Among Others

Individual differences in the neurobiology of children with ADHD

Branko Mark van Hulst

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Among others
Individual differences in the neurobiology of children with ADHD

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Individuele verschillen in de neurobiologie van kinderen met ADHD

(met een samenvatting in het Nederlands)

Proefschrift

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Contents

Chapter 1	Introduction	7
Chapter 2	Children with ADHD symptoms show deficits in reactive but not proactive inhibition, irrespective of their formal diagnosis	27
Chapter 3	What to expect and when to expect it: an fMRI study of expectancy in children with ADHD symptoms	45
Chapter 4	Reward anticipation in ventral striatum and individual sensitivity to reward: A pilot study of a child-friendly fMRI task	69
Chapter 5	Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward irrespective of ADHD diagnosis	87
Chapter 6	Distinct neuropsychological profiles within ADHD: A latent class analysis of cognitive control, reward sensitivity and timing	107
Chapter 7	Can we use neuroimaging data to identify distinct subgroups among children with ADHD symptoms: a proof of concept study using latent class analysis of brain activity	131
Chapter 8	Discussion	153
NL	Nederlandstalige samenvatting	169
D	Dankwoord	183
P	Publications	191
CV	Curriculum Vitae	195

1

Introduction

Introduction

On the one hand, children who share a diagnosis are still unique and different from each other in many respects. On the other hand, basic scientific principles have taught us to group individuals in order to make better, generalizable predictions. This grouping of individuals (e.g. by diagnosis) is debatable as long as specific causal mechanisms underlying the disorder are unclear. One could argue that a diagnosis is as strong as its prognostic value and its boundaries should be optimized accordingly. So far, a fully behavioral definition of attention-deficit/hyperactivity disorder (ADHD) has shown most value to children that are hindered by a pattern of inattentive, hyperactive and impulsive behavior. A promising next step is to enrich this behavioral definition with knowledge from neurobiological studies in a way that accounts for individual differences among children with ADHD.

Scope of this thesis

An important motivation behind studying individual differences in the neurobiology of children with ADHD is that these differences may carry prognostic value. Neurobiological profiles could help to predict which child will follow which developmental trajectory, or eventually, to predict which child will benefit from which therapy. This thesis addresses different aspects of individual differences: trans-diagnostic mechanisms, dimensionality and heterogeneity.

To make clinically meaningful predictions, it might be effective to model ADHD-related behavior as a dimensional trait that transcends diagnostic categories (Coghill & Sonuga-Barke, 2012). If indeed the underlying individual neurobiology is better aligned with dimensional measures of ADHD than with a categorical diagnosis of ADHD, such measures could provide a model that better accounts for inter-individual neurobiological differences. In this thesis, we tested whether more ADHD-related behavior was associated with more neurobiological dysfunction in a way that transcends diagnostic categories. To test this, we included children with ASD and symptoms of ADHD, in addition to children with ADHD and typically developing children. As for heterogeneity, we tested individual differences across neurobiological domains. In short, we investigated whether multiple, in part independent neurobiological pathways were associated with similar ADHD-related behavior. Such causal heterogeneity would have great implications for the clinical applicability of findings on the neurobiology of ADHD. If there is causal heterogeneity underlying ADHD, predictions on the basis of a core dysfunction theory might be systematically inaccurate for a subgroup of children with ADHD.

These general questions about inter-individual differences in the neurobiology of ADHD led us to the following research questions:

1. Are neurobiological differences specific to the diagnosis ADHD, or a more general feature of children with similar problems? (Chapters 2, 3 and 5)
2. Do neurobiological differences scale with ADHD symptom levels in a trans-diagnostic way? (Chapters 2, 3 and 5)
3. Are multiple, separable neurobiological pathways involved in ADHD? (Chapters 6 and 7)

What is ADHD?

ADHD is a developmental disorder that is defined by the Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5) as: "a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development" (American Psychiatric Association, 2013). Three types of presentations of ADHD are defined: a combined presentation if inattention and hyperactivity-impulsivity are both present, a predominantly inattentive presentation if only inattention is present and a predominantly hyperactive-impulsive presentation if only hyperactivity-impulsivity is present. The exact symptoms are listed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (see Table 1) (American Psychiatric Association, 2013). According to this DSM-5 definition the symptoms of ADHD should be present prior to age 12, but typically symptoms are already present in early childhood. ADHD is a common disorder with an estimated worldwide prevalence of around 5%, with boys more often affected than girls (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Treatment options depend on the severity of ADHD symptoms. In mild to moderately affected children, psychosocial interventions are indicated. When psychosocial interventions do not bring enough improvement or when children are more severely affected, psychostimulant treatment is indicated. These drugs increase dopamine availability in the synaptic cleft and reduce symptoms of both inattention and hyperactivity-impulsivity (Berridge et al., 2006; Volkow et al., 2001; Volkow, Wang, Fowler, & Ding, 2005). Only symptomatic improvements are found, no medication has a proven effect that continues after discontinuation of treatment (Banaschewski et al., 2006). In addition, at group level analyses, behavioral interventions have no effect on core ADHD symptoms when assessed by a rater that is blinded from the type of intervention used (Sonuga-Barke et al., 2013). However there may be beneficial effects on other relevant measures such as improved parenting and reduced conduct problems (Daley et al., 2014). On average, ADHD is associated with a wide range of disadvantageous long-term consequences such as reduced

academic performance, reduced occupational performance and increased chances of unemployment (Adamou et al., 2013; Barkley, Fischer, Smallish, & Fletcher, 2006; Kessler et al., 2006). Moreover, ADHD is associated with co-morbid disorders such as oppositional defiant disorder and conduct disorder. Less frequently, but more often than in the general population, individuals with ADHD have anxiety disorders or major depressive disorder (Willcutt et al., 2012). In all, it seems fair to conclude that children can be hampered in developing their full potential by having ADHD.

Table 1. DSM-5 criteria for the diagnosis ADHD

A A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2)

(1) Six (or more) of the following symptoms* have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Inattention

a. Often fails to give close attention to details or makes careless mistakes in school work, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
d. Often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., school work or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

(2) Hyperactivity and impulsivity: Six (or more) of the following symptoms* have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Hyperactivity-Impulsivity

a. Often fidgets with or taps hands or feet or squirms in seat.
b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
d. Often unable to play or engage in leisure activities quietly.
e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or
f. Uncomfortable being still for extended time, as in restaurants, meetings; may be

experienced by others as being restless or difficult to keep up with).

g. Often talks excessively.

h. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).

i. Often has difficulty waiting his or her turn (e.g., while waiting in line).

j. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

- 314.01 (F90.2) Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- 314.00 (F90.0) Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- 314.01 (F90.1) Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

- In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

- Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.
- Moderate: Symptoms or functional impairment between "mild" and "severe" are present.
- Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

* The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

The history of ADHD

Over the course of the last 100 years different names and definitions have been given to behavior we now consider part of ADHD. The history of ADHD is cited here as it tells a story about how researchers and clinicians have continuously renewed and refined their definitions in order to most adequately help a group of children with a disadvantageous pattern of behavior. We start in the early twentieth century when the term Minimal Brain Damage (MBD) came to be a popular choice to describe these children. At that time, an encephalitis lethargica pandemic took place (Taylor, 2011). Among children affected by the pandemic, clinicians identified a group of children with hyperactive, impulsive, disinhibited and irritable behavior. This behavior was thought to be a result of residual brain damage after suffering from encephalitis (Matthews, Nigg, & Fair, 2014; Taylor, 2011). Consequently, children that presented with this cluster of symptoms were diagnosed with Minimal Brain Damage. In the following decades criticism of this term grew as there was no proven brain damage in children presenting with hyperactive, impulsive, disinhibited and irritable behavior. The term Minimal Brain Dysfunction (again abbreviated MBD) was coined as an alternative that did not make any assumptions about underlying neurological damage (Taylor, 2011). Not only was this term vague and non-specific, it still included a reference to an unknown neurological etiology. The next big step in redefining the behavioral syndrome conveyed an important conceptual change. The DSM-III definition of Attention Deficit Disorder, was the first definition to focus on a description of overt behavior, instead of making reference to an uncertain etiology (Taylor, 2011). Paradoxically, after the etiology of the syndrome was removed from its name, an extensive body of literature started off trying to unravel the neuropsychological foundation of ADHD (Efron, 2015). In a way, letting go of an etiological definition made way for new theoretical models of the disorder. Since this point, only minor changes to the diagnosis have been implemented on for example the primacy of attention deficits over hyperactivity-impulsivity (Efron, 2015). However, the rationale behind the definition of ADHD remains the same. A syndrome is described on the basis of a similar profile of behavior, and questions about its etiology are left open for research.

Neurobiology

The etiology of ADHD can be seen as a pathway from a genetic disposition, via neurobiological functioning to the behavioral expression that is known as ADHD (see figure 1) (Durston, 2010). Notably, all neurobiological factors in this model interact with environmental influences. Ultimately, mapping this pathway across development will result in a gene by environment model of the etiology of ADHD. So, how far along are we in mapping this pathway? What do we know about the neurobiology of ADHD?

We know that on average, children with ADHD show differences in brain structure and function, in comparison to same-aged peers. In the next sections of this introduction, these differences will be discussed in more detail. But first, it is important to realize that when neurobiological differences are found to be associated with ADHD, we cannot yet speak of a full etiological model. To know what 'causes' ADHD we need to think about causality and how this takes shape in etiological models. There is a vast literature on the neurobiology of ADHD, but only genetic studies can distinguish between cause and consequence. Other neurobiological fields mainly focus on associations, they describe which neurobiological characterization fits ADHD without addressing causality (Weinberger & Radulescu, 2015). It is important to mention here that likewise we have tried to delineate neurobiological profiles associated with ADHD, but have left the question about cause or consequence unaddressed. Large, long-term longitudinal studies are needed to disentangle causes and consequences related to the development of ADHD (Sonuga-Barke, 2005). However, cross-sectional studies are needed to generate specific hypotheses for such large-scale projects.

Genes versus environment in ADHD

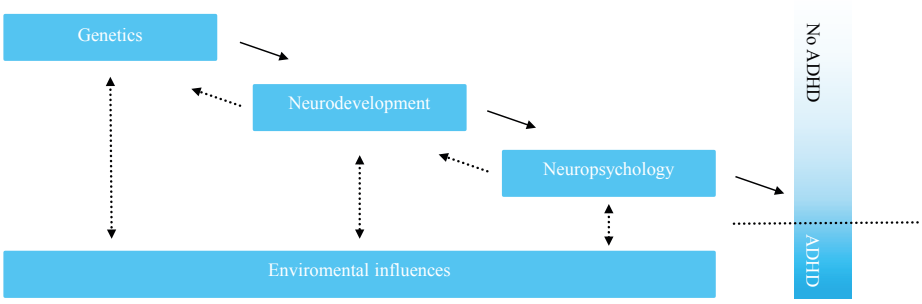
One of the strongest indications that ADHD is in part caused by an innate neurobiological set-up comes from twin studies. Monozygotic siblings of individuals with ADHD show a higher prevalence of ADHD than dizygotic siblings of individuals with ADHD (Levy, Hay, McStephen, Wood, & Waldman, 1997; Willcutt, Pennington, & DeFries, 2000). This indicates a causal influence of genes on the prevalence of ADHD symptoms across the population. This is expressed in the high heritability of ADHD (76%), a figure that is comparable with the heritability of body height (Faraone et al., 2005). These studies provide an indication of the overall influence of genes, but give no further directions on which genes are involved. Candidate gene studies have identified a number of genes potentially involved in the etiology of ADHD, however, these genes only account for a limited proportion of the total variance (Franke et al., 2011; Gizer, Ficks, & Waldman, 2009). One way to comprehend the variety of associated genes is to look at common molecular pathways. Genes that code for different proteins can contribute to the same molecular mechanism. For example, a number of genes that have been found to be associated with ADHD all have a role in neurite outgrowth (Poelmans, Pauls, Buitelaar, & Franke, 2011). Another way to go about the genetics of ADHD is to screen large parts of the genome for genes associated with ADHD. So far, these so called genome wide association studies have not identified new genetic loci (Hawi et al., 2015; Neale et al., 2010). In all, genetic studies of ADHD provide evidence for causal neurobiological mechanisms in ADHD. However, genetic influences do not at all preclude environmental influences, nor do they (at this point in time) provide

direct information on which neurobiological mechanisms are involved.

Brain structure in ADHD

Since the application of magnetic resonance imaging (MRI) in studies of ADHD, it is possible to make images of brain structure and function in live human participants in a non-invasive manner (e.g. no radioactive materials are needed). Structural MRI can inform us on the size and shape of brain structures, but provides no information on the functioning of these structures. Functional MRI on the other hand, gives a dynamic indication of brain functioning, but recordings are less stable over time than recordings from structural MRI. Initial structural imaging studies in ADHD showed reductions in total brain volume and gray matter volume (Castellanos et al., 2002). Brain regions that are established to be smaller in ADHD at the group level, are the prefrontal cortex, the striatum and the cerebellum (Valera, Faraone, Murray, & Seidman, 2007). Later studies have looked more closely at different aspects of brain structure and differentiated measures of cortical thickness, gyrification and surface

Figure 1. A gene by environment model of the etiology of ADHD



Note. Figure 1 shows a model of the etiology of ADHD. It can be read from left to right: a genetic disposition in combination with environmental influences leads to a particular pattern of neurodevelopment (brain structure and function). This neurodevelopment, again in combination with environmental influences, leads to a certain neuropsychological profile (e.g. pattern of cognitive performance), which, again in combination with environmental influences, leads to a behavioral profile that can be classified as ADHD. Note that the arrows indicate a bidirectional relationship between the different levels of analysis.

area. Individual studies report on reductions in cortical thickness (Shaw et al., 2007, 2012) or surface area (Batty et al., 2015; de Zeeuw, Schnack, et al., 2012; Shaw et al., 2012), but replication studies and large meta-analytical studies have yet to confirm these results. Another aspect of brain structure that has been quantified in ADHD (using Diffusion Tensor Imaging) is the microstructural organization of white matter fibers. On average, children, adolescents and adults with ADHD show disruptions in white matter integrity (de Zeeuw, Mandl, Hulshoff Pol, van Engeland, & Durston, 2012; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). After two decades of studying brain structure in ADHD we know that the average brain of a group of children with ADHD is different from the average brain of a group of typically developing children. However, inferences about volumetric differences being a cause or a consequence of ADHD cannot be made. Moreover, even for the most robust group differences, sensitivity and specificity are low: Children with large brains can have ADHD and vice versa, children without ADHD can have small brains.

Brain function in ADHD

Neural activity results in an initial decrease of blood oxygenation, followed by an increase in blood oxygenation (overcompensation). As levels of blood oxygenation locally influence the magnetic field, they can be detected by functional magnetic resonance imaging (fMRI). This way, local blood oxygenation levels are used as an indicator for neural activity (Logothetis, 2008). Consequently, fMRI studies are able to show which brain areas are active during which part of the task and, importantly, how this differs between individuals or groups. FMRI has been used to identify brain regions with atypical functioning in ADHD. In task-based fMRI studies participants perform a task while lying still in an MRI-scanner. The localization of this brain activity is highly dependent on the type of task used: different tasks probe different brain regions (Cortese et al., 2012). This is important to take into account as the choice of tasks used in fMRI studies has been strongly guided by neuropsychological theories on the etiology of ADHD (Dickstein, Bannon, Castellanos, & Milham, 2006). One could say that fMRI studies have created a topological mapping of known neuropsychological deficits in ADHD. Where fMRI results are specific to certain neuropsychological theories, they will be described in the upcoming sections on neuropsychological theories of ADHD. In general, meta-analytical studies have found diffuse hypoactivity in ADHD in brain networks such as the frontoparietal executive control network, the putamen, and the ventral attention network (Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; McCarthy, Skokauskas, & Frodl, 2014). Hyperactivity has been found in the default mode network and visual areas (Cortese et al., 2012). Again group differences are neither specific nor sensitive enough to have direct clinical implications. However, findings on brain activity during neuropsychological tasks can

inform mechanistic theories on the neurobiology of ADHD.

Heterogeneity in ADHD

It is well recognized that ADHD is a clinically heterogeneous disorder (Nigg & Casey, 2005; Sonuga-Barke, 2002), with dreamy inattentive children at one end of the spectrum and rowdy hyperactive children at the other. Recently it has been recognized that the underlying neuropsychology and even neurobiology, might equally be heterogeneous (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2003, 2005). More specifically, it has been proposed that multiple, separable neurobiological pathways could lead to a similar behavioral profile (Durston, van Belle, & de Zeeuw, 2011). For example, one child with ADHD could be affected in its reward processing, but not in its response inhibition; while another child with ADHD might be affected in its response inhibition, but not in its reward processing and both children would show similar ADHD-related behavior. This notion can be considered one of the starting points of this thesis and is represented in the third research question: Can multiple, separable neurobiological pathways be involved in ADHD? (Chapters 6 and 7). If there is causal heterogeneity, the search for a neurobiological basis of ADHD might have been hampered by the assumption of a homogeneous diagnostic group. Effects that only hold for a subgroup of participants might be diluted or even cancelled out when assuming a uniform relationship between ADHD-related behavior and neurobiology for the group as a whole. Techniques to model and quantify this neurobiological heterogeneity are needed to allow for differential relationships between behavior and neurobiology within one clinical group (Fair, Bathula, Nikolas, & Nigg, 2012; van Hulst, de Zeeuw, & Durston, 2015). Multiple pathway theories of the neurobiology of ADHD hypothesize that neuropsychological functions such as inhibitory control, reward sensitivity and timing can all be affected in ADHD (Nigg et al., 2005; Sonuga-Barke, Bitsakou, & Thompson, 2010; Sonuga-Barke, 2003). These theories can be seen as a continuation of the work of single pathway neuropsychological theories of ADHD, where deficits in inhibitory control, reward sensitivity and timing have been described separately. In the following sections these different neuropsychological theories of ADHD will be discussed.

Neuropsychological theories of ADHD

For decades, researchers conceptualized ADHD as the heterogeneous behavioral expression of a single, homogeneous deficit in neuropsychological and/or neurobiological functioning (Sonuga-Barke, 2005). Under this assumption, the main question for research was: which neuropsychological dysfunction leads to ADHD-related behavior? Neuropsychological theories of ADHD can be broadly divided

into two categories: top-down and bottom-up models of neuropsychological dysfunctioning in ADHD (Casey, Tottenham, Liston, & Durston, 2005). One influential top-down theory is Russel Barkley's Unifying Theory of ADHD (Barkley, 1997). He proposed that behavioral inhibition is the core neuropsychological function that is impaired in ADHD and that an upstream deficit in behavioral inhibition leads to a range of downstream deficits in domains such as arousal, motor control, motivation and working memory. Neuropsychological paradigms have operationalized behavioral inhibition as response inhibition, which in turn is defined as: 'the ability to inhibit or suppress an inappropriate, prepotent response in favor of a more appropriate alternative' (Matthews et al., 2014). Well known tasks to test this are the stop-signal task and the go/nogo task (both tasks are used in parts of this thesis: the go/nogo task in chapter 3, 6 and 7; the stop-signal task in chapter 2). Deficits in response inhibition in children with ADHD have been shown with a relatively high degree of consistency (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Lipszyc & Schachar, 2010). Moreover, during tasks of response inhibition, hypoactivity has been found in a network of inhibitory brain regions including the inferior frontal cortex, the striatum and the anterior cingulate cortex (Aron, Robbins, & Poldrack, 2014; Hart et al., 2013; McCarthy et al., 2014).

A second class of models that has been influential in trying to find a causal neuropsychological account of ADHD are the motivational or reward-based theories. These include the delay-aversion theory (Sonuga-Barke, 1994), the dynamic developmental theory (Sagvolden, Johansen, Aase, & Russell, 2005) and the dopamine transfer deficit theory (Tripp & Wickens, 2008). The first has its basis in the behavioral observation that children with ADHD favor smaller immediate rewards over larger delayed rewards. This theory poses that ADHD-related behavior can be in part explained by attempts to avoid or ameliorate periods of delay. The latter two theories have in common that they place a dopaminergic deficit in the processing of reward at the core of ADHD. Dopamine is a neurotransmitter and neuromodulator known to be involved in the anticipation and receipt of reward. Both theories give a multi-level account of the basis of ADHD, describing molecular neurobiology as well as neuropsychology and behavior. The dynamic developmental theory poses that ADHD may be associated with a general hypodopaminergic state, where deficits in dopamine signaling lead to a strong preference for immediate reward (Sagvolden, Johansen, et al., 2005; Sagvolden, Russell, Aase, Johansen, & Farshbaf, 2005). By contrast, the dopamine transfer deficit theory poses that the dopamine problem may be more specific. It states that the processing of rewarding events itself is not affected, but the transfer of the signal from rewarding events to the cues that predict reward is attenuated; this would then result in atypical reward learning (Tripp & Wickens, 2008,

2009). Adolescents and adults with ADHD have lower ventral striatum activity during the anticipation of reward, in accordance with (but not distinguishing between) both theories (Plichta & Scheres, 2014). In chapter 5 we investigated if ventral striatum hypoactivity could also be found in school-aged children with ADHD. Next to this main dichotomy in neuropsychological theories, another influential neuropsychological model considers ADHD a problem of state-regulation (Sergeant, 2005). That is: a problem in maintaining or switching to appropriate levels of arousal or vigilance according to situational demands, may underlie ADHD.

Lastly, it should be mentioned that both theoretical and empirical papers have implicated timing as a candidate neuropsychological pathway to ADHD symptoms (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Noreika, Falter, & Rubia, 2013; Sonuga-Barke et al., 2010; van Hulst et al., 2015). A wide variety of timing-related constructs have been assessed in ADHD (Toplak, Dockstader, & Tannock, 2006). Specifically, a meta-analytical study showed deficits in timing across multiple domains (e.g. motor timing, perceptual timing) and timescales (e.g. sub-second, supra-second timescale) in ADHD (Hart, Radua, Mataix-Cols, & Rubia, 2012). Temporal processing is known to be associated with dopamine signaling (Allman & Meck, 2012; Buhusi & Meck, 2005), but a comprehensive neuropsychological theory on how deficits in temporal processing would lead to ADHD is still lacking.

Outline of this thesis

The different chapters of this thesis all study the neurobiology underlying the heterogeneous disorder that is ADHD. In addition, they explore if neurobiological changes are a general feature of children with ADHD-symptoms, irrespective of the primary diagnosis. Chapter 2 starts off by disentangling different aspects of the well-established deficit in response inhibition in ADHD. We assessed whether this represents a deficit in outright stopping (reactive inhibition), whether it relates to a deficit in anticipatory response slowing (proactive inhibition), or both. Moreover, we included a group of children with similar levels of parent-rated ADHD symptoms, but a different primary diagnosis (autism spectrum disorder) to assess if findings were specific to children with ADHD. This also allowed us to look for an association between levels of ADHD symptoms and levels of inhibitory control, within a heterogeneous group of children with ADHD symptoms (a mixed group of children with ADHD and children with ASD). In chapter 3, we considered cognitive control and timing as special cases of the same construct and analyzed them in concert. Both domains encompass making and monitoring predictive models of the environment, as well as the ability to alter behavior when these predictions are violated. We used a timing

manipulated go/nogo task to test brain activity related to predictions about what (cognitive control) and when (timing) events will happen. Again we tested if results were specific to children with ADHD and whether a trans-diagnostic association between activity and symptoms of ADHD could be found. Chapter 4 describes how we modified an existing fMRI task that measures reward anticipation (a monetary incentive delay paradigm) to be suitable for use in children. In order to better be able to interpret differences in brain activity, we also tested the association between task performance and brain activity. Subsequently, this child-friendly task of reward anticipation was used in the study described in chapter 5. We tested whether children with ADHD would show hypoactivity during reward anticipation. Also, we tested how brain activity during reward anticipation was related to reward sensitivity in daily life as rated by parents. As in chapter 2 and 3, we tested the specificity of results to children with the diagnosis ADHD and tested for a trans-diagnostic association between brain activity during reward anticipation and ADHD symptom levels. The last two chapters deal with techniques to formally address causal heterogeneity in ADHD. In chapter 6 we used latent class analysis (LCA) to identify subgroups within a group of children with ADHD on the basis of task performance during tasks of cognitive control, reward sensitivity and timing. In a final, exploratory step we tested if the subgroups we found would show differences on parent-rated measures of behavior. Chapter 7 describes a continuation of this work. Here subgroups of children with ADHD are defined on the basis of their brain activity profiles during the performance of two tasks. Again we tested if the children in the different subgroups would differ in their every-day behavior as assessed by their parents.

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2

Children with ADHD symptoms show deficits in reactive but not proactive inhibition, irrespective of their formal diagnosis

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Abstract

Attenuated inhibitory control is one of the most robust findings in the neuropsychology of ADHD. However, it is unclear whether this represents a deficit in outright stopping (reactive inhibition), whether it relates to a deficit in anticipatory response slowing (proactive inhibition), or both. In addition, children with other development disorders, such as autism spectrum disorder, often show symptoms of inattention, impulsivity and hyperactivity similar to children with ADHD. These may relate to similar underlying changes in inhibitory processing. In this study, we used a modified stop-signal task to dissociate reactive and proactive inhibition. We included not only children with ADHD, but also children primarily diagnosed with an autism spectrum disorder and high parent-rated levels of ADHD symptoms. We replicated the well-documented finding of attenuated reactive inhibition in children with ADHD. In addition, we found a similar deficit in children with ASD and a similar level of ADHD symptoms. In contrast, we found no evidence for deficits in proactive inhibition in either clinical group. These findings re-emphasize the role of reactive inhibition as a separable neuropsychological function that is affected in children with ADHD. Moreover, our findings stress the importance of a trans-diagnostic approach to the relationship between behavior and neuropsychology.

Introduction

Attenuated inhibitory performance is one of the most robust findings in the neuropsychology of ADHD (Alderson, Rapport, & Kofler, 2007; Lipszyc & Schachar, 2010). However, it is unclear whether this represents a deficit in outright stopping (reactive inhibition), whether it relates to a deficit in strategic response slowing (proactive inhibition) or both (Bhaijiwala, Chevrier, & Schachar, 2014; Chevrier, Noseworthy, & Schachar, 2007). In addition, children with other development disorders, such as autism spectrum disorder, often show symptoms of inattention, impulsivity and hyperactivity similar to children with ADHD. These may relate to similar underlying changes in inhibitory processing. Indeed, it is unclear if inhibitory deficits are specific to the diagnosis ADHD or related to symptoms of ADHD irrespective of the formal diagnosis. Here, we set out to dissociate reactive and proactive inhibition in children with symptoms of ADHD, using a modified stop-signal task, called the stop-signal anticipation task (Zandbelt & Vink, 2010).

The stop-signal task (SST) assesses how participants stop a response that has already been initiated (Frederick Verbruggen & Logan, 2008). A stream of go-signals is presented that all require a response. Infrequently, a go-signal is followed by a stop-signal indicating that the participant should withhold his or her response. The ability to stop is conceptualized in terms of a race between two independent processes: a go process that produces the response and a stop process that cancels it (Logan & Cowan, 1984). If the go process finishes first, a response is produced; if the stop process finishes first, the response is canceled. Furthermore, this model provides methods for the estimation of the speed of the (covert) stop-process - the stop-signal reaction time (SSRT) - on the basis of the response rate on stop trials and response times on go trials. SSRT is a measure of reactive inhibition, but does not address proactive inhibition.

To measure proactive inhibition, the ability to adapt ongoing responses in relation to contextual cues, researchers have adapted the stop-signal task by introducing cues that inform the participant about the possibility of an upcoming stop-signal (Frederick Verbruggen & Logan, 2009; Zandbelt & Vink, 2010). For example, in the stop-signal anticipation task (SSAT), a visual cue indicates the probability that a stop-signal will occur (Vink, Kaldewaij, Zandbelt, Pas, & du Plessis, 2015; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013; Zandbelt & Vink, 2010). Participants respond to this manipulation by adjusting their response strategy, slowing down as stop-signal probability increases. Another prominent feature of this task is that it requires participants to make a timed response, rather than a speeded response as

in the standard stop-signal task. As a result, response latency (i.e. RT) differences between groups are usually small or absent (e.g. Zandbelt, van Buuren, Kahn, & Vink, 2011). Thus, the SSAT enables the quantification of proactive response slowing and reactive stopping, while minimizing group differences in baseline response latencies.

In light of the ongoing debate about dimensional approaches versus categorical approaches in psychiatry (Coghill & Sonuga-Barke, 2012), we decided to include not only children with ADHD, but also children primarily diagnosed with an autism spectrum disorder and high parent-rated levels of ADHD symptoms. This permitted us to determine if any differences were specific to ADHD or rather to the broader dimension of ADHD symptoms. Moreover, by relating performance measures to parent-rated ADHD symptoms across clinical groups, we could analyze neuropsychological functioning in a trans-diagnostic fashion.

We first tested if the well-documented finding of slower inhibitory speed (i.e. SSRT) in children with ADHD could be replicated, in the context of timed responding (SSAT) as opposed to speeded responding (standard stop-signal task). Second, we investigated whether children with ADHD showed a deficit in proactive inhibition in addition to a deficit in reactive inhibition. Third, we tested if the findings were specific to children with a diagnosis of ADHD or rather were also present in children with ASD and ADHD symptoms. Finally, we tested for an association between parent-rated ADHD symptoms and inhibitory performance across diagnostic groups.

Methods

Participants

108 Right-handed boys aged 8-12 years met full inclusion criteria. An initial screening for off-task behavior, based on mean response times (RT) and/or percentage omission errors, yielded five extreme outlier subjects (three interquartile ranges above the third quartile of the sample as a whole). As such, data from 103 children were available for final analyses: 39 Children with ADHD, 32 children with ASD and ADHD symptoms and 32 typically developing controls. Table 1 provides demographic information. The institutional review board of the University Medical Center Utrecht (UMCU) approved all study procedures. Both parents and children aged 12 years provided written informed consent, younger children provided verbal assent. Participants with ADHD or ASD and ADHD symptoms were recruited through schools for special education and the UMCU outpatient clinic for developmental disorders. Control participants were recruited through primary schools. Only children using no medication or short-acting psychostimulants (e.g. methylphenidate) were included; all parents were

instructed not to administer medication in the 24 hours prior to testing. A majority (76 out of 103) of participants included in this study also participated in a set of two fMRI experiments. Results from these tasks were analyzed separately and have been submitted for publication elsewhere (van Hulst et al., submitted for publication).

Table 1. Demographic characteristics

	Control (SD)	ADHD (SD)	ASD (SD)	F-value	p-value
N (total = 103)	32	39	32	-	-
Age	10.1 (1.1)	10.5 (1.2)	10.7 (1.4)	1.69 (2,100)	0.190
IQ	112.9 (15.8)	105.4 (16.8)	106.4 (18.0)	1.95 (2,100)	0.147
SWAN-hyp	0.36 (0.66)	-1.06 (0.66)	-1.02 (0.77)	44.08 (2,96)	<0.001*
SWAN-att	0.27 (0.53)	-1.33 (0.66)	-1.36 (0.65)	73.76 (2,96)	<0.001*

SD, standard deviation; ADHD, Attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; SWAN-hyp, Strengths and Weaknesses of ADHD and Normal Behavior hyperactivity/ impulsivity subscale; SWAN-att, Strengths and Weaknesses of ADHD and Normal Behavior inattention subscale.

* Significant after FDR correction.

In/exclusion criteria

The Diagnostic Interview Schedule for Children (DISC-IV, parent version) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was administrated to parents of all participants. In addition, children participated in a four-subtest short-form of the WISC-III in order to estimate full-scale IQ. General in- and exclusion criteria were: age 8 through 12 years, an (estimated) IQ equal to or higher than 70, no history of or present neurological disorder and the ability to speak and comprehend Dutch. Additional criteria for children with ADHD included a clinical DSM-IV diagnosis of ADHD confirmed by the DISC-IV. Children with ASD and parent-rated ADHD symptoms, were included if they met criteria for a clinical DSM-IV diagnosis of ASD and showed clinical or subclinical scores on the attention problems subscale of the Child Behavior Checklist (CBCL) (Verhulst, Van Der Ende, & Koot, 1996). The absence of psychiatric disorders in typically developing children was confirmed using DISC-IV (with an exception of specific phobia and enuresis). Furthermore, typically developing children were required to have normal (not clinical or subclinical) scores on any of the CBCL subscales.

Questionnaires

In addition to the CBCL, parents completed the Strenghts and Weaknesses of ADHD and Normal Behavior (SWAN) questionnaire (Lakes, Swanson, & Riggs, 2012). This questionnaire assesses all symptoms listed in the DSM-IV definition of ADHD across the complete spectrum of functioning (both below and above average behavior is quantified).

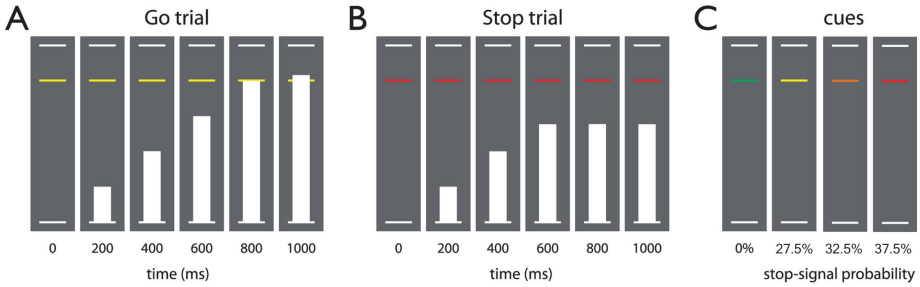
Stop-signal anticipation task (SSAT)

The SSAT is a variation on a classic stop-signal paradigm and was designed to assess both reactive and proactive inhibition (Zandbelt & Vink, 2010). We introduced the task in a storyline format, where children were asked to help a spaceship land on the moon (see next paragraph). During all trials, three horizontal lines were shown on a grey background (see Figure 1). The second line (i.e. target line) was placed at 80% of the distance from the bottom line to the top line. During every go-trial a bar moved from the bottom to the top line in 1000 milliseconds (ms). The first objective was to press a button with the right index finger to halt the bar as close to the target line as possible (i.e. go trial with a target response time of 800ms). Stop trials were identical to go trials, except that the program made the bar stop before it reached the target line (i.e. stop-signal). In this case participants had to withhold the button press. The probability that a stop-signal would appear was manipulated across trials (randomly interspersed) and the color of the target line provided information on this stop-signal probability. The task consisted of four blocks. In each block, there were 41 green trials with 0% stop-signal probability (41 go trials, 0 stop trials), 40 yellow trials with 27.5% stop-signal probability (29 go trials, 11 stop trials), 40 orange trials with 32.5% stop-signal probability (27 go trials, 13 stop trials) and 40 red trials with 37.5% stop-signal probability (25 go trials, 15 stop trials), so that there were 122 go trials and 39 stop trials per block. The stop-signal onset time was initially set to 500 ms after trial onset (i.e. 300 ms before the target response time). During the experiment, stop-signal onset time was adjusted in steps of 25 ms for each stop-signal probability level separately, depending on stopping performance. Specifically, if stopping was successful on the previous stop trial within a probability level, then stopping was made more difficult by shifting the stop-signal onset time 25 ms towards the target response time. This process was reversed when stopping failed. This staircase procedure ensures roughly equal numbers of successful and unsuccessful stop trials.

We explained the SSAT to the children in a storyline format. We told them that the first objective was to ensure a soft landing of the spaceship. To achieve this, children were asked to stop the bar as close to the target line as possible (go trial). The second

objective was to cancel a landing if circumstances became too dangerous. To achieve this, children were asked to withhold the button press whenever the bar stopped before it reached the target line (stop-trial). We instructed the children that a green line indicated that the bar would never be stopped before the target line, a yellow line represented "occasionally", an orange line represented "sometimes" and a red line indicated "quite often". We instructed children that the go and stop trials were equally important and that it would not always be possible to suppress a response when a stop-signal occurred. Furthermore, we did not give children any instructions on how to adapt their task strategy in response to this information. All participants performed three practice levels (of respectively 30, 60 and 161 trials) to get acquainted with the paradigm.

Figure 1. Task design of the stop-signal anticipation task



Note. Three horizontal lines formed the background displayed continuously during the task. (A) In each trial, a bar moved at constant speed from the bottom up, reaching the middle line in 800 ms. The main task was to stop the bar as close to the middle line as possible by pressing a button with the right index finger. These trials are referred to as Go trials. (B) In a minority of trials, the bar stopped moving automatically before reaching the middle line, indicating that a response had to be stopped. These trials are referred to as Stop trials. Stop-signal onset was adjusted in steps of 25 ms based on stopping performance, according to a 1-up-1-down staircase procedure (see Methods section). (C) The probability that a stop-signal would occur was manipulated across trials and was indicated by the color of the target response line. There were four stop-signal probability levels: 0% (green), 27.5% (yellow), 32.5% (orange) and 37.5% (red).

Caption and figure (with minor modifications) reprinted with permission from "On the Role of the Striatum in Response Inhibition" by Zandbelt & Vink, 2010, PLoS ONE 5(11): e13848. doi:10.1371/journal.pone.0013848

A basic differentiation could be made between two types of trials: baseline go-trials (stop-signal probability = 0%) and uncertain go and stop-trials (stop-signal probability > 0%). Uncertain go and stop-trials occurred with three different stop probabilities (27.5%, 32.5% and 37.5%). Mean response times (RT), standard deviations of response times (SDRT) and percentage of omission errors (OMISS) were computed separately for certain go-trials and for uncertain go-trials (pooled across stop-signal probability conditions). SSRT, pooled across stop-signal probability conditions, was computed using the integration method (Logan & Cowan, 1984). To test the basic assumptions of the stop-signal task, mean response times of stop failure trials (stop-failure RT) and percentage stop-accuracy were computed pooled across all stop-signal probability conditions.

Statistical analyses

According to the race model, a stop failure trial occurs when the go process finishes before the stop process (i.e. the go process escapes inhibition). As a result, a prediction of the model is that stop-failure RT is shorter than go RT. We tested this prediction using a repeated-measures ANOVA. Second, we tested whether the staircase procedure had indeed produced 50% stop accuracy across all stop signal probabilities using a one-sample t-test.

We tested for an effect of diagnosis on SSRT, RTcertain-go, RTuncertain-go, SDRTcertain-go, SDRTuncertain-go, OMISScertain-go, OMISSuncertain-go, using ANCOVA including age as a covariate. Post-hoc testing was applied as appropriate. Proactive inhibition was operationalized as within-subject slowing of response times with increasing stop-signal probability. We quantified this using repeated measures ANCOVA with stop-signal probability as within-subject factor, diagnosis as between-subject factor and age as covariate. In addition, we tested for an association between ADHD-symptoms (i.e. SWAN subscale scores) and all outcome measures. If there were no between-group differences, this was tested on the entire sample. For measures that did show between-group differences, we tested within clinical and comparison groups separately. Again, age was included as a covariate.

All outcome measures except SSRT were not distributed normally. ANCOVA is fairly robust for deviations from normality, especially when group sizes are approximately equal (Schmider, Ziegler, Danay, Beyer, & Bühner, 2010). Therefore, we chose to report ANCOVA results and provide a supplement (see supplementary Table S1) with additional non-parametric (Kruskal-Wallis) analyses. These analyses did not include age as a covariate. All reported results were replicated in the non-parametric analyses.

Results

Model assumptions

We first tested the assumptions underlying the stop-signal paradigm on the group as a whole. As expected, mean response times were shorter on stop-failure trials (M = 796ms, SD = 30.34) than on uncertain go-trials (M = 837ms, SD = 23.35) ((F(1,102) = 407.24, p < 0.001). Stop accuracy was close to 50% but differed from it statistically (M = 49.5%, SD = 1.63) (t(102) = -2.97, p = 0.004).

Response time measures

We found main effects of group and age on the standard deviation of response times (SDRT) in both conditions (certain-go and uncertain-go), and on the percentage of omission errors in both conditions (see Table 2 for descriptive and inferential statistics). We found no group by age interactions. Post-hoc analyses showed higher SDRT and more omission errors in both clinical groups compared to typically developing children, independent of age. We found no group differences in RTcertain-go and RTuncertain-go.

Inhibition measures

For reactive inhibition, we found group differences and a main effect of age on SSRT (see Figure 1 and Table 2 for detailed results). We found no group by age interactions. Post-hoc analysis showed longer SSRTs in both clinical groups than in typically developing children. For proactive inhibition, we found a within-subject main effect of stop-signal probability on mean response time (F(2.71,271) = 57.92, p <0.001), where an increase in stop-signal probability was associated with proactive slowing of response times (see supplementary Figure S1). However, we found no group by stop-signal probability interaction and thus no evidence for differential proactive inhibition between groups (F(5.43,271) = 1.25, p =0.285).

Within-group effect of ADHD symptoms

We found no association between measures of task performance and attention problems (SWAN attention problems subscale) or hyperactivity/impulsivity (SWAN hyperactivity/impulsivity subscale). We tested this separately in the combined clinical group (ADHD and ASD with ADHD symptoms) and in the comparison group. In typically developing children, the association between attention problems and SSRT (F(1,29) = 4.43, p = 0.044) was nominally significant, but this did not survive FDR-correction for multiple comparisons. For those performance measures that did not show between-group differences in the initial ANCOVA, the effect of ADHD symptom

scores on task performance was tested across all groups. In this analysis we found no association between the subscales of the SWAN and RTcertain-go, RTuncertain-go or the within-subject main effect of stop-signal probability on mean response times (i.e. proactive inhibition).

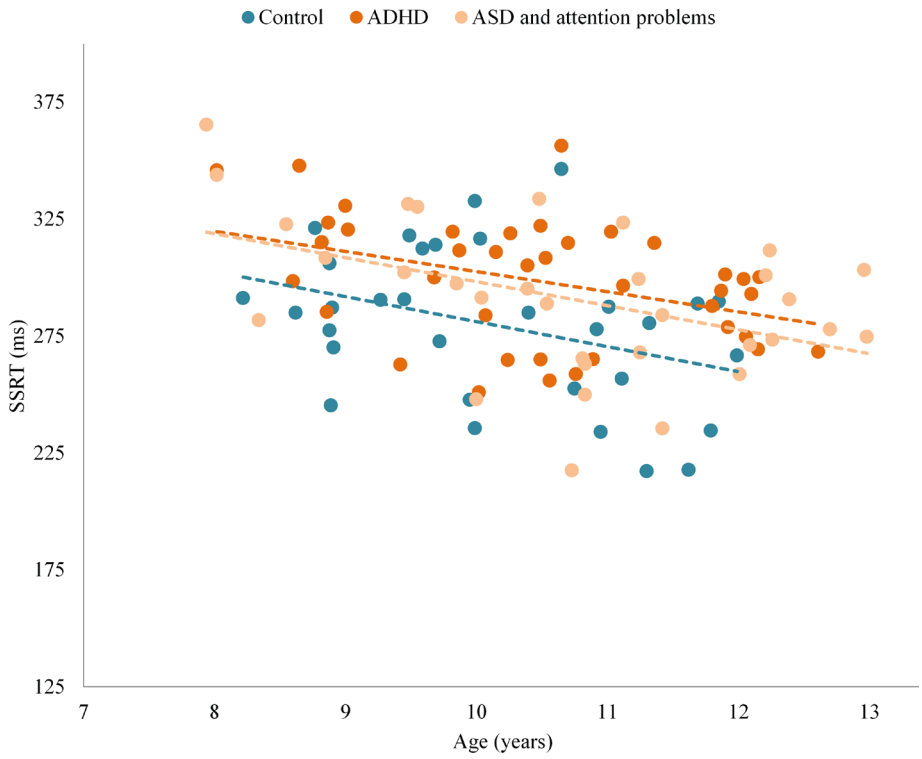
Table 2. ANCOVA results for Task performance – reactive inhibition

		F-value	p-value	Control M(SD)	ADHD M(SD)	ASD M(SD)
RTcertain-go	Group	1.56 (2,99)	0.216	821 (22.2)	824 (21.3)	829 (21.8)
	Age	2.03 (1,99)	0.158	-	-	-
RTuncertain-go	Group	1.48 (2,99)	0.234	836 (24.5)	833 (20.1)	842 (25.6)
	Age	2.03 (1,99)	0.158	-	-	-
SDRTcertain-go	Group	5.43 (2,99)	0.006*	57.9 (14.2)	73.6 (26.3)	68.9 (31.3)
	Age	12.54 (1,99)	0.001*	-	-	-
SDRTuncertain-go	Group	5.50 (2,99)	0.005*	58.7 (12.9)	73.3 (22.0)	70.0 (30.4)
	Age	9.76 (1,99)	0.002*	-	-	-
OMISScertain-go	Group	7.87 (2,99)	0.001*	2.10 (2.35)	5.36 (3.91)	4.52 (5.61)
	Age	10.76 (1,99)	0.001*	-	-	-
OMISSuncertain-go	Group	7.64 (2,99)	0.001*	2.80 (2.56)	5.80 (3.65)	4.96 (4.89)
	Age	9.92 (1,99)	0.002*	-	-	-
SSRT	Group	5.67 (2,99)	0.005*	280 (32.7)	298 (26.6)	291 (32.6)
	Age	19.34 (1,99)	<0.001*	-	-	-

SD, standard deviation; ADHD, Attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; RT, mean response time; SDRT, standard deviation of response times; OMISS, percentage of omission errors; SSRT, stop-signal reaction time; SSD, stop-signal delay.

* Significant after FDR correction.

Figure 2. Group differences in reactive inhibition across the age range



ADHD, Attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; SSRT, stop-signal reaction time; ms, milliseconds.

Discussion

We used a modified stop-signal task to disentangle proactive inhibition (strategic response slowing) and reactive inhibition (outright stopping) in ADHD. We replicated the well-documented finding of poorer reactive inhibition in children with ADHD compared to typically developing children. In addition, we found this inhibitory deficit in children with ASD and a similar level of ADHD symptoms. We found no evidence for a deficit in proactive inhibition in either clinical group.

Markedly, we found deficits in reactive inhibition (i.e. increased SSRT) in children with ADHD in a task that involves timed as opposed to speeded responding. Possibly as a result of these timed responses, we found no evidence for differences in mean response times (RT) on go-trials between children with ADHD and typically developing children. This argues against suggestions that increased RT may confound changes in SSRT in ADHD (Alderson et al., 2007).

The standard stop-signal task assesses reactive inhibition only (Aron, 2011; Zandbelt et al., 2013; Zandbelt & Vink, 2010). To facilitate a distinction between proactive and reactive processes, a task-based manipulation of proactive inhibition was developed by Zandbelt and Vink (Zandbelt & Vink, 2010). They found that, without any explicit instructions, healthy adults slowed their responses when stop-signal probability increased (Zandbelt et al., 2011; Zandbelt & Vink, 2010). Here, we replicated this finding in children, showing a similar effect of proactive inhibition overall. However, we found no evidence for a deficit in proactive inhibition in children with symptoms of ADHD. Thus children with symptoms of ADHD did seem to engage a response-set in which they anticipated infrequent stop-trials, yet they still showed reduced inhibitory processing. Such a deficit in reactive inhibition could be mediated by a neurobiological deficit in the hyperdirect pathway of motor control (including right inferior frontal gyrus, subthalamic nucleus and globus pallidus pars interna) subserving fast, global motor inhibition (Aron, 2011; Frank, Samanta, Moustafa, & Sherman, 2007; Nambu, Tokuno, & Takada, 2002). Alternatively, this deficit could be due to impairments in attentional processing that manifest when multiple signals (go and stop) are processed in parallel.

We did not find the deficits in reactive inhibition to be specific to children with a primary diagnosis of ADHD. Children with similar levels of parent-rated ADHD symptoms but a primary diagnosis of ASD showed similar deficits in reactive inhibition. We hypothesized that if an inhibitory deficit was found across both clinical groups, inhibitory performance was likely to be related to ADHD symptoms in a dimensional

way. Such a linear relationship has previously been reported in population based studies (Crosbie et al., 2013; Tillman, Thorell, Brocki, & Bohlin, 2007). Surprisingly we found no such trans-diagnostic relationship within our clinical groups. One possible explanation may be that the linear relationship does not hold for the extreme ends of the distribution. As an example, a diathesis-stress model of nature-nurture interactions could imply that above a certain threshold of inhibitory problems, environmental factors have more impact on the expression of ADHD symptoms than inhibitory problems themselves (Belsky & Pluess, 2009; Monroe & Simons, 1991). Another explanation could be that different neurobiological mechanisms lead to reduced inhibitory control in either group (i.e. ADHD and ASD).

In this study, we were able to dissociate reactive and proactive inhibition. However, we did not dissociate reactive inhibition from attentional switching. Psychophysiological measures such as event related potentials (ERP's) have been used to disentangle different aspects of response inhibition as measured by the stop-signal paradigm (Kenemans, 2015). Because of the high temporal resolution of EEG, distinctions can be made between different phases of processing. These studies point toward a deficit in the switching of attention to the stop-signal as a possible cause for inhibitory problems (Bekker et al., 2005; Kenemans et al., 2005; F. Verbruggen, Aron, Stevens, & Chambers, 2010). One could even argue that as per definition reactive inhibition is a task of attentional switching.

In sum, we found evidence for a deficit of reactive inhibition in children with ADHD symptoms in the absence of evidence for deficits in proactive inhibition. These findings re-emphasize the role of reactive inhibition as a separable neuropsychological domain that is affected in children with ADHD. Moreover, our findings in children with ASD and symptoms of ADHD stress the importance of a trans-diagnostic approach to the relation between behavior and neuropsychology.

Acknowledgments

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Supplementary information

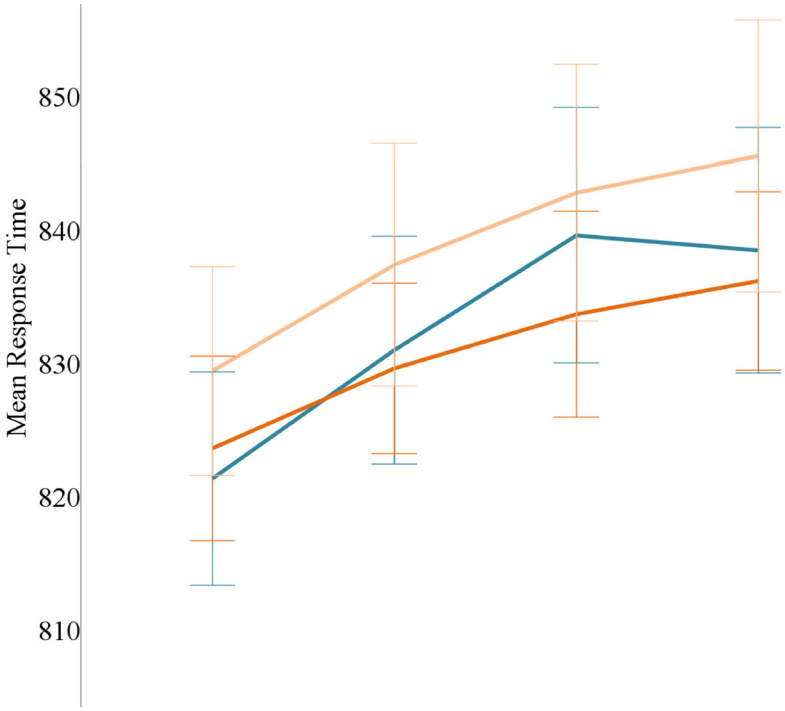
Supplementary Table S1. Non-parametric test of group differences in task performance

	Control (mean rank)	ADHD (mean rank)	ASD (mean rank)	Chi-squared (df)	p-value
RTcertain-go	45.45	52.08	58.45	3.030 (2)	0.220
RTuncertain-go	49.89	48.81	58.00	1.895 (2)	0.388
SDRTcertain-go	40.78	62.05	50.97	16.212 (2)	<0.001
SDRTuncertain-go	39.81	63.12	50.64	13.846 (2)	0.001
OMISScertain-go	36.95	65.45	50.66	8.964 (2)	0.011
OMISSuncertain-go	38.00	64.44	50.84	10.789 (2)	0.005

Note. For the six task performance measures that showed a non-normal distribution, we replicated the between group analysis using the non-parametric Kruskal-Wallis test by rank. For each group the mean rank is shown along with the Chi-squared and p-value for the group difference.

ADHD, Attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; df, degrees of freedom; RT, mean response time; SDRT, standard deviation of response time; OMISS, percentage omission errors.

Supplementary Figure S1. Proactive inhibition: response slowing as a function of stop-signal probability



Note. Supplementary Figure S1 shows response time slowing as a function of increasing stop-signal probability. We found a main within-subject effect of stop-signal probability on mean response time, but no evidence for any interaction between group and response time slowing. The error bars show mean response times plus and minus one standard error, separately for each group.

ADHD, Attention-deficit/hyperactivity disorder; ASD+, autism spectrum disorder and symptoms of ADHD.

3

What to expect and when to expect it: an fMRI study of expectancy in children with ADHD symptoms

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Submitted for publication

Abstract

Changes in cognitive control and timing have both been implicated in ADHD. Both are involved in making and monitoring predictions about the environment, and altering behavior if those predictions are violated. In ADHD, problems with predicting events have high face validity, as this would be associated with behavior that is inappropriate only given a certain context, similar to what is seen in the disorder. In this fMRI study, we used a timing manipulated go/nogo task to assess brain activity related to predictions about what (cognitive control) and when (timing) events would occur. We hypothesized that problems in predicting the environment are a more general, trans-diagnostic characteristic of children with hyperactive, impulsive and inattentive symptoms. To address this, we included children with ASD and symptoms of ADHD, in addition to children with ADHD and typically developing children. We found group differences in brain activity related to predictions about when (timing), but not what events will occur (cognitive control). Specifically, we found timing-related hypo-activity that was in part unique to children with a primary diagnosis of ADHD (left pallidum) and in part shared by children with similar levels of ADHD symptoms and a primary diagnosis of ASD (left subthalamic nucleus). Moreover, we found poorer task performance related to timing, but only in children with ASD and symptoms of ADHD. Ultimately, such neurobiological changes in children with ADHD symptoms may relate to a failure to build or monitor predictive models and thereby hinder their efficient interaction with the environment.

Introduction

The observation that the behavior of children with Attention-deficit/hyperactivity disorder (ADHD) is inappropriate only in certain contexts has led to suggestions that children with ADHD may be particularly impaired in their ability to predict events (Nigg & Casey, 2005). Indeed both cognitive control, important for predicting what events will occur, and timing, important for predicting when they will occur, are involved in ADHD (Lipszyc & Schachar, 2010; Noreika, Falter, & Rubia, 2013). However, it is unclear if these psychological processes are specific to the diagnosis ADHD or related to ADHD symptoms in a more general, trans-diagnostic way. In this study, we analyzed cognitive control and timing in concert, using a single child-friendly fMRI paradigm in children with ASD and symptoms of ADHD, children with ADHD and typically developing children.

Nigg and Casey have integrated both neuropsychological features by proposing that ADHD is characterized by a deficient ability to form predictions about what (cognitive control) and when (timing) events will happen (Nigg & Casey, 2005). This ties in with theories of attention that propose that predictive models about the environment, and related anticipatory brain activity, form the foundation of attention processes (Ghajar & Ivry, 2009). From a clinical perspective, such a failure to make or monitor contextual predictions could explain behavior that is inappropriate only given a certain context, as is seen in ADHD (Nigg & Casey, 2005). From a neurobiological perspective, this theory could have a cellular basis in an existing model of reduced anticipatory dopamine signaling in ADHD (Tripp & Wickens, 2008, 2009).

Cognitive control is defined as 'the ability to override an inappropriate response in favor of another' (Casey, Tottenham, Liston, & Durston, 2005) and encompasses a variety of closely related constructs such as behavioral inhibition, response inhibition and inhibitory control (Aron, 2007). Deficits in cognitive control have been suggested to be one of multiple, partially separable pathways to ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Solanto et al., 2001; Sonuga-Barke, 2002, 2005). Neuropsychological studies of ADHD have shown deficits in cognitive control with relatively high consistency (Hervey, Epstein, & Curry, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), although it has also been estimated that at least 50% of children with ADHD do not show any deficits in cognitive control (Nigg et al., 2005). Moreover, neuroimaging studies have found evidence of hypo-activity in a fronto-striatal network involved in cognitive control at the group level (Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; McCarthy, Skokauskas, & Frodl, 2014).

Analogous to cognitive control, timing is an overarching term that encompasses different aspects of temporal processing. A wide variety of timing-related constructs have been assessed in ADHD (Toplak, Dockstader, & Tannock, 2006) and both theoretical and empirical papers have implicated timing as a candidate neuropsychological pathway to ADHD symptoms (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Noreika et al., 2013; Sonuga-Barke, Bitsakou, & Thompson, 2010; van Hulst, de Zeeuw, & Durston, 2015). Moreover, a meta-analysis showed deficits in timing across multiple domains (e.g. motor timing, perceptual timing) and timescales (e.g. sub-second, supra-second timescale) in ADHD (Hart, Radua, Mataix-Cols, & Rubia, 2012).

As neuropsychological changes found in children with ADHD are not necessarily specific to the diagnosis (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011) and deficits in cognitive control and timing have been reported across multiple disorders (Allman & Meck, 2012; Geurts, van den Bergh, & Ruzzano, 2014; Lipszyc & Schachar, 2010), we assessed diagnostic specificity by including a third group of participants: children with a similar level of parent-rated ADHD symptoms, but a different primary diagnosis (autism spectrum disorder (ASD)).

Using a timing manipulated go/nogo task, we hypothesized we would find changes in brain activity in fronto-striatal networks involved in motor control. We expected to find these changes in children with symptoms of ADHD, irrespective of their primary diagnosis (ASD or ADHD) and that they would be related to unexpected stimulus type and unexpected stimulus timing. Moreover, we expected that changes in brain activity would correlate more with trait ADHD symptoms than diagnosis per se. In addition, we expected children with ADHD symptoms to benefit less from the expected timing of trials and thus to show less speeding of response times on expected trials as compared to response times on unexpected trials (i.e. less response time benefit) (Durston et al., 2007; Mulder et al., 2008).

Methods

Participants

A total of 111 right-handed boys, aged 8-12 years were included in the study: 36 typically developing boys and 75 boys with ADHD symptoms. Children with ADHD symptoms were recruited in two groups: 38 with a primary diagnosis of ADHD (all presentations) and 37 with a primary autism spectrum disorder (ASD) diagnosis. Typically developing children were recruited through schools in the wider Utrecht area. Children with ADHD symptoms were recruited through schools for special education and the University Medical Center Utrecht (UMCU) outpatient clinic

for developmental disorders. Only children using no medication or short-acting psychostimulants (e.g. methylphenidate) were included; all parents were instructed not to administer medication in the 24 hours prior to testing. All children completed a timing manipulated go/nogo paradigm (Durston et al., 2007). After screening data quality, 29 participants were excluded on the basis of excessive head motion and three participants were excluded due to anatomical abnormalities (for details see Online Resource 1, supplementary text S1). High quality data from 76 participants were available for final analyses. Participants were matched at the group level for age and IQ. Demographics are provided in Table 1.

Table 1. Demographics per group

	Control (SD)	ADHD (SD)	ASD (SD)	F-value	p-value
N (76)	26	24	26		
Age	10.5 (1.0)	11.2 (1.1)	10.8 (1.4)	(2,73) 1.76	0.179
IQ	117.3 (18.5)	105.6 (15.9)	109.6 (17.7)	(2,72) 2.92	0.060
SWAN-hyp	0.43 (0.75)	-1.07 (0.63)	-1.01 (0.61)	(2,70) 40.63	<0.001*
SWAN-att	0.40 (0.63)	-1.22 (0.64)	-1.50 (0.46)	(2,70) 79.48	<0.001*

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SD, standard deviation; SWAN-hyp, Strengths and Weaknesses of ADHD and Normal Behavior hyperactivity/impulsivity subscale; SWAN-att, Strengths and Weaknesses of ADHD and Normal Behavior inattention subscale.

* Significant group difference.

In- and exclusion criteria

Inclusion criteria for typically developing children were: no psychiatric diagnoses on the DISC-IV interview (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) (with an exception of specific phobia and enuresis) and no scores in the clinical range on any scale of the Child Behavior Checklist (CBCL) (Verhulst, Van Der Ende, & Koot, 1996), as reported by one of the parents. Inclusion criteria for children with ADHD symptoms were either a clinical DSM-IV diagnosis of ADHD, which was confirmed using the Diagnostic Interview Schedule for Children (DISC) or a DSM-IV autism spectrum diagnosis and a score in the (sub)clinical range of the CBCL subscale of Attention Problems. For all participants, major illness, present or past neurological illness, IQ below 70 and presence of metal objects in or around the body that would preclude MRI, were grounds for exclusion.

Questionnaires

Parents completed two questionnaires: The Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) questionnaire (Lakes, Swanson, & Riggs, 2012). This questionnaire assesses symptoms listed in the DSM-IV definition of ADHD across the complete spectrum of functioning (behavior that is below and behavior that is above that of typically developing peers is quantified).

Timing manipulated go/nogo paradigm

We used a timing-manipulated go/nogo task (Durston et al., 2007). Participants were instructed to help a mouse collect cheese. First, a picture of a door was shown. In a majority of trials (82%), this door opened with an interstimulus interval (ISI) of 4 seconds (expected timing), in a minority of trials (18%) the door opened with a 2 second ISI (unexpected timing). Behind the door was either a piece of cheese (go-trials; 82% of 264 trials) or a cat (nogo-trials; 18% of 264 trials). Subjects were asked to press a button as fast as possible when a piece of cheese was shown and to withhold their response when a cat was shown. These two manipulations created four types of trials: go-trials with expected timing, go-trials with unexpected timing, nogo-trials with expected timing and nogo-trials with unexpected timing. Participants included in this study performed two different tasks in a single scan session, interrupted by a short (15 minute) break. Results from the other task (a child-friendly monetary incentive delay paradigm) were analyzed separately (van Hulst et al., submitted for publication).

fMRI acquisition

The study was run on a 3.0 T Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) using an eight-channel sensitivity-encoding (SENSE) parallel imaging head coil. For anatomical reference, we acquired a whole-brain three-dimensional fast field echo T1-weighted scan (200 slices; repetition time = 10 ms; echo time = 4.6 ms; flip angle = 8°; field of view, 240 x 240 x 160 mm; voxel size: 0.75 x 0.8 x 0.75 mm isotropic). In addition, we acquired whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast (4 sessions; 135 volumes per session; 36 slices per volume; interleaved acquisition; TR = 2.02 s; TE = 35 ms; field of view = 232 × 123 × 256 mm; flip angle = 70°; voxel size = 2.67 × 2.67 × 3.43mm) oriented in a transverse plane. We collected six dummy scans to allow for T1 equilibration effects.

Preprocessing of fMRI data

We analyzed FMRI data using SPM8 (r4290) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) as implemented in Matlab 7.12 (Mathworks Inc., Natick, MA, USA). To correct for between-scan head motion, we realigned all images to the first volume using rigid body transformations. Next, the anatomical image was co-registered to the first fMRI image using the mutual information criteria method and subsequently normalized to Montreal Neurological Institute (MNI) space using unified segmentation. We then resliced the image at a voxel size of 1.0 x 1.0 x 1.0mm. Functional images were normalized using the normalization parameters generated in this step, the images were resliced at a voxel size of 3.0 x 3.0 x 3.0mm. Finally, we spatially smoothed the fMRI images using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm. In addition, we assessed scan-to-scan movement using ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009). Scans with more than 1.0 mm scan-to-scan movement or more than 1.5% deviation from the average global signal, were replaced using a linear interpolation of the values of neighboring scans. Participants with more than 30% corrected scans were excluded from further analyses (for details, see Online Resource 1, supplementary text S1).

Statistical analyses – task performance

We tested for an effect of diagnosis on five measures of task performance: baseline mean response times (MRTexpected-go), baseline standard deviation of response times (SDRTexpected-go); percentage of correct go-trials (accuracygo), percentage of correct nogo-trials (accuracynogo) and response time benefit (RTbenefit). RTbenefit denotes the difference in MRT between expected and unexