# Cognitive Control and Decision Making
## in ADHD

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cognitieve controle en beslisprocessen in ADHD

(met een samenvatting in het Nederlands)

**Proefschrift**

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door

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**Co-promotor:** Dr. S. Durston

*voor Pa en Ma*
*en Doriene*

# Contents

# Introduction

Attention-deficit hyperactivity disorder (ADHD) has a heterogeneous phenotype. The disorder is defined by inappropriate, impulsive or inattentive behavior, often within social contexts. For example, subjects with ADHD may have trouble staying in their seat in the classroom, or may blurt out comments while at the movies, or may have difficulty waiting their turn in a conversation. In addition, subjects with ADHD often are distracted easily, making it hard to stay focused on a task at hand. However, to some extent impulsive and inattentive behavior is a normal part of childhood, making it sometimes difficult to distinguish between symptoms of the disorder and typical development. In other words: how impulsive or how distractible does a child have to be in order to receive a diagnosis of ADHD? Criteria have been drawn up to define the disorder (see Table 1; American Psychiatric Association, 1994 & ICD-10). In addition to classifying symptoms, they provide a measure of the severity of impairment: a child can only be diagnosed when a minimum level of the impairment is met. Such criteria are useful in the clinic, as they objectify the disorder. However, they also emphasize the phenotypic heterogeneity of ADHD. Such heterogeneity makes it hard to identify the neurobiological mechanisms underlying the disorder. Nevertheless, research has shown that ADHD is heritable and that genetic factors account for a substantial part of the phenotypic variance. Studies have suggested that different biological pathways may underlie the disorder, where, e.g., different genotypes and environmental factors result in similar phenotypes that are covered by the ADHD diagnosis.

## Prevalence & Treatment

ADHD is a neurodevelopmental disorder that is characterized by disorganized, inattentive behavior as well as inappropriate levels of impulsivity and hyperactivity (American Psychiatric Association, 2000; Kaplan, et al., 1994). It is the most commonly diagnosed psychiatric disorder in childhood (Brown, et al., 2001; Faraone, et al., 2003; Levy, et al., 1997), with a worldwide prevalence of 5.3% (Polanczyk, et al., 2007). The age of onset is usually around age of 6 or 7 years (American Psychiatric Association, 1994; WHO, 1992) and the disorder can persist into adulthood (Asherson, 2009; Wilens, et al., 2002).

Treatment for the disorder includes pharmacotherapy and non-pharmacological therapy such as education remediation and psychotherapy. Stimulants, such as methylphenidate and amphetamine are effective, but have sometimes been questioned due to putative adverse effects. Alternative therapies, such as food supplementation with poly-unsaturated fatty acids are gaining popularity, but to date, the effects are not convincing enough to replace psycho or drug therapy (Dopheide & Pliszka, 2009).

## Etiology

ADHD is a heritable psychiatric disorder (Dopheide & Pliszka, 2009). The disorder has a tendency to cluster in families and up to 75-80% of the variance in ADHD symptoms can be explained by genetic effects (Albayrak, et al., 2008; Faraone, et al., 2005; Rasmussen, et al., 2004; Thapar, et al., 1999). Furthermore, twin and adoption studies suggest a substantial genetic component for ADHD, with 50-80% concordance for monozygotic twins and 30% for dizygotic twins (Bradley & Golden, 2001; Hechtman, 1994; Thapar, et al., 1999).

Genetic studies of ADHD have been conducted. Two popular methods are linkage and association studies. In linkage studies, the whole genome is scanned for each subject, to look for genetic markers that all subjects share. It is then suggested that the shared behavior (or disorder) across subjects is linked to the area around that marker. However, as these markers often represent large parts of a chromosome, it is hard to pinpoint the exact genes that are associated with the disorder. In association studies, two discordant groups are compared to each other, to investigate whether a certain genotype (or allele) is present more often in the affected than in the unaffected group. Often, candidate genes are selected on theoretical grounds and used in association studies to investigate if they are involved in the disorder.

Several candidate genes have been implicated in ADHD. These include genes related to dopamine and serotonin systems (Faraone, et al., 2005). Both neurotransmitter systems have been implicated in ADHD in a variety of studies (for review see Durston, et al., 2009). For example, it has been shown that a hypodopaminergic state of the striatum is related to ADHD symptoms. Stimulant medication normalizes these decreased dopamine levels by blocking dopamine transporter (DAT) receptors (Shafritz, et al., 2004; Spencer, et al., 2007; Vaidya, et al., 1998). This has been confirmed in animal studies using DAT1 knock-out mice, where the initial hyperactive behavior improved when stimulant

*Table 1.* Diagnostic Criteria for ADHD, according to the DSM-IV (APA, 1994)

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 or homework)
   g. Often loses things necessary for tasks or activities (e.g. toys, school assignments, 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 situations 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 blurts out answers before questions have been completed
   h. Often has difficulty awaiting turn
   i. Often interrupts or intrudes on others (e.g. butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before 7 years of age.

C. Some impairment from the symptoms is present in 2 or more settings (e.g. at school [or work] or 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 other psychotic disorder and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, or 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

**314.00 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

**314.9 Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified**

medication was administered. Interestingly, this effect was mediated by serotonin systems, showing the involvement of both dopamine and serotonin systems in these improvements (Gainetdinov, et al., 1999).
Genes that have most often been associated with ADHD are the dopamine D4 receptor gene (DRD4) and dopamine transporter gene (DAT1) (see for review Durston, et al., 2009). Furthermore, across studies that used the less detailed method of linkage mapping, the link with region 5p13 was replicated in two independent samples; the region that includes the candidate DAT1 gene (Friedel, et al., 2007; Hebebrand, et al., 2006). A second region that is replicated is 17p11, which lies close to 17q11, a region that covers the serotonine transporter gene (Ogdie, et al., 2003).

Despite these convincing results, findings of association and linkage studies are not consistent, suggesting that ADHD may be related to combinations of genes, each of which have a limited effect (Faraone, et al., 2005). Furthermore, even for the best-replicated candidate genes (DAT1 and DRD4) nearly as many negative as positive associations have been found (Durston, et al., 2009).
It has been suggested that gene x environment interactions may explain some of the inconsistent findings in genetic studies of ADHD (Plomp, et al., 2009; Rutter & Silberg, 2002). For example, an increased risk for ADHD has been reported for carriers of the polymorphism of DAT1 that is most often associated with ADHD, but only when they were exposed to psychosocial adversity (Laucht, et al., 2007), maternal smoking during pregnancy (Becker, et al., 2008; Kahn, et al., 2003; Todd & Neuman, 2007) or maternal use of alcohol during pregnancy (Brookes, et al., 2006). Similar findings have been reported for carriers of the DRD4 polymorphism (Neuman, et al., 2007; Todd & Neuman, 2007).

In sum, although etiology data suggest an underlying heritable biological basis for ADHD, only a few genes have been confirmed repeatedly, both with and without an interaction with environmental factors. A possible explanation for these inconsistent findings is that the heterogeneous symptoms in ADHD do not map onto the neurobiological effects of gene variations. The use of endophenotypes may help to address this problem.

## Endophenotypes

Diagnostic classification criteria are often extensive and diverse. As such, investigating the neurobiology of the disorder at this level is extremely difficult since links between the behavioral data and the underlying biological mechanisms are diverse and noisy (Gottesman & Gould, 2003). An endophenotype is a quantifiable component between biology and behavior that reduces the heterogeneity of psychiatric symptoms (Gottesman & Gould, 2003; Gould & Gottesman, 2006). Measures of such quantity allows to identify biological pathways that are less susceptible for noisy variations of the phenotype (see Figure 1). For example, with functional magnetic resonance imaging (fMRI) one can measure brain activity during tasks that probe disabilities associated with the disorder.

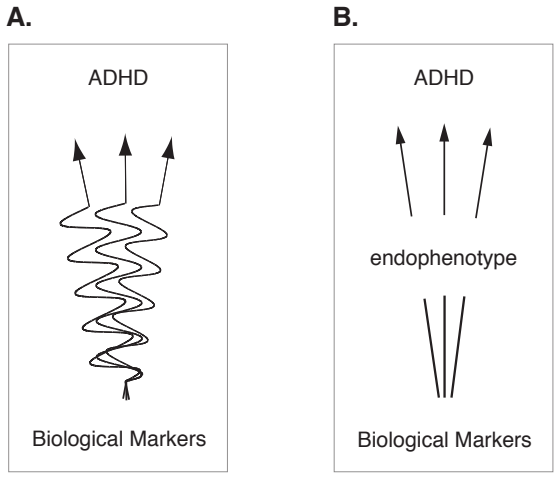


*Figure 1.* Links between the disorder and the underlying biological mechanisms are diverse and noisy (A). Use of an endophenotype reduces the heterogeneity in the phenotype of interest allowing research to identify biological pathways that are shorter and thus less susceptible to variations in the phenotype (B).

Such a measure will likely be closer to genetic influences, producing a more homogeneous measure for investigating causative agents. As such, it may be useful to identify measures that can serve as endophenotype in investigating the neurobiology of ADHD. There are a number of criteria that a measure should meet in order to serve as an endophenotype (see Table 2; for review see Durston, et al., 2009). One such criterion is that the endophenotype should also be found in non-affected family members, at a higher rate than in the general population.

## Cognitive control in ADHD

A sensible starting point to elucidate gene-behavior pathways is to reduce the phenotype to measurable units. This is necessary to link neurobiological mechanisms to the heterogeneous symptoms of ADHD. A measure that has been used successfully for this purpose is cognitive control. Cognitive control is the ability to control behavior in response to contextual and temporal cues and adjust behavior accordingly (Nigg & Casey, 2005). According to this model, the brain makes predictions about *what* is going to happen and *when* it is going to happen. When these predictions are violated, behavior needs to be adjusted in order to act toward a specific goal (see Figure 2). It has been suggested that two important brain circuits are involved in regulating these processes: The fronto-striatal circuit, involved in the detection of novel events (*what* events; Berns, et al., 1997; Schultz, et al., 1997), and the fronto-cerebellar circuit, involved in monitoring and detecting violations in the timing of events (*when* events; Ivry, et al., 2002; R. M. Spencer, et al., 2003). Both circuits are believed to play an important role in the development of the ability to adjust behavior in response to contextual cues (Casey, 2005).

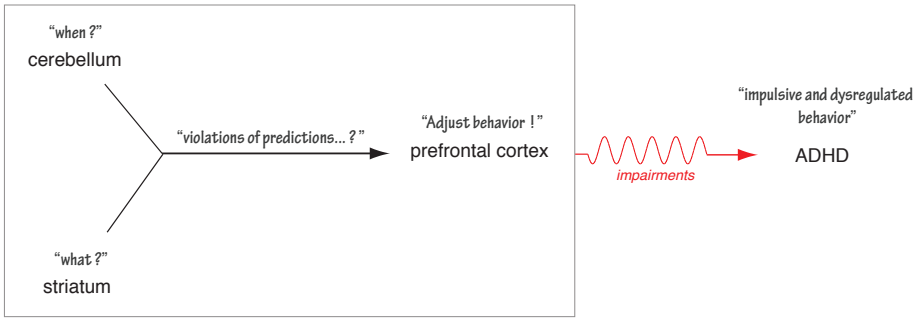


*Figure 2*. Schematic representation of aspects of cognitive control and their relationship to ADHD. The brain makes predictions about *what* is going to happen (fronto-striatal system) and *when* it is going to happen (fronto-cereblellar system). When these predictions are violated, behavior needs to be adjusted in order to act toward a specific goal (prefrontal cortex). Impairments in these systems can lead to impulsive and dysregulated behavior as seen in the ADHD phenotype. Modified with permission from Nigg & Casey, 2005.

It has been suggested that impairments in cognitive control may explain a substantial part of the ADHD phenotype (Barkley, 1997; Durston, 2003; Durston, et al., 2009; Nigg & Casey, 2005; Sergeant, et al., 2002; Willcutt, et al., 2005). Subjects with ADHD often perform worse than typically developing children on tasks that probe cognitive control. Furthermore, neuroimaging studies have shown deficits in brain functioning underlying these behavioral differences. Specifically, during tasks where subjects are required to inhibit a prepotent response, the ventro-lateral prefrontal cortex, anterior cingulate cortex and striatum showed decreased activity for subjects with ADHD compared to control subjects (for review see Bush, et al., 2005; Castellanos & Tannock, 2002; Dickstein, et al., 2006; Durston, et al., 2009). Furthermore, structural neuroimaging in ADHD has shown volume reductions

in prefrontal cortex (gray matter), striatum and cerebellum (for review see Durston, 2003; for meta analyses Valera, et al., 2007). As these regions are involved in cognitive control (Aron & Poldrack, 2005; Botvinick, et al., 2004; Nigg & Casey, 2005), it is not surprising that impairments in activity of these regions are associated with ADHD.

These findings suggest that neuroimaging measures of cognitive control could be a candidate endophenotype, as they meet a number of the criteria (see Table 2): behavioral and neuroimaging measures of cognitive control are continuous quantities (*criterion 1*); deficits are stable and well established in the ADHD phenotype (*criteria 2 & 4*) (Lijffijt, et al., 2005; Nigg, et al., 2005); behavioral changes in cognitive control are heritable (*criteria 6 & 7*) (Rasmussen, et al., 2004; Slaats-Willemse, et al., 2003) and deficits in cognitive control are grounded in neuroscience (*criterion 8*) (for review see Durston, et al., 2009).

*Table 2.* Criteria for endophenotypes for investigating gene effects in psychiatry

| *Criteria for intermediate phenotypes in psychiatric research* | |
|---|---|
| (1) | Continuously quantifiable |
| (2) | Stable (a trait as opposed to a state measure) |
| (3) | Closer to the causative agent (e.g., genes and gene expression) than the disorder |
| (4) | Associated with disorder |
| (5) | Probabilistically predictive of the disorder |
| (6) | Cluster in families where the disorder is found |
| (7) | Found in unaffected relatives of affected individuals |
| (8) | Grounded in neuroscience |

(adapted from Almasy & Blangero, 2001; Castellanos & Tannock, 2002; Durston, et al., 2009; Gottesman & Gould, 2003)

## Perceptual Decision Making

As noted, theoretical accounts have often linked the ADHD phenotype to deficits in cognitive control, where children with ADHD have problems responding to contextual and temporal cues and adjusting their behavior accordingly. Tasks that tap cognitive control are often designed to manipulate various aspects of cognition, but at the trial level they have often one thing in common: they require the subject to make a perceptual decision before choosing the most appropriate course of action. It is an open question whether these basic processes are also affected by the disorder.

Mathematical models have been developed to describe the process of perceptual decision making. One class of these models is the drift-diffusion models (DDM; see for review Bogacz, 2007; Gold & Shadlen, 2007). These models describe the decision process as an accumulation of noisy sensory information towards a decision threshold. For example, imagine a task that requires a subject to choose whether the perceived motion of a ‘cloud’ of moving dots is directed to the right or to the left. Here, the sensory information is determined by the number of dots moving coherently towards a direction.

Suppose that 80% of the dots is moving to the left, and 20% is moving randomly, then the DDM predicts that the accumulation towards the decision threshold will be more likely to end at the 'left'-threshold, because the sensory evidence for this direction is larger per time unit, as opposed to its 'right' alternative (see Figure 3).

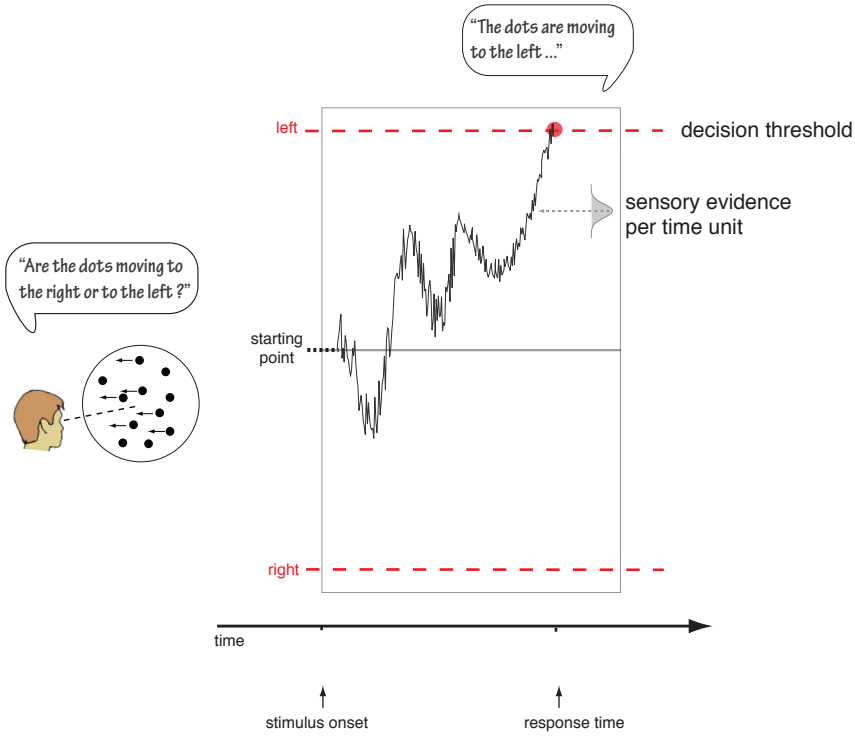


*Figure 3.* Schematic representation of the drift-diffusion model. This model assumes that decisions between two alternatives are based on the accumulation of noisy evidence over time towards a fixed threshold (decision threshold). As the process is noisy, there is variability in the time to reach the threshold, leading to variable RTs and possibly incorrect choices.

These simple predictive models are successful as they can account for both response time (RT) and accuracy data from various experimental manipulations (Bogacz, et al., 2006; Gomez, et al., 2007; Palmer, et al., 2005; Ratcliff, 1978, 2006; Ratcliff & McKoon, 2008; Ratcliff & Rouder, 1998; Simen, et al., 2009; Voss, et al., 2004). Furthermore, studies from both humans and non-human primates are showing neural correlates that map on the assumptions made by the DDM, suggesting that they are ecologically valid (Aston-Jones & Gold, 2009; Beck, et al., 2008; Ditterich, 2006a, 2006b; Forstmann, et al., 2008; Gold & Shadlen, 2001, 2002; Grossberg & Pilly, 2008; Heekeren, et al., 2004; Mazurek, et al., 2003; Philiastides & Sajda, 2007; Schall, 2001; Wang, 2002). In addition to an overall model for

RT and accuracy data, the DDM provides insight in the dynamics of the decision process, as changes in the model parameters have an unique effect on the adjustment of choice behavior (Ratcliff & McKoon, 2008).
An example for such adjustments involves balancing between fast and accurate choices: When information is noisy, errors are more likely to be made and more time is needed for a correct decision. As such, manipulating speed and accuracy instructions in a perceptual decision making paradigm is an excellent tool to assess possible deficits in behavioral optimization related to ADHD. Furthermore, by biasing behavior towards one decision, for example by favoring it with reward, these models can address how the brain uses this information to bias behavior.

## Aim of this thesis

The overall aim of this thesis is to address how aspects of cognitive control and decision making contribute to ADHD symptoms. In the first part of this thesis we address whether deficits in brain activity during different aspects of cognitive control are vulnerable to familial risk for ADHD. By doing so, we can identify candidate endophenotypes for ADHD. The second part of the thesis focuses on basic perceptual decision making. Here, we investigate whether impairments associated with ADHD are limited to higher-order cognitive processes or if more basic processes are also affected. Furthermore, we address where in the brain basic decisions are biased by environmental factors, such as expected reward.

## Outline of this thesis

Neuroimaging of cognitive control may be a candidate endophenotype for ADHD research. In the first section (**part 1**) of this thesis we investigate this by using functional MRI to measure changes in brain activation during tasks that tap cognitive control in typically developing children, subjects with ADHD and their unaffected siblings. If deficits have a heritable component, unaffected siblings of subjects with ADHD will show changes similar to their siblings with ADHD or intermediate between them and typically developing controls (see Table 1, *criteria 7*). In **chapter 2** we investigate whether deficits in brain functioning underlying cognitive control are sensitive to a familial risk for ADHD. We use functional MRI during a go/no-go paradigm to measure changes in the brain activity in boys with ADHD, their unaffected siblings and typically developing controls. In **chapter 3** we investigate whether cerebellar systems are sensitive to a familial risk for ADHD, in addition to fronto-striatal circuitry. As it has been shown that the fronto-cerebellar circuit is involved in cognitive control in situations where *when* predictions are violated, we will use a variation of the go/no-go paradigm where both stimulus timing (*when*) and stimulus identity (*what*) are manipulated. In **chapter 4**, we investigate whether functional connectivity between regions underlying cognitive control is affected by familial risk and if changes are specific to these regions. We will use correlational seed analyses to investigate temporal co-variance across brain regions within cognitive control and motor networks in two independent data-sets to address whether it is the level of activity per se that is under familial risk, or whether changes in connectivity in cognitive control are also affected.
In the second section of this thesis (**part 2**), we focus on decision making. As tasks that tap cognitive control often involve perceptual decisions, we address the question whether these basic processes are affected by ADHD in **chapter 5**. We use a basic perceptual decision making task where speed and accuracy instructions are manipulated to investigate whether subjects with ADHD are able to optimize decision parameters to changing task demands. In **chapter 6**, we address where in the brain such decision processes are influenced by environmental factors such as expected reward.

Is neuroimaging of cognitive control a suitable endophenotype for ADHD research? Are basic perceptual decisions affected by the disorder, in addition to higher-order processes such as cognitive control? If so, what does it tell us about ADHD as a neurobiological disorder? In **chapter 7**, we discuss the results from this thesis to address these questions.

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# Part 1

In **Part 1** of this thesis (**chapters 2, 3 & 4**) we address whether deficits in brain activity during different aspects of cognitive control are vulnerable to familial risk for ADHD. By doing so, we are able to identify candidate endophenotypes for ADHD.

# Chapter 2

## Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for ADHD

**Background**. Attention-deficit hyperactivity disorder (ADHD) is a heritable neuropsychiatric disorder, associated with atypical patterns of brain activation in functional imaging studies. Neuroimaging measures may serve as an intermediate phenotype in genetic studies of ADHD, as they are putatively more closely linked to gene expression than a clinical diagnosis.

**Methods**. We used rapid, mixed-trial, event-related functional magnetic resonance imaging (fMRI) to investigate changes in brain activation during a go/no-go task in boys with ADHD, their unaffected siblings, and matched control subjects.

**Results**. On the hardest inhibitory trials in our task, children and adolescents with ADHD had lower accuracy than control subjects, whereas their unaffected siblings did not. Control subjects activated a network of regions, including ventral prefrontal and inferior parietal cortex. Both children and adolescents with ADHD and their unaffected siblings showed decreased activation in these areas, as well as fewer correlations between performance and activation.

**Conclusions**. These findings suggest that the magnitude of activation during successful inhibitions is sensitive to genetic vulnerability for ADHD in a number of regions, including ventral prefrontal cortex. If this can be replicated in future studies, this suggests that neuroimaging measures related to inhibitory control may be suitable as intermediate phenotypes in studies investigating gene effects in ADHD.

*Biol Psychiatry, 2006*

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## Introduction

Attention-deficit hyperactivity disorder (ADHD) is a heritable neuropsychiatric disorder, with increased incidence in biological relatives of affected individuals. The siblings of children with ADHD have a three- to fivefold increased risk of having ADHD compared to the siblings of healthy control subjects (Biederman, et al., 1992; Faraone, et al., 1993) and the risk is even greater for monozygotic twins with 50-80% concordance compared with up to 33% in dizygotic twins (Bradley and Golden, 2001). As full siblings share on average 50% of their genes, even the unaffected siblings of children with ADHD would be expected to share some of the genes involved in the disorder. The genes involved are not yet known, although several candidates have been proposed (see Faraone, et al., 2005; Heiser, et al., 2004 for review). One of the key neuropsychological features of ADHD is that affected individuals are impaired on tasks that tap executive functioning, in particular those that involve cognitive, or inhibitory, control (see Sergeant, et al., 2002; Willcutt, et al., 2005 for reviews). Studies using go/no-go, stop- and Stroop paradigms have consistently shown poorer performance and slower reaction times for children with ADHD relative to healthy controls (e.g. Grodzinsky and Diamond, 1992; Schachar, 1995; Seidman, et al., 1995, 1997; for meta-analysis see Oosterlaan, 1998). It has been proposed that deficits in executive functioning associated with ADHD may even be due to a core deficit in inhibitory control (Barkley, 1997). In this view, the ability to inhibit inappropriate behaviors is central to the successful execution of other neuropsychological functions, such as working memory (by inhibiting responses to interfering thoughts or external events), goal- directed behavior (acting towards a future reward and inhibiting actions towards immediate gratification) or emotional self-control (by inhibiting emotional responses in favor of more thought-out reactions). In ADHD, lack of such behavioral control may then explain the deficits in cognitive functioning and impulsive behaviors associated with the disorder. Imaging studies have shown that cognitive or inhibitory control is associated with a pattern of brain activation involving ventral prefrontal areas, anterior cingulate cortex and parietal cortex, where ventral prefrontal activation has been suggested to be particularly critical to successful task performance (e.g., Bellgrove, et al., 2004; Casey, et al., 1997; Durston, et al., 2002a, 2002b, 2003; Garavan, et al., 1999; Konishi, et al., 1999; Liddle, et al., 2001; Rubia, et al., 2000).

ADHD has been associated with atypical patterns of brain activation relative to healthy controls (see Durston, 2003 for a review). Functional imaging studies consistently show atypical activation in individuals with ADHD, in particular in prefrontal regions (Booth, et al., 2005; Bush, et al., 1999; Durston, et al., 2003; Liotti, et al., 2005; Rubia, et al., 1999, 2005; Schulz, et al., 2004, 2005; Schweitzer, et al., 2000; Tamm, et al., 2004; Vaidya, et al., 1998; Zang, et al., 2005). While most of these studies show hypofrontality, some have shown localized increases in activation for some prefrontal regions, suggesting that the more frequently reported hypofrontality may be region or task-specific, and that behavioral improvement on medication, and possibly the remission of ADHD symptoms in adolescence may be related to prefrontal increases in activation (e.g., Durston, et al., 2003; Schultz, et al., 2004, 2005; Vaidya, et al., 1998).

Neuroimaging measures may potentially serve as an intermediate phenotype in genetic studies of ADHD (Castellanos and Tannock, 2002). Intermediate or endophenotypes are putatively more closely

related to gene expression than a psychiatric diagnosis, such as ADHD and as such, the effects of risk genes may be greater in these intermediate measures, making them easier to detect. In order to qualify as a potential endophenotype, neuroimaging measures should meet several criteria, such as being heritable, being stable over time, as well as being grounded in neuroscience (Castellanos and Tannock, 2002). In ADHD, catecholaminergic modulation of prefrontal functioning may be a good candidate, as it has been implicated in numerous studies of ADHD (see Durston, 2003 for review). We previously showed that unaffected siblings of boys with ADHD display subtle reductions in cortical gray matter volume, including in prefrontal cortex, comparable to their affected siblings (Durston, et al., 2004), suggesting that MRI-based brain measures may be suitable as intermediate phenotypes in ADHD research. To further examine this association, we assessed catecholaminergic gene effects on gray matter volumes, and were able to link prefrontal gray matter to a dopamine gene expressed preferentially in that region (DRD4), as well as show a similar effect in the striatum for a gene expressed preferentially in that region (DAT1) (Durston, et al., 2005). Recently, it has been suggested that inhibitory control and associated activation in inferior frontal gyrus (IFG) may serve as an endophenotype for ADHD, as this appears to be a stable and heritable trait in this disorder (Aron and Poldrack, 2005). Therefore, we set out to address this question by investigating whether changes in inhibitory control and associated brain activation in ADHD could be found in individuals with a genetic vulnerability for the disorder, but free of symptomatology.

In a previous study, we used a go/no-go task to show that children with ADHD display atypical patterns of brain activation compared to typically developing children (Durston, et al., 2003). In that study, we manipulated task difficulty by systematically varying the number of go-trials preceding no-go trials (Durston, et al., 2002a, 2002b). This manipulation provided an opportunity to examine trials on which the groups had comparable performance. As such, we showed that differences in activation were not solely due to differences in performance of the task. In the present study, we used the same task to investigate inhibitory control and brain activation patterns in a new sample of boys with ADHD, their unaffected siblings and matched control subjects. To maximize our ability to separate ADHD symptoms (in probands) from genetic vulnerability (in probands and unaffected siblings), we required 1) affected siblings to be free of medication at the time of the scan, and 2) unaffected siblings to be free of ADHD-symptomatology, as assessed by structured interview and symptom-rating scales.

## Methods

*Subjects.* A total of 41 boys, aged 8 to 20 years, participated in the current study. This included 33 individuals who had previously participated in a structural MRI study at our department (Durston, et al., 2004). Sibling pairs were recruited through the University Medical Center in Utrecht, whereas controls were recruited through schools in the area. All assessments and study participation were conducted in Dutch. After a complete description of the study, written informed consent was obtained from a parent for all subjects. In addition, all subjects were asked to sign for assent. The procedure was approved by the Central Committee on Research involving Human Subjects in the Netherlands. Subjects with major physical or neurological illness, such as migraine, epilepsy, endocrine disorders, head trauma in the past or IQ of below 70 were excluded. All subjects that met the inclusion criteria were

*Table 1.* Descriptive Variables per Group

| | Controls | Unaffected siblings | siblings with ADHD |
|---|---|---|---|
| Age (years) | 15.27 (1.92)<br>12.70 - 19.00 | 14.45 (2.58)<br>10.50 - 20.40 | 13.97 (3.14)<br>8.20 - 18.20 |
| Total IQ | 106 (14)<br>91 -127 | 107 (15)<br>80 - 127 | 100 (10)<br>86 - 114 |
| Verbal IQ | 100 (19)<br>76 - 124 | 105 (14)<br>80 - 128 | 99 (16)<br>74 - 124 |
| Performance IQ | 110 (10)<br>95 -125 | 108 (20)<br>85 - 152 | 101 (12)<br>88 - 123 |
| Father's eduction (years) | 10.9 (3.9)<br>6.0- 17.0 | 12.2 (2.4)<br>10.0 - 15.0 | 12.2 (2.4)<br>10.0 - 15.0 |
| Mother's education (years) | 11.8 (2.5)<br>10.0- 17.0 | 11.3 (1.9)<br>10.0 - 15.0 | 11.3 (1.9)<br>10.0 - 15.0 |
| Handpreference (no. lefthanded) | 0 | 0 | 2 |
| ADHD (no. meeting criteria) | 0/11 | 0/11 | 10/11 combined<br>1/11 hyperactive |
| ODD (no. meeting criteria) | 0/11 | 0/11 | 3/11 |
| ADHD Symptoms (no. on DISC) | | | |
| Inattentive | .8 (.8)<br>0–2 | .0 (.0)<br>0–0 | 6.5 (2.1) **<br>4–9 |
| Hyperactive / Impulsive | .4 (.7)<br>0–2 | .3 (.9)<br>0–3 | 7.4 (1.4) **<br>6–9 |
| CBCL score | | | |
| ADHD | 2.0 (1.5) | 2.7 (2.3) | 7.3 (3.0) ** |
| ODD | 1.5 (1.6) | 2.0 (2.1) | 4.5 (1.8) ** |
| CD | 0.5 (0.8) | 2.0 (2.5) | 5.3 (4.1) ** |
| affective problems | 1.0 (1.8) | 1.0 (1.2) | 3.8 (3.8) * |
| anxiety | 0.4 (0.5) | 0.9 (1.0) | 1.9 (1.6) * |
| somatic problems | 0.3 (0.5) | 0.6 (0.7) | 1.4 (1.4) * |
| attention problems | 2.6 (2.0) | 2.6 (2.9) | 4.1 (3.5) ** |
| delinquency | 0.8 (0.8) | 2.5 (2.5) | 5.0 (3.0) ** |
| aggression | 1.9 (2.5) | 3.0 (4.3) | 4.9 (5.5) ** |
| withdrawn | 1.2 (1.7) | 2.0 (1.8) | 2.6 (2.9) |
| anxious-depressed | 0.7 (1.1) | 1.7 (1.9) | 4.0 (3.2) ** |
| social problems | 0.5 (0.8) | 1.2 (2.0) | 1.9 (3.0) ** |
| thought problems | 0.5 (0.7) | 0.7 (1.1) | 4.2 (3.5) ** |
| somatic complaints | .0.4 (0.7) | 0.9 (0.8) | 1.3 (1.9) ** |
| Methylphenidate at Scan, no/group | 0/11 | 0/11 | 6/11 |
| Performance on Task | | | |
| Reaction time (msec) | 587 (66) | 567 (102) | 581 (94) |
| Accuracy (overall) | .92 (.06) | .88 (.08) | .84 (.12) |
| after 1 go trial | .96 (.04) | .88 (.12) | .89 (.09) |
| after 3 go trials | .88 (.12) | .86 (.09) | .86 (.12) |
| after 5 go trials | .90 (.09) | .87 (.07) | .79 (.17) * |

Values are mean (standard deviation) and range. ADHD, attention deficit hyperactivity disorder; ODD, opporitional defiant disorder; CBCL, Child Behavior Checklist; DISC, Diagnostic Interview Schedule for Children.
* $p < .05$. ** $p < .01$.

asked to participate in a one-hour functional magnetic resonance imaging (fMRI) scanning session and a neuropsychological assessment in order to estimate full-scale IQ (Similarities, Vocabulary, Block Design and Object Assembly subtests of the Wechsler Intelligence Scale for Children - Revised [WISC-R]) (Wechsler, 1974). (Dutch norms were not available for more recent versions of the WISC at the time this study was conducted.) For each subject a parent was asked to participate in a semi-structured interview session with a trained rater to objectively determine psychiatric diagnosis (Diagnostic Interview Schedule for Children [DISC-P]) (Shaffer, et al., 2000). In addition, parents were asked to fill out the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock, 1983). ADHD subjects were required to meet DSM-IV criteria (American Psychiatric Association, 1994) for ADHD, as assessed by DISC-interview. Subjects with co-morbid disorders other than oppositional defiant disorder (ODD) were excluded. Unaffected siblings and control subjects were excluded if they met DSM-IV criteria for any psychiatric diagnosis, as assessed by DISC interview. In addition, they were excluded if they scored in the clinical range on the CBCL. Control subjects were excluded if they had first-degree relatives who had been diagnosed with ADHD or another disruptive disorder. Functional MRI data from eight subjects were excluded from further analysis, due to excessive motion or, in one case, artifact on the MRI scan caused by dental implants. Data for 11 discordant sibling pairs and 11 matched control subjects were included in the fMRI analyses. Subjects were matched at a group level for age, IQ, and socio-economic status (operationalized as parental education level) for both samples. Ten of eleven subjects with ADHD met DISC-criteria for ADHD, combined subtype. One subject scored subthreshold on the inattention scale of the DISC (4 symptoms) and therefore met criteria for ADHD, hyperactive subtype. In addition, three of the ADHD subjects met DISC-criteria for ODD. There were significant differences between groups on several CBCL scales, including ADHD and attention problems scales. Subjects with ADHD had higher mean values on all significantly different measures (all $F > 4.0$; $p < .03$ for subjects with ADHD; $p > .05$ for unaffected siblings). Six of 11 subjects with ADHD were on stimulant medication at the time they were approached for this study. All discontinued medication for at least 24 hours prior to the scan (see Table 1).

*Paradigm.* All subjects participated in an fMRI session using a go/no-go paradigm as previously described (Durston, et al., 2002a, 2002b, 2003, 2006). The subjects' task was to press a button in response to visually presented stimuli, but to avoid responding to a rare nontarget. The task consisted of 5 runs, which lasted 3 min and 56 sec each. Each run contained a total of 57 trials, with 75% go trials, resulting in a total of 70 no-go trials, including 20 of each type (with 1, 3 or 5 preceding go trials) per subject. Foil trials (no-go trials after 2 or 4 go trials) were also included, to prevent subjects learning the pattern. The order of presentation of the different types of no-go trials was pseudorandomized. In order to make the task more interesting for children, characters from the Pokemon cartoon series were used as stimuli. Stimulus duration was 500 msec and the interstimulus interval was 3500 msec (total trial length = 4000 msec). Stimuli were projected using a through-projection screen and slide projector. Responses were collected using an MRI compatible air pressure button box.

*Analysis of behavioral data.* All behavioral data were analyzed using the SPSS statistical package (version 11.5, SSPS Inc., Chicago, Illinois). Differences in behavior were investigated in the total sample of 41 subjects, as well as in the smaller sample of 33 subjects for whom imaging data were included. Differences were investigated using a two-tailed General Linear Model (multivariate)

analysis of variance ([M]ANOVA), with separate dummy variables coding for ADHD and sibling status (Durston, et al., 2004). As we hypothesized that there would be a correlation between the number of errors on no-go trials and the number of preceding go-trials, we investigated this using Fisher's R to Z transformation and a one-tailed Z-test. As the age-range included in this study was quite wide, and we have previously shown that the ability to perform this task increases with age (Durston, et al., 2002b), we re-ran all behavioral and functional MRI analyses including age as a covariate.

*Scan acquisition.* All subjects participated in a practice session prior to scanning, using an MRI simulator, housed at the Department of Child and Adolescent Psychiatry, at the University Medical Center in Utrecht, the Netherlands. The purpose of this session was to acquaint subjects with the scanner environment, the task, and the researchers present during the MRI-session. All subjects successfully participated in both the practice and actual MRI sessions. MRI images were acquired on a 1.5-T Philips Gyroscan (Philips Medical Systems, Best, the Netherlands), housed at the Department of Radiology in the same hospital. Functional MRI scans consisted of a navigated three-dimensional (3D)-PRESTO pulse sequence (time to echo [TE] 11 msec, repetition time [TR] 21.74 msec, flip angle 9.0°, matrix 64 x 64 x 24, field of view [FOV] 256 x 256 x 96 mm, voxel size 4 mm isotropic, and scan duration 2.0 sec per 24-slice volume), covering the whole brain. Anatomical T1-weighted 3D fast field echo (FFE) scans with 130 to 150 1.5 mm contiguous coronal slices of the whole head (TE 4.6 msec, TR 30 msec, flip angle 30°, FOV 256 mm, in plane voxel size 1 mm x 1 mm) were also acquired. A FA30 scan with contrast more similar to the T1 weighted scans was also acquired to aid in the alignment of PRESTO images to the template (TE 12.10 msec, TR 24.24 msec, flip angle 30°, matrix 64 x 64 x 24, FOV 256 x 256 x 96 mm, voxel size 4 mm isotropic). During anatomical scans the projection system was used to play cartoons, to prevent the subjects becoming bored or restless.

*Functional MRI analysis.* All data were analyzed using a random effects model in Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London). PRESTO images were realigned and normalized to a standard stereotactic space (Montreal Neurological Institute (MNI) template). Estimated motion parameters were examined on a subject-by-subject basis to ensure that the amount of absolute motion did not exceed 4 mm, or the size of 1 voxel. There were no differences between groups in the average amount of motion.
At the first level, six event types were defined (initial fixation, correct and incorrect go trials and no-go trials and a parametric factor representing the number of go trials preceding a no-go trial (1-5). These included three effects of interest (go trials, no-go trials and the parametric factor) and three effects of no interest (initial fixation, omission errors and comission errors). The event types were time-locked to stimuli by a canonical synthetic haemodynamic response function (HRF) and its first-order temporal derivative.
For the second-level analysis, random effects analyses were performed for each group separately. The first analysis compared no-go to go-trials (one-sample *t*-test), whereas the effect of the parametric contrast was evaluated in a second analysis, using a one-way ANOVA with no-go and parametric factors entered (see Henson, et al., 2002). Differences in activation were tested at a threshold of $p < .001$, uncorrected, with a minimum extent of 10 voxels. Correlations between MR-signal change and performance on the task were investigated in an ANCOVA-design, with performance entered as the covariate. Changes in MR signal related to task performance were then investigated using a

masking approach, where the no-go > go contrast was calculated using brain activation associated with performance as an inclusive mask at a more lenient threshold ($p < .01$; extent 5 voxels).
For the between-group analysis, three planned contrasts were performed, comparing subjects with ADHD to controls, siblings to controls and subjects with ADHD to their unaffected siblings.

Whole-brain, between-group analyses were followed up by a region-of-interest (ROI) analysis, implemented in the MarsBaR package (Brett, et al., 2002) to investigate changes between groups. ROIs included all voxels activated by the control group in the no-go > go condition at the threshold of $p < .001$ with minimum extent of 10 voxels.
As the age-range included in this study was quite wide, all functional MRI analyses were re-run including age as a covariate. MNI stereotactic coordinates were transformed to Talairach and Tournoux space.

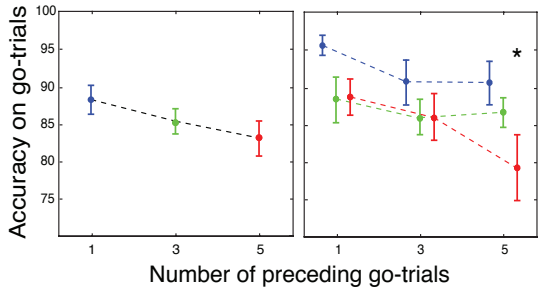


*Figure 1.* Accuracy on no-go trials for the group as a whole (left panel) and control subjects, children and adolescents with ADHD and their unaffected siblings separately (right panel). In the left panel there is a significant relationship between the number of preceding go-trials and accuracy on no-go trials for the group as a whole. In the right panel accuracy is significantly lower for individuals with ADHD for no-go trials preceded by five go-trials. Differences for other types of no-go trials do not reach significance.

## Results

*Behavioral results.* In the total sample of 41 subjects, there was a significant increase in errors on no-go trials as a function of the number of preceding go trials ($r = .17$; p = .034; see Figure 1).
This increase did not reach significance for individual subgroups (control subjects, children and adolescents with ADHD, or their unaffected siblings; $p > .05$). There was a trend for differences in accuracy on no-go trials between groups ($F = 3.76$, $p = .061$ for children and adolescents with ADHD

*Table 2.* Regions of activation for controls.

| Region | Side | BA | Talairach | Max t-value |
|---|---|---|---|---|
| *Go > No-go* | | | | |
| Precentral G | L | 4 | -55, -25, 53 | 7.22 |
| Cerebellum | R | | 24, -45, -41 | 8.39 |
| *No-go > Go* | | | | |
| *Inf frontal G ** | *R* | *47* | *40, 20, -8* | *11.12* |
| | L | 47 | -36, 19, -7 | 6.41 |
| Ant cingulate G | R | 24/32 | 4, 40, 16 | 4.98 |
| | L | 24/32 | -8, 40, 24 | 4.57 |
| Inf/mid frontal G | L | 10/46 | -36, 43, 13 | 6.82 |
| Mid frontal G | R | 9 | 44, 13, 36 | 6.11 |
| Premotor cortex | L | 6 | -44, 6, 51 | 5.89 |
| Mid/sup frontal G | R | 10 | 28, 55, 8 | 5.68 |
| *Inf parietal lobule** | *L* | *40* | *-60, -49, 29* | *8.04* |
| *Parametric effect of preceding number of go trials* | | | | |
| Inf frontal G | R | 44 | 55, 1, 26 | 4.92 |
| Cingulum | L | | -16, -28, -12 | 5.45 |
| | | | -36, -31, -2 | 4.64 |

*Table 3*. Regions of activation for unaffected siblings of children and adolescents with ADHD.

| Region | Side | BA | Talairach | Max t-value |
|---|---|---|---|---|
| *Go > No-go* | | | | |
| Precentral G | L | 4 | -55, -20, 38 | 8.56 |
| Cerebellum | R | | 40, -48, -18 | 6.65 |
| Sup temporal G | L | 22 | -55, 0, 4 | 9.90 |
| *No-go > Go* | | | | |
| *Inf frontal G ** | *R* | *44* | *44, 16, 14* | *15.05* |
| Ant cingulate G | R | 32 | 4, 40, 16 | 7.06 |
| | L | 24/32 | -27, -23, -1 | 6.15 |
| Inf parietal lobule | R | 40 | 51, -56, 43 | 9.69 |
| Sup/Mid temporal G | R | 21/38 | 44, 2, -30 | 4.96 |
| *Parametric effect of preceding number of go trials* | | | | |
| Inf frontal G | R | 47 | 36, 31, -5 | 6.62 |
| Cingulum | L | | -4, -15, 4 | 5.71 |

Tables 2 & 3: Values are $p < .001$; min extent 10 vox; $T > 4.14$. G, gyrus; Ant = anterior; Inf = inferior; Mid = middle; Sup = superior; ADHD = attention-deficit hyperactivity disorder; BA = Brodmann's area; MR = magnetic resonance.* Regions where MR signal change on no-go trials correlated w/ no-go accuracy.

*Table 4*. Regions of activation for children and adolescents with ADHD.

| Region | Side | BA | Talairach | Max t-value |
|---|---|---|---|---|
| *Go > No-go* | | | | |
| Precentral G | L | 4 | -55, -25, 49 | 5.91 |
| Cerebellum | R | | 20, -51, -18 | 5.40 |
| *No-go > Go* | | | | |
| Mid frontal G | R | 8 | 48, 18, 43 | 6.18 |
| *Inf parietal lobule ** | *R* | *40* | *44, -40, 46* | *5.47* |
| *Parametric effect of preceding number of go trials* | | | | |
| None | | | | |

Values are $p < .001$; min extent 10 vox; $T > 4.14$. G, gyrus; Ant = anterior; Inf = inferior; Mid = middle; Sup = superior; ADHD = attention-deficit hyperactivity disorder; BA = Brodmann's area; MR = magnetic resonance.* Regions where MR signal change on no-go trials correlated w/ no-go accuracy.

*Table 5*. Significant differences in activation between children and adolescents with ADHD, and their unaffected siblings and control subjects (for nine clusters from no-go > go condition for controls).

| Region | Side | BA | Talairach | Max t-value |
|---|---|---|---|---|
| *Controls > ADHD* | | | | |
| Inf frontal G | L | 47 | -36, 19, -7 | 2.80 |
| Ant cingulate G | L | 24/32 | -8, 40, 24 | 2.25 |
| Premotor cortex | L | 6 | -44, 6, 51 | 1.86 |
| Mid/sup frontal G | R | 10 | 28, 55, 8 | 1.93 |
| Inf parietal lobule | L | 40 | -60, -49, 29 | 1.90 |
| *Controls > unaffected siblings* | | | | |
| Inf frontal G | R | 47 | 40, 20, -8 | 2.41 |
| Mid frontal G | R | 9 | 44, 13, 36 | 3.26 |
| Premotor cortex | L | 6 | -44, 6, 51 | 2.07 |
| Inf parietal lobule | L | 40 | -60, -49, 29 | 4.38 |
| *Unaffected siblings > ADHD* | | | | |
| None | | | | |
| *ADHD > unaffected siblings* | | | | |
| None | | | | |

Values are for nine clusters from No-go > Go condition for controls. G = gyrus; Ant = anterior; Inf = inferior; Mid = middle; Sup = superior; ADHD = attention-deficit hyperactivity disorder; BA = Brodmann's area.

and $F = 1.12$, $p = .30$ for their unaffected siblings) that was largely due to a significant difference in the no-go after 5 preceding go-trials condition ($F = 4.72$, $p = .03$ for children and adolescents with ADHD and $F = .57$, $p = .46$ for their unaffected siblings; see Table 1 and Figure 1). There were no significant differences between accuracy on go-trials or reaction time between groups, even when age was included as a covariate ($p > .05$). In the sample of 33 subjects for whom fMRI data were included in the analyses, differences between groups in accuracy and reaction time did not reach significance, even after including age as a covariate ($p > .05$). The increase in the number of errors to no-go trials as a function of the number of preceding go -trials no longer exceeded trend level ($r = .14$; $p = .08$).

*Functional MRI results.* All groups showed increased activation in left motor cortex and right cerebellum for the go versus no-go comparison (see Table 2, 3 and 4). For the no-go versus go condition, control subjects showed increased activation bilaterally in inferior frontal gyrus (IFG), anterior cingulate gyrus (ACG), regions in the middle and superior frontal gyri and the left inferior parietal lobe, similar to patterns of activation previously described (Durston, et al., 2002a, 2002b, 2006). Regions in the right inferior frontal gyrus and in the left cingulum area showed an increase in activation with increasing number of preceding go-trials. MR signal change correlated with performance for regions in the right inferior frontal gyrus and left parietal lobe (see Table 2; Figures 2 and 3).

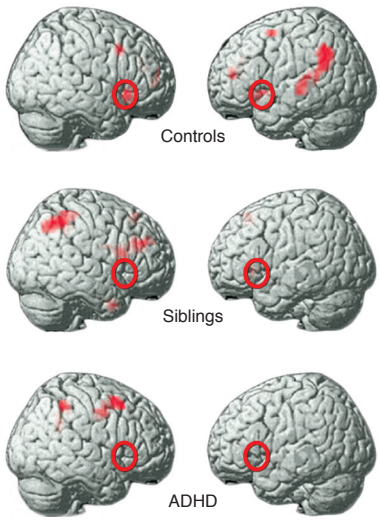


*Figure 2.* Patterns of activation for no-go > go trials for control subjects, unaffected siblings of children and adolescents with ADHD and children and adolescents with ADHD. Red circles indicate bilateral inferior frontal gyrus, a region critical to performance of this task in control subjects, as activation in this region correlates with performance (40, 20, -8) and is sensitive to manipulations of task difficulty. All images are thresholded at $T > 4.14$; $p < .001$; extent > 10 voxels. ADHD, attention deficit hyperactivity disorder.

Unaffected siblings of children and adolescents with ADHD showed increased activation in right inferior frontal gyrus, bilateral anterior cingulate gyrus, the right inferior parietal lobule and the right superior temporal gyrus. Here again, the only regions to show an effect of increasing number of preceding go-trials on activation levels were regions in the right inferior frontal gyrus and in the left cingulum area. Similar to the controls, MR signal change correlated with performance for the region in the right IFG only (see Table 3; Figures 2 and 3).

Children and adolescents with ADHD showed increased activation in right middle frontal gyrus and right inferior parietal lobule for no-go versus go trials, but not in inferior frontal gyrus or anterior cingulate gyrus. No regions showed an effect of increasing number of preceding go-trials for this group, but MR signal change correlated with performance for the region in the inferior parietal lobule (see Table 4; Figures 2 and 3).

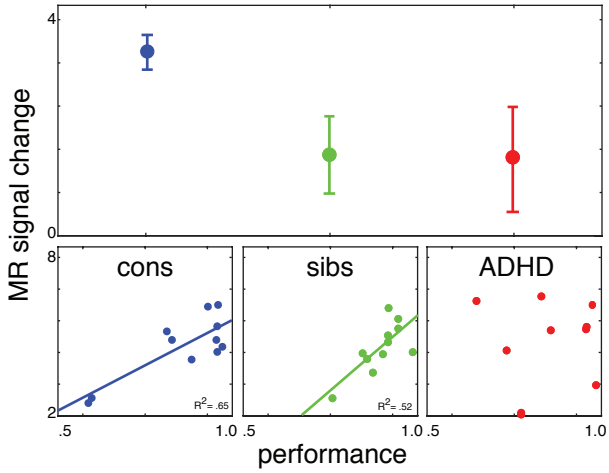


*Figure 3*. Signal change in right (R) IFG for controls, unaffected siblings, and siblings with ADHD (top panel) and correlations with performance on this task in this region (bottom panel). For the purpose of comparison, signal change was also plotted against performance for siblings with ADHD, although there was no significant correlation. For this group, individual MR signal change values are taken from the ROI defined in the control comparison. ADHD = attention deficit hyperactivity disorder; IFG = inferior frontal gyrus; MR = magnetic resonance; ROI = region of interest.

Whole-brain analyses yielded no regions that were significantly different between groups at the $p <$ .001, extent, 10 voxels threshold. A region of interest approach, investigating differences between groups in regions that were significantly activated for the control group for no-go trials compared to go-trials, showed greater activation for controls than children and adolescents with ADHD in inferior frontal gyrus, anterior cingulate gyrus, middle frontal gyrus and inferior parietal lobule.

Activation was greater for controls than unaffected siblings in regions in inferior frontal gyrus, middle frontal gyrus and inferior parietal lobule, but not anterior cingulate gyrus. There were no regions where activation was greater for either siblings with or without ADHD than controls. Differences between siblings with and without ADHD were not significant in any region (see Table 5). Patterns of activation from the analyses treating age as a covariate were similar to the initial results, and thus not reported separately.

## Discussion

In this study, we investigated the effect of genetic vulnerability for ADHD on performance of and brain activation during an inhibitory control task. We showed that unaffected siblings of children and adolescents with ADHD displayed no significant detriment in their performance of this task, whereas children and adolescents with ADHD showed decreased accuracy in the hardest condition of this task. Furthermore, we show differences in their patterns of brain activation, where both children and adolescents with ADHD and their unaffected siblings showed less activation than control subjects in regions in ventral prefrontal and inferior parietal cortex. For control subjects, IFG appeared central to successful inhibitory control in this task, as activation in this region was related to both accuracy on no-go trials and task difficulty. Both children and adolescents with ADHD and their unaffected siblings showed decreased activation in this region, relative to controls. However, for unaffected siblings, activity in this region was associated with performance and task difficulty, similar to controls, whereas for individuals with ADHD, it was not.
Behaviorally, all subjects in this study showed an effect of task difficulty on performance, as accuracy on no-go trials decreased as a function of the number of preceding go-trials. This finding is consistent with previous studies using this manipulation (Durston, et al., 2002a, 2002b, 2003, 2006). However, this effect did not reach significance for the individual sub-groups, probably due to limited power (see Figure 1). There was a trend-level decrease in accuracy for individuals with ADHD that was significant for the hardest condition of this task. As such, these results are consistent with the numerous reports in the literature of impaired inhibitory control in individuals with ADHD (e.g. Grodzinsky and Diamond, 1992; Schachar, et al., 1995; Seidman, 1995, 1997; for meta-analysis see Oosterlaan, 1998).

On successfully inhibited no-go trials, control children activated a network of regions, including IFG, ACG and the parietal cortex, very similar to previous normative pediatric imaging studies (Durston, et al., 2002b). Furthermore, those studies showed a correlation between performance on this inhibitory control task and activation in IFG and inferior parietal cortex, suggesting that these areas are central to performance of this task, at least in typically developing children. In addition, activation in IFG increased on no-go trials as a function of the number of preceding go-trials, confirming previous reports that this region is critical for inhibitory control, in the context of this (Durston, et al., 2002a, 2002b, 2006) and other inhibitory tasks (e.g., Bellgrove, et al., 2004; Casey, et al., 1997; Durston, et al., 2003; Garavan, et al., 1999; Konishi, et al., 1999; Liddle, et al., 2001; Rubia, et al., 2000).
For children and adolescents with ADHD, successful inhibition on no-go trials was not significantly associated with activation of IFG (see Figure 2). Furthermore, no regions were sensitive to the manipulation of no-go difficulty, and the only region where activation was correlated with performance on this task was in parietal cortex. This confirms our previous report of atypical activation in prefrontal and cingulate cortex for individuals with ADHD (Durston, et al., 2003), as well as other reports of atypical prefrontal activation in ADHD (Booth, et al., 2005; Bush, et al., 1999; Liotti, et al., 2005; Rubia, et al., 1999, 2005; Schulz, et al., 2004, 2005; Schweitzer, et al., 2000; Tamm, et al., 2004; Vaidya, et al., 1998; Zang, et al., 2005). The lack of significant activation of IFG, taken together with the association between parietal activation and performance, suggest that individuals with ADHD may be activating only part of the network associated with this task in controls, or may be relying on

additional brain areas to perform this task. Parietal cortex is associated with attentional processes, and activation in this region in the ADHD group may represent compensatory activation, as may the activation in more dorsolateral prefrontal areas that are implicated in working memory and other tasks of executive functioning.

Interestingly, unaffected siblings of individuals with ADHD did show a correlation between task performance and IFG activation similar to the control subjects (see Figure 3), as well as a similar association between MR signal change in IFG and no-go difficulty. However, they did not show any association between performance and activation in parietal cortex. In a direct comparison of activation between groups, the control subjects showed significantly more activation in IFG than both children and adolescents with ADHD and their unaffected siblings, whereas there was no difference between the affected and unaffected siblings. Taken together, these results suggest that the unaffected siblings may be employing the prefrontal-parietal network in a manner that is qualitatively similar to control subjects, but less efficiently, as the magnitude of activation in IFG is reduced and correlations with performance do not reach significance in parietal areas. The unaffected siblings included in this study did not have behavioral symptoms of ADHD, as assessed by symptom rating scales and parental interview. As such, these results suggest that the observed changes in IFG and parietal cortex are related to familial risk for ADHD, rather than subthreshold symptomatology. However, as unaffected siblings do show modulation of activation in IFG in response to task difficulty, as well as a relationship between activation and performance in this region, the effect on IFG function may be less severe for at-risk individuals.
Direct comparisons with control subjects were very similar for siblings with and without ADHD, as both groups displayed reductions in activation for no-go trials in prefrontal and parietal regions. Interestingly, the only region that differentiated between the groups was the ACG, where activation was significantly reduced for subjects with ADHD compared to controls, but not for their unaffected siblings. Tentatively, this could be taken to suggest that activation in this region may be related to compensatory or spared functioning in the unaffected siblings. However, a direct comparison between siblings with and without ADHD did not reach significance in the current study. Therefore this result should be treated with caution until it can be confirmed in a larger sample.
Another noticeable finding was that activation in parietal cortex was left-lateralized for control subjects, but right-lateralized for both affected and unaffected siblings. Potentially, the right-hemisphere findings could be related to compensatory mechanisms with increased activation in attentional areas in both sibling-groups. However, these findings are preliminary and should be treated with caution until they have been confirmed in other studies.

Although our results are consistent with both the inhibitory control and the ADHD literature, there are a number of limitations in our study that need to be acknowledged. First, although the number of subjects included in this study is not atypical of the functional neuroimaging literature, the sample size is relatively small with 11 subjects in each group. As such, we cannot exclude the possibility of type II errors, where we may have missed existing differences. Indeed, differences between groups only reached significance in the post-hoc ROI-analysis, while the between-group whole-brain comparisons yielded no significant results. Second, we have used group averages rather than investigating differences at an individual level. As such, we cannot rule out that differences in activation between groups could be related to increased anatomic variability in the ADHD and

unaffected sibling samples, rather than functional differences. An approach that combines anatomical and functional imaging may be better able to tease apart anatomical and functional differences in ADHD. However, our previous study of brain anatomy suggests that volumetric reductions of cortical gray matter are subtle and widespread in both affected and unaffected siblings (Durston, et al., 2004). It seems unlikely that such global differences in anatomy should result in relatively focal differences in activation, in particular as global scaling procedures, such as implemented in SPM2, remove gross differences between groups. A related concern is the use of a standard adult template, as well as the Talairach atlas in pediatric populations, as adult neuroanatomy does not necessarily generalize well to children. However, there is evidence to suggest that anatomic differences between school-aged children and adults are only modest in their effects on detecting functional differences (Burgund, et al., 2002). Furthermore, the age range of the sample included in this study spans 12 years and extends into early adulthood, meaning that a child or adolescent template brain would have been equally problematic. Third, although subjects with ADHD were not on medication, or discontinued treatment prior to participating in an MR scan, most were not stimulant-naive. Therefore we cannot rule out the possibility that some of the observed changes in brain activation are due to long-term effects of stimulant medication. However, the unaffected siblings in this study had never taken stimulants, suggesting that changes shared between both groups are unlikely to be fully explained by stimulant treatment. Nevertheless, this point does stress the need for studies of medication-naive subjects, preferably including large samples and multiple methodologies to tease apart these issues. Finally, we have investigated full siblings of individuals with ADHD. As the genetic relatedness is similar (approximately 50%) for all sibling-pairs in this study, we cannot estimate the heritability of phenotypic measures, such as reduced IFG activation, based on these data. Future studies including both monozygotic and dizygotic twin pairs discordant for ADHD will be better able to address this issue.

In summary, we have shown that individuals with ADHD show detriments in performance and atypical patterns of brain activation during an inhibitory control task. During successful inhibitions, they activate regions in ventral prefrontal cortex less than control subjects. For control subjects, ventral prefrontal and inferior parietal regions appear to be critical in inhibitory control, as activation in these regions is correlated with performance on this task. Unaffected siblings of children and adolescents with ADHD did not show the behavioral deficit evident in their affected counterparts. Furthermore, the relationship between activation in ventral prefrontal cortex and task performance was similar to that for control subjects. However, reductions in activation in a number of regions, including ventral prefrontal areas were similar to those in subjects with ADHD, and there were fewer significant correlations between performance and activation. These findings suggest that the magnitude of activation during successful inhibition is sensitive to genetic vulnerability to ADHD in a number of regions, including ventral prefrontal cortex, even in the absence of differences at a behavioral level. If this can be replicated in future studies, these results suggest that neuroimaging measures related to inhibitory control may be suitable as an intermediate phenotype in studies investigating gene effects in ADHD.

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# Chapter 3

## Familial vulnerability to ADHD affects activity in the cerebellum in addition to the prefrontal systems

**Background**. Familial vulnerability to attention-deficit hyperactivity disorder (ADHD) has been shown to be related to atypical prefrontal activity during cognitive control tasks. However, ADHD is associated with deficits in the cerebellum as well as deficits in fronto-striatal circuitry and associated cognitive control. In this study, we investigated whether cerebellar systems are sensitive to familial risk for ADHD in addition to fronto-striatal circuitry.

**Methods**. We used an event-related, rapid mixed-trial functional magnetic resonance imaging design. The paradigm was a variation on a go/no-go task, with expected (go) and unexpected (no-go) events at expected and unexpected times. A total of 36 male children and adolescents completed the study, including 12 sibling pairs discordant for ADHD and 12 matched controls.

**Results**. Children and adolescents with ADHD were less accurate on unexpected events than control subjects. Performance by unaffected siblings was intermediate, between that of children and adolescents with ADHD and controls. Functional neuroimaging results showed dissociation between activation in the cerebellum and anterior cingulate cortex: Activity in the anterior cingulate cortex was decreased for subjects with ADHD and their unaffected siblings compared with controls for manipulations of stimulus type (no-go trials), but not timing. In contrast, cerebellar activity was decreased for subjects with ADHD and their unaffected siblings for manipulations of timing, but not stimulus type.

**Conclusion**. These findings suggest that activity in both the prefrontal cortex and cerebellum is sensitive to familial vulnerability to ADHD. Unaffected siblings of individuals with ADHD show deficits similar to affected probands in prefrontal areas for unexpected events and in cerebellum for events at unexpected times.

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## Introduction

Attention-deficit hyperactivity disorder (ADHD) is a developmental disorder in which familial effects are estimated to explain up to 70% of the phenotypic variance (Castellanos & Tannock, 2002). Evidence from family, twin, and adoption studies shows that family members of individuals with ADHD are at increased risk for developing the disorder (Faraone, et al., 2005). For example, full siblings of individuals with ADHD have a three- to fivefold increased chance of developing ADHD (Biederman, et al., 1992). Although association studies have implicated a large number of candidate genes in ADHD, their relative contributions are not yet understood (Faraone, et al., 2005). Behaviorally defined phenotypes, such as ADHD, are complex and are likely to be affected by multiple genes as well as gene-gene and gene-environment interactions. Investigating intermediate phenotypes can be useful to reduce the complexity in etiology and genetic background (Gottesman & Gould, 2003; Gould & Gottesman, 2006). Deficits at the neuronal level may serve as intermediate phenotypes and may therefore be useful in investigating familial risk for ADHD (Castellanos & Tannock, 2002).

In ADHD, obvious candidates as neuronal intermediate phenotypes are deficits in fronto-striatal circuitry and cognitive control. Cognitive control can be defined as the ability to control behavior in a constantly changing environment by inhibiting inappropriate thoughts or actions in favor of more appropriate ones. Behaviorally, individuals with ADHD perform worse than matched controls on tasks that probe cognitive control (for meta-analysis, see Oosterlaan, et al., 1998; for review, see Sergeant, et al., 2002). Functional magnetic resonance imaging (MRI) studies have shown decreased neural activity in fronto-striatal areas in the context of cognitive control tasks, and reductions in volume have been shown in these areas in morphological MRI studies (Bush, et al., 2005; Durston, 2003; Seidman, et al., 2005).

We previously showed that changes in fronto-striatal functioning may be a potentially useful intermediate phenotype for ADHD, as we showed that individuals at familial risk for ADHD activated fronto-striatal regions less than typically developing controls during a cognitive control task (Durston, et al., 2006). In this study, subjects with ADHD, their unaffected siblings, and controls participated in a go/no-go task in the context of a functional MRI study. Behaviorally, individuals with ADHD had lower accuracy on the most challenging no-go trials, whereas performance by siblings was no different from that of controls. However, activation in prefrontal areas was decreased for both subjects with ADHD and their unaffected siblings, suggesting that these regions are sensitive to familial vulnerability to ADHD (Durston, et al., 2006). In a second study, we used this observation to directly investigate the effect of genotype on fronto-striatal measures. Here, dopamine transporter (DAT1) genotype effects were found on striatal activity for individuals at familial risk for ADHD (affected and unaffected siblings), but not controls, implicating this region in translating familial risk into a neurobiological substrate (Durston, et al., 2008). We found similar evidence of ADHD candidate gene effects on fronto-striatal regions using anatomical MRI (Durston, et al., 2005). Here, DAT1 genotype affected caudate volume, whereas a much-studied polymorphism in the dopamine-4 receptor gene affected prefrontal gray matter volume.

The cerebellum has been increasingly implicated in ADHD, both in morphological studies and in studies of time estimation (Berquin, et al., 1998; Castellanos, et al., 2001; Castellanos, et al., 1996; Castellanos, et al., 2002; Durston, et al., 2004; Hill, et al., 2003; Mostofsky, et al., 1998; Rubia, et al., 2003; Smith, et al., 2002; van Meel, et al., 2005). To date, two studies have suggested indirectly that the cerebellum may be less sensitive to familial risk for ADHD than fronto-striatal areas. In a study of effects of familial risk on brain anatomy, we found that, whereas cortical gray matter was decreased in both boys with ADHD and their unaffected siblings, a reduction in cerebellar volume was only present in siblings with ADHD but not their unaffected counterparts (Durston, et al., 2004). Furthermore, in our study of DAT1 gene effects on brain activation, the only other region where activity was influenced by genotype was the cerebellar vermis. There was no interaction between genotype and familial risk, suggesting that this effect is independent of familial risk for ADHD (Durston, et al., 2008). Taken together, these results suggest that deficits in the cerebellum may be related more to the ADHD phenotype than to a familial risk for the disorder.

Recently, we investigated the effects of ADHD on fronto-cerebellar and fronto-striatal regions during expectancy violation (Durston, et al., 2007). Subjects with ADHD showed diminished activation in cerebellum during violations of stimulus timing and diminished ventral prefrontal cortex and anterior cingulate activity to violations in stimulus timing and identity. In the present study, we investigated whether cerebellar systems are sensitive to the familial risk for ADHD in certain contexts, in addition to fronto-striatal circuits. Subjects with ADHD, their unaffected siblings and matched, typically developing control subjects participated in a functional MRI study, using a variation of a go/no-go paradigm where the predictability of stimulus type and stimulus timing was manipulated: expected and unexpected events (go and no-go trials) were presented at expected or unexpected times. We hypothesized that prefrontal regions would be sensitive to familial vulnerability for ADHD, as previously shown (Durston, et al., 2006). Both subjects with ADHD and their unaffected siblings were hypothesized to show less activation in prefrontal regions less during violations of stimulus type. In contrast, we hypothesized that the cerebellum would not show sensitivity to familial vulnerability to ADHD. We expected unaffected siblings to show activation similar to that of controls to violations of stimulus timing in contrast to the diminished activation in the cerebellum of subjects with ADHD (Durston, et al., 2007).

## Methods

*Participants.* A total of 36 male children and adolescents participated in the present study. Demographic information is listed in Table 1. Controls were matched to subjects with ADHD and their unaffected siblings for age, sex, IQ, hand preference, and socio- economic status, operationalized as the number of years of parental schooling.

Subjects were recruited through the Department of Child and Adolescent Psychiatry at the University Medical Center Utrecht in the Netherlands (sibling pairs) and local schools (controls). Twelve male children and adolescents with ADHD, their unaffected full siblings, and 12 matched, typically developing control subjects were included. Eight of 36 subjects had previously participated

*Table 1.* Descriptive variables for controls, unaffected siblings and siblings with ADHD.

| | controls (N=12) | siblings (N=12) | ADHD (N=12) |
|---|---|---|---|
| Age | | | |
| mean | 15.0 (2.1) | 14.1 (2.7) | 14.9 (2.3) |
| range | 11.9 - 19.7 | 10.2 - 18.2 | 9.6 - 17.6 |
| IQ | | | |
| mean | 107 (20) | 115 (20) | 108 (22) |
| range | 75 - 151 | 81-147 | 84-156 |
| Hand preference | | | |
| (L/R) | 3/9 | 1/11 | 3/9 |
| ADHD (N on DISC) | | | |
| combined | 0 | 0 | 9 [a] |
| hyperactive | 0 | 0 | 3 [b] |
| ODD | 0 | 0 | 4 [b] |
| CBCL | (N=12) | (N=12) | (N=12) |
| ADHD | 52.2(3.3) | 54.3(5.8) | 60.9(10.0) [a] |
| ODD | 50.9(1.6) | 51.3(2.3) | 60.6(9.2) [b] |
| CD | 50.4(0.5) | 51.9(3.1) | 59.8(7.9) [b] |
| Affective problems | 52.5(3.6) | 55.3(6.6) | 58.3(9.6) |
| Anxiety problem | 55.3(7.3) | 52.8(4.8) | 53.9(5.8) |
| Somatic problems | 54.6(4.1) | 54.3(5.0) | 55.2(6.1) |
| Anxious/depressed | 52.9(4.9) | 52.8(5.4) | 53.3(8.3) |
| Withdrawn/depressed | 52.6(3.8) | 59.2(8.9) | 58.3(8.5) |
| Somatic Complaints | 53.3(3.6) | 55.8(4.1) | 55.2(5.0) |
| Social problems | 52.8(5.6) | 52.7(4.0) | 58.8(9.8) |
| Thought problems | 53.5(5.1) | 52.8(5.3) | 57.7(8.3) |
| Attention problems | 52.6(3.6) | 54.8(5.6) | 59.3(8.3) [a] |
| Rule-breaking behavior | 50.4(0.7) | 52.2(3.0) | 58.4(5.6) [b] |
| Aggressive behavior | 50.5(1.5) | 51.8(3.9) | 62.3(10.7) [b] |
| SES | | | |
| mothers's education (years) | 13.2 | 13.5 | 13.5 |
| father's education (years) | 14.0 | 14.1 | 14.1 |
| On medication | 0 | 0 | 7 [a] |

Legend: ADHD = attention deficit hyperactivity disorder; ODD = oppositional defiant disorder; CD = Conduct Disorder; SES = socio-economic status; DISC = Diagnostic Interview Schedule for Children; CBCL = Child Behavior Checklist.
[a] $p < .01$; [b] $p < .05$

in another functional MRI study at our laboratory (four subjects with ADHD and their unaffected counterparts). Furthermore, data for 24 subjects (12 subjects with ADHD and 12 controls) were also included in the previous study in which we investigated the effects of expectancy violations in two samples of subjects with and without ADHD (Durston, et al., 2007). In the present study, data from discordant siblings of subjects with ADHD were included to investigate the familial effects of ADHD on the cerebellum. Subjects with major physical or neurological illness, learning disabilities, or IQ < 70 were excluded. Neurological illness and learning disabilities were assessed based on report from the primary clinician, chart review, and parental report. All of the subjects participated in a standardized IQ assessment using the WISC-III or WISC-Revised (Wechsler, 1974, 1991), and a parent participated in a semistructured interview session to confirm or disconfirm clinical psychiatric diagnosis using the Diagnostic Interview Schedule for Children (DISC-P) (Schaffer, et al., 2000). A full DISC interview was administered for all subjects. ADHD subjects were required to have received a clinical diagnosis of ADHD from our department and to meet DSM-IV criteria for ADHD, as assessed by DISC interview. Furthermore, they were required to have no comorbid disorders other than oppositional defiant disorder. Siblings and control subjects were excluded if they met DSM-IV criteria for any psychiatric diagnosis, as assessed by DISC interview. In addition, Child Behavior Checklist scores were obtained to ascertain the presence of ADHD-related symptoms in siblings and control subjects.

Subjects on short-acting medication for ADHD discontinued treatment for a minimum of 24 hours before the scan. After a full description of the study, informed assent/consent was obtained from all of the subjects and their parents before study participation was commenced. Before the MRI scan, participants were acclimated to the scanning environment using an MRI simulator located in our laboratory. All of the procedures were conducted in accordance with guidelines established by the Dutch Central Committee on Research involving Human Subjects.

*Behavioral Paradigm.* Subjects were asked to perform a visual target detection task by pressing a single response button with their right index finger whenever a target stimulus was presented (Davidson, et al., 2004; Durston, et al., 2007). The task was a variation of a go/no-go task, in which the temporal predictability of events was manipulated, in addition to the predictability of the type of the stimulus (i.e., no-go versus go-stimuli). Two subjects with ADHD and their unaffected siblings and three control subjects performed a slightly different version of the task, without trials at unexpected times. Therefore, analyses of the timing manipulation include 10 subjects with ADHD, 10 unaffected siblings, and 9 control subjects. Group effects were comparable for both versions of the task. The task was designed to build up the expectancy of an event occurring (the frequent and predictable go-trial). Subjects were required to adjust their behavior when that prediction was violated (i.e., inhibit a prepotent button press on no-go trials or press the button at an unexpected time on unpredictable go trials). The task was presented in the context of a computer game, where subjects were asked to “help feed a hungry little mouse as much cheese as possible”. The target stimulus was a cartoon drawing of a piece of cheese, whereas the unexpected stimulus was a cartoon drawing of a cat. During the interstimulus interval, a mouse hole remained on the screen, briefly opening to reveal one of the experimental stimuli in a continuous stream of trials (Davidson, et al., 2004).

The task involved five blocks of 72 trials (360 trials total). On the majority of trials (67% of 360 = 240 trials), the target stimulus (cheese) was presented at the expected time (every 4 seconds). On the remainder of the trials (33% of 360 = 120 trials), unpredictable trials (30 of each type) were presented: an unexpected stimulus at the expected time (cat at 4 seconds; temporally predictable no-go trial); an expected target stimulus at an unexpected time (cheese at 2 seconds; temporally unpredictable go-trial); and an unexpected stimulus at the unexpected time (cat at 2 seconds; temporally unpredictable no-go trial). A fourth unpredictable trial type, in which no stimulus was presented at the predictable time (a nontrial) was also included to help prevent subjects learning any pattern other than that of the predictable go trials. Trial types were mixed pseudorandomly in equal numbers throughout each block. The stimuli were presented for 500 milliseconds, with an interstimulus interval of either 1500 or 3500 milliseconds.

*Analysis of Behavioral Data.* All of the behavioral data were analyzed using the SPSS statistical package (version 14.0, SPSS Inc., Chicago). Accuracy scores were calculated as the percentage of hits to targets (predictable and unpredictable go trials) and correct omissions to nontargets (no-go trials) relative to the total number of trials of each type. Mean reaction times were calculated for the condition for which a response was required (i.e., expected stimulus at the expected or unexpected time). Differences between groups were investigated using analysis of variance techniques with post hoc *t*-tests, using Tukey's honestly significant difference test.

*Image Acquisition.* MR images were acquired on a 1.5-T Philips Allegra MR scanner (Philips Medical Systems, Best, the Netherlands). Functional MRI scans consisted of a navigated three-dimensional PRESTO pulse sequence (TE [echo time] 11 milliseconds, TR [recovery time] 21.74 milliseconds, flip angle 9.0-, matrix 64 × 64 × 36, FOV [field of view] 256 × 256 × 144 mm, voxel size 4 mm isotropic, and scan duration 2.0 seconds per 36-slice volume), covering the whole brain. Anatomical T1-weighted three-dimensional fast field echo scans with 170 1.2-mm contiguous coronal slices of the whole head (TE 4.6 milliseconds, TR 30 milliseconds, flip angle 30 degrees, FOV 256 mm, in-plane voxel size 1 × 1 mm) were also acquired. An FA30 scan with contrast more similar to the T1-weighted scans was also acquired to aid in the alignment of PRESTO images to the template (TE 11 milliseconds, TR 1.74 milliseconds, flip angle 30 degrees, matrix 64 × 64 × 36, FOV 256 × 256 × 144 mm, voxel size 4 mm isotropic).

*Image Analysis.* Data were analyzed using a random effects model in Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London). For the analyses, functional MR images were realigned and normalized to a standard stereotactic space (Montreal Neurological Institute template). Estimated motion parameters were examined on a subject-by-subject basis to ensure that the amount of motion did not exceed the size of one voxel.
At the first level, six event types were defined (expected and unexpected stimuli at expected and unexpected times, the omission of an event and incorrect trials). These included four effects of interest (correct trials for expected and unexpected stimuli at expected and unexpected times). Events were time- locked to the stimulus by a canonical synthetic hemodynamic response function and its first-order temporal derivative. At the second level, three separate analyses were conducted. Only correct trials were included in the analyses.

First, one-sample *t*-tests were performed for control subjects. Three conditions of interest were investigated, all of which compared unpredictable events that required subjects to adapt their behavior to predictable events (expected stimulus at unexpected time [temporally unpredictable go trial]; unexpected stimulus at expected time [temporally predictable no-go trial]; unexpected stimulus at unexpected time [temporally unpredictable no-go trial]). An uncorrected threshold of $p < .005$, with a minimum extent of 10 voxels was used in each case (Forman, et al., 1995). This analysis was conducted to allow the definition of functional regions of interest (ROIs) for comparisons with other groups.

Second, an ROI analysis was performed to investigate differences between controls, subjects with ADHD, and unaffected siblings in regions of a priori interest. Three regions were functionally defined from one-sample *t*-tests for control subjects (Table 2), using the MarsBaR package (Brett, et al., 2002): The anterior cingulate gyrus (ACG) and inferior frontal gyrus were defined from the manipulation of the stimulus type and the inferior cerebellum from the manipulation of timing. Subjects who differed in activation level by more than 2 SDs for any ROI were defined as outliers. ROI analyses were performed with and without one outlier in the ADHD group. For each ROI, signal change per subject was extracted from the Statistical Parametric Mapping software contrast files. Individual average values for ROIs represent intrasubject differences between activation for the condition of interest minus the control condition (expected event at expected time). The SPSS statistical package (version 14.0) was used to analyze between-group differences with analysis of variance techniques and post hoc *t*-tests, using Tukey's honestly significant difference test. Power analyses were performed to determine the effect size of the observed differences.

Finally, whole-brain differences between subjects with ADHD and controls and siblings without ADHD and controls were investigated using exploratory two-sample *t*-tests for the same three conditions of interest. An uncorrected threshold of $p < .005$, with a minimum extent of 10 voxels was used (Forman, et al., 1995). The results of the whole-brain two-sample *t*-test comparing subjects with ADHD to controls was included in an earlier article (Durston, et al., 2007) and is shown again here to allow for a direct comparison to the results for unaffected siblings.

## Results

Subjects with ADHD had significantly higher scores on ADHD symptoms compared with their unaffected siblings and matched controls, according to both Child Behavior Checklist scales and the DISC interview. There were no significant differences between unaffected siblings and matched controls (Table 1).

### Behavioral Results

*Accuracy*. There were significant differences between groups in accuracy for manipulations of stimulus type (unexpected stimuli at the expected and unexpected time; $F_{2,33} = 4.51$; $p = .019$) and for manipulations of timing (expected and unexpected stimuli at the unexpected time; $F_{2,26} = 3.64$; $p = .04$; Figure 1). For stimulus manipulations, accuracy was significantly lower for subjects with ADHD

than for control subjects (54 ± 22% for ADHD, 78 ± 18% for controls; $p = .026$). Differences between unaffected siblings and control subjects reached trend level (57 ± 24% for unaffected siblings; $p = .051$). For timing manipulations, accuracy was significantly lower for subjects with ADHD than control subjects (78 ± 11% for ADHD, 92 ± 8% for controls; $p = .049$). Differences between unaffected siblings and control subjects reached trend level (80 ± 14% for unaffected siblings; $p = .092$). There were no differences in performance between subjects with ADHD and unaffected siblings.

*Reaction Time.* There were no differences in reaction time between groups ($F < .71$; $p > .5$). All of the subjects were faster for expected than unexpected go trials (459.1 milliseconds versus 533.8 milliseconds; $t_{28} = -13.1$; $p < .001$).

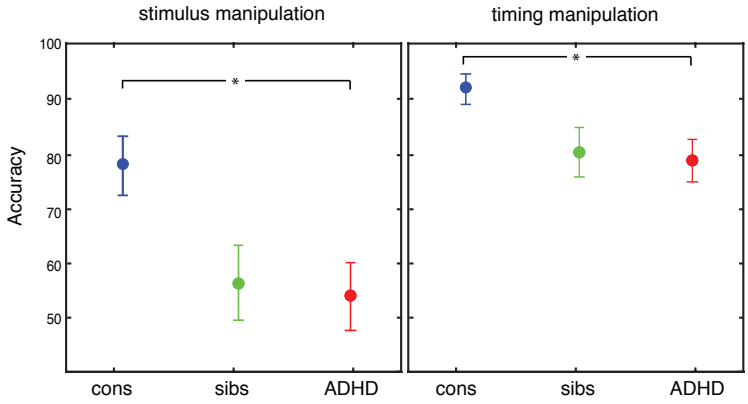


*Figure 1.* Accuracy for stimulus and timing manipulations are sensitive to familial risk for attention-deficit/hyperactivity disorder (ADHD). * Significant at $p < .04$.

## Functional MRI Results

*One-sample t-tests for control subjects.* Results for control subjects are summarized in Table 2. Regions in prefrontal cortex, including the inferior frontal gyrus and ACG (extending into superior frontal gyrus), were activated for unexpected stimuli at the expected and unexpected times. Inferior cerebellum was activated for presentations of expected stimuli at the unexpected time. These data were included in a previous study (Durston, et al., 2007).

*ROI Analysis.* Between-group differences in the right inferior frontal gyrus, ACG, and cerebellum were investigated using an ROI approach. ACG activation differed between groups for the manipulation of stimulus type, but not stimulus timing ($F_{2,32} = 3.67$; $p = .037$; effect size $\eta = .187$ for stimulus type; ($F_{2,26} = 1.21$; $p = .314$; effect size $\eta = .097$ for stimulus timing; Figure 2). In contrast, activation in the cerebellum differed between groups for the manipulation of stimulus timing, but not stimulus type ($F_{2,26} = 8.38$; $p = .002$; effect size $\eta = .375$ for timing; $F_{2,32} = .856$; $p = .434$; effect size $\eta = .098$ for stimulus type; Figure 2). Differences in IFG did not reach significance for any comparison.

For manipulations of stimulus type, activation in ACG was significantly decreased for subjects with ADHD compared with controls (–4.37 ± 1.65; $p = .032$). When one outlier in the ADHD group was

included in the analyses, between-group differences no longer reached significance ($F_{2,32}$ = 1.42; $p$ = .256). Differences between unaffected siblings and controls and between affected and unaffected siblings did not reach significance.

For manipulations of stimulus timing, activation in the cerebellum was decreased for both subjects with ADHD and their unaffected siblings compared to controls (–10.51 ± 2.87; $p$ = .003 for ADHD versus controls and 8.27 ± 2.80; $p$ = .018 for siblings versus controls). There were no differences between unaffected siblings and the subjects with ADHD.

*Table 2.* Functional MRI results for control subjects.

| Region | Side | BA | Talairach | | | Max T-value |
|---|---|---|---|---|---|---|
| *unexpected stimulus, expected time* | | | | | | |
| **IFG** | R | 47 | 40 | 19 | -8 | 5.62 |
| **ACG** | R | 32 | 8 | 21 | 36 | 7.57 |
| MFG | R | 10 | 40 | 47 | 16 | 6.02 |
| | L | 8/9 | -36 | 44 | 31 | 5.78 |
| FG | R | 20/37 | 44 | -43 | -8 | 7.36 |
| STG | R | 21/22 | 59 | -19 | 1 | 5.64 |
| *expected stimulus, unexpected time* | | | | | | |
| **Cerebellum** | L | | -20 | -53 | -44 | 5.59 |
| **IFG** | R | 47 | 36 | 23 | -1 | 4.74 |
| **STG** | R | 44 | 44 | -23 | -2 | 7.83 |
| LG | med | 17 | 0 | -85 | 4 | 9.42 |
| *unexpected stimulus, unexpected time* | | | | | | |
| IFG | R | 47 | 32 | 29 | -8 | 5.98 |
| ACG | med | 32 | 4 | 29 | 39 | 5.19 |
| SFG | R | 8 | 8 | 37 | 42 | 9.07 |
| MFG | R | 6 | 36 | 18 | 51 | 3.74 |
| IPL | L | 40 | -55 | -49 | 28 | 8.14 |
| | R | | 63 | -45 | 28 | 4.84 |

$p$ < .005; minimum extent = 10 voxels; $t$ > 3.36. Bold type indicates regions of a priori interest. MRI = magnetic resonance imaging; IFG = inferior frontal gyrus; R = right; L = left; ACG = anterior cingulate gyrus; MFG = middle frontal gyrus; FG = fusiform gyrus; STG = superior temporal gyrus; LG = lingual gyrus; Med = medial; SFG = superior frontal gyrus; IPL = inferior parietal lobule.

*Two-sample t-tests*. Exploratory, whole-brain *t*-tests were used to investigate differences between groups. For the manipulation of stimulus type, activation in an area in the lateral prefrontal cortex was attenuated for subjects with ADHD compared with control subjects (Talairach: –36, 47, 9; $t$ = 4.01; $df$ = 22; $p$ < .005; minimum extent = 10 voxels). For siblings, activation in the ACG was attenuated compared with control subjects (Talairach: 24, 25, 32; $t$ = 4.43; $df$ = 22; $p$ < .005; minimum extent = 10 voxels). This effect was not significant for subjects with ADHD, although present at subthreshold level (Talairach: 20, 21, 32; $t$ = 3.49; $df$ = 22; $p$ < .005; minimum extent = five voxels).

For the manipulation of stimulus timing, activity in the inferior cerebellum was attenuated for subjects with ADHD compared with control subjects (ADHD: Talairach: –16, –56, –41; $t$ = 4.50; $df$ = 17; p < .005; minimum extent = 10 voxels). For unaffected siblings compared with control subjects, decreased activity in the cerebellum did not exceed subthreshold level (siblings: Talairach: 32, –48, –31; $t$ = 3.63; $df$ = 17; $p$ < .005; minimum extent = five voxels).

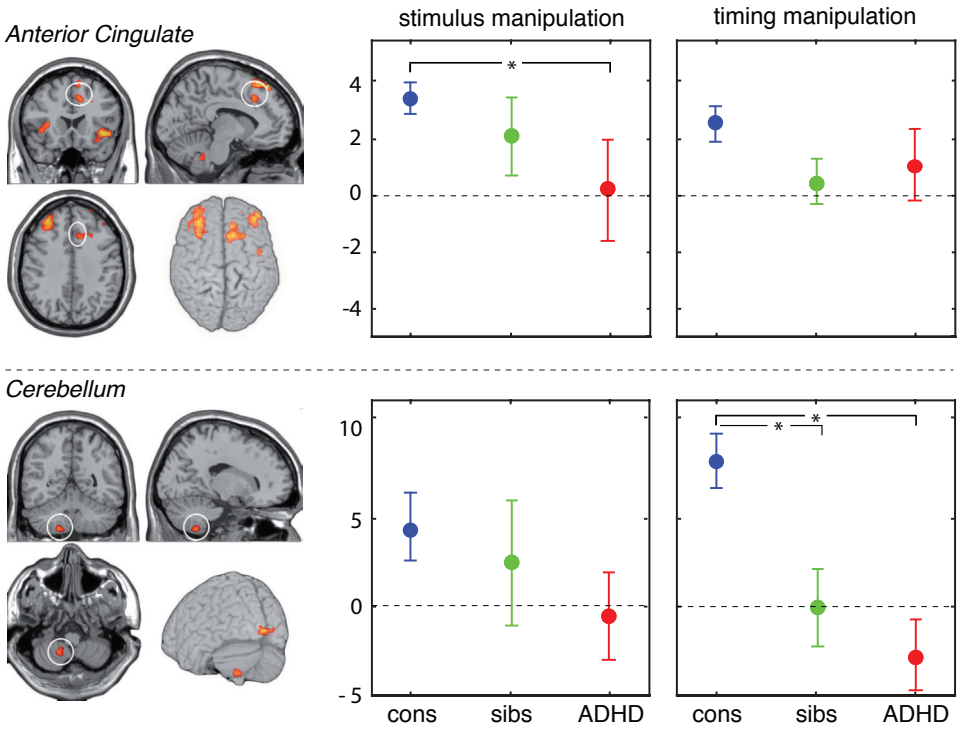


*Figure 2*. Dissociation between activity in the anterior cingulate gyrus and cerebellum, in which both regions show sensitivity to familial vulnerability to ADHD. Left, Activation in the anterior cingulate gyrus and cerebellum is decreased for subjects with attention-deficit hyperactivity disorder (ADHD) compared to control subjects. Circled areas represent regions of interest (ROIs). Right, Signal change for ROIs circled on the right for manipulations of stimulus type and stimulus timing. y-Axis represents MR signal change (arbitrary units). *Significant difference between groups ($p$ < .05).

## Discussion

In this study, we investigated whether cerebellar systems are sensitive to the familial risk for ADHD in certain contexts in addition to fronto-striatal circuits. Behaviorally, we found evidence of effects of familial vulnerability to ADHD on unexpected events and expected events at unexpected times: In both cases, accuracy was decreased for both subjects with ADHD compared with control subjects and intermediate for the unaffected siblings of subjects with ADHD. Functional neuroimaging showed less activity in critical brain areas, associated with both types of unpredictable events for both groups. Furthermore, attenuations in activation were context specific. During stimulus manipulations (no-go trials), both subjects with ADHD and their unaffected siblings showed decreased activity in the ACG and prefrontal areas, whereas during timing manipulations, both groups showed decreased activation in the inferior cerebellum. These results suggest that cerebellar regions are sensitive to familial vulnerability to ADHD in certain contexts, in addition to prefrontal systems.

The finding that the cerebellum was sensitive to familial risk for ADHD was unexpected. Based on earlier findings, we had hypothesized that deficits in the cerebellum would be specific to ADHD because we had found that decreases in the cerebellar volume were only present in siblings with ADHD but not their unaffected counterparts (Durston, et al., 2004). Furthermore, in a study of DAT1 gene effects on brain activation, there was an interaction between vulnerability to ADHD and genotype for activity in the striatum, but not the cerebellum (Durston, et al., 2008). However, in the present study, we found that activation in the cerebellum was sensitive to familial vulnerability to ADHD in certain contexts because both siblings with and without ADHD showed decreased activation in this region to events at unexpected times.

For controls, the ACG was active for unexpected events (no-go trials) and the cerebellum was active for events at the unexpected time, whereas activity in these regions was decreased for subjects with ADHD. However, we found no evidence of decreased activation in the inferior frontal gyrus for subjects with ADHD, likely related to diminished power to detect differences between groups as a result of fewer no-go trials in comparison to previous studies using go/no-go paradigms (e.g., see Durston, et al., 2006).

There are some important limitations to our study. First, although subjects with ADHD were either not taking medication or discontinued treatment 24 hours before undergoing the functional MRI scan, most were not stimulant naïve. As such, we cannot rule out that some of the observed changes in brain activation were due to long-term effects of stimulant medication. However, recent evidence suggests that long-term effects of stimulant medication on brain activity patterns are small, if present at all (Pliszka, et al., 2006; Smith, et al., 2006). Furthermore, the unaffected siblings in this study had never taken stimulants, suggesting that changes shared by both groups are unlikely to be fully explained by stimulant treatment. Second, as we were careful to include only truly discordant sibling pairs in the study, the sample size is relatively small. With larger groups, statistical power would have been greater and our findings would likely have appeared stronger. As such, we cannot be certain

that null findings in the present study are not due to low power. However, effect sizes (0.19 - 0.38) in ROIs (ACG and cerebellum) suggest that these findings are fairly robust. Certainly, in a previous study that included both subjects with ADHD and controls from this study, as well as an independent sample, differences between controls and ADHD were found in both these regions in both samples (Durston, et al., 2007). Third, we used group averages rather than investigated differences at an individual level. As such, we cannot rule out that differences in activation between groups could be related to increased anatomical variability in the ADHD and unaffected sibling samples rather than functional differences. Finally, here we investigated full siblings of individuals with ADHD. Because the familial relatedness is similar (approximately 50%) for all of the sibling pairs in this study, we cannot estimate the heritability of phenotypic measures based on these data. Future studies including both monozygotic and dizygotic twins will be better able to address this issue.

In sum, the present study suggests that activity in both the prefrontal cortex and cerebellum is sensitive to familial vulnerability to ADHD. Accuracy was lower for unexpected events (no-go trials) and expected events at unexpected times for subjects with ADHD compared with control subjects and intermediate for their unaffected siblings. Furthermore, unaffected siblings of individuals with ADHD showed decreased activity in prefrontal areas for unexpected events and in cerebellum for events at unexpected times, similar to their affected counterparts.

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# Chapter 4

## Functional connectivity in cognitive control networks is sensitive to familial risk for ADHD

**Background**. Familial risk for attention-deficit hyperactivity disorder (ADHD) has been associated with changes in brain activity related to cognitive control. However, it is not clear whether changes in activation are the primary deficit or whether they are related to impaired communication between regions involved in this ability. We investigated whether (1) functional connectivity between regions involved in cognitive control is affected by familial risk and (2) changes are specific to these regions.

**Methods**. Correlational seed analyses were used to investigate temporal covariance across the brain within cognitive control regions and motor networks in two independent samples of typically developing controls, subjects with ADHD and their unaffected siblings.

**Results**. In both samples, correlations within the cognitive control network were greater for typically developing controls than for subjects with ADHD, with intermediate correlations for unaffected siblings. Within the motor network, unaffected siblings had correlations equal to typically developing children. There were no differences in activity between the brain regions involved.

**Conclusion**. These data show that functional connectivity of cognitive control networks is sensitive to familial risk for ADHD. Results suggest that changes in connectivity associated with cognitive control may be suitable as an intermediate phenotype for future studies.

*Under review*

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## Introduction

Attention-deficit hyperactivity disorder (ADHD) is a developmental disorder characterized by poor behavioral control and impairments in attention. These problems are often conceptualized as related to cognitive control. However, the heterogeneous symptoms associated with ADHD make it hard to pinpoint neurobiological mechanisms underlying them (Castellanos & Tannock, 2002; Gottesman & Gould, 2003). Measures at a level intermediate between behavior and biology can be useful to reduce the behavioral complexity. For example, brain imaging measures have been shown to be useful as intermediate phenotypes in ADHD-research, as they represent reproducible, quantitative measures of phenotypic changes that are not state-dependent (Durston, et al., 2009). Magnetic resonance imaging (MRI) studies have shown deficits in brain functioning during tasks that tap cognitive control (Bush, et al., 2005; Castellanos & Tannock, 2002; Dickstein, et al., 2006; Durston, et al., 2009). Recent findings have suggested that neural connectivity is changed in ADHD, both during tasks and when the brain is at rest (Casey, et al., 2007; Castellanos, et al., 2008; Fassbender, et al., 2009; Murias, et al., 2007; Tian, et al., 2006; Uddin, et al., 2008; Wang, et al., 2009; Wolf, et al., 2009; Zang, et al., 2007). This raises the question whether well-established changes in brain activity in ADHD are related to changes in connectivity between brain regions.

Studies of typically developing children, subjects with ADHD and their unaffected siblings have already shown that changes in activity related to cognitive control are sensitive to familial risk for the disorder (Durston, et al., 2006; Mulder, et al., 2008). However, it is not clear whether it is the level of activity per se that is under familial influences, or whether changes in connectivity in cognitive control circuits may be driving these findings. We set out to address this by investigating familial effects on connectivity between regions of the cognitive control network: We identified regions that temporally covaried during a cognitive control paradigm and investigated differences in the strength of these task-dependent connections between typically developing children and adolescents, subjects with ADHD and their unaffected siblings. We hypothesized that task-dependent functional connectivity of cognitive control networks would be decreased for subjects with ADHD compared to typically developing controls. Furthermore, we hypothesized that connectivity in these networks would be sensitive to familial risk (i.e., correlation coefficients for unaffected siblings would be intermediate between subjects with ADHD and controls). To ensure that changes in connectivity were not related to changes in activity levels in the brain regions involved, we selected seed regions where the BOLD-signal did not differ between groups. Furthermore, we tested whether findings were specific to regions of the cognitive control network by investigating temporal covariation within the motor network during the same task. Finally, to lend confidence to our findings, we sought to replicate our results in an independent sample.

*Table 1*. Descriptive variables for controls, unaffected siblings and siblings with ADHD

| | sample 1 | | | sample 2 | | |
|---|---|---|---|---|---|---|
| | controls (N=11) | siblings (N=11) | ADHD (N=11) | controls (N=12) | siblings (N=12) | ADHD (N=12) |
| Age | | | | | | |
| Mean | 15.27 (1.92) | 14.45 (2.58) | 13.97 (3.14) | 15.0 (2.1) | 14.1 (2.7) | 14.9 (2.3) |
| IQ | | | | | | |
| Mean | 106 (14) | 107 (15) | 100 (10) | 107 (20) | 115 (20) | 108 (22) |
| Hand preference | | | | | | |
| (L/R) | 0/11 | 0/11 | 2/9 | 3/9 | 1/11 | 3/9 |
| ADHD (N on DISC) | | | | | | |
| Combined | 0 | 0 | 10 | 0 | 0 | 9 |
| Hyperactive | 0 | 0 | 1 | 0 | 0 | 3 |
| ODD | 0 | 0 | 3 | 0 | 0 | 4 |
| CBCL | | | | | | |
| ADHD | 51.6 (1.8) | 52.7 (3.7) | 62.1 (6.7) ** | 52.2 (3.3) | 54.3 (5.8) | 60.9 (10.0) ** |
| ODD | 52.2 (3.0) | 53.3 (5.2) | 60.3 (6.1) ** | 50.9 (1.6) | 51.3 (2.3) | 60.6 (9.2) * |
| CD | 50.7 (1.2) | 53.7 (5.0) | 59.7 (6.9) ** | 50.4 (0.5) | 51.9 (3.1) | 59.8 (7.9) * |
| Affective problems | 52.5 (4.9) | 52.5 (3.8) | 59.5 (9.2) * | 52.5 (3.6) | 55.3 (6.6) | 58.3 (9.6) |
| Anxiety problem | 51.1(1.5) | 52.8 (3.7) | 56.7 (6.3) * | 55.3 (7.3) | 52.8 (4.8) | 53.9 (5.8) |
| Somatic problems | 51.6 (2.8) | 53.5 (3.6) | 56.9 (6.3) * | 54.6 (4.1) | 54.3 (5.0) | 55.2 (6.1) |
| Anxious/depressed | 50.5 (1.2) | 52.1 (4.2) | 56.7 (7.2) ** | 52.9 (4.9) | 52.8 (5.4) | 53.3 (8.3) |
| Withdrawn/depressed | 53.2 (4.5) | 55.7 (6.2) | 57.4 (8.5) | 52.6 (3.8) | 59.2 (8.9) | 58.3 (8.5) |
| Somatic Complaints | 51.5 (2.7) | 53.5 (3.2) | 57.5 (7.8) ** | 53.3 (3.6) | 55.8 (4.1) | 55.2 (5.0) |
| Social problems | 50.8 (1.6) | 52.2 (5.0) | 58.6 (8.6) ** | 52.8 (5.6) | 52.7 (4.0) | 58.8 (9.8) |
| Thought problems | 50.7 (1.5) | 51.7 (2.9) | 60.8 (8.1) ** | 53.5 (5.1) | 52.8 (5.3) | 57.7 (8.3) |
| Attention problems | 52.1 (2.3) | 52.5 (4.1) | 59.2 (5.9) ** | 52.6 (3.6) | 54.8 (5.6) | 59.3 (8.3) ** |
| Rule-breaking behavior | 50.8 (0.8) | 54.8 (5.3) | 59.5 (5.7) ** | 50.4 (0.7) | 52.2 (3.0) | 58.4 (5.6)* |
| Aggressive behavior | 51.0 (2.4) | 52.8 (5.0) | 60.9 (7.8) ** | 50.5 (1.5) | 51.8 (3.9) | 62.3 (10.7) * |
| SES | | | | | | |
| mothers's education (years) | 11.8 | 11.3 | 11.3 | 13.2 | 13.5 | 13.5 |
| father's education (years) | 10.9 | 12.2 | 12.2 | 14.0 | 14.1 | 14.1 |
| On medication | 0 | 0 | 6 | 0 | 0 | 7 |

Legend: ADHD = attention-deficit hyperactivity disorder; ODD = oppositional defiant disorder; CD = Conduct Disorder; SES = socio-economic status; DISC = Diagnostic Interview Schedule for Children; CBCL = Child Behavior Checklist;
** $p < .01$; * $p < .05$

## Methods

*Subjects.* fMRI-data from two independent samples from previously published fMRI-studies were reanalyzed for the purposes of this paper. Sample 1 included 33 male subjects (11 sibling pairs discordant for ADHD and 11 typically developing, matched controls), between the ages of 8 and 20 years (Durston, et al., 2006). Sample 2 included 36 male subjects (12 sibling pairs discordant for ADHD and 12 typically developing, matched controls), between the ages of 9 and 19 years (Mulder, et al., 2008). All subjects performed a variation of a go/no-go paradigm. Subjects with ADHD were required to have received a clinical ADHD diagnosis from our department and to meet DSM-IV criteria for ADHD, as assessed by DISC interview. Siblings and control subjects were excluded if they met DSM-IV criteria for any psychiatric diagnosis, as assessed by DISC interview. In addition, Child Behavior Checklist scores were obtained to ascertain the presence of ADHD-related symptoms in siblings and control subjects (for details see Table 1).

*MRI scan acquisition & preprocessing.* All subjects participated in a practice session prior to scanning, using an MRI simulator at the Department of Child and Adolescent Psychiatry, University Medical Center Utrecht, the Netherlands. For sample 1, MRI images were acquired on a 1.5-T Philips Gyroscan (Philips Medical Systems, Best, the Netherlands), housed at the Department of Radiology in the same hospital. Functional MRI scans consisted of a navigated three-dimensional PRESTO pulse sequence (time to echo [TE] 11 msec, repetition time [TR] 21.74 msec, flip angle 9.0°, matrix 64 × 64 × 24, field of view [FOV] 256 × 256 × 96 mm, voxel size 4 mm isotropic, and scan duration 2.0 sec per 24-slice volume), covering the whole brain. For sample 2, MR images were acquired on a 1.5-T Philips Allegra MR scanner (Philips Medical Systems, Best, the Netherlands). Functional MRI scans consisted of a navigated three-dimensional PRESTO pulse sequence (TE = 11 milliseconds, TR = 21.74 milliseconds, flip angle 9.0°, matrix 64 × 64 × 36, FOV: 256 × 256 × 144 mm, voxel size 4 mm isotropic, and scan duration 2.0 seconds per 36-slice volume), covering the whole brain. Anatomical T1-weighted three-dimensional fast field echo scans with 170 1.2-mm contiguous coronal slices of the whole head (TE = 4.6 milliseconds, TR = 30 milliseconds, flip angle 30 degrees, FOV 256 mm, in-plane voxel size 1 × 1 mm) were also acquired.
MR images were preprocessed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London). First, functional time-series were realigned to the first image to correct for motion artifacts using a 6-parameter (rigid body) spatial transformation (Friston, et al., 1995). In addition, the T1-weighted anatomical image was co-registered to the functional time-series by using Mutual Information (Collignon, et al., 1995; Wells, et al., 1996). Time-series were normalized to standard stereotactic space (Montreal Neurological Institute template) and resliced with a voxelsize of 4 × 4 × 4 (same as raw voxelsize). Finally, functional images were smoothed with an 8 × 8 × 8 kernel FWHM. Global effects were removed using a voxel-level linear model of the global signal (LMGS; Macey, et al., 2004).

*Correlational seed analyses.* All analyses were run for each sample separately. Seed regions were determined by a whole brain second-level one-sampled *t*-test over all subjects to avoid selection bias

toward a specific group ($p = .0001$, extent 10 voxels; corresponding to $p = .05$ corrected at the cluster level). Three seed regions were chosen: two associated with cognitive control (anterior cingulate gyrus [ACG] and right inferior frontal gyrus [rIFG]; contrast no-go > go) and one region, associated with motor responses (motor cortex [MTC]; contrast go > no-go). For each seed region, the peak of activity was used to define 10mm spheres (see Figure 1). For each seed, a one-way ANOVA was run to ensure that there were no differences between groups in blood oxygenation level-dependent (BOLD) signal. There was no difference between groups (controls; unaffected siblings; siblings with ADHD) in BOLD level in the seed regions for either sample ($F < 2.5$, $p > .1$).

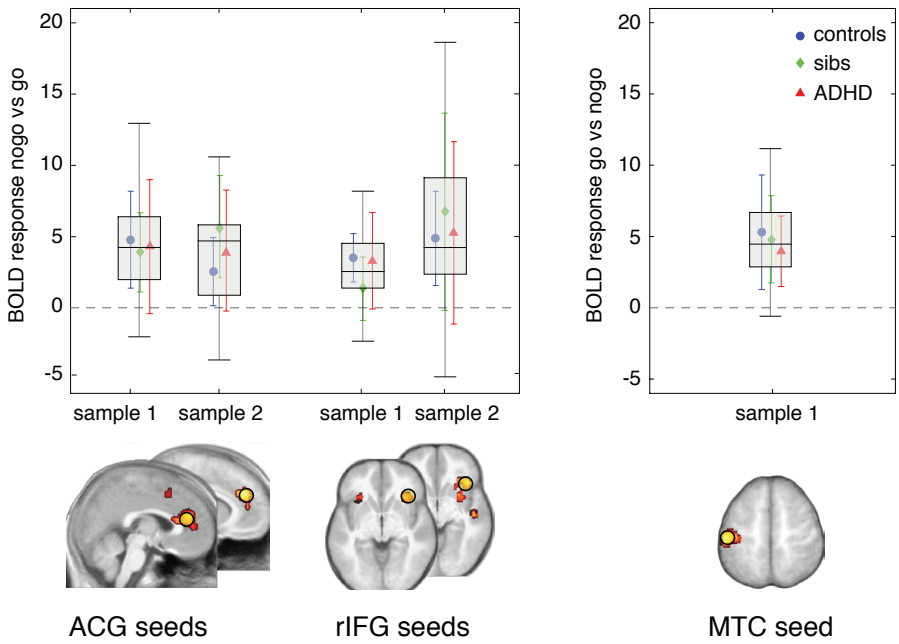


*Figure 1*. Seed points selected from whole group analyses. Seed regions were taken from a whole group one-sample *t*-test at $p = .0001$, extent 10 voxels (corresponding to $p = .05$ corrected at the cluster level) for each sample. For each seed region, the peak activity was used to define 10mm spheres (yellow circles). Grey boxes represent the interquartile range (difference between first and third quartiles) for the whole group. The colored datapoints represent mean (SD) BOLD activity level for each group separately (healthy controls - blue; unaffected siblings -green and subjects with ADHD - red). Legend: ACG = anterior cingulate gyrus; BOLD = blood oxygenation level dependent; IFG = inferior frontal gyrus; MTC = motor cortex.

For each sphere separately, averaged individual timeseries were extracted and entered in a general linear model (GLM) with the six motion parameters for each subject. *T*-maps were created for the covariate of interest from these individual GLM analyses and converted to *R*-maps, using the Volumes toolbox for SPM. These *R*-maps reflect individual maps of the correlation strength (correlation coefficient r) with the seed region per voxel. To allow for second level analyses of correlations,

individual *R*-maps were converted to *Z*-maps using Fisher's *R* to *Z* transformation. Two sample *t*-tests were run to test for differences in correlation patterns between typically developing controls and subjects with ADHD at $p = .001$, extent 10 voxels. For replication in the second sample, a more lenient threshold of $p = .005$, extent 5 voxels was allowed. Fisher transformed correlation coefficients were extracted for each ROI , and entered in a general linear model (univariate) analysis of variance (UNIANOVA) to test for sibling effects. Dummy variables were used to code for patient and sibling status, thus comparing siblings to all other subjects while controlling for patient effects, and vice versa. To control for possible developmental effects, we reran the analyses with age included as covariate (Lee et al., 2009). Additionally, for each ROI BOLD responses for the no-go > go and go > no-go contrasts were extracted to explore whether there were between-group differences in the task-related BOLD signal.

## Results

*ACG-seed.* Differences between typically developing individuals and subjects with ADHD in correlations with ACG were found for cerebellum (CB) ($p < .001$; $k = 24$, Figure 2*A*). This was replicated in sample 2 ($p = .002$; $k = 5$, see Figure 2*B*). For both samples, correlation coefficients for unaffected siblings were intermediate between those of controls and subjects with ADHD, with significant lower correlation coefficients compared to controls in sample 1 ($F_{1, 30} = 4.97$; $p < .05$). In sample 2, correlation coefficients for siblings did not differ from controls or subjects with ADHD ($p > .5$). Results did not change when age effects were controlled for. There were no differences between groups in the BOLD response in the region found in cerebellum ($p > .44$).

*rIFG-seed.* Differences between typically developing children and subjects with ADHD in correlations between rIFG and left inferior frontal gyrus (lIFG) did not exceed the statistical threshold of $p = .001$; $k = 10$.

*MTC-seed.* Differences between typically developing children and subjects with ADHD in correlations with motor cortex were found in striatum ($p < .001$; $k = 12$). Correlation coefficients for unaffected siblings were similar to those of the control group ($p > .7$), but significant different from the patient group ($t = 3.5$; $p < .01$; see Figure 2*C*). Results did not change significantly when age effects were controlled for.

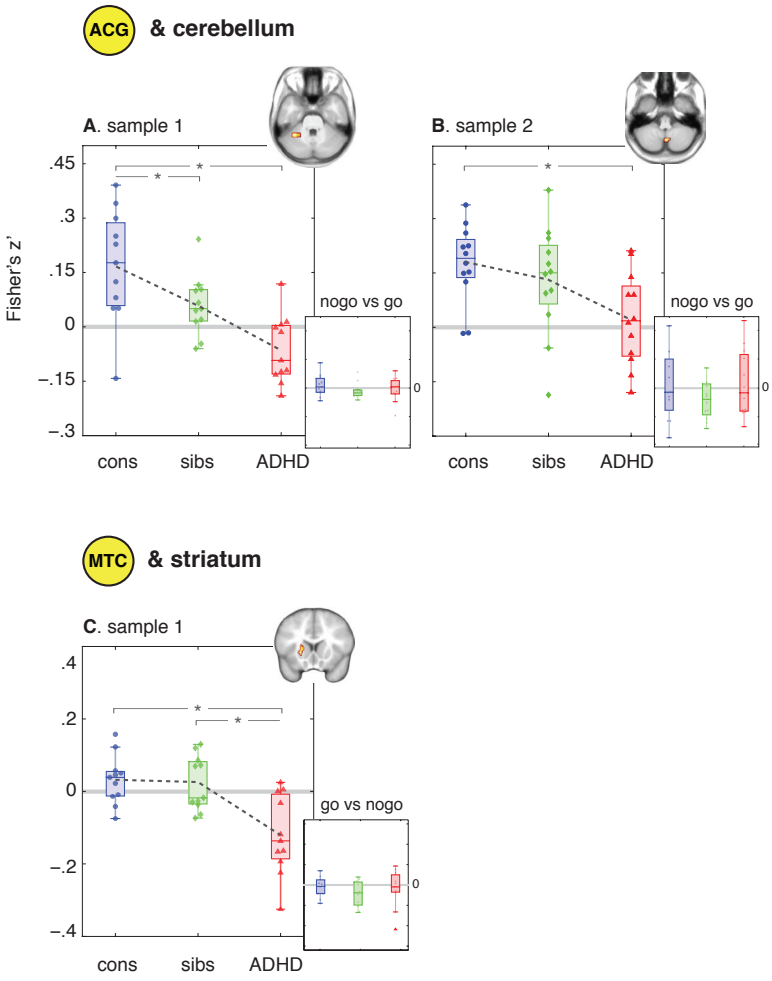


*Figure 2.* Group differences in functional connectivity. Boxes represent the interquartile range, dashed lines connect means for each group. Functional connectivity between ACG and CB differs between subjects with ADHD (red) and typically developing controls (blue). Correlation coefficients for unaffected siblings (green) are intermediate (**A & B**). Functional connectivity between motor cortex and striatum differed between subjects with ADHD (red) and healthy controls (blue), but the correlation coefficients for unaffected siblings are similar to those of healthy controls (green) (**C**). There are no differences between groups in the BOLD response in any of the regions (small graphs). * = p <.05

## Discussion

We found that functional connectivity in cognitive control networks was sensitive to familial risk for ADHD: Functional connectivity between ACG and cerebellum was decreased for subjects with ADHD. Unaffected siblings of boys with ADHD showed correlation coefficients intermediate between their affected counterparts and typical controls. These differences were present in the absence of differences in activity in ACG or CB. There was no effect of familial risk on the motor network during the same task, suggesting that familial effects are specific to functional connectivity within cognitive control networks, and not merely a consequence of differences in task-related activity. Replication in a second sample lends further confidence to these results.

Our findings tie in with recent findings of atypical functional connectivity of cerebellum and ACG during a working memory task in ADHD (Wolf, et al., 2009). Findings of changes in connectivity in ADHD in two such different tasks suggest that this may be an integral part of the ADHD-phenotype. Further support comes from studies of the brain's resting state in ADHD: These have suggested that moment-to-moment fluctuations in the low-frequency range (representing the brain's resting state or default mode) may interfere with high-frequency, task-specific processes, thereby contributing to variability in task performance and interruption of goal-directed activity (Sonuga-Barke & Castellanos, 2007). Indeed, subjects with ADHD appear to have difficulty to suppress default network activity (Fassbender, et al., 2009) and have been shown to have increased connectivity between regions in this network (Tian, et al., 2006). Here, cerebellum shows higher functional connectivity with dorsal ACG during rest. Although our results of task-related decreases in connectivity between these regions initially appear contrary to this finding, they support suggestions that subjects with ADHD may be impaired in switching between task-positive and task-negative processes.

There are some limitations to our study. First, we operationalized functional connectivity as statistical dependence (correlations) between remote neurophysiological events. As such, no causal inferences can be drawn from these analyses (Friston, 2005).
Second, our seeds were selected to not be biased towards a specific group; both subjects with ADHD and their unaffected siblings showed activity levels similar to controls, both in the seed regions and in the regions found to correlate with them. However, other studies have shown reduced activity in these regions, both in ADHD (for review see Bush, et al., 2005; Dickstein, et al., 2006; Durston, 2003; Durston, et al., 2009) and in unaffected family members (Durston, et al., 2006; Mulder, et al., 2008). These findings underline that the whole cognitive control system is likely to be involved in ADHD and that changes are not likely to be entirely due to differences in connectivity. However, our approach does make it unlikely that the current finding of reduced connectivity is secondary to changes in activity in the regions involved.

In sum, we show that functional connectivity of cognitive control networks is sensitive to familial risk for ADHD, in two independent samples. These results suggest that changes in cognitive control in ADHD are at least in part related to changes in connectivity in these networks. Furthermore,

they suggest that changes in connectivity associated with cognitive control may be suitable as an intermediate phenotype for future studies.

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# Part 2

In **Part 2** (**chapters 5 & 6**), we investigated whether deficits are limited to higher-order processes, or if basic perceptual decisions are also affected by ADHD. Furthermore, we addressed where in the brain basic decisions are biased by reward expectations.

# Chapter 5

## Basic impairments in regulating the speed-accuracy tradeoff predict symptoms of ADHD

**Background**. ADHD is characterized by poor optimization of behavior in the face of changing demands. Theoretical accounts of ADHD have often focused on higher-order cognitive processes and typically assume that basic processes are unaffected. It is an open question whether this is indeed the case.

**Method**. We explored basic cognitive processing in twenty-five subjects with ADHD and thirty typically developing children and adolescents using a perceptual decision making paradigm. We investigated whether individuals with ADHD were able to balance the speed and accuracy of decisions.

**Results**. We found impairments in optimization of the speed-accuracy tradeoff. Furthermore, these impairments were directly related to the hyperactive and impulsive symptoms that characterize the ADHD-phenotype.

**Conclusion**. These data suggests that impairments in basic cognitive processing are central to the disorder. This calls into question conceptualizations of ADHD as a 'higher-order' deficit, as such simple decision processes are at the core of almost every paradigm used in ADHD research.

*Under review*

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## Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common child neuropsychiatric disorder. It is has a great impact on affected individuals and their families, as individuals with ADHD have trouble adapting their behavior appropriately to social and environmental demands. For example, children with ADHD may have trouble waiting their turn in conversation, staying in their seat in the classroom (impulsive symptoms) or they may have trouble focusing on the task at hand and become distracted easily (inattentive symptoms). Such symptoms can be conceptualized as poor adaptation of behavior to social or environmental demands and have often been attributed to deficits in higher-order cognitive processes. Indeed, functional imaging studies have shown changes in brain activity on tasks that tap these processes (see Bush, et al., 2005; Castellanos & Tannock, 2002; Dickstein, et al., 2006; Durston, et al., 2009 for review). However, these studies have one thing in common: They use paradigms where subjects respond differentially to different classes of stimuli. As such, these tasks require the subject to make a perceptual decision in choosing the most appropriate course of action. A basic assumption of these paradigms is that children with ADHD are capable of making such basic perceptual decisions as well as typically developing children. It is an open question whether this is indeed the case. If children with ADHD are impaired in balancing the speed and accuracy with which they make such decisions, this will affect their behavior. For example, a child that decides prematurely that their friend has finished talking, may blurt out a response too quickly.

Decision making processes can be described using the *drift-diffusion model* (e.g. Glimcher, 2003; Gold & Shadlen, 2007; Luce, 1986; Ratcliff, 1978; Reddi & Carpenter, 2000; Usher & McClelland, 2001). This model conceptualizes decision making as the accumulation of sensory information over time towards a decision threshold (see Figure 1; see Bogacz, 2007; Gold & Shadlen, 2007 for review): The sensory evidence builds up towards a decision until the threshold is reached, at which point the decision is made. One particularly useful property of this model is that it simultaneously accounts for response time (RT) and accuracy data (Palmer, et al., 2005; Ratcliff, 1978, 2006; Ratcliff & McKoon, 2008; Simen, et al., 2009). A second useful property is that studies from both humans and non-human primates have found evidence for neural correlates of the model's components, demonstrating that they have ecological validity in addition to theoretical appeal (Beck, et al., 2008; Forstmann, et al., 2008; Gold & Shadlen, 2000, 2001; Grossberg & Pilly, 2008; Heekeren, et al., 2004; Philiastides & Sajda, 2007; Schall, 2001; Wang, 2002). In addition to integrating RT and accuracy data into a single model, the drift-diffusion model permits the decomposing of data into parameters that are related to decision making and those that are related instead to sensory or motor processing. Each parameter has a unique effect on behavior, and subjects are required to adjust the parameters of the model to comply with task demands (Ratcliff & McKoon, 2008). The rate of drift towards a decision threshold depends on the difficulty of the decision at hand, but subjects can adapt the decision threshold to favor speed or accuracy.

One important aspect of optimizing behavior in response to environmental demands involves the speed-accuracy tradeoff (Bogacz, et al., 2009; Palmer, et al., 2005; Rinkenauer, et al., 2004; Roitman

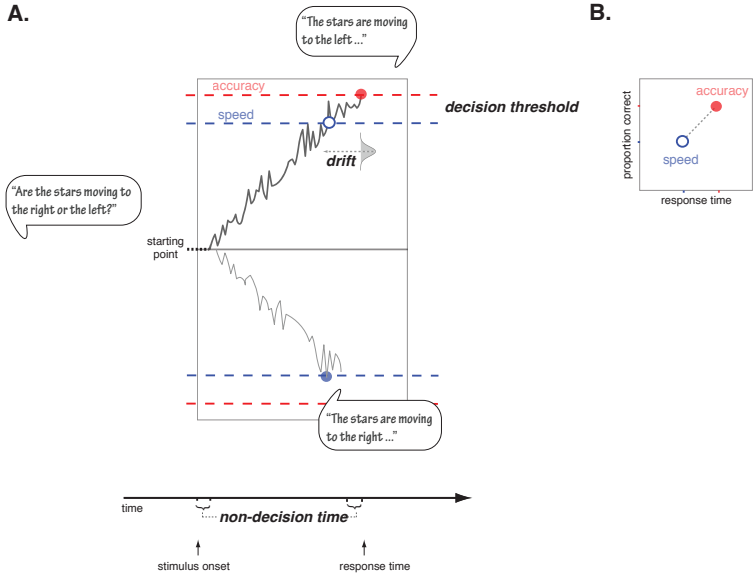


*Figure* 1. Schematic representation of the drift-diffusion model. **A.** This model assumes that dichotomous decisions are based on the accumulation of noisy evidence over time to a fixed threshold (*decision threshold*). As the process is noisy, there is variability in the time to reach threshold, leading to variable RTs and possibly incorrect choices. *Drift rate* represents the average amount of evidence accumulated per time unit. *Non-decision time* is the time for processes other then the decision process, such as stimulus encoding and motor responses. **B.** The drift-diffusion model provides a model for the speed-accuracy tradeoff: When the decision threshold is low, responses are fast, but involve a higher risk of an incorrect choice (open blue circle). When the decision threshold is higher, more time is used to collect evidence, increasing the chance of a correct choice (solid red circle). As such, flexible adaptation of the decision threshold is crucial in optimizing speed and accuracy in response to environmental demands.

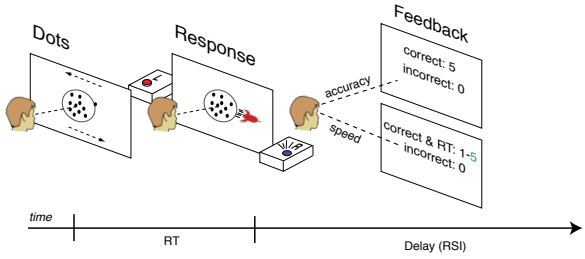


*Figure 2*. Random-dot motion task. Subjects were instructed to indicate the direction of an array of randomly moving dots by a button press. The motion stimulus stayed on until a button was pressed. After the response, feedback showing the number of points earned was given. During accuracy sessions, subjects earned five points for each correct choice. During speed sessions, subjects earned between one and five points, depending on the speed of their response. To stress the importance of speed, 5-point rewards were displayed in a green font and accompanied by a special winning bleep.

& Shadlen, 2002; Simen, et al., 2006; Simen, et al., 2009): Errors are more likely when information is noisier, meaning more time is required to reach a correct decision. Trading speed (slowing down) for accuracy is useful in contexts where errors are costly, but accuracy can be sacrificed to gain speed and a higher rate of reward if rewards for correct responses outweigh the cost of errors. The drift-diffusion model provides a mechanism to conceptualize the speed-accuracy tradeoff by flexibly adapting the decision threshold. When the decision threshold is low, responses are fast, but more errors are made. When the threshold is high, more time is taken to collect evidence, thus increasing the chance of a correct decision (Figure 1). As such, flexible adaptation of the decision threshold is crucial to adapting behavior in response to environmental demands. As subjects with ADHD have difficulty adapting their behavior in response to environmental demands and are prone to impulsiveness, we hypothesized that this may arise from a basic inability to adapt the decision threshold. This inability could manifest itself as a tendency to make impulsive and speedy decisions, behavior that is associated with ADHD at a phenotypic level.

We set out to investigate this hypothesis using a basic perceptual decision making task, where either accuracy or speed was stressed in the instructions. Specifically, we hypothesized that subjects with ADHD would display an overall preference for speed over accuracy, reflected by a lower decision threshold than controls under conditions where accuracy was stressed. Furthermore, we hypothesized that subjects with ADHD would show a smaller speed-accuracy tradeoff across levels of accuracy emphasis, reflecting the inability to optimize performance in response to changing task demands. This smaller adjustment in the speed-accuracy tradeoff should be reflected in the difference between decision thresholds in tasks conditions where either speed or accuracy was emphasized. Finally, we hypothesized that if optimizing behavior at this basic cognitive level is indeed central to ADHD, then these deficits should correlate with symptoms of the disorder.

Thirty typically developing children and adolescents and twenty-five subjects with ADHD performed a perceptual decision making task, where the instructions were manipulated to stress accuracy in one condition and speed in another (Figure 2). We used a child-friendly version of a random-dot motion task, embedded in a computer game. Subjects were told that a small red rocket was lost in space, and that they needed to bring the rocket back home to earth safely, by following the stars. “Stars” were depicted as a cloud of randomly moving dots on a screen. Subjects had to decide whether the ‘stars’ were moving to the left or to the right. Stimuli were similar to those used in a variety of experiments (Britten, et al., 1992; Gold & Shadlen, 2000; Heekeren, et al., 2006; Palmer, et al., 2005; Simen, et al., 2009). In the *accuracy* sessions, subjects were instructed that they would gain points by being as accurate as possible. In the *speed* sessions, they were instructed to respond as fast as they could and were told that they would receive more points for doing so. To examine whether differences between groups were specific to the speed-accuracy tradeoff or whether other components of the decision process were also affected, we manipulated difficulty by changing the number of coherently moving ‘stars’ across five difficulty levels.

## Methods & Materials

**Participants**. A total of 57 children participated in the study, including 25 children diagnosed with ADHD. Two control subjects were excluded from the analyses due to poor performance on the task, where more than two thirds of the data constituted fast guesses (impulsive choices based on a guess or caused by a distraction). Demographic information is listed in Table 1.

*Table 1*. Descriptive statistics for typically developing controls and subjects with ADHD (mean ± SD).

| | controls (N=30) | ADHD (N=25) |
|---|---|---|
| Sex (M/F) | 21/9 | 22/3 |
| Age | 12.9 (4.0) | 11.8 (3.1) |
| Tanner (A) stage | 2.7 (1.8) | 2.4 (1.7) |
| IQ | 110 (18) | 102 (16) |
| Hand preference (L/R) | 3/27 | 2/23 |
| ADHD - type (number of subjects) | | |
| Inattentive | 0 | 9 ** |
| Hyperactive | 0 | 4 ** |
| Combined | 0 | 12 ** |
| DISC – total symptom scores | | |
| inattentiveness | .6 (1.3) | 6.3 (2.0) ** |
| hyperactivity/ impulsivity | .5 (1.2) | 5.5 (2.2) ** |
| ODD | 0 | 7 ** |
| SES | | |
| maternal education (years) | 13.2 (2.1) | 13.7 (1.8) |
| paternal education (years) | 13.9 (2.3) | 13.6 (2.6) |

ADHD = attention-deficit hyperactivity disorder; ODD = oppositional defiant disorder; CD = conduct disorder; DISC = Diagnostic Interview Schedule for Children; F= female; L = left; M = male; R=right, SES = socioeconomic status, ** $p < .01$, * $p < .05$.

ADHD subjects were matched to typically developing control subjects, for age, gender, IQ, hand preference, and socio-economic status (operationalized as years of parental education). Subjects were recruited through the Department of Child- and Adolescent Psychiatry at the University Medical Center Utrecht in the Netherlands (children with ADHD) and local schools (typically developing controls). The procedure was approved by the Medical Ethical Review Board at the UMC Utrecht and informed consent was obtained from a parent for each child, as well as assent from the subject. Children with major physical or neurological illness, learning disabilities or IQ < 70 were excluded from participating. IQ was assessed using Wechsler intelligence tests (WISC-II, WISC-R or WAIS). Subjects with ADHD were required to have a clinical diagnosis for ADHD from our department, as well as meet criteria for ADHD according to the Diagnostic Interview Schedule for Children (DISC-P). Control subjects were not permitted any diagnosis on DISC-P. Nineteen subjects with ADHD were on short-acting medication and were asked to discontinue treatment for a minimum of 24 hours before participating in the study.

**Paradigm**. To manipulate the speed-accuracy tradeoff we used a version of the random-dots motion paradigm (e.g. Britten, et al., 1992; Forstmann, et al., 2008; Gold & Shadlen, 2000; Hanks, et al., 2006; Heekeren, et al., 2006; Palmer, et al., 2005; Ratcliff & McKoon, 2008; Simen, et al., 2009). Subjects were instructed to maintain fixation on the middle of the screen and to decide the direction of motion of a cloud of randomly moving white dots. They were further instructed to indicate their decision at any time during motion viewing with a button press. Task difficulty was manipulated by manipulating the percentage of coherently moving dots, where the task was easier for trials with more coherently moving dots and harder for trials with fewer coherently moving dots.

For the current study we developed a child friendly version of the task: The paradigm was embedded in a simple game, where children were told that they needed to help a red rocket that was lost in space by following the stars. Children were asked to point the rocket in the direction of the moving 'stars' (dots), by pressing a red (left) or blue (right) button. When a button was pressed (i.e., a choice was made) a small red rocket flashed through the dots in the direction of the button press, accompanied by a flashy sound. Feedback was displayed immediately following the trial: The number of points earned on the preceding trial was displayed in the middle of the screen. To prevent anticipatory responses, the response-stimulus interval (RSI) was varied. On any given trial, the RSI was selected from an exponential distribution with a mean of 0.75 s (range 0.3 - 2.4 s) to ensure stimulus onset was unpredictable and to secure a refractory period. In addition, a penalty delay of 4 s was imposed for responses made within 100 ms of stimulus onset and accompanied by a buzzing error tone (Simen, et al., 2009).
Subjects were instructed to keep their head at a steady distance of 60 cm from the screen, and to maintain fixation on the middle of the screen, where feedback was displayed. Subjects were first instructed to perform as accurately as possible in order to earn maximum points. Correct choices triggered a rewarding beep. Incorrect choices produced no auditory feedback. After each set of 25 trials, a subtotal score was displayed in a large green font, accompanied by the number of points missed due to incorrect responses in a smaller red font. After each session of 125 trials, subjects had a rest, while the sub-total was displayed on the screen and followed by a picture of the rocket landed on planet, accompanied by an ambient soundtrack. This rest was provided to avoid lapses in attention due to fatigue.

*Pre-practice session*. To become familiar with the task, subjects practiced during the first set of task instructions. Ten practice trials were displayed with relatively easy coherence levels (12.8, 25.6, or 51.2 percent coherently moving dots). If performance was poorer than 60% correct, more trials were displayed until performance reached at least 60% correct trials.

*Practice session & difficulty levels*. After the pre-practice session, subjects performed 80 practice trials to estimate their individual discrimination threshold. Two randomly interleaved adaptive staircases were used to estimate the 82% performance level (Klein, 2001). The first staircase started at a high motion coherence level (80%), the second staircase at very low motion coherence level (5%). Based on the estimated discrimination threshold, a Weibull function was used to determine the proportion coherently moving dots for each difficulty level. For each subject, the proportion of coherently moving dots was obtained corresponding to performance levels of 50%, 63%, 71%, 95%

and 99% correct choices. These five difficulty levels were then used in the experimental 'accuracy' and 'speed' sessions (see Figure 3).

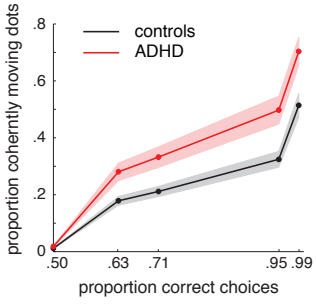


*Figure 3.* Proportion of coherently moving dots, corresponding to different performance levels in the random dots motion task. For each subject, the proportion of coherently moving dots was obtained corresponding to performance levels of 50%, 63%, 71%, 95% and 99% correct choices. These five difficulty levels were then used in the experimental sessions. Lines represent mean motion coherence. Shaded areas represent standard error of mean (SEM). Overall, subjects with ADHD required a higher proportion of coherently moving dots (red) to obtain the same level of performance as the control subjects (black).

*Accuracy sessions*. In the accuracy sessions, subjects were instructed to be as accurate as possible in order to show the rocket the correct way home. Subjects earned five points for each correct, and zero points for each incorrect answer. Subjects performed two sessions of 125 trials each, resulting in a total of 250 trials, with 50 trials per difficulty level. Difficulty levels were randomly distributed over each session.

*Speed sessions.* The two accuracy sessions were followed by the two speed sessions. Here, subjects were instructed to respond as quickly as possible. Subjects could earn between one and five points for a correct choice, where five points were awarded for the fastest responses, and one point for the slowest responses. No points were given for incorrect choices. For each subject, fast and slow responses were defined using the RT distribution for each difficulty level obtained in the accuracy sessions. For each coherence-sample a gamma function was fit to the RT data data (McGill, 1963; Ratcliff, 1978). From this distribution, RTs at the 20$^{th}$, 40$^{th}$, 60$^{th}$, 80$^{th}$ percentiles were calculated. In the speed version of the task, subjects could earn 5 points for RTs that fell within the first 20$^{th}$ percentile, 4 points for RTs between the 20$^{th}$ and 40$^{th}$ percentile, etc. When RT fell above the 80$^{th}$ percentile, subjects earned 1 point. An individual reward scheme was used to ensure that each subject had equal likelihood of maximizing scores within the speed session, and that the score of 5 points was within each subject's capability. To stress the importance of speed, 5-point rewards were displayed in a green font and accompanied by a special winning–beeb. Subjects performed two blocks of 125 speed trials, resulting in a total of 50 trials per difficulty level. Difficulty levels were randomly distributed over each session.

*End of the experiment*. The game ended with a feedback display showing all four scores from the previous sessions, summed to a total score. This was followed by a picture of the rocket on earth, accompanied by the text "Thank you, we are back home!". Total task duration was a maximum of 25 minutes (depending on time taken for breaks).

**Behavioral analyses**. The *drift diffusion model* (DDM) assumes that for each dichotomous choice, sensory evidence accumulates in favor of one of the alternatives. When this accumulation of evidence reaches a threshold value (decision threshold), the choice is made. When the threshold is low, decisions are faster, but errors are more likely to occur since the decision is based on a smaller amount of evidence. Setting a higher threshold increases the probability of making the correct choice, at the cost of speed (see Figure 1). This speed-accuracy tradeoff is controlled by the height of the decision threshold that can be estimated by fitting the drift-diffusion model to the data, while permitting the decision threshold to vary between speed and accuracy conditions. However, speed and accuracy may also be affected by other parameters, such as difficulty (Ratcliff & McKoon, 2008; Rinkenauer, et al., 2004; Voss, et al., 2004): In this task, the coherence of the motion stimulus reflects decision difficulty, meaning that drift-rate (the speed at which evidence accumulates; Fig 1) is likely to covary with coherence of the motion stimulus (Palmer, et al., 2005; Ratcliff & McKoon, 2008). Furthermore, the speed of the motor response could theoretically differ between speed and accuracy conditions. As such, we allowed three parameters of the model to fluctuate within subjects across conditions: decision threshold, drift-rate and non-decision time (which includes the motor response). We used the DMAT toolbox to fit the drift-diffusion model to the individual data and select the best suitable model (Vandekerckhove & Tuerlinckx, 2007, 2008), as outlined below.

*DDM fitting.* The DMAT toolbox maximizes the likelihood of observing a proportion of responses with a given number of reaction time (RT) bins with a multinomial likelihood function (MLF). Here, RT-bins are defined by the $1^{th}$, $2^{th}$, $5^{th}$, $10^{th}$, $30^{th}$, $50^{th}$, $70^{th}$, and $90^{th}$ quantiles of the RT-distribution. The DDM model fit by the DMAT toolbox consists of seven parameters: three parameters for the decision process (decision threshold *a*, starting point *z* and drift rate *v*), a parameter for non-decision processes (non-decision time *Ter*), and three parameters for intertrial variability (variability in bias $s_z$, variability in non-decision time $s_t$, and variability in stimulus quality $\eta$, see Ratcliff, 1978; Ratcliff & McKoon, 2008; Vandekerckhove & Tuerlinckx, 2007, 2008). Additionally, two parameters were fit to account for outlier trials (Ratcliff & Tuerlinckx, 2002). We used the DMAT Nelder-Mead SIMPLEX optimization algorithm to fit the DDM. To reduce possible local minima, the algorithm restarts six times performing a number of short runs with 250 iterations, before the final run of 5000 iterations.

*Fast guesses.* The DMAT toolbox provides a method to account for fast guesses, defined as impulsive choices based on a guess or caused by a distraction. As these data can bias the decision parameters, it is important to correct for such contaminant data (Ratcliff & Tuerlinckx, 2002). Fast guesses are determined by the DMAT toolbox using the Exponentially Weighted Moving Average (EWMA) method. This method assumes that fast guesses can be identified by very short RTs with accuracy levels at chance level. In short, all RTs are sorted to find the minimal RT at which accuracy data starts to deviate from chance. All responses faster than this minimal RT are then excluded from further analyses (Ratcliff & Tuerlinckx, 2002; Vandekerckhove & Tuerlinckx, 2007).
Most subjects made more fast guesses in the speed than in the accuracy sessions ($F_{1,53} = 66.5$, $P < .001$). Subjects with ADHD made more fast guesses than control subjects in both the accuracy and speed sessions (8% vs 16%; $F_{1,53} = 5.74$, $P < .05$). Exclusion of fast guesses had a minimal effect on accuracy and RT and did not affect the significance of the between-group effects described. When correcting for fast guesses, scores per minute were lower for both groups, especially in the

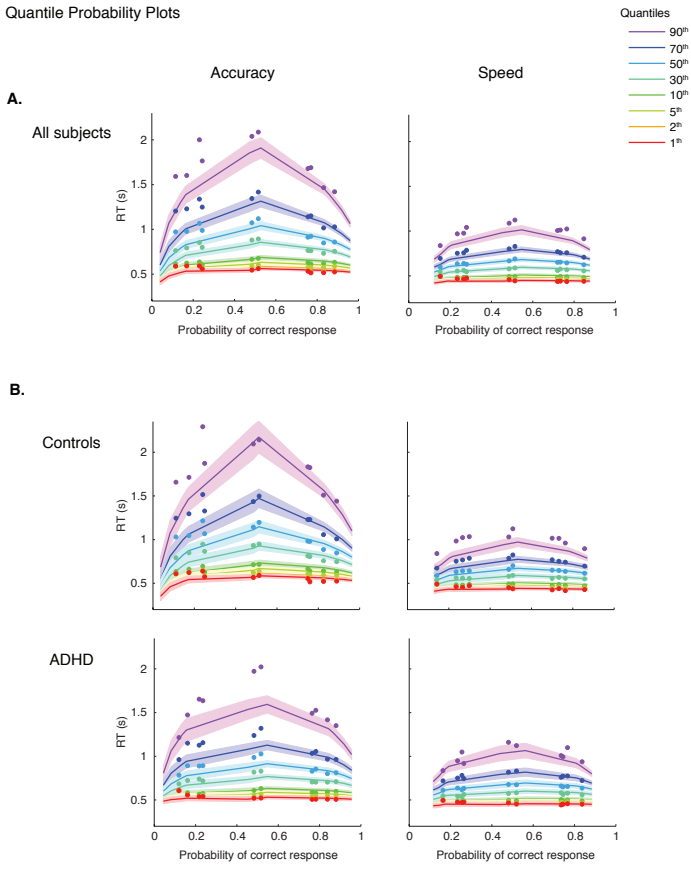


*Figure 4*. Group Quantile Probability Plots for accuracy (left) and speed (right) sessions. Each graph represents group averages of the proportion correct choices and RT distributions for each difficulty level (datapoints) and the DDM quantile probability functions describing them (lines). RT distributions are represented by eight quantiles (colors), plotted along the y-axis for each condition. Coherence conditions are split into correct and incorrect responses and divided over the x-axis, representing response probability: i.e., if correct responses occurred on 80% of trials within a condition, then correct RT quantiles would be plotted above the point 0.8 on the x-axis, and incorrect RT quantiles from the same condition would appear above the point 0.2 on the x-axis. Lines connecting the quantiles between conditions represent changes in RT distributions across difficulty levels, for incorrect and correct responses. Shaded areas around each line are the standard error of mean (SEM). Distances between quantiles, across the y-axis reflect the effect of decision threshold a on RT. Distances and slope of the lines between conditions represent the effect of drift rate v. Non-decision time Ter determines the placement of RT distributions on the y-axis. **A.** Group Quantile Probabilty plots for all subjects. **B**. Group Quantile Probability plots for control subjects and subjects with ADHD. Most graphs show a dramatic change of accuracy across difficulty. The inverted U-shapes indicate that drift rates were changing across conditions (Ratcliff & Tuerlinckx, 2002). Differences between accuracy and speed sessions show a large reduction of RTs, representing the effects of the speed instructions. Although the quantile probability functions sufficiently describe the data, they do deviate from the data at some points. Specifically, fits are worse for the incorrect data and for the higher quantiles in the accuracy sessions. This is possibly due to the lower number of incorrect trials for the accuracy sessions.

speed sessions. Between-group effects on scores per minute did not change after correcting for fast guesses.

*Model selection*. We fit four different models for each subject separately, to find the best balance between fit-error reduction and power. Each model permitted one or more parameters to vary within individual subject data to detect changes in parameters across speed and accuracy conditions: Model 1 constrained all parameters to be equal across conditions. Model 2 allowed decision threshold and drift rate to vary between, but not within, speed and accuracy conditions. Model 3 allowed decision threshold, drift rate and non-decision time to vary between speed and accuracy conditions and allowed drift-rate to co-vary with motion-strength within these conditions. Model 4 allowed decision threshold, non-decision time and drift rate to vary freely between and within speed and accuracy conditions.
For all models, starting point (*z*) was fixed at half of the decision threshold (*a*), as no differences in prior information (bias) were expected. All other parameters were kept constant across conditions, allowing for between, but not within subject comparisons. Previous studies have shown that despite these within-subject restrictions, the DDM model can account for changes in accuracy and RT data due to manipulations in speed and accuracy instructions and difficulty (Ratcliff & McKoon, 2008).

For each subject and each model, the Akaike information criterion (AIC) and Bayesian information criteria (BIC) were calculated to determine the model with the best tradeoff between fit quality and model complexity (Vandekerckhove & Tuerlinckx, 2007). Results are summarized in Table 2. For both subjects with and without ADHD, mean AIC and BIC scores were lowest for model 3. As such, we chose this model for our further analyses.

*Quantile Probability Plots*. For each condition of the experiment the proportion correct choices and RT distributions are plotted in a quantile probability plot. These plots represent all the data, together with the quantile probability functions, showing the diffusion model that describes the data. On the x-axis, conditions are split in the proportion incorrect (left) and correct (right) responses. For each condition the RT distribution is plotted on the y-axis, divided into eight quantiles. As such the plot represents how accuracy changed across different levels of difficulty (coherence) and how speed instructions affected the data (Ratcliff & McKoon, 2008; Ratcliff & Tuerlinckx, 2002) (see Figure 4).

The group quantile probability plots were generated as follows: First, for each subject, each condition was split into incorrect and correct responses. Then for each of these datasets the proportion correct choices and the $1^{th}$, $2^{th}$, $5^{th}$, $10^{th}$, $30^{th}$, $50^{th}$, $70^{th}$, and $90^{th}$ quantiles of the RT-distribution were calculated. These were then averaged across subjects (Ratcliff, 1979). To generate the group quantile probability functions, we used the DMAT toolbox to generate 1000 simulated data-sets based on the individual DDM parameters for each subject. From each simulated dataset, RT quantiles and proportion correct responses were calculated and averaged within and across subjects.

**Statistical analyses**. Group differences were investigated using the SPSS statistical package (version 16.0, SPSS inc., Chicago). Summary data of accuracy, speed and total points scored (see Fig. 3) were analyzed using a Mixed-Model ANOVA, with speed-accuracy tradeoff (2 levels) and

difficulty (5 levels) as within-subject factors and group (ADHD vs control) as a between-subject factor. Performance data were corrected for fast guesses before entering the ANOVA. Fast guesses were determined by the DMAT toolbox as described above. DDM parameters (decision threshold, non-decision time and drift rate) were analyzed using a Mixed-Model ANOVA.

*Table 2.* Model selection.

| | AIC | | | | BIC | | | |
|---|---|---|---|---|---|---|---|---|
| **model** | 1 | 2 | **3** | 4 | 1 | 2 | **3** | 4 |
| **controls (n=30)** | 2267.7 (366.2) | 2168.7 (333.5) | **2066.5 (345.1)** | 2078.5 (356.2) | 2300.3 (366.8) | 2209.4 (334.4) | **2115.2 (346.1)** | 2216.6 (359.8) |
| **ADHD (n=25)** | 1906.7 (463.4) | 1852.8 (441.5) | **1769.2 (430.4)** | 1791.0 (428.7) | 1938.4 (464.9) | 1892.2 (443.3) | **1816.4 (432.6)** | 1923.9 (436.1) |

Mean values of Akaike information criterion (AIC) and Bayesian information criteria (BIC) across subjects for each group. AIC and BIC values were calculated for each model to determine which model had the best tradeoff between fit quality and model complexity. Model 3 had the lowest AIC and BIC values, indicating the best fit to the data.

Constrained parameters, variability in non-decision time ($s_z$), variability in starting point ($s_t$) and variability in drift rate ($\eta$) were compared between groups using two-sample *t*-tests. Finally, a regression analysis was run to test whether changes in decision parameters could predict ADHD symptoms, as assessed by the DISC-p. For this purpose we calculated the difference between accuracy and speed sessions for each main parameter. These values together with the variability parameters ($s_z$, $s_t$ & $\eta$) were entered as independent variables in the two separate regression analyses with cumulative DISC symptom scores (for inattentiveness or hyperactivity/impulsivity respectively) as the dependent variable.

## Results

*Speed-accuracy tradeoff.* To test for group differences in performance, we ran a Mixed-Model ANOVA with *session* (accuracy vs speed), *difficulty* (five levels) and *group* (controls vs ADHD) as factors. Most subjects had fewer correct choices and faster RTs for speed than accuracy sessions, reflecting the speed-accuracy tradeoff ($F_{1,53} > 60.7$, $p < .0001$) (Figure 5*A*). Furthermore, most subjects made more errors and responded more slowly when choices were more difficult ($F_{1,53} > 21.5$, $p < .0001$). For RT, there was an interaction between *group* x *session*, where subjects with ADHD were faster than control subjects on accuracy but not speed sessions ($F_{1,53} = 8.5$, $p = .005$). There were no differences between groups in the proportion of correct choices made for both accuracy and speed sessions ($p > .5$). In sum, all subjects show the speed-accuracy tradeoff to some degree. However, subjects with ADHD show a preference for speed, even in the accuracy sessions.

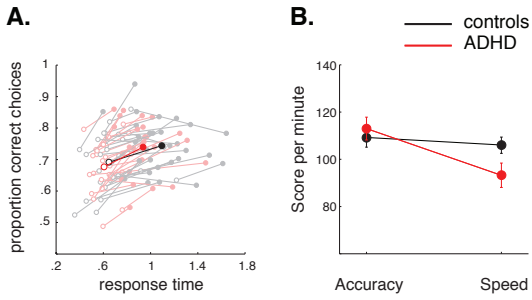


*Figure 5.* **A**. The speed-accuracy tradeoff between accuracy and speed sessions. Each data-point represents mean RT vs mean proportion correct choices for accuracy (solid dots) and speed sessions (open dots). The dim lines show data for individual subjects, whereas bright lines indicate group means. Subjects with ADHD (red) have faster responses than controls (black) in accuracy sessions, but are equally fast in the speed sessions. **B**. Average (SE) points scored per minute (reward rate) on accuracy and speed sessions. Subjects with ADHD (red) had reward rates similar to controls (black) in accuracy sessions, but lower reward rates in speed sessions.

*Optimizing the speed-accuracy tradeoff.* Subjects with ADHD scored fewer points per minute than controls in the speed sessions, as reflected by an interaction between *group* x *session* ($F_{1,53} = 12.3$, $p = .001$) (Figure 5*B*). This lower rate of reward suggests that they may have failed to optimize the speed-accuracy tradeoff. If so, this should be reflected by a smaller difference in decision threshold between the two sessions. To investigate whether this was the case, we fitted the drift diffusion model to the data of each individual subject and tested for differences in *decision threshold*, reflecting the

speed-accuracy tradeoff, and *drift rate*, reflecting difficulty. We further tested for differences in *non-decision time* to assess group differences in other, non-decision processes.

Results are shown in Table 3 and Figure 6. All subjects had lower decision thresholds for speed than accuracy sessions ($F_{1,53}$ = 216.6, $p$ < .001). An interaction between *group* and *session* showed that subjects with ADHD had lower decision thresholds than controls in the accuracy sessions, but higher decision thresholds in the speed sessions ($F_{1,53}$ = 14.7, $p$ < .001). This interaction was suggestive of smaller speed-accuracy tradeoff's for subjects with ADHD compared to controls (Figure 6*A*). To

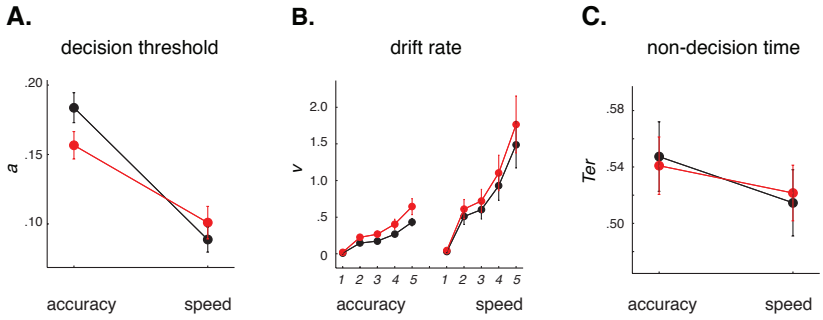


*Figure 6.* Differences between subjects with ADHD (red) and healthy controls (black) on the three main parameters of the drift diffusion model for accuracy and speed sessions. Data-points represent means (SE). **A**. Decision threshold is a measure of regulation of the speed-accuracy tradeoff. Compared to controls, subjects with ADHD showed a lower decision threshold on accuracy sessions, but not speed sessions. This indicates a smaller adjustment of the speed-accuracy tradeoff for subjects with ADHD, possibly as a result of impaired regulation of the decision threshold. **B**. Drift-rate represents the accumulation of sensory information per unit time (quality of the stimulus). Drift rates co-varied with the motion coherence, with larger drifts-rates for stronger coherence (easier trials). For each motion-strength, drift rates were significantly larger in speed sessions than in accuracy sessions, indicating faster processing of sensory information when speed is required. There were no differences in drift-rate between subjects with ADHD and controls. **C**. Non-decision time represents time involved processes other then the decision process (e.g. encoding and motor processes). Non-decision times were lower for all subjects in the speed version of the task. There were no differences between groups.

explore this further, we determined each subject's individual speed-accuracy tradeoff, by calculating the difference between the height of the decision threshold for the accuracy and speed sessions. Subjects with ADHD had a smaller speed-accuracy tradeoff than typically developing controls ($t_{53}$ = 3.8 , $p$ < .0001; see Table 3).

Overall, subjects had higher drift rates for speed sessions than accuracy sessions ($F_{1,53}$ = 23.7, $p$ < .001. Non-decision time was shorter for speed than accuracy sessions ($F_{1,53}$ = 8.3, $p$ < .005). There were no group differences or interaction effects for drift rate or non-decision time. In all, these data show that subjects with ADHD do not optimize the speed-accuracy tradeoff to the same degree as controls (see *Supportive Information* for details).

*Table 3*. Mean (SD) parameter values of the drift diffusion model (DDM), for typically developing controls and subjects with ADHD.

| | | controls (n=30) | | | ADHD (n=25) | | |
|---|---|---|---|---|---|---|---|
| **DDM parameter** | | Accuracy | Speed | *difference* | Accuracy | Speed | *difference* |
| decision threshold | *a* | .184 (.06) | .089 (.05) | ***.095 (.04)*** | .157 (.05) | .101 (.06) | ***.056 (.04)*** |
| drift rate | | | | | | | |
| difficulty level 1 | *v1* | .007 (.06) | .031 (.07) | – .023 (.04) | .022 (.06) | .046 (.07) | – .025 (.03) |
| difficulty level 2 | *v2* | .146 (.10) | .509 (.60) | – .362 (.60) | .226 (.18) | .610 (.66) | – .384 (.53) |
| difficulty level 3 | *v3* | .174 (.11) | .604 (.71) | – .430 (.71) | .266 (.21) | .722 (.78) | – .456 (.62) |
| difficulty level 4 | *v4* | .269 (.17) | .928 (1.08) | – .659 (1.09) | .404 (.33) | 1.103 (1.21) | – .700 (.96) |
| difficulty level 5 | *v5* | .432 (.28) | 1.489 (1.74) | – 1.057 (1.74) | .644 (.55) | 1.765 (1.95) | – 1.121 (1.54) |
| non-decision time | $T_{er}$ | .547 (.14) | .515 (.13) | .033 (.07) | .541 (.10) | .522 (.10) | .019 (.06) |

Values for drift rates are shown for each difficulty level with difficulty decreasing from level 1 to 5. Bold oblique reflects a significant difference in the shift of decision threshold a, representing speed-accuracy tradeoff, $p < .0001$

However, subjects with ADHD made faster decisions than controls during accuracy sessions. As such, one hypothesis could be that subjects with ADHD are closer to a physical RT limit, resulting in a floor effect for RT in the speed sessions. Accordingly, lower speed-accuracy tradeoffs for subjects with ADHD may reflect this physical RT limit. We addressed this by determining the RT-windows for scoring points individually: The highest points were awarded for RTs within the fastest 20% from the accuracy session (see Methods). Even very fast responses were therefore well within the capacity of the subjects. Furthermore, the RT windows (20$^{th}$ percentile - fastest RT) were not narrower for subjects with ADHD than controls ($F_{1,53} = .14$, $P > .71$). Finally, we included the RTs from the accuracy sessions as a co-variate in the ANOVA to test whether differences in the speed-accuracy tradeoff were dependent on them. This did not change the finding of a *group* x *session* interaction for the decision threshold ($F_{1,53} = 9.6$, $P = .003$), suggesting that faster RTs in the accuracy condition did not account for the smaller speed-accuracy tradeoff adjustment for subjects with ADHD. In all, these additional analyses indicate that group differences in optimizing the speed-accuracy tradeoff reflect a difference in adapting the decision threshold rather than a group difference in RT.

*Relationship to ADHD symptoms.* To explore whether optimizing behavior at this basic level of perceptual decision making was related to the ADHD behavioral phenotype, we tested whether differences in decision parameters were related to symptoms of the disorder. Two regression analyses were run: The first included overall inattentive symptoms and the second overall hyperactive/impulsive symptoms as the dependent variable. Both scores were taken from a structured interview (see Methods). The difference in decision threshold between speed and accuracy sessions (speed-accuracy tradeoff), drift rates (difficulty) and non-decision times were entered as predictors, along with variability-parameters (see Methods). None of the parameters predicted inattentiveness ($p > .58$). However, two parameters predicted the variance in impulsivity/hyperactivity symptoms: speed-accuracy tradeoff ($\beta = –.58$; $p < .05$), and a parameter reflecting variability in the decision threshold ($s_z$; regression coefficient $\beta = –.47$; $p < .05$; see Methods). However, across subjects the variance in $s_z$ was minimal, making this finding less reliable (only 13 of 25 subjects had $s_z > 0$, median

~0, variance = .003). The linear relationship between speed-accuracy tradeoff and impulsivity / hyperactivity symptom scores (corrected for the effects of all other parameters in the drift-diffusion model) is plotted in Figure 7. In sum, impairments in the basic ability to regulate the speed-accuracy tradeoff were predictive of hyperactive and impulsive symptoms in ADHD.

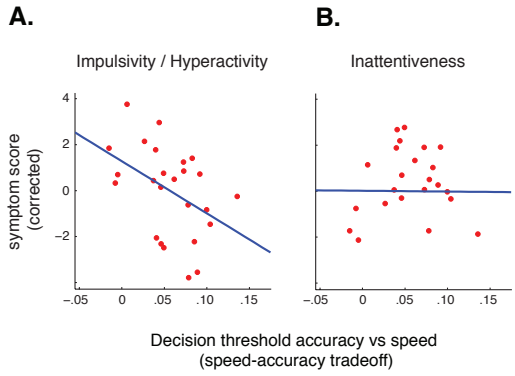


*Figure 7*. Relationship between the speed-accuracy tradeoff (as reflected by decision threshold) and ADHD symptoms. On the x-axis, the ability to flexibly regulate the speed-accuracy tradeoff in response to task demands is reflected by the difference in decision threshold between the accuracy and speed sessions. **A**. The speed-accuracy tradeoff predicts hyperactive/impulsive symptoms scores on the impulsivity / hyperactivity scale (y-axis), but not inattentive symptoms (**B**). Data are corrected for the effects of other parameters of the drift-diffusion model.

## Discussion

We explored basic cognitive processing in ADHD using a perceptual decision making paradigm. We investigated whether individuals with ADHD were able to balance the speed and accuracy of decisions. We found impairments in this basic regulation that predicted hyperactive and impulsive symptoms.

Interestingly, individuals with ADHD were not impaired on all aspects of task performance (Figure 5): Although they showed a preference for speed, they did not make more errors than controls in either speed or accuracy sessions. As such, the lower speed accuracy tradeoff was not problematic in terms of their accuracy: Their preference for speed did not result in more mistakes. However, the cost of a poorer speed-accuracy tradeoff became apparent in the speed sessions: Although individuals with ADHD were as accurate as controls, they scored fewer total points per minute. As such, the smaller adaptation of the decision threshold was not optimal in terms of reward maximization. This failure to optimize was not due to an inability to make fast choices in general, but rather seemed to be due to a basic maladaptive setting of the decision threshold. The specificity of these impairments in performance underscores the basic level of these findings: It is not cognition in general that is impaired, but rather an ability to optimize behavior, even at a basic cognitive level.

Our findings tie in with findings from neuroimaging studies in ADHD that have stressed the involvement of fronto-striatal circuitry in this disorder (see Durston, 2008). In ADHD, problems in this circuitry have been linked to a range of cognitive and behavioral problems. Recently a perceptual decision making task, similar to the one here, was used to show that striatum is involved in adapting the decision threshold to balance the speed-accuracy tradeoff. When speed is stressed, activity in striatum increases, with the greatest increases for those individuals who adjust their decision threshold most (Forstmann, et al., 2008). These results make it plausible that similar neurobiological mechanisms may underlie problems in optimizing behavior both at the basic level shown here and at the behavioral level of ADHD-symptoms.

In sum, theoretical and experimental accounts of ADHD have typically highlighted higher-order cognitive processes. Such accounts make the assumption that basic, perceptual processes are not impaired in this disorder. We reasoned that this may not be the case. Rather, we hypothesized that if basic cognitive processes, such as perceptual decision making are indeed characterized by problems in optimization, this may be directly tied to the ADHD phenotype. Indeed, we found that the performance of individuals with ADHD on a perceptual decision making task was characterized by poor optimization of the speed accuracy tradeoff, where they demonstrated an overall preference for speed. Furthermore, these impairments were directly related to the hyperactive and impulsive symptoms that characterize the ADHD-phenotype. In all, these data show that ADHD is associated with impairments in basic cognitive processing. The relationship with ADHD symptoms suggests that these impairments are central to the disorder. This calls into question conceptualizations of ADHD as a ‘higher-order’ deficit, as simple decision processes are at the core of almost every paradigm used in ADHD research.

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## Supporting Information

*Drift rate & Non-decision time.* We found higher drift rates for speed compared to accuracy sessions for all subjects, across all difficulty levels (Figure 6*B*). These results possibly reflect practice effects, showing increased sensitivy to the motion stimulus in speed sessions. Overall drift rates tended to be larger for subjects with ADHD, which was consistent with the higher proportion of moving dots in the motion stimuli for this group (Figure 3). However, between-group or interaction effects were not significant ($P > .23$).

We found no group effect on non-decision time. However, there was an overall effect of session on non-decision time, with both groups showing shorter non-decision times in the speed sessions. Stressing speed has been shown to impact (pre)motor responses and post-decision processes, in addition to the decision threshold (Rinkenauer, et al., 2004; Voss, et al., 2004). However, in our findings, impulsive and hyperactive symptoms were not related to differences in non-decision time, but rather to differences in decision threshold.

*Variability in decision threshold, drift rate and non-decision time.* We used non-parametric Mann-Whitney tests to investigate group differences for parameters that capture inter-trial variability of the main parameters of the drift-diffusion model ($s_z$, $s_t$ & $\eta$; Table S1). $s_z$ usually reflects inter-trial variability at starting point $z$; the time point where no evidence for either alternative has yet been collected (Ratcliff, 1978; Vandekerckhove & Tuerlinckx, 2007). However, in our data starting point $z$ was fixed at $z = a / 2$. As such, any variability in starting point ($s_z$) is driven by variability in the decision threshold $a$. There were no differences between groups on these measures, although there was a trend-level effect for $s_z$ ($t_{53} = 1.7$, $P = .091$). To test whether permitting within subject-variance in $s_z$ produced a better fit to the data, we performed an exploratory analysis, where $s_z$ was allowed to vary across all conditions between and within speed and accuracy sessions. Mean AIC and BIC values were higher for this model than for the model chosen (model 3). As such, allowing increased variability in this parameter did not lead to a better model.

*Table S1.* Mean (SD) values of DDM parameters for typically developing controls and subjects with ADHD reflecting variability of main parameters decision threshold, drift rate and non-decision time.

| DDM parameter | | controls (n=30) | ADHD (n=25) |
|---|---|---|---|
| variability in $a$ | $s_z$ | .023 (.04) | .048 (.06) |
| variability in $T_{er}$ | $s_t$ | .240 (.17) | .205 (.16) |
| variability in $v$ | $\eta$ | .048 (.09) | .064 (.08) |

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# Chapter 6

## BOLD correlates of reward-related decision bias on a visual discrimination task

The speed and accuracy of even simple perceptual decisions can be influenced by internal factors like reward expectation. However, little is known about how and where in the brain information about expected reward is incorporated into the decision process. We used functional MRI to identify brain regions that represent biasing effects of reward expectation on computations related to forming a simple visuo-motor decision. Eighteen adult human subjects performed a reaction time (RT) version of a random-dot motion discrimination task with asymmetric rewards. Subjects tended to choose the higher-rewarded alternative more often and with shorter RTs. We used the blood-oxygen-level-dependent (BOLD) response to identify brain regions that were involved in deciding the direction of random-dot motion and that were modulated by task difficulty and RT. These regions included portions of the prefrontal and cingulate cortex and the thalamus. Among these regions, only the bilateral inferior frontal gyrus showed effects of reward expectation consistent with its effects on choice. These effects included a systematic relationship between the BOLD response and the magnitude of reward-induced choice bias in left inferior frontal gyrus, suggesting a possible site for integrating reward information into decisions that guide behavior. These results help to clarify where in the brain sensory and reward information are combined for instructing a choice between competing behavioral responses.

*Under review*

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## Introduction

A car in front of you is driving slowly. Do you pass the car? Making this decision can be easy on a clear day or if you are not in a hurry. But poor visibility or stress can make the decision more difficult. How the brain makes these kinds of decisions, which require a rapid and complex weighing of diverse factors including sensory input and internal preference and expectation, is a central issue in neuroscience (Glimcher, 2003). Neural mechanisms that accumulate and weigh sensory evidence have been identified in the brains of both human and non-human primates (Gold & Shadlen, 2007; Heekeren, et al., 2008). Mechanisms of reward processing have also been identified in a wide range of cortical and subcortical brain areas (Montague, et al., 2006; O'Doherty, 2004; Schultz, et al., 2000; Wallis, 2007). However, little is known about how the brain combines sensory input with reward expectation to influence behavior. In this study we used functional magnetic imaging (fMRI) to identify brain regions that encode a combination of sensory, motor, and reward factors and therefore likely contribute to reward-biased decision-making.

Human subjects performed a task requiring them to decide the direction of random-dot motion and respond with a button press as soon as a decision was reached. Unlike most previous versions of the motion task, we used a version in which rewards were predictably asymmetric, with one of the two direction choices corresponding to a larger reward than the other in a given session (Figure 1). This manipulation of reward magnitude can affect both reaction time (RT) and motor accuracy on simple sensory-motor tasks (Landy, et al., 2007; Milstein & Dorris, 2007). For the motion task, optimal reward harvesting under asymmetric-reward conditions involves more choices and shorter RTs for the higher-reward alternative (Feng, et al., 2009). In monkeys, correlates of the biasing influence of asymmetric rewards on RT have been found in the parietal and prefrontal cortex and the caudate nucleus (Coe, et al., 2002; Ding & Hikosaka, 2006; Lauwereyns, et al., 2002; Leon & Shadlen, 1999; Platt & Glimcher, 1999). In humans, BOLD correlates of reward expectation have been identified in numerous brain regions, including orbital frontal, ventromedial prefrontal, and visual cortex and the striatum (Daw, et al., 2006; Hampton & O'Doherty, 2007; Knutson, et al., 2005 Gläscher, et al., 2009; Heekeren, et al., 2007; Rushworth & Behrens, 2008; Serences, 2008).

We identified brain regions with BOLD responses that correlated with both decision and reward processing in subjects performing the motion task. To identify decision-related activity, we assumed that the process of converting motion input into the decision that instructs the behavioral response would elicit BOLD responses that reflect both the strength of the motion input and the time of the response, with stronger activation on trials with weaker evidence and longer RTs (Figure 2; Binder, et al., 2004; Grinband, et al., 2008; Hanes & Schall, 1996; Thielscher & Pessoa, 2007; Yarkoni, et al., 2009). We then looked for effects of reward expectation on these decision-related signals.

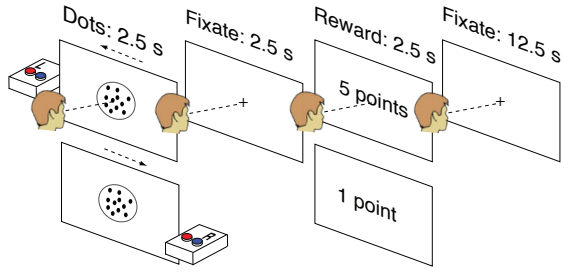


*Figure 1.* Random-dot motion task with asymmetric rewards. Subjects were required to decide the direction of random-dot motion and indicate their decision at any time during motion viewing with a button press. The motion stimulus was always shown for a full 2.5 s regardless of the time of the button press, followed by 2.5 s of fixation, 2.5 s of feedback (1 or 5 points for a correct choice, with each point value associated with a particular choice within a given session, or 0 points for an incorrect choice), and 12.5 s of additional fixation. Subjects were instructed to amass as many points as possible.

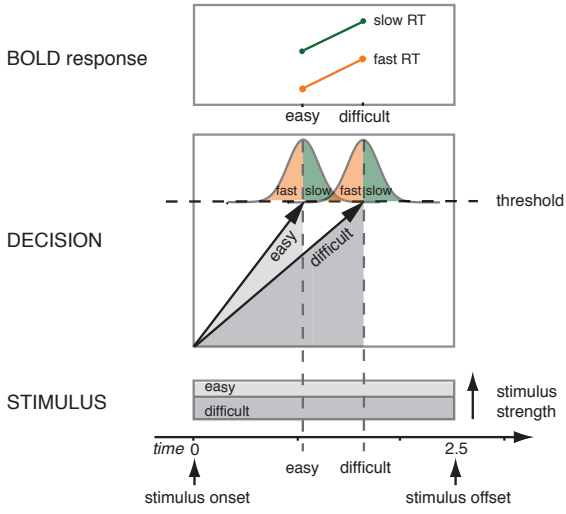


*Figure 2.* Schematic representation of the decision process in terms of difficulty and RT. The direction decision is thought to be based on an accumulation of noisy motion information over time to a fixed threshold. Because the process is noisy, there is variability in the time to reach threshold, leading to variable RTs. Nevertheless, strong motion tends to be accumulated more quickly. Accordingly, because blood-oxygen-level-dependent (BOLD) signals reflect integrated brain activity, these signals in brain regions that represent the decision process are expected to be higher on trials with slow versus fast RTs and difficult versus easy stimuli.

## Methods

**Participants**. Twenty-one right-handed adults participated in the fMRI experiment. MRI-compatible corrective glasses were used for subjects with corrected-to-normal vision. Two subjects were excluded from analyses because of scanner-induced imaging artifacts. A third subject showed large lapses in the middle of the experiment, causing the staircase procedure to produce unreliable results throughout the rest of the paradigm, and therefore was excluded. Data were analyzed for the remaining eighteen subjects (8 females, aged 22–30 years, with a mean age of 25.2 years; 10 males, aged 20–31 years, with a mean age of 25.0 years). Subjects had no self-reported history of psychiatric or neurological disorder. Each participant gave informed consent, according to procedures approved by the Institutional Review Board of Weill Cornell Medical College. A mock scanner was used to acclimate subjects to the scanner environment prior to the experiment.

**Random-dot motion task**. Subjects performed an RT, asymmetric-reward version of a random-dot motion direction-discrimination task (Figure 1). Subjects were instructed to maintain fixation on a cross on the middle of the screen, then decide the direction of motion of a cloud of randomly moving white dots and indicate their decision at any time during motion viewing with a button press. The motion stimulus was presented for 2.5 s, regardless of RT, followed by a fixation cross for 2.5 s, which was followed by a feedback display shown for 2.5 s that consisted of a large reward (5 points), small reward (1 point), or the word “incorrect” for an error choice or “missed” for no response. The feedback display was followed by 12.5 s of fixation. Each subject performed 40 practice trials (~3 minutes) and 114 experimental trials, divided over 6 runs of 19 trials (~6 minutes) each. During the experimental trials, subjects were instructed to collect as many points as possible. During the practice trials, no reward manipulation was used and only feedback as to whether the trial was correct, incorrect, or missed was given.

Visual stimuli were generated on a Macintosh computer (‘Mac-mini’ 1.5 Ghz PowerPC G4, Mac OS X 10.4.5) using custom software and the Psychophysics Toolbox Version 3.0.8 (Brainard, 1997; Pelli, 1997) for Matlab (version 7.3, Mathworks, MA) and presented on a 13.5 cm wide LCD screen at a viewing distance of 39.0 cm. E-prime (Psychology Software Tools, Inc., Pittsburgh, PA) was used to control stimulus timing and response logging. E-prime was installed on the integrated functional imaging system (IFIS) (PST, Pittsburgh) with an LCD video display in the bore of the MR scanner and a fiber optic response collection device. Stimuli were presented by sending commands from the IFIS system to the Mac-mini, while scanner and subject responses were handled by the E-prime code on the IFIS system. The motion stimuli were similar to those used elsewhere (Heekeren, et al., 2006; Palmer, et al., 2005): white dots, with a size of 3 x 3 pixels, moved within a circle with diameter of 6˚ with a speed of 5˚/s and a density of 16.7 dots/deg2/s on a black background.

Easy and difficult trials were pseudo-randomly divided over a total of 114 trials. Difficult trials were defined as the motion strength at which subjects performed at 63% accuracy. Easy trials were defined as the motion strength at 92% accuracy. Before the actual experiment started, 40 trials were acquired using QUEST to estimate the 63% and 92% percent performance level (King-Smith, et al., 1994; Watson & Pelli, 1983). These motion strengths were used as starting points for each difficulty level.

During the experiment, a staircase procedure was used to keep performance levels at the 63% and 92% level. There were 72 difficult and 44 easy trials, resulting with an equal total (~40) of correct trials for each level.
Large- and small-reward trials were pseudo-randomly divided over the 114 trials, such that 50% of the trials were followed by a large reward. Large reward was always associated with the same direction for each subject, with leftward and rightward counterbalanced across subjects. To resemble as closely as possible prior non-human primate reward studies, subjects were not informed of the direction that was associated with large reward prior to the experiment (e.g., Lauwereyns, et al., 2002). On correct, large-reward trials, subjects earned 5 points. On correct, small-reward trials, subjects earned 1 point. Incorrect trials were followed by a display of the word 'incorrect', missed trials (no response) were followed by the word 'miss'. Missed trials were excluded from further analyses.

**Behavioral data**. As a control for our difficulty manipulation, median motion strength was computed per difficulty level and tested for significant differences between easy and difficult choices. We further quantified performance by fitting a psychometric function to the binomial decision data, using maximum likelihood estimation. The probability of a correct large rewarded choice is given by:

$$P_{\text{large}} = \frac{1}{1 + e^{-(\beta 0 + \beta 1 \cdot C)}} \qquad (1)$$

Where $C$ is motion strength in percentage coherent moving dots (signed such that positive values correspond to motion towards large-reward choices, negative values to motion towards small-reward choices), and the fit parameters are $\beta 0$, which governs the horizontal shift of the curve and represents choice bias (positive values indicate biases towards large-reward choices), and $\beta 1$, which governs the steepness of the curve and represents perceptual sensitivity (larger values indicate higher sensitivity to weak motion).

**Imaging data**. Imaging was performed on a 3.0 T Signa Excite HDx MRI scanner (General Electric, Milwaukee, WI) using a quadrature head coil. We chose a slow event-related design to minimize between-trial dependencies including interference of reward outcome from the previous trial.
Functional scans were acquired using a spiral-in/out sequence (Glover & Thomason, 2004). The parameters were: repetition time (TR) = 2500 ms, echo time (TE) = 30 ms, 64 × 64 matrix, 34 4-mm coronal slices, 3.125 × 3.125 mm in-plane resolution, flip angle = 90°, 95 repetitions for the first 40 trials and 155 repetitions for the actual experiment, including 2 discarded acquisitions at the beginning of each run. In addition, a high-resolution, T1-weighted anatomical scan (3D Magnetization Prepared Rapid Acquisition Gradient Echo [MPRAGE] 256 × 256 in-plane image resolution, 240-mm FOV; 124 1.5-mm sagittal slices) was acquired for each subject and used to co-register and normalize functional images to the standard stereotactic space (Montreal Neurological Institute template).

*Preprocessing*. Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London) was used to preprocess functional and anatomical images. First, functional time-series were realigned to the first image to correct for motion artifacts using a six-parameter (rigid body) spatial transformation (Friston, et al., 1995). In addition, the T1-weighted anatomical

image was co-registered to the functional time-series by using Mutual Information (Collignon, et al., 1995; Wells, et al., 1996). Next, the anatomical image was segmented using the Unified Segment procedure to produce spatial normalization parameters that were used to normalize the functional time-series (Ashburner & Friston, 2005). Time-series were normalized and re-sliced with a voxel size of 3.125 × 3.125 × 4 (same as the raw voxel size). Finally, functional images were smoothed with an 8 × 8 × 10 kernel FWHM (full width at half-maximum).

**Functional imaging analyses**. We conducted first-level analyses of fMRI data using general linear models (GLMs; SPM5 software package) to identify decision- and reward-related BOLD activity in individual subjects. We then used beta maps from the first-level analyses for second-level (random effects) analyses to determine the locations of these effects in the group data.

*First-level analyses.* We identified decision-related activity in the brain by finding BOLD responses related to task difficulty and RT. This analysis was based on the assumption that the decision about motion direction was based on an accumulation of motion information over time (Ditterich, 2006a, 2006b; Grossberg & Pilly, 2008; Mazurek, et al., 2003; Palmer, et al., 2005; Roitman & Shadlen, 2002; Wang, 2002).
Accordingly, because BOLD signals reflect integrated brain activity (Boynton, et al., 1996; Logothetis, 2008; Logothetis & Wandell, 2004), these signals in brain regions corresponding to the decision process should be larger on trials with higher difficulty (lower motion strength) and longer RTs (Figure 2). In contrast, BOLD signals that encode the sensory input alone should reflect motion strength but not RT. Likewise, BOLD signals that encode the motor output alone should be insensitive to motion strength but possibly reflect RT. However, task difficulty and RT were not independent (see Figure 3). For example, a straightforward implementation of the “accumulation-to-bound” model depicted in Figure 2 might give rise to BOLD signals that reflect RT (which corresponds to the accumulation time) primarily and task difficulty only insofar as it affects RT. However, given the relatively small number of trials we obtained per subject as compared to prior nonhuman primate studies, the unreliability of RT effects in our behavioral data (see Figure 3), and the fact that RT can reflect factors other than the perceptual decision process (Luce, 1986), we opted not to rely entirely on RT effects and instead conducted two-factor analyses, as follows:

*Design 1*: difficulty and RT. For each subject, correct trials were divided into slow or fast responses using a median split. A GLM model was constructed with four categorical regressors: difficult and easy trials, with slow or fast responses. Regressors were modeled using a box-car function with a duration of 2.5 s, which was convolved with the hemodynamic response function (HRF) and its temporal derivative.
Motion strength was modeled as parametric factor to account for between-subject differences in motion strength variability over conditions, leaving mean effects modeled by each regressor. Five categorical regressors were added: three for model feedback (‘1 point’, ‘5 points’ or ’incorrect’), and two to model missed and incorrect choices. To control for a main effect of, and interaction effects with, expected reward, a regressor was created for the main effect of reward (with 1 for large and -1 for small-reward correct choices). This regressor was multiplied by a regressor for the effect of difficulty (with 1 for difficult and -1 for easy correct choices), to account for the interaction expected reward x

difficulty. Similarly, a third regressor for the interaction expected reward x response time was created with response time as a continuous variable (mean centered), with RT measured at each correct trial. These three regressors were convolved with the HRF and its temporal derivative, and added as nuisance regressors to the GLM model.

*Design 2*: difficulty and expected reward. A similar GLM model was created for difficulty and expected reward effects. Four regressors were used to model stimuli conditions (difficult and easy trials with small or large expected reward, with motion strength as a parametric modulation) and five for feedback ('1 point', '5 points' or 'incorrect'), missed, and incorrect choices. To control for the main effect of, and interaction effects with, RT, additional similar regressors were created as mentioned in design 1, but this time using regressors for the main effect of RT (continuous variable), the interaction effect of difficulty x RT, and the interaction effect of expected reward x RT. These regressors were convolved with the canonical HRF and its temporal derivative (Friston, et al., 1998), and added as nuisance regressors to the GLM model.

For both designs, six motion parameters were modeled to account for motion susceptibility (three translation, three rotation parameters). BOLD curves were fitted using the canonical hemodynamic response function together with its temporal derivative. This procedure was used to account for possible variability in time, making canonical curve fitting at stimulus onsets more reliable. Three-factor analyses (difficulty, RT, and expected reward) did not yield reliable results because of the relatively small number of trials per regressor in this model.

**Second-level analyses**. First, random-effects (RFX) whole-brain group analyses were done using first-level beta-maps from design 1 (difficulty and RT). A beta map for each condition per subject was entered in a full factorial design with two factors. To account for within-subject effects, factor levels were treated as dependent, with equal error variance. To obtain all voxels showing a change in BOLD response related to the motion task, an F-map was created by running an F-test over all four conditions (effects of interest) at a appropriate statistical threshold to control for multiple comparisons using a family-wise error rate (FWE) at $p = .05$ and an extent threshold of 10 voxels. Note that this test does not contain any prior information about the direction of a possible effect of difficulty or RT, because the F-test is two sided, for each condition separately. Regions of interest were then defined by 12mm -radius spheres at the peak activity for each cluster from the F-map.

**ROI-analyses**. Regions of interest were selected using design 1, which identified effects of difficulty and RT independent of expected reward. BOLD responses from these ROIs for each condition in design 1 (to test for effects of difficulty and RT) and design 2 (to test for effects of difficulty and expected reward) were extracted and averaged over voxels using the Volumes toolbox for SPM5.
Extracted average beta values were then entered in a two-way repeated measures ANOVA, using the SPSS statistical package (version 16.0, SPSS inc., Chicago), to test for significant main or interaction effects. Error-bars were corrected for within subject effects (Morey, 2008). In addition, interaction graphs were plotted for low- and high-bias groups, using averaged beta values of subjects that feel into either the 25$^{th}$ (low) or 75$^{th}$ (high) percentile of the choice-bias distribution, respectively (see Figures 5,6*B*). This procedure allowed us to examine possible BOLD differences that resulted from

differences in choice bias as estimated by the psychometric function (see Figure 3 and Equation 1).

Activation maps were created using a group-averaged anatomical image as a template in Mango (Research Imaging Center, University of Texas Health Science Center San Antonio). Talairach labels were obtained by entering the created spheres as clusters into the MSU toolbox (Sergey Pakhomov's MNI space utility) that generates reports about localization of clusters in terms of Talairach Deamon anatomical region labels.

## Results

We examined fMRI correlates of reward-biased decision-making in human subjects performing an asymmetric-reward direction-discrimination task. We first show how performance depended on both stimulus strength and expected reward. We then identify neural correlates of the decision process, using task difficulty, RT, and expected reward as predictors of BOLD activation. Finally, we analyze in more detail brain areas that showed BOLD correlates of both decision and reward processing, in particular the bilateral IFG, and look for a relation with behavioral performance.

*Behavioral performance.* Performance accuracy depended on both motion strength and expected reward magnitude. Each session consisted of easy (~92% correct responses) and difficult (~63% correct) conditions, which corresponded to motion strengths with a median [interquartile range, or IQR] of 28.6 [20.6 – 46.9] and 6.0 [2.8 – 12.4] % coherence, respectively (Wilcoxon signed rank test for $H_0$: difference of paired values = 0, $p < .0001$). For both conditions, subjects tended to choose the large-reward option more often. Specifically, the median [IQR] choice bias (in units of difference in proportion correct for large- versus small-reward choices, with positive values corresponding to more large-reward choices) across subjects was .17 [-.03 – .24] and .08 [-.05 – .18] for difficult and easy conditions, respectively (one-sample *t*-test for $H_0$: mean = 0, $p < .05$). However, four of the eighteen subjects were somewhat counter-intuitively biased towards the small-reward choice (ranges of choice biases for these subjects = -.39 to -.14 and -.17 to -.04 for difficult and easy conditions, respectively).

To further quantify these effects, we fit logistic functions to the psychometric data (Equation 1 and Figure 3*A,B*). These functions included two terms, a coherence-dependent term that reflected sensitivity to the motion stimulus and a coherence-independent term that reflected a choice bias. Sensitivity varied slightly across subjects (median [IQR] value of $\beta 1$ from Equation 1 = 5.80 [9.30 12.67]% $coh^{-1}$) but did not depend on reward magnitude (paired Wilcoxon test for H0: equal median sensitivity from fits using only trials in which the stimulus moved towards the large- or small-reward target in individual sessions, $p = 1.00$). In contrast, reward magnitude did affect choice bias, which across the population of subjects tended to be >0, reflecting a tendency to choose the large-reward alternative (median [IQR] value of $\beta 0$ from Equation 1 = .47 [.05 .55], Mann-Whitney test for $H_0$: median value of $\beta 0 = 0$, $p < .05$).
RT also depended on motion strength and reward magnitude. The median [IQR] RT across subjects

= 1.30 [1.17 – 1.50] s for easy conditions and 1.55 [1.46 – 1.68] s for difficult conditions (Wilcoxon signed rank test for H0: difference of paired values = 0 s, $p$ = .001).
Moreover, RT tended to be faster for most, but not all, subjects for larger-reward choices: the median

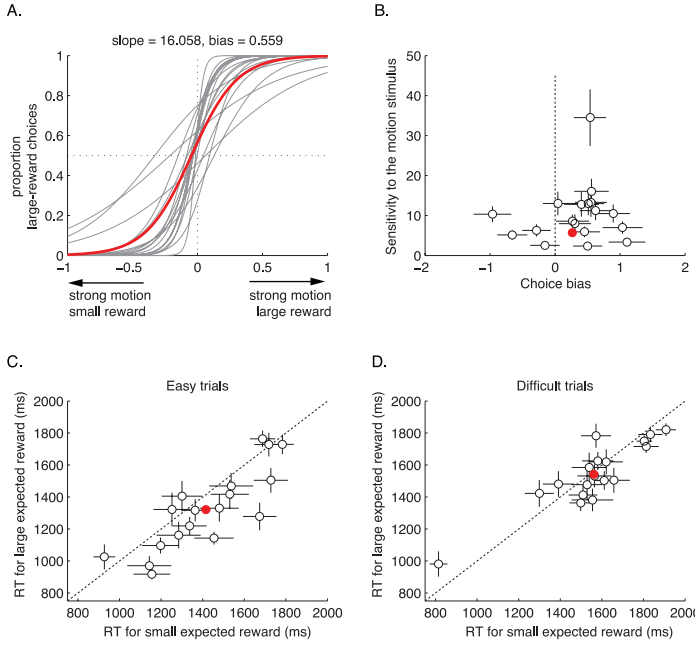


*Figure 3*. Performance. **A**. Psychometric curves (Equation 1) computed for each subject separately (grey) and across all subjects (red). The proportion of large-reward choices is plotted as a function of signed motion strength (positive for motion in the large-reward direction, negative for motion in the small-reward direction). The point on the ordinate where the curve crosses zero on the abscissa corresponds to the choice bias (β0 in Equation 1): an upward shift corresponds to an overall tendency to choose the large-reward alternative. The steepness of the curve (β1 in Equation 1) reflects perceptual sensitivity. **B**. Summary of choice bias and sensitivity. Points and error bars represent best-fitting parameters and SEM from Equation 1 fit to data from individual subjects (black) or the population (red). **C**, **D**. Summary of effects of expected reward on reaction times (RT). Each point represents mean and SEM RT for large and small rewarded choices per subject. Subjects tended to be faster for easy (C) than for difficult (D) choices. Most data points fall under the line of equality between large- and small-reward choices, particularly on easy trials, indicating faster responses to the large-reward choices.

[IQR] difference in RT for large- versus small-reward choices was .07 [-.08 – .11] s for difficult ($p$ = .33) and .06 [-.02 – .17] s for easy conditions (one-sample $t$-test for $H_0$: mean = 0, $p < .05$).

Together, the accuracy and RT data are consistent with an underlying decision process based on an accumulation of motion information over time to a threshold value (Palmer, et al., 2005; Roitman & Shadlen, 2002). The logistic fits suggest that reward expectation biases this decision process, possibly by changing the starting or ending point of the evidence accumulation. We attempted to support this idea further using the LATER method, which can help to distinguish between changes in the rate-of-rise versus threshold of this kind of decision process (Carpenter & Williams, 1995), but these analyses were ambiguous given the limited number of trials we could obtain in this human imaging experiment.

*BOLD correlates of reward-biased decisions.* We identified decision-related activity in the brain by looking for main effects of difficulty and RT in regions that showed changes in BOLD signal related to the random-dot motion task. As illustrated in Figure 2, we assumed that an underlying "accumulate-to-bound" decision process would correspond to larger BOLD responses on trials with lower motion strength and longer RTs, when the process of evidence accumulation takes longer and thus has larger integrated activity. Using both task difficulty and RT as factors in this analysis helps to distinguish decision-related activity from activity related to either the motion stimulus (i.e., sensitive to stimulus strength but not RT) or the motor response (i.e., possibly sensitive to RT but not stimulus strength) alone.

Of the extensive network of cortical and subcortical regions that were active during task performance (Figure 4*A*), several structures encoded aspects of task difficulty and RT (Figures 4–6 and Table 1).

*Table 1*. Summary of main effects. BOLD signals were extracted from 12mm -radius spheres at the peak activity for each cluster from *F*-map and entered in a 2 way repeated measures ANOVA.

| spheres (12 mm radius) | | | | | | Difficulty & RT design | | | Difficulty & Reward design | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Brain region | Side | BA | MNI (x,y,z) | | | difficulty (F) | RT (F) | interaction (F) | difficulty (F) | reward (F) | interaction (F) |
| **IFG** | L | 47 | -41 | 19 | -4 | **+** (11.8) | **+** (18.4) | . | **+** (14.3) | . | . |
| **IFG** | R | 47 | 41 | 22 | -4 | **+** (15.4) | **+** (32.1) | . | **+** (16.8) | . | . |
| **Thalamus** | L | | -9 | -28 | 0 | **+** (8.2) | **+** (17.5) | . | **+** (4.7) | . | . |
| **SFG** | R | 9/10 | 12 | 58 | 29 | **+** (8.0) | . | (7.3) | **+** (5.5) | . | . |
| MFG | R | 8 | 28 | 34 | 52 | **–** (5.5) | . | . | **–** (5.0) | . | . |
| **MFG** | L | 8 | -26 | 26 | 50 | *– (3.4)* | . | . | *– (4.0)* | **+** (5.3) | . |
| **medFG** | L/R | 10/11 | 0 | 53 | -8 | . | . | . | . | **+** (10.0) | . |
| **pre/post- central gyrus (motor)** | L | 3/4/6 | -41 | -19 | 56 | . | **+** (14.3) | . | . | . | . |
| PCG | L | 29/30 | -6 | -44 | 8 | . | **+** (9.9) | . | . | . | . |
| Cerebellum | R | | 19 | -50 | -20 | . | **+** (27.2) | . | . | . | . |
| **CG** | L/R | 8/32 | 3 | 22 | 48 | . | **+** (23.4) | . | . | . | . |
| Caudate | | | 9 | 6 | 8 | . | **+** (12.8) | . | . | . | . |

Main and interaction effects of both designs are shown for each sphere. Direction of effects are indicated with a + or - sign for each factor where: + difficulty = difficult > easy, + RT = slow>fast and + reward = large > small *expected* reward. *F*(1,17) value corresponding to the main effect is shown in brackets. Bold type indicates regions of interest. IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; ACG = anterior cingulate gyrus; medFG = medial frontal gyrus; PCG = Posterior Cingulate Gyrus; BA = Brodmann's Area; MNI = Montreal Neurological Institute.

In particular, BOLD activation tended to be higher for difficult versus easy trials in portions of the prefrontal cortex including right superior frontal gyrus (SFG) and bilateral inferior frontal gyrus (IFG), along with the left thalamus (Th; Figure 4*B*, top). In contrast, activation tended to be higher for easy versus difficult trials in the left middle frontal gyrus (MFG). Moreover, activation tended to be higher on trials with slow versus fast RTs in right SFG, bilateral IFG, and left Th, in addition to the anterior cingulate gyrus (CG) and right premotor and motor areas (Figure 4*B*, middle).

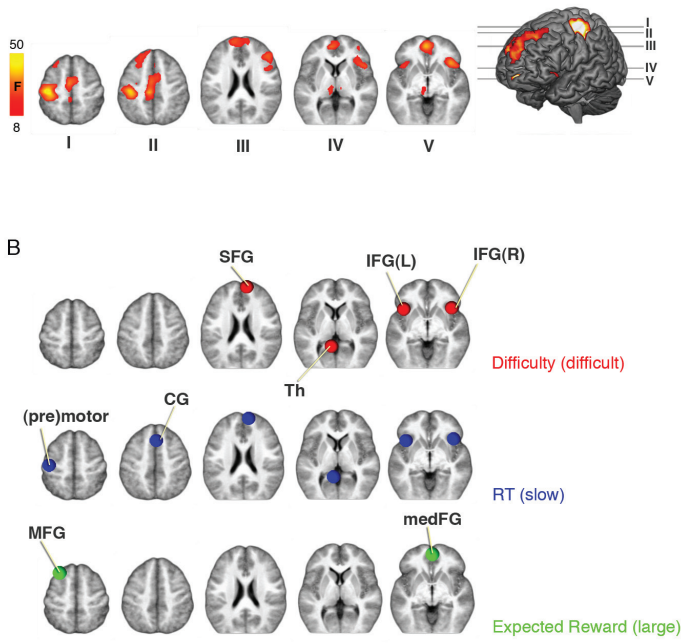


*Figure 4*. Imaging results. **A**. Activation map showing BOLD responses related to the random-dot motion task. **B**. Effects of difficulty, RT, and expected reward. Red spheres represent regions showing a main effect of difficulty, with larger responses for difficult choices. Blue spheres represent regions showing a main effect of RT, with larger responses for slow choices. Green spheres represent regions showing a main effect of expected reward, with larger responses for large-reward choices. CG=cingulate gyrus; IFG=inferior frontal gyrus; medFG=medial frontal gyrus; MFG=middle frontal gyrus; L=left; SFG=superior frontal gyrus; R=right; RT=reaction time; Th=thalamus.

We identified five regions of interest (ROIs) based on patterns of activity similar to those hypothesized in Figure 2 (Figure 5*A*). Bilateral IFG and left Th each showed significant main effects of both difficulty and RT. CG showed a similar pattern, albeit with only a significant main effect of RT (see Table 1). The right SFG did not show these main effects but instead showed a significant interaction effect between difficulty and RT, with larger responses for slow, difficult choices.

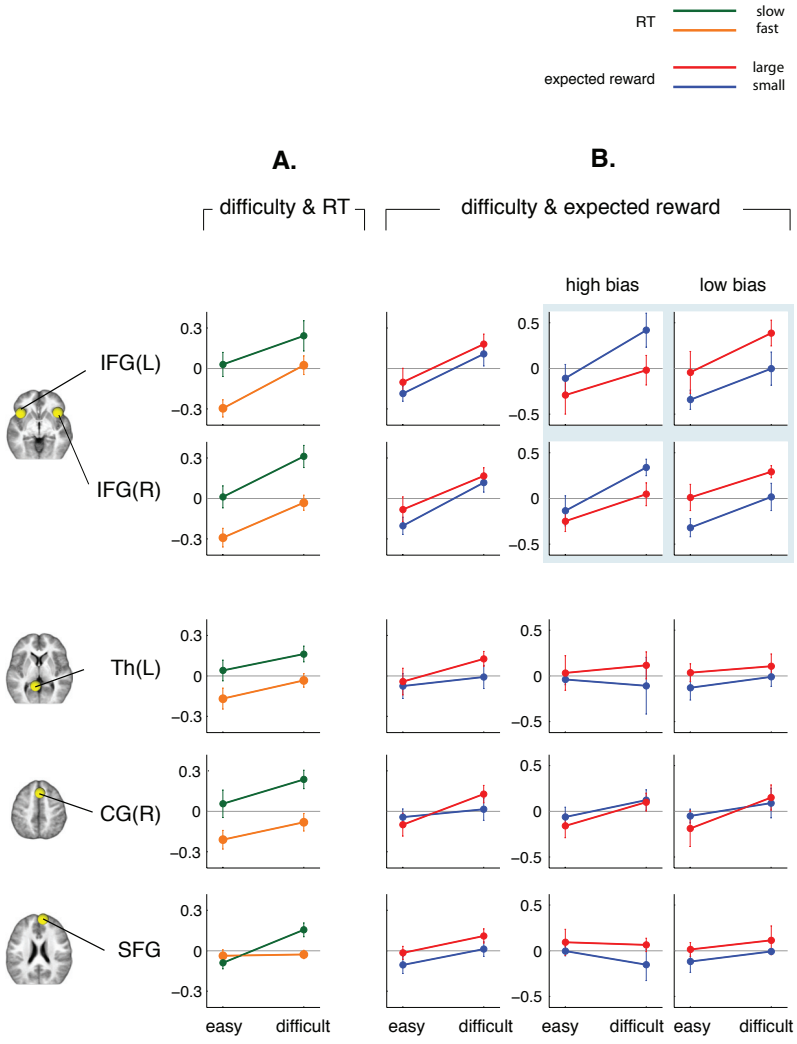


*Figure 5*. Summary plots of main effects of difficulty, RT, and expected reward on BOLD in decision-related brain areas. For comparison purposes, for each graph data points are centered around their mean. Error-bars represent standard error (corrected for within-subject effects). High-bias group was defined as greater sensitivity to large reward, the low-bias group as less sensitivity to large reward (the 75th and 25th percentiles of the choice-bias distribution, respectively). **A**. Main effects of difficulty and RT that served as our selection criteria: regions showing a main effect of slow and difficult choices. **B**. Main effects of difficulty and expected reward across subjects, and for high- and low-bias subjects separately. Highlighted interaction plots show differences in the effect of expected reward on BOLD response between subjects with high and low bias to large rewarded choices for bilateral IFG (note the flip of the blue and red lines). CG=cingulate gyrus; IFG=inferior frontal gyrus; L=left; SFG=superior frontal gyrus; R=right; RT=reaction time; Th=thalamus.

In addition to these five ROIs identified based on activity related to both task difficulty and RT, we included three other ROIs (Figure 6). Trials with higher expected reward produced larger activations in left MFG, which was also sensitive to easy choices on a trend level (Table 1), and the medial frontal gyrus (medFG). A pair of neighboring regions (right premotor and motor areas) that for simplicity we analyzed as a single "motor" area were sensitive to RT only, showing a main effect for larger activation on slow versus fast choices.

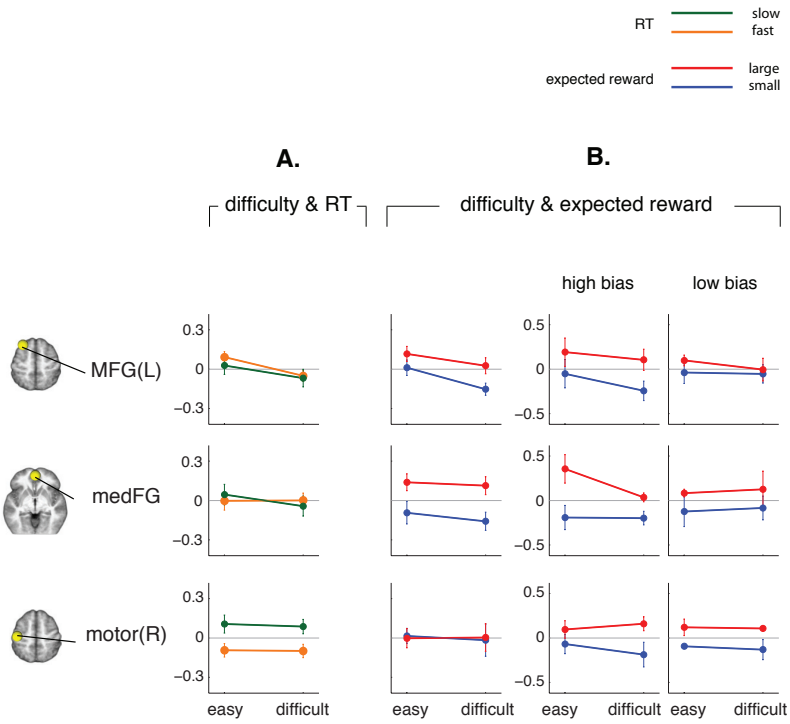


*Figure 6.* Other BOLD effects of difficulty, RT, and expected reward. For comparison purposes, for each graph data points are centered around their mean. Error-bars represent standard error (corrected for within subject effects). A main effect of expected reward was found for MFG and medFG, showing larger BOLD responses for large rewarded choices. A small effect for difficulty was found in MFG (easy>difficult; at trend level). Motor regions only showed a main effect of RT.

Of the eight ROIs, only the left MFG and the medFG showed effects of expected reward (large>small) across all subjects (Table 1 and Figure 6*B*). No such effect of expected reward was found in decision-related regions (Figure 5*B*). However, these results were based on analyses that averaged data across all subjects and therefore may have been confounded by heterogeneity in the effects of

expected reward on behavior: most subjects tended to choose the large-reward alternative, but some preferred the small-reward alternative (Figure 3*B*). Thus, we examined the effects of reward magnitude on BOLD responses separately for subjects with the strongest large-reward bias (above the 75$^{th}$ percentile of choice bias from the psychometric fits; see Methods) and those with the weakest large-reward bias (below the 25$^{th}$ percentile of choice bias from the psychometric fits, corresponding to subjects who tended to be biased towards the small-reward alternative; Figure 5*B* and 6*B*, rightmost two columns).

Left and right IFG were the only ROIs that were sensitive to these bias-selected reward effects (Figure 5B; Mann-Whitney test for $H_0$: difference in median activations in high- versus low-bias group, $p <$ .05). We calculated the effect of large reward on BOLD (large – small expected reward) for easy and difficult choices and compared those between the high- and low-bias groups. For both left and right IFG, subjects in the high-bias group, who tended to make the large-reward choice more often, had higher BOLD activations for trials in which they made the small-reward choice. Consistent with a role in behavior, these effects flipped in the low-bias group, who tended to make the small-reward choice more often and had higher BOLD activations for trials in which they made the large-reward choice.

*Relationship between IFG activation and choice bias.* To further understand the representation of reward-related choice bias in IFG, we analyzed the relationship between BOLD signals in this region and choice bias on a subject-by-subject basis (Figure 7).
There was a significant, linear relationship between BOLD responses and reward bias in the left IFG for correct, difficult trials. In particular, subjects with stronger biases towards the large-reward alternative tended to have a smaller difference in BOLD activation for large- versus small-reward choices ($r = -.55$, $p = .02$). Similar trends were evident in the right IFG for difficult choices and, to an even lesser extent, in both right and left IFG for easy choices, but these effects did not exceed trend level ($p > .15$ for $H_0$: $r = 0$).

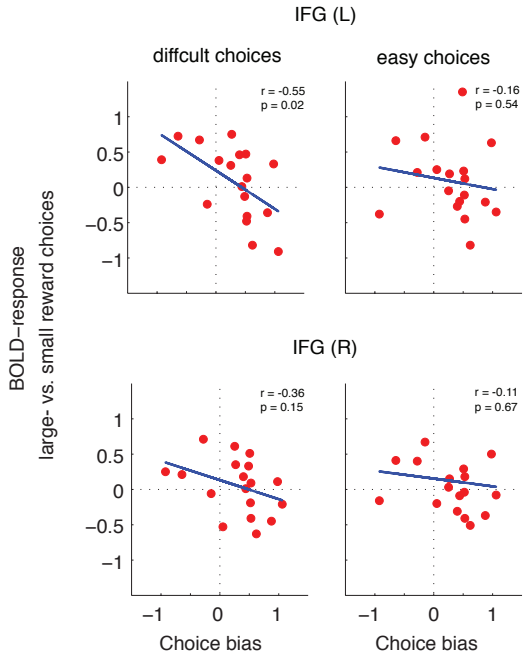


*Figure 7*. Relationship between BOLD response and choice bias for difficult (left) and easy (right) choices in the left IFG (top) and right IFG (bottom). Points are data from individual subjects. Lines are linear fits. Insets show correlation coefficients and *p* values for $H_0$: $r = 0$.

## Discussion

We examined where in the brain reward expectation is combined with sensory evidence to form decisions that guide behavior. Healthy adult participants performed an RT version of a random-dot motion task in which both perceptual difficulty and expected reward were manipulated. We used fMRI to identify brain activity related to the speed and difficulty of a decision about the direction of motion. We identified five regions of interest with elevated activity for difficult choices and slow responses: bilateral IFG, left thalamus, right CG and right SFG. There was no reliable effect of expected reward in these regions across the population of eighteen subjects. However, there was considerable variability in the effects of reward expectation on behavior across the population. Therefore, we analyzed BOLD responses in subjects with the highest and lowest bias toward large rewarded choices separately. These data showed substantial and opposite effects of expected reward in IFG, suggesting processing of choice bias in this region.

These results extend findings from previous studies that implicate the IFG and insular cortex in decision processes related to choice uncertainty or difficulty (Binder, et al., 2004; Grinband, et al., 2006; Philiastides & Sajda, 2007; Rolls, et al., 2008; Thielscher & Pessoa, 2007). Further, IFG has been implicated in attentional processes and cognitive control when there are competing responses (Aron, et al., 2003; Badre, et al., 2005; Casey, et al., 2002; Corbetta & Shulman, 2002; Durston, et al., 2006; Hampshire, et al., 2009; Heekeren, et al., 2008; Konishi, et al., 1999; Pessoa & Ungerleider, 2004; Rahm, et al., 2006; Ullsperger & von Cramon, 2001; Zhang, et al., 2004). Our findings extend these results and show that IFG might play a unique role in combining external (sensory) and internal (reward preference) information to form decisions that guide behavior.

A key question is: what are the underlying neural computations that give rise to these decision-related BOLD effects in IFG. One possibility is that IFG is primarily involved in computing or monitoring reward expectation and preference, consistent with previous reports of IFG function (Ballard & Knutson, 2009; McClure, et al., 2004; Serences, 2008). Under this assumption, decision time and difficulty affect IFG activity insofar as they affect the predicted time and probability of receiving a reward. This information would then be integrated into decision processes elsewhere in the brain, possibly in areas including thalamus, SFG, and other areas, to govern behavior.

A second possibility is that IFG plays a role in the decision process itself. The decision process is thought to involve the accumulation of noisy sensory information to a fixed threshold (Bogacz, et al., 2006; Gold & Shadlen, 2007). Accumulation-to-bound models typically predict a psychometric function in the form of a logistic equation like we used (Equation 1 and Figure 3*A*) and the trade-off between accuracy and RT that is similar to what we report (Palmer, et al., 2005). Electrophysiological studies in monkeys have sufficient spatial and temporal resolution to measure the dynamic decision processes directly in the activity of single neurons (Roitman & Shadlen, 2002) BOLD responses lack this precise spatial and temporal resolution but can be used to make indirect inferences, like our predictions based on task difficulty and RT (Figure 2). The results in IFG, like in left thalamus,

right anterior CG and right SFG, are consistent with these predictions: higher difficulty and longer RT correspond to longer accumulations and therefore larger BOLD responses.

The effects of reward expectation on the BOLD responses in IFG are roughly consistent with an accumulation-to-bound model. We found that for both the high- and low-bias groups, there was less BOLD activity in IFG for the preferred choices (large-reward choices for the high-bias group, small-reward choices for the low-bias group). This effect was largest for difficult choices. In addition, the magnitude of this effect in left IFG was negatively correlated with the magnitude of behavioral bias on a subject-by-subject basis. These results are consistent with a change in the distance between the starting and ending point of a process of evidence accumulation, which under similar conditions can be an optimal strategy to maximize reward (Bogacz, et al., 2006; Feng, et al., 2009; Ratcliff, et al., 1999; Simen, et al., 2006; Simen, et al., 2009). According to this idea, a preferred choice would correspond to a smaller distance than for the non-preferred choice, giving rise to more preferred choices with shorter RTs and smaller BOLD signals (Figure 8*A*).

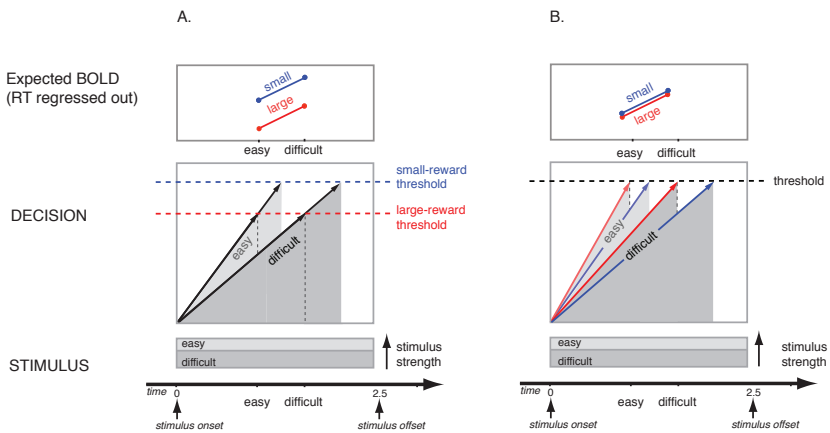


*Figure 8.* Schematic representation of two alternatives for how expected reward affects the dynamics of decision-making. A. Changes in decision threshold are expected to affect BOLD responses for both easy and difficult trials, even after accounting for effects of RT, because they change the area under the decision curve for a given RT. B. Changes in the rate of evidence accumulation are expected to affect BOLD responses for both easy and difficult trials only insofar as they affect RT, because for a fixed threshold the area under the decision curve corresponds to a particular RT.

Alternatively, a preferred choice could correspond to a change in the rate of evidence accumulation (Figure 8*B*; Feng, et al., 2009). According to this idea, a preferred choice would correspond to a faster accumulation than for the non-preferred choice, also giving rise to more preferred choices with shorter RTs and smaller BOLD signals. However, the fact that the BOLD signals in IFG depended on both RT and reward expectation argues against at least the simplest form of this idea. That is, the effects of reward expectation were measured after accounting for the effects of RT (see Methods). If reward expectation affected only the rate of rise and not the starting or ending levels of the decision

process, then the effects of reward expectation on the BOLD signals should be accounted for entirely by effects of RT: for a fixed threshold, the area under the curve of the decision process is uniquely determined by the time of the decision process (see Figure 8). However, it is difficult to rule out this interpretation, because the RTs we measured for this task were highly variable, only sparsely sampled, and may have reflect factors other than just the time of the decision process (Sternberg, 2001).

Our results are consistent with the idea that no single, but rather numerous brain regions contribute to task performance. For example, medFG and left MFG appear to encode information about reward expectation, with larger signals for large- versus small-reward choices. The medFG was the only region we found with reward-related activity in the absence of effects of task difficulty or RT. This result supports the idea that this region is involved in monitoring expected outcome value rather than forming the decision that guides behavior (Gläscher, et al., 2009; Montague, et al., 2006; Rushworth & Behrens, 2008). The left MFG showed effects of expected reward and, at a trend level, task difficulty. MGG is part of the dorsolateral prefrontal cortex, which has been shown previously to encode both reward expectation decision-related processing (Barraclough, et al., 2004; Heekeren, et al., 2004; Heekeren, et al., 2006; J. N. Kim & Shadlen, 1999; Leon & Shadlen, 1999; Wallis & Miller, 2003; Ichihara-Takeda & Funahashi, 2008; S. Kim, et al., 2008; Seo, et al., 2007), suggesting that further work is needed to determine its exact role in this kind of task, requiring the brain to combine sensory and reward information to form decisions. In addition, we found RT-sensitive processes in several other brain areas, including motor areas, but most of these were not also sensitive to task difficulty suggesting a role in motor but not necessarily decision processing.

Although our findings are consistent with the decision model as shown in Figure 2, an important factor to consider for interpreting BOLD signals in these high-order cortical areas is the role of attention. Many of the regions we identified, including IFG, are associated with attentional processes or cognitive control (Corbetta & Shulman, 2002). In this view, difficult stimuli could elicit less stimulus activation in the visual cortex, causing frontal and parietal regions to work harder to detect and process the data, with longer RT and larger BOLD responses as a result (Weissman, et al., 2006). Alternatively, many detection tasks possibly implicate a decision process, in which subjects have to make a choice to respond to a specific target (cue) or not (Corbetta & Shulman, 2002). In order to distinguish neural correlates of decision and attention processes more in detail, combining neuroimaging techniques with computational models can be useful to test specific hypotheses of decision or attention related activity.

To return to our example of encountering a car in front of you driving slowly: Whether or not you decide to pass the car depends on the accumulation of perceptual evidence and the expected value you attribute to the outcome. We show that subjects make more errors and need more time to decide when less evidence is available. Furthermore, for most subjects, decisions are biased toward the choice with the greatest expected value. We have begun to identify several components of a distributed network of brain regions, centered in prefrontal cortex, that appear to contribute to this phenomenon. The results will help to clarify where in the brain sensory information is combined with psychological factors like reward expectation to form decisions that guide behavior in choosing between competing responses.

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# Discussion

The overall aim of this thesis was to address how aspects of cognitive control and decision making contribute to ADHD symptoms. As the disorder is characterized by a heterogeneous symptomatology, investigating the neurobiology of the disorder is difficult. The use of endophenotypes may help to address this problem: a quantifiable component between biology and behavior reduces the heterogeneity of the disorder and will help to investigate bio-behavioral pathways underlying it. In **Part 1** (**chapters 2, 3 & 4**) we addressed whether deficits in brain activity during different aspects of cognitive control are vulnerable to familial risk for ADHD. By doing so, we were able to identify candidate endophenotypes for ADHD. We found changes in brain activity for both fronto-striatal and fronto-cerebellar circuits in subjects with ADHD and their unaffected siblings. Furthermore, functional connectivity between regions of these circuits was affected as well. These data suggest that impairments in fronto-striatal and fronto-cerebellar circuits are suitable as an endophenotype for ADHD. In **Part 2** (**chapters 5 & 6**), we investigated whether deficits are limited to higher-order processes, or if basic perceptual decisions are also affected by ADHD. Furthermore, we addressed where in the brain basic decisions are biased by reward expectations. We found that subjects with ADHD were impaired in adjusting the balance between speed and accuracy, and as such were disabled in optimizing their behavior to task demands. In addition, we found BOLD correlates of reward-related choice bias in the inferior frontal gyrus, a region implicated in cognitive control and ADHD. These findings suggest that impairments in basic processes such as perceptual decision making may contribute to the ADHD phenotype. Below we discuss the main findings of the thesis and address possible implications for future research.

## Part 1

Neuroimaging of cognitive control may be a candidate endophenotype for ADHD research. According to criteria for endophenotypes (see **chapter 1**; Table 1), an endophenotype should be present in unaffected relatives of affected individuals (*criteria 7*). As such, the aim of **Part 1** (**chapter 2, 3 & 4**) of this thesis was to investigate whether deficits in brain functioning underlying cognitive control are sensitive to familial risk for ADHD. We used functional MRI to measure changes in brain activation during tasks that tap cognitive control in typically developing children, subjects with ADHD and their unaffected siblings.

In **chapter 2** we showed that both subjects with ADHD and their unaffected siblings show decreased activity of ventro-lateral prefrontal cortex during events that tap cognitive control. Interestingly, this similarity between family members was not found at the behavioral level, where subjects with ADHD but not their unaffected brothers had worse performance than the control group. These findings suggest that the activation associated with cognitive control is sensitive to familial vulnerability to ADHD, even in the absence of differences at a behavioral level.

In **chapter 3**, we found similar patterns of activity for the prefrontal cortex and cerebellum. Specifically, unaffected siblings of subjects with ADHD showed decreased activity in prefrontal areas for unexpected events and in cerebellum for events at unexpected times, similar to their affected counterparts. Contrary to the behavioral results in **chapter 2**, we did find poorer performance for both subjects with ADHD and their unaffected siblings using this paradigm.

The involvement of cerebellum in ADHD was confirmed by findings in **chapter 4**. Here, we showed that functional connectivity of cognitive control networks is sensitive to familial risk for ADHD, in two independent samples. Specifically, we found differences between controls and subjects with ADHD in functional connectivity between anterior cingulate gyrus and cerebellum, with intermediate levels for the unaffected siblings. These results suggest that changes in cognitive control in ADHD are, at least in part, related to changes in connectivity in these networks. Furthermore, we found that this connectivity was sensitive to familial risk for ADHD.

In sum, the results of **Part 1** of this thesis show that deficits in brain functioning underlying cognitive control are sensitive to familial risk for ADHD.

### Imaging cognitive control as an endophenotype

Neuroimaging studies have suggested that neuroimaging measures of cognitive control could be a candidate endophenotype, as they meet a number of the criteria for endophenotypes (see **chapter 1**; Table 1): behavioral and neuroimaging measures of cognitive control are continuous quantities (*criterion 1*); deficits are stable and well established in the ADHD phenotype (*criteria 2 & 4*); behavioral changes in cognitive control are heritable (*criteria 6 & 7*) and deficits in cognitive control are grounded in neuroscience (*criterion 8*). Results of **chapters 2, 3** and **4** show that brain function associated with cognitive control is vulnerable to familial risk for ADHD. As such, neuroimaging in ADHD meets the criterion that an endophenotype should be expressed in siblings of the affected subjects (see **chapter 1**; Table 1; *criterion 7*). These findings also suggest that deficits in brain functioning cluster

in families where the disorder is found (*criterion 6*). This, together with criteria already established in the literature (see for review Durston, et al., 2009), suggests that neuroimaging of cognitive control is suitable as an endophenotype for ADHD research. A straightforward step in investigating these bio-behavioral pathways is to investigate how the genotype is expressed in the endophenotype. Studies that combined neuroimaging with genetics have already made progress in doing so.

**From genotype to endophenotype - Imaging genetics**

Studies using structural MRI have shown subtle anatomical differences between controls and discordant sibling pairs: both affected and unaffected siblings showed reductions of cortical gray matter, with the largest effect found in the prefrontal lobe (Durston, et al., 2004). Interestingly, when groups were categorized by genotype on DRD4 and DAT1 polymorphisms, anatomical differences were found in regions associated with the expression of these candidate genes. Specifically, carriers of the DAT1 9R allele showed a reduction in caudate nucleus volume whereas carriers of a variant DRD4- allele showed a decrease in prefrontal gray matter volume (Durston, et al., 2005). Furthermore, in a similar study using functional MRI we showed that the DAT1 genotype affected activity of the striatum and the cerebellar vermis (Durston, et al., 2008). However, only for the striatum we found an interaction effect between genotype and familial risk for ADHD: both affected and unaffected siblings that carried the DAT1 9R allele, showed increased striatal activity during events that tap cognitive control compared to carriers of the DAT1 10R variant. These findings suggest that DAT1 gene effects could be involved in translating a genetic risk for ADHD in a neurobiological substrate.

These results of imaging genetics studies illustrate how we can begin to map the effects of ADHD risk genes on the brain. However, results do not always appear to be consistent, as it was the DAT1 10R allele that was related to decreased activity of the striatum for subjects with ADHD, whereas the 9R variant was found to be associated with smaller caudate volumes. Furthermore, genetic effects on the cerebellum are not consistent across studies, as we found effects of familial risk for ADHD on cerebellar functioning (**chapters 3 & 4**), whereas other studies did not (Durston, et al., 2005; Durston, et al., 2008; Durston, et al., 2004). This suggests that subtle effects of gene-gene interaction or gene-environment interaction might contribute differently to specific aspects of the disorder, leading to changes in brain functioning that might be related to different types of ADHD. The complexity of these processes becomes even more evident in studies investigating effects of genes on developmental trajectories of the disorder. For example, recently polymorphisms of candidate genes have been shown to differentially impact the course of ADHD (Biederman, et al., 2009). The DRD4 7-repeat variant was found to be associated with a more persistent course of ADHD, whereas no such effect was found for the DAT1 10-repeat allele.

These findings suggest that candidate genes have specific, subtle effects that contribute to the heterogeneity of the ADHD phenotype. Reducing this complexity requires studies that investigate smaller steps of the bio-behavioral pathways underlying the disorder. Animal models might provide methods toward a more detailed understanding of the gene-endophenotype associations. For example, findings of imaging DAT1 gene knock-out mice can be associated with a specific behavioral outcome (Trinh, et al., 2003). In addition, it might be possible to look at the effects of stimulants on

mice without the dopamine transporter (Giros, et al., 1996). As such, subtle changes at the (endo) phenotype level related to a specific change in genotype can be investigated and be used for theory-driven human studies in psychiatry. However, as gene-endophenotype correlations provide only a part of the bio-behavioral pathway, detailed understanding of endophenotype-phenotype relationships will also be necessary in investigating ADHD.

**From endophenotype to phenotype - across disorders**

In **Part 1** we used variations of the go/no-go paradigm where we operationalized cognitive control as a measure of response inhibition. This is based on the assumption that during no-go trials a prepotent response is overruled by a top-down mechanism, providing control over the selection of competing actions. As response inhibition is an operationalization of cognitive control, imaging of tasks using response inhibition is believed to be a suitable candidate as endophenotype in ADHD research (Aron & Poldrack, 2005; Durston, et al., 2009). The results of studies in **chapters 2, 3** and **4** confirm this.

Although brain functioning underlying cognitive control was sensitive to familial risk for ADHD, familial effects were not necessarily found at the behavioral level (**chapters 2 & 3**). A possible explanation for this could be that a deficit in brain functioning can lead to different behavioral outcomes. That is: as a network of several brain regions underlies cognitive control (Badre, et al., 2005), deficits in one or more of these regions can lead to a variety of behavioral changes, resulting in deficits in different aspects of cognitive control (Casey, 2005). As such, detailed investigation of endophenotype-phenotype pathways is necessary to understand how a specific endophenotype might be related to symptoms associated with a psychiatric disorder.

A good starting point to address this is to develop tasks that tap different aspects of cognitive control. For example, we showed that violations in temporal expectations are associated with changes in cerebellar activity, whereas a more classic form of a violation in expectancy, such as a no-go stimulus, was associated with changes in striatal regions (**chapters 2 & 3**; Durston, et al., 2007). These findings show that it is useful to operationalize cognitive control in distinguishable measures at the behavioral level, in order to find dissociations in the brain related to these. As such, it can be argued that the reduction of symptoms into task-related measures is useful to relate the phenotype to underlying biological markers.

A next step in understanding the relation between endophenotype and phenotype is to classify task-related measures across psychiatric disorders. For example, a set of tasks that each tap different aspects of cognitive control will create a pallet of measures that represent the behavioral blue-print for cognitive control in a disorder. These measures can then be associated with underlying brain activity which in turn can be associated with specific genetic variations: Pattern recognition, or classification software can then be used to search for clusters among genes that predict a specific blue-print in the endophenotype, leading to a symptoms underlying one or more psychiatric disorders.
A challenge for neuroscience is to develop clever paradigms that tap different aspects of behavioral constructs such as cognitive control. Below we will discuss findings of **chapters 5** and **6**, and will relate these to a more comprehensive and more detailed understanding of cognitive control.

The aim of the **Part 1** (**chapter 2, 3 & 4**) of this thesis was to investigate whether deficits in brain functioning underlying cognitive control are sensitive to familial risk for ADHD. We used functional MRI to measure brain activity during tasks that tap cognitive control in typically developing children, subjects with ADHD and their unaffected counterparts. We showed that fronto-striatal and fronto-cerebellar circuits are sensitive to familial risk for ADHD, suggesting that these circuits are susceptible to ADHD gene effects. As such, imaging cognitive control can be used as an endophenotype for ADHD research.

## Part 2

The ADHD phenotype has often been linked to deficits in cognitive control: The ability to guide and adapt behavior to meet particular goals. Tasks that tap cognitive control are often designed to manipulate various aspects of cognition, but at the trial level they have often one thing in common: They require the subject to make a perceptual decision before choosing the most appropriate course of action. The aim of **Part 2** (**chapters 5 & 6**) of this thesis was to investigate whether basic processes like this are affected in ADHD. Furthermore, we attempted to find BOLD correlates of changes in these processes due to environmental factors.

In **chapter 5** we investigated whether ADHD impairments are limited to higher-order processes or if basic decision processes are also affected by the disorder. We used a basic perceptual decision making paradigm where either accuracy or speed was stressed. We had two hypotheses. First, we expected subjects with ADHD to show a preference for fast decision making. Second, we expected that subjects with ADHD would show a smaller speed-accuracy tradeoff, causing them to be unable to optimize performance in response to task demands. We found that subjects with ADHD chose to respond faster, even when accuracy was stressed. In addition, we found that subjects with ADHD were disabled in optimizing the decision process, as they showed deficits in adapting the decision threshold to balance the speed-accuracy tradeoff. These impairments were predictive for impulsivity and hyperactivity symptoms in ADHD, suggesting that very basic impairments in optimizing behavior are directly related to the ADHD phenotype. Additionally, in **chapter 6**, we tried to answer the question where in the brain such basic decisions were biased by environmental factors such as expected reward. We used functional imaging with a perceptual decision making task where expected reward was manipulated by assigning rewards with different magnitude to correct choices. We found BOLD correlates of reward-related choice bias in the inferior frontal gyrus, a region implicated in cognitive control and ADHD. Below we will discuss a possible relation between perceptual decision making and cognitive control and its implication for psychiatric research.

In sum, the results of **Part 2** of this thesis show that deficits in ADHD are not limited to higher-order cognition. We found deficits in regulating the speed-accuracy tradeoff in basic decision making. In addition, we showed BOLD correlates of reward-related decision bias in the inferior frontal gyrus, a region associated with cognitive control and ADHD (Aron & Poldrack, 2005; **chapter 2**).

### The dynamics of perceptual decision making and control

Psychology and neuroscience studies have designed clever tasks to operationalize cognitive control and to quantify predictions about performance on tasks that tap this ability. Often these tasks use instructions that appeal to some form of cognitive control: e.g. inhibit a prepotent response (go/no-go or stop-signal task) or ignoring salient information of a stimulus (flanker and stroop tasks). Although these tasks theoretically provide a measure of aspects of cognitive control, it is not clear how the brain is using task instructions (top-down) to adjust behavior. That is: Within a single trial, it is still an open question how the mechanisms of cognitive control regulate behavioral outcome. Possibly, computational modeling of perceptual decisions can help to investigate this.

Most of the tasks used in ADHD research involve a perceptual decision at the level of a single trial, where a race between two alternatives determines the outcome of a simple choice (see Instructions; Figure 3): e.g. press the button or not on basis of stimulus information (go/no-go task), name the color of a font or name the word itself (stroop task). Simple decision processes like these can be described by a class of sequential-sampling models in which sensory evidence is accumulated over time until a decision threshold is reached (Beck, et al., 2008; Ditterich, 2006a, 2006b; Gold & Shadlen, 2001, 2002; Grossberg & Pilly, 2008; Mazurek, et al., 2003; Wang, 2002). For example, in **chapter 5** we used a simple decision making task to investigate whether basic decision processes were affected by ADHD. We fitted the drift-diffusion model to the data, which allowed us to measure differences in the underlying dynamics of simple decision processes. This model describes and predicts both accuracy and RT on a specific task, taking into account the whole distribution of a data-set. Subtle changes in behavior are reflected in changes of the shape of these distributions, which can be captured by model-parameters that each explains specific aspects of the decision process. These parameters have proven to be ecological valid as both animal and human studies have shown that model parameters map on the underlying neurobiology of decision processes (see for review Gold & Shadlen, 2007; Heekeren, et al., 2008). In **chapter 6** we used predictions of the drift-diffusion model to identify decision related regions in the brain. We then investigated if these regions were sensitive for expected reward, and found a correlation between BOLD signals and choice bias obtained from drift-diffusion related analyses.
In sum, by using this model-based approach, one is able to investigate the dynamics of decision processes that can explain how subjects control their behavior to the demands of the environment. To elaborate further on the relation between perceptual decision making and control, we will discuss optimization of behavior within the field of perceptual decision making.

### Controlling the decision parameters to optimize behavior

It has been shown that humans adapt their behavior to approximate optimal performance (Bogacz, et al., 2009). Optimal can be defined as gaining as much reward possible within a certain time unit. This reward rate often depends on the demands of the environment and the balance between how fast and how accurate a response is required to be. In **chapter 5** we showed that subjects with ADHD were impaired in finding the optimal reward rate, when speed was stressed. Specifically, when faster decisions were required, subjects with ADHD were not able to select the appropriate decision threshold to gain the most reward possible per time unit. It has been suggested that the ability to select an optimal decision threshold is a simple form of control (Bogacz, et al., 2009; Morsella, et al., 2009; Mozer & Kinoshita, 1997). According to this idea, for each given trial of the decision task, a speed-accuracy tradeoff is selected to optimize the reward rate. As such, regulating the decision threshold might underlie ‘cognitive control’ when decision processes are to be optimized in terms of speed and accuracy: behavior is adjusted to the demands of the environment in a way that is most beneficial for the subject.
Optimization decision processes can not only be optimized by altering the decision threshold; other decision parameters, such as the drift rate or the starting point of the decision process, can also explain aspects of behavioral control (see **chapter 1**; Figure 3). The drift rate is the amount of

sensory signal per time unit. When drift rate is low, more attention is needed to gain as much sensory information as possible in order to make the correct choice. As such, the drift rate may be controlled by attentional resources (Bogacz, et al., 2009). When the starting point of a decision process is shifted toward either one of the decision thresholds, a choice bias toward this alternative is likely to occur since the process is more likely to terminate at the threshold that is closest to the starting point. As such, regulating the starting point has a large impact on the probability of a correct choice, and can account for choice bias (Bogacz, et al., 2009; Simen, et al., 2009). In **chapter 6** we looked at BOLD correlates of this choice bias and found inferior frontal gyrus (IFG) to be involved in this process. IFG has been associated with cognitive control (e.g. Aron & Poldrack, 2005). Possibly, with respect to our findings in **chapter 6**, an area such as IFG is combining expected reward and sensory evidence that are used to compute a top-down signal towards regions that code for the distance between decision threshold and starting point. It has been shown that the striatum is a good candidate for such a role (Forstmann, et al., 2008). Further research is needed to map predictions of the drift diffusion model onto the neurobiological substrate.

In sum, a model-based framework like the drift diffusion model allows us to measure changes in processes that might underlie different aspects of behavioral or cognitive control. Furthermore, it can help to operationalize these aspects in a more detailed and subtle way. In brain imaging, these measures can be used to distinguish brain regions that underlie specific aspects of control. As such, it can be useful for the characterizing endophenotype-phenotype relation in ADHD and maybe in psychiatric disorders in general.

The aim of the **Part 2** (**chapter 5 & 6**) of this thesis was to investigate whether impairments in ADHD are limited to higher-order processes or if basic decision processes are also affected by the disorder. We showed that deficits are not limited to higher-order cognition. We found deficits in regulating the speed-accuracy tradeoff in basic decision making. In addition, we showed BOLD correlates of reward-related decision bias in the inferior frontal gyrus, a region associated with cognitive control and ADHD (**chapter 2**; Aron & Poldrack, 2005).

## Conclusion

The overall aim of this thesis was to address how aspects of cognitive control and decision making contribute to ADHD symptoms. In **Part 1** (**chapter 2, 3 & 4**) we addressed whether deficits in brain activity during different aspects of cognitive control are vulnerable to familial risk for ADHD. By doing so, we were able to identify candidate endophenotypes for ADHD. We showed that neuroimaging of cognitive control is useful as an endophenotype in investigating ADHD. Fronto-striatal and fronto-cerebellar circuits were sensitive to familial risk for ADHD, suggesting that these circuits are susceptible to ADHD gene effects. In **Part 2** (**chapter 5 & 6**), we investigated whether deficits are limited to higher-order processes, or if basic perceptual decisions are also affected by ADHD. Additionally, we addressed where in the brain basic decisions are biased by reward expectations. We showed that ADHD was not limited to impairments in higher-order cognition, but that basic decision processes were also affected. Furthermore, brain regions involved in cognitive control and ADHD showed BOLD correlates of reward-related decision bias, suggesting that impairments in such basic processes might have a larger contribution to the phenotype of this disorder than has been thought up until now.

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# Samenvatting

In dit proefschrift onderzoeken we hoe aspecten van cognitieve controle en perceptuele beslissingen bijdragen aan het gedrag dat we zien bij personen met ADHD. In **deel 1** hebben we door middel van hersenscans de hersenactiviteit tijdens een 'cognitieve controle' taak vergeleken tussen jongens met ADHD, hun broertjes zonder ADHD en een controlegroep. We vonden dat fronto-striatale en fronto-cerebellaire circuits gevoelig zijn voor een verhoogd risico op ADHD door genetische overlap tussen de familieleden. Dit geeft aan dat het meten van hersenactiviteit in deze gebieden een nuttig endofenotype voor ADHD kan zijn. In **deel 2** hebben we laten zien dat basale beslisprocessen zijn ontregeld bij personen met ADHD. Ook laten we zien dat hersengebieden die worden geassocieerd met cognitieve controle en ADHD zijn betrokken bij dit soort basale processen. De resultaten veronderstellen dat processen onderliggend aan perceptuele beslissingen mogelijkerwijs een belangrijkere rol spelen bij ADHD dan tot nu toe werd aangenomen.

# Cognitieve controle en beslisprocessen in ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is een neuropsychiatrische aandoening die wordt gekenmerkt door veel verschillende symptomen. Deze symptomen kunnen worden ingedeeld in twee categorieën; *aandachtsproblemen* en het *impulsief of hyperactief* handelen. Een kind met ADHD kan bijvoorbeeld moeite hebben zich te concentreren tijdens een taak of tijdens het stil zitten in de klas. Echter, dit gedrag komt ook voor bij kinderen zonder ADHD waardoor de grens tussen normaal en afwijkend gedrag niet altijd duidelijk zichtbaar is.

Binnen de psychiatrie gelden criteria waar het gedrag aan moet voldoen alvorens tot de diagnose ADHD te komen (zie hoofdstuk 1, Tabel 1). Deze classificatiesystemen (DSM-IV, ICD-10) zijn nuttig voor klinische doeleinden. Echter, ze benadrukken ook de verscheidenheid van het gedrag binnen de stoornis (zie hoofdstuk 1, Tabel 1). Deze verscheidenheid of *heterogeniteit* maakt het moeilijk om de biologische mechanismen te bestuderen die ten grondslag liggen aan ADHD. Desondanks is het aangetoond dat genetische factoren een grote rol spelen bij ADHD. Maar duidelijkheid over welke genen dat precies zijn, of hoe genen het gedrag precies beïnvloeden, is er nog niet. Doordat er vaak verschillende resultaten worden gevonden in genetica studies lijkt het erop dat genen met elkaar en met de omgeving interacteren, waardoor het traject (*pathway*) van genen naar het gedrag complex en onoverzichtelijk wordt. Om de complexiteit te reduceren is het nuttig om tussenliggende stappen in kaart te brengen. Zo kan hersenonderzoek inzicht geven in de relatie tussen de hersenen en het gedrag en tegelijkertijd de stap naar de genetica verkleinen: de hersenen liggen als biologisch substraat dichter bij de genen dan het gedrag. Door de grote stap van genen naar gedrag op te delen in kleine stappen, kunnen de *pathways* in kaart worden gebracht waarlangs genen het gedrag mogelijkerwijs beïnvloeden. Deze kleinere stappen worden endofenotypen genoemd: het zijn biologische maten die ten grondslag liggen aan een stoornis en dichter bij het genotype liggen. Endofenotypen zijn vooral nuttig omdat ze de verscheidenheid binnen een stoornis kunnen reduceren tot meetbare eenheden, wat kan helpen om de stoornis beter te begrijpen (zie Hoofdstuk 1; Figuur 1).

Voordat men de relatie tussen genen en gedrag kan onderzoeken moet eerst het gedrag meetbaar worden gemaakt (operationaliseren). Dat wil zeggen: kunnen we meten of er verschillen zijn tussen iemand met en zonder ADHD? En zo ja, kan deze meting het gedrag dat we zien verklaren? Uit onderzoek is gebleken dat het meten van verstoorde *cognitieve controle* een goede maat is die past bij het kenmerkende gedrag van personen met ADHD.

Cognitieve controle is het vermogen om het gedrag aan te passen in reactie op veranderingen in de omgeving. Er wordt hierbij verondersteld dat de hersenen proberen te voorspellen wat er gaat gebeuren en wanneer. Wanneer deze voorspellingen niet uitkomen, wordt het gedrag aangepast aan de nieuwe situatie om het doel alsnog te behalen (*controle*; zie Hoofdstuk 1; Figuur 2). Twee belangrijke hersencircuits zijn hierbij betrokken: het fronto-striatale circuit, en het fronto-cerebellaire circuit. Het fronto-striatale circuit is betrokken bij de detectie van nieuwe, contextuele gebeurtenissen (*wat*), terwijl het fronto-cerebellaire circuit betrokken lijkt te zijn bij onverwachte gebeurtenissen in de tijd (*wanneer*). Wanneer deze systemen niet goed werken kunnen er gedragsproblemen ontstaan

zoals wordt gezien bij ADHD: het gedrag wordt niet goed afgestemd op veranderingen in de omgeving, waardoor er impulsief en hyperactief wordt gehandeld. Dit bemoeilijkt vervolgens het behalen van doelen, zoals bijvoorbeeld het afmaken van een taak.

Onderzoek heeft aangetoond dat mensen met ADHD minder goed presteren op computertaken waarbij er een beroep wordt gedaan op het vermogen om het gedrag aan te passen (cognitieve controle). Ook heeft men met hersenscans kunnen aantonen dat de hersengebieden die betrokken zijn bij een dergelijke taak minder actief zijn bij mensen met ADHD, in vergelijking met mensen zonder ADHD (controlegroep). Daarnaast zijn er in deze gebieden ook anatomische verschillen gevonden, zoals minder grijze stof in de prefrontale cortex en een kleiner volume van het striatum en cerebellum. Deze verschillen in hersenactiviteit en hersenvolume veronderstellen dat het meten van cognitieve controle, door middel van hersenscans mogelijk een goede kandidaat kan zijn als endofenotype binnen het onderzoek naar ADHD. In deel 1 van dit proefschrift onderzoeken we dit.
In deel 2 van dit proefschrift richten we ons op eenvoudige beslisprocessen. Dit soort processen liggen vaak ten grondslag aan allerlei computertaken die worden gebruikt in het onderzoek naar ADHD. We onderzoeken of deze basale processen zijn verstoord bij personen met ADHD. Ook kijken we waar in de hersenen dit soort processen mogelijk worden beïnvloed door externe factoren.

## Deel 1

Er zijn een aantal criteria waaraan een endofenotype moet voldoen. Een van die criteria is dat het endofenotype vaker wordt gevonden bij broers of zussen van personen met ADHD, dan in de algemene populatie (zie criteria in hoofdstuk 1, Tabel 2). Dit komt omdat broers of zussen 50% van de genetische informatie met elkaar delen. Omdat er een relatie bestaat tussen het endofenotype en de onderliggende genen zal de kans dus hoger zijn dat het endofenotype wordt gevonden bij familieleden van iemand met ADHD, dan bijvoorbeeld bij een willekeurig persoon uit de Nederlandse bevolking.

In **deel 1** van dit proefschrift onderzoeken we of we zo'n *familie-effect* zien bij het meten van hersenactiviteit tijdens een cognitieve controle taak. Dit leert ons iets over de vraag of dit soort metingen nuttig zijn als endofenotype voor ADHD. We doen drie onderzoeken met drie groepen proefpersonen: jongens zonder ADHD, jongens met ADHD en hun gezonde broers. Door de hersenactiviteit tussen deze drie groepen te vergelijken, kunnen we onderzoeken of er een familie-effect is in het functioneren van de hersenen tijdens een taak. We willen weten of de hersenactiviteit van jongens met ADHD anders is dan bij de controlegroep. Ook willen we weten of de hersenactiviteit bij de gezonde broers verschillend is. In hoofdstuk 2 richten we ons op hersenactiviteit gerelateerd aan het *wat*-aspect van cognitieve controle. In hoofdstuk 3 kijken we naar het *wanneer*-aspect. In hoofdstuk 4 onderzoeken we hoe de hersengebieden die betrokken zijn bij cognitieve controle met elkaar communiceren en of deze communicatie gevoelig is voor een familie-effect.
In **hoofdstuk 2** onderzoeken we of hersenactiviteit bij het *wat* aspect van cognitieve controle gevoelig is voor een familie-effect. We hebben kinderen en adolescenten gevraagd om een zogenaamde go/

no-go taak uit te voeren in de scanner. De opdracht was om alle 'pokemon' plaatjes te vangen die elke vier seconden op het scherm verschenen. Dit konden ze doen door op de knop te drukken zodra er een plaatje van een pokemon-figuur op het scherm verscheen (*go*). Echter, één pokemon-figuur mocht niet worden gevangen: de kat 'Meowth'. Wanneer dit plaatje op het scherm verscheen mocht er niet op de knop worden gedrukt (*no-go*: verandering op de *wat*-gebeurtenis). Het is gebleken dat dit soort taken moeilijk is voor kinderen met ADHD omdat zij moeite hebben hun gedrag (op de knop drukken) plotseling aan te passen aan een nieuwe situatie (niet op de knop drukken).
In hoofdstuk 2 tonen we aan dat hersendelen die betrokken zijn bij de momenten waarop er niet op de knop mag worden gedrukt een verlaagde activiteit laten zien bij jongens met ADHD. Dit effect werd vooral gevonden in de rechter inferior frontal gyrus (rIFG). Interessant genoeg vonden we deze verlaagde activiteit ook in de rIFG van de gezonde broertjes. Dit familie-effect veronderstelt dat hersenactiviteit onderliggend aan cognitieve controle een mogelijke kandidaat is voor een endofenotype in het onderzoek naar ADHD.

In **hoofdstuk 3** onderzoeken we op vergelijkbare wijze het *wanneer*-aspect van cognitieve controle. In deze studie deden opnieuw drie groepen kinderen en adolescenten (gezonde controles, broers met en zonder ADHD) mee in een taak waarbij hersenscans werden gemaakt. De bedoeling van de taak was om zo veel mogelijk stukjes kaas te vangen voor de muis. Er verscheen een deurtje op het scherm, dat elke vier seconden open ging. Wanneer er achter het deurtje een stukje kaas lag moesten de proefpersonen op de knop drukken (*go*). Maar wanneer er een kat achter het deurtje lag, mocht dat niet (*no-go*: verandering op de *wat* gebeurtenis). Echter, soms verscheen het stukje kaas eerder dan normaal gedurende het experiment, namelijk na twee in plaats van vier seconden. Om toch het stukje kaas te vangen moesten de proefpersonen dus anticiperen op de vroege stimulus en sneller op de knop drukken dan werd verwacht (verandering in de *wanneer* gebeurtenis).
De resultaten van de studie uit hoofdstuk 3 laten voor zowel de jongens met ADHD als hun gezonde broertjes een verlaagde activiteit zien in hersendelen die betrokken zijn bij onverwachte *wat* en *wanneer*-gebeurtenissen. Voor de *wat*-gebeurtenissen wordt dit effect vooral gevonden in gebieden uit het fronto-striatale circuit (specifiek: de anterior cingulate gyrus). Voor de *wanneer*-gebeurtenissen vinden we dit effect in gebieden uit het fronto-cerebellaire circuit (cerebellum). Deze resultaten veronderstellen dat hersenactiviteit onderliggend aan zowel het *wat* als het *wanneer*-aspect van cognitieve controle gevoelig is voor een familie-effect.

In **hoofdstuk 4** onderzoeken we of de bevindingen in **hoofdstuk 2 & 3** misschien te maken hebben met de communicatie tussen hersengebieden die betrokken zijn bij cognitieve controle. Voor elke proefpersoon hebben we onderzocht welke gebieden tegelijkertijd 'aan' of 'uit' gaan tijdens de experimenten van hoofdstuk 2 & 3. Wanneer gebieden een vergelijkbaar patroon volgen gedurende de taak, kan dit een indicatie zijn dat gebieden met elkaar communiceren. Wanneer er dus verschillen worden gevonden tussen personen met en zonder ADHD in de mate waarin gebieden tegelijk actief zijn, kan dit betekenen dat de communicatie tussen deze gebieden verstoord is bij personen met ADHD.
In hoofdstuk 4 tonen we aan dat sommige hersendelen anders met elkaar communiceren bij personen met ADHD dan bij de controlegroep. Ook zien we dat de gezonde broers van de jongens met ADHD een communicatiepatroon laten zien dat tussen de controle- en de ADHD-groep in ligt. Dit effect

wordt gevonden in het fronto-cerebellaire circuit, tussen gebieden die betrokken zijn bij cognitieve controle. Echter, dit familie-effect wordt niet gevonden in het communicatiepatroon tussen gebieden die zijn betrokken bij het drukken op de knop (*go*). Deze resultaten veronderstellen dat naast een ontregeld functioneren van hersengebieden bij cognitieve controle, ook de communicatie tussen deze hersengebieden verstoord kan zijn. Daarnaast is deze communicatie ook gevoelig voor familie-effecten, wat suggereert dat deze maten een mogelijk endofenotype zijn voor ADHD.

Samengevat hebben we in **deel 1** van dit proefschrift aangetoond dat hersengebieden die betrokken zijn bij cognitieve controle gevoelig zijn voor een erfelijke component, en dat het meten van hersenactiviteit in deze gebieden een goede kandidaat kan zijn als endofenotype in het onderzoek naar ADHD.

Voor toekomstig onderzoek zou het een logische stap zijn om de relatie tussen een specifiek genetische achtergrond en het endofenotype te onderzoeken. Op die manier kunnen de *pathways* van genen naar gedrag beter in kaart worden gebracht. Daarnaast is het ook belangrijk om de relatie tussen het endofenotype en het fenotype beter in kaart te brengen, zodat ook dat deel van de relatie tussen genen en gedrag beter in kaart kan worden gebracht. Zo kan er een duidelijker beeld worden verkregen van ADHD en de onderliggende biologische mechanismen, wat weer belangrijke kennis kan opleveren voor de behandeling van de stoornis.

## Deel 2

In het onderzoek naar ADHD worden veel taken gebruikt waarbij op basis van een plaatje een actie moet worden ondernomen. Bij veel van dit soort taken ligt een (perceptuele) beslissing ten grondslag: ‘druk ik wel of niet op de knop bij het zien van het plaatje?’. Er wordt in het onderzoek naar ADHD vaak verondersteld dat dit soort basisprocessen niet zijn verstoord, maar is dit wel waar? In **deel 2** van dit proefschrift onderzoeken we dit. Ook kijken we waar in de hersenen dit soort processen worden beïnvloed door externe factoren, zoals het krijgen van een beloning bij een goed antwoord.

In deze studies hebben we gebruik gemaakt van een eenvoudige beslistaak, waarbij de proefpersoon een ‘wolk’ met bewegende stippen op het scherm ziet, en moet beslissen of de stippen naar rechts, dan wel naar links bewegen. Soms bewegen alle stippen naar dezelfde kant, wat de keuze makkelijk maakt: het is duidelijk te zien in welke richting de stippen bewegen. Echter, wanneer maar een klein deel van de stippen in dezelfde richting beweegt en de rest van de stippen door elkaar heen, is het een stuk moeilijker om de richting te bepalen (zie Hoofdstuk 1; Figuur 3). Gedrag op dit soort taken kan goed worden beschreven door het *drift diffusion model* (DDM). Met behulp van wiskundige formules kan dan bijvoorbeeld worden voorspeld en worden beschreven hoe goed en hoe snel een persoon een keuze maakt.
Het DDM gaat uit van het idee dat een keuze tussen ‘links’ of ‘rechts’ bewegende stippen wordt bepaald door de hoeveelheid (sensorische) informatie die stap-voor-stap binnen enkele seconden wordt verzameld. Bijvoorbeeld, wanneer een persoon kijkt naar stippen die naar links bewegen, stapelt de informatie over de richting zich op, totdat een drempelwaarde (*decision threshold)* wordt

bereikt en er op de linkerknop wordt gedrukt om het juiste antwoord te geven. Echter, tijdens het verzamelen van informatie wordt er ook veel ruis verwerkt, bijvoorbeeld doordat sommige stippen willekeurig door elkaar bewegen. De hoeveelheid aan nuttige informatie die per tijdseenheid wordt verzameld, wordt aangeduid met de term *drift rate* (zie Hoofdstuk 1; Figuur 3). Hoe meer informatie per tijdseenheid, hoe hoger de *drift rate* en hoe makkelijker de beslissing.

In het kort: het maken van een beslissing kan worden beschreven als een race tussen 'links' en 'rechts' bewegende stippen. Voor beide alternatieven wordt er informatie verzameld. Wanneer er meer informatie wordt verzameld voor het ene alternatief (links) dan voor het andere (rechts), dan zal de *drift rate* zich in de richting van dit alternatief (links) bewegen. Wanneer er genoeg informatie is verzameld en de *decision threshold* wordt overschreden, wordt de keuze gemaakt door op de (linker) knop te drukken.

Het bijzondere aan het gebruik van dit soort wiskundige modellen bij het beschrijven van gedrag, is dat het inzicht geeft in *hoe* het gedrag tot stand komt: veranderingen in de snelheid of nauwkeurigheid van het gedrag kunnen worden gemeten aan de hand van de modelparameters. Deze parameters bepalen als het ware de 'vorm' van het model dat het beste bij het gedrag past. Bij het DDM bepaalt bijvoorbeeld de parameter *decision threshold* hoe snel en hoe nauwkeurig een beslissing moeten worden gemaakt. Wanneer tijdens de taak wordt gevraagd om zo snel mogelijk te beslissen, zal de tijd van een beslissing korter zijn, maar zullen er ook meer fouten worden gemaakt. Dit gedrag kan goed worden verklaard door een verschuiving van de *decision threshold*: het verlagen van de *threshold* zal snellere beslissingen opleveren omdat er minder tijd en informatie nodig is om de *threshold* te overschrijden. Dit gaat echter ten koste van de nauwkeurigheid omdat de kans groter is dat de *decision threshold* wordt overschreden zonder dat er genoeg informatie is verzameld (zie Hoofdstuk 5; Figuur 1). Onderzoek heeft aangetoond dat mensen tijdens een taak de snelheid en nauwkeurigheid in evenwicht proberen te brengen zodat ze binnen een bepaalde tijd snelle maar ook nauwkeurige beslissingen maken. Dit evenwicht wordt ook wel *speed-accuracy tradeoff* genoemd.

In **Hoofdstuk 5** onderzoeken we of kinderen en adolescenten met ADHD in staat zijn de *speed-accuracy tradeoff* optimaal aan te passen aan verschillende experimentele condities. We gebruiken een kindvriendelijke versie van de taak met de bewegende stippen, met twee verschillende condities. In de ene conditie wordt nauwkeurigheid beloond (*accuracy*), in de andere snelheid (*speed*). De resultaten laten zien dat kinderen en adolescenten met ADHD in het algemeen geneigd zijn snelle beslissingen te maken. Dit gaat echter niet ten koste van de nauwkeurigheid in de *accuracy*-conditie. Maar in de *speed*-conditie kan de optimale snelheid niet worden vastgehouden door proefpersonen met ADHD, wat resulteert in een lagere puntenscore (per minuut). Om te onderzoeken hoe deze verschillen tot stand komen hebben we het *drift diffusion model* toegepast op de data. Hieruit blijkt dat personen met ADHD de *decision threshold* niet kunnen aanpassen voor een optimale *speed-accuracy tradeoff*. Een interessante bevinding hierbij is dat personen met de laagste *speed-accuracy tradeoff*, tevens ook hoog scoren op impulsiviteit en hyperactiviteit symptomen. Deze resultaten laten zien dat verstoringen in basale beslisprocessen mogelijk ten grondslag liggen aan de symptomen van ADHD. Omdat bij veel taken waarmee ADHD wordt onderzocht vaak een perceptuele beslissing moet worden gemaakt heeft dit mogelijk consequenties voor de manier waarop resultaten worden geïnterpreteerd.

In **Hoofdstuk 6** onderzoeken we welke hersengebieden ten grondslag liggen aan perceptuele beslissingen en hoe omgevingsfactoren zoals beloning deze processen beïnvloeden. We gebruiken hiervoor een versie van de taak met de bewegende stippen waarbij de beloning voor een juiste 'links' beslissing hoger was dan de beloning voor een juiste 'rechts' beslissing (of vice versa). Deze asymmetrische beloning zorgt ervoor dat proefpersonen een voorkeur ontwikkelen voor de richting die het meeste oplevert: personen kiezen vaker en sneller voor de richting met de hoogste beloning (*bias*). In hoofdstuk 6 hebben we met hersenscans onderzocht waar mogelijkerwijs deze *bias* tot stand komt in de hersenen.
De taak werd afgenomen bij volwassen personen waarvan de hersenactiviteit werd gemeten gedurende het experiment. De resultaten laten zien dat de *inferior frontal gyrus* (IFG), een hersengebied dat vaak wordt geassocieerd met cognitieve controle en ADHD, is betrokken bij het genereren van een voorkeur: hoe hoger de *bias*, hoe lager de activiteit in dit gebied. Deze relatie komt overeen met voorspellingen uit het DDM: hoe hoger de *bias*, des te sneller de beslissing, des te korter de periode waarin de hersenactiviteit wordt opgebouwd. Aldus verwacht je minder signaal voor de richting van de bewegende stippen waarbij de bias het hoogst is.

Samengevat hebben we in **deel 2** van dit proefschrift aangetoond dat ADHD meer is dan een aandoening met verstoorde hogere cognitieve processen, maar dat ook de ontregeling van basale beslissingen een belangrijke rol spelen. Tevens hebben we aangetoond dat dit soort processen worden verwerkt door hersengebieden die zijn betrokken bij cognitieve controle en ADHD.

In **dit proefschrift** onderzoeken we hoe aspecten van cognitieve controle en perceptuele beslissingen bijdragen aan het gedrag dat we zien bij personen met ADHD. In **deel 1** hebben we door middel van hersenscans de hersenactiviteit tijdens een 'cognitieve controle' taak vergeleken tussen jongens met ADHD, hun broers zonder ADHD en een controlegroep. We vonden dat fronto-striatale en fronto-cerebellaire circuits gevoelig zijn voor een verhoogd risico op ADHD door genetische overlap tussen de familieleden. Dit geeft aan dat het meten van hersenactiviteit in deze gebieden een nuttig endofenotype voor ADHD kan zijn. In **deel 2** hebben we laten zien dat basale beslisprocessen zijn ontregeld bij subjecten met ADHD. Ook laten we zien dat hersengebieden die worden geassocieerd met cognitieve controle en ADHD zijn betrokken bij dit soort basale processen. De resultaten veronderstellen dat processen onderliggend aan perceptuele beslissingen mogelijkerwijs een belangrijkere rol spelen bij ADHD dan tot nu toe werd aangenomen.

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# Publications

# Publications

**Mulder, M. J**., Bos, D., Weusten, J. M. H., van Belle, J., van Dijk, S. C., Simen, P., van Engeland, H., Durston, S. Basic Impairments in Regulating the Speed-Accuracy Tradeoff Predict Symptoms in ADHD. *Under review*.

**Mulder, M. J.**, Gold, J.I., Durston, S., Heasly, B, Millner, A., Simen, P., Getz, S., Voss, H., Ballon, D., Berge, R., Casey, B. J. BOLD correlates of reward-related decision bias on a visual discrimination task. *Under review*.

**Mulder, M. J.**, van Belle, J., van Engeland, H., Durston, S. Functional connectivity in cognitive control networks is sensitive to familial risk for ADHD. *Under review*.

**Mulder, M. J.**, Baeyens, D., Davidson, M., Casey, B. J., van den Ban, E., van Engeland, H., Durston, S. (2008). Familial Vulnerability to ADHD Affects Activity in the Cerebellum in Addition to the Prefrontal Systems. *J Am Acad Child Adolesc Psychiatry, 47* (1), 68-75

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**Mulder, M. J.**, Bos, D., Weusten, J. M. H., van Belle, J., van Dijk, S. C., Simen, P., van Engeland, H., Durston, S. (2010). Basic Impairments in Regulating the Speed-Accuracy Tradeoff Predict Symptoms in ADHD. *Eunethydis ADHD Conference*.

**Mulder, M. J.** (2009). Functional correlates of cognitive control in children with attention-deficit hyperactivity disorder and their unaffected siblings. *World Congress of Biological Psychiatry Congress;* Oral presentation

**Mulder, M. J.**, Gold, J.I., Durston, S., Heasly, B, Millner, A., Simen, P., Getz, S., Voss, H., Ballon, D., Berge, R., Casey, B. J. (2009). BOLD correlates of reward-related decision bias on a visual discrimination task. *Organization for Human Brain Mapping OHBM*.

**Mulder, M. J.**, Baeyens, D., Davidson, M., Casey, B. J., van der Ban, E., van Engeland, H. and, Durston, S. (2007). Effects of genetic vulnerability for ADHD on brain activation are sensitive to context. *Organization for Human Brain Mapping OHBM*; travel award

**Mulder, M. J.**, Durston, S., Hulshoff Pol, H. E., Schnack, H. G., Buitelaar, J. K., Steenhuis, M. P., Minderaa, R. B., Kahn, R. S., van Engeland, H. (2005): An MRI study of the effect of familial risk for ADHD on the cerebellar vermis. *Eur Neuropsychopharmacol*, *15* sup 3:S601-S602; travel award, poster award

# Curriculum Vitae

Martijn Mulder werd op 18 April 1974 geboren te Ossendrecht. In 1992 deed hij eindexamen Atheneum aan het Moller Lyceum te Bergen op Zoom. In dat zelfde jaar begon hij met de studie Medische Biologie aan de Universiteit Utrecht. Echter, zijn interesse richtte zich steeds meer op het menselijk brein en in 1994 stapte hij over naar de studie Psychologie. Na een kleine schijnbeweging richting het bedrijfsleven behaalde hij in 2003 zijn doctoraal aan de faculteit Psychonomie in 'de theorie van cognitie en emotie'. In 2004 begon Martijn als onderzoeksassistent bij NICHE, het neuroimaging lab van de afdeling Kinder- en Jeugdpsychiatrie van het Universitair Medisch Centrum Utrecht. Onder begeleiding van Sarah Durston en Herman van Engeland begon hij in 2005 aan zijn promotietraject. In 2007 werkte hij zes maanden op het Sackler Institute for Developmental Psychobiology van Weill Cornell University Medical Center in New York. Hier werkte hij in samenwerking met Princeton University en University of Pennsylvania aan een onderzoeksproject naar perceptuele *decision making*. In 2010 promoveert Martijn aan de Universiteit Utrecht en begint hij als postdoctoraal onderzoeker bij het *Spinoza Center for Neuroimaging* van de Universiteit van Amsterdam waar hij onderzoek gaat doen naar de biologische grondslag van *decision making* met Birte Forstmann en Eric-Jan Wagenmakers.

Martijn Mulder was born on the 18th of April 1974 in Ossendrecht, the Netherlands. In 1992 he graduated from high-school (A-Levels) at het Moller Lyceum in Bergen op Zoom. In the same year, he started his undergraduate program at the University of Utrecht where he studied Medical Biology. As his interest moved more and more towards the human brain he switched to Psychology in 1994. After a small feint towards the business world, he received an MSc from the department of Psychonomics on 'the theory of cognition and emotion' in 2003. In 2004, Martijn began work as a research assistant at NICHE, the neuroimaging lab at the Department of Child and Adolescent Psychiatry of the University Medical Center Utrecht. He began his PhD-project with Sarah Durston and Herman van Engeland in 2005. In 2007, he spent six months at the Sackler Institute of Psychobiology, at the Weill Cornell University Medical Center in New York. Here, he worked on a collaborative project with Princeton University and the University of Pennsylvania on perceptual decision-making. In 2010, Martijn will defend this thesis and will begin a position at the Spinoza Center for Neuroimaging at the University of Amsterdam, working as a post-doctoral researcher on the neural correlates of decision making with Birte Forstmann and Eric-Jan Wagenmakers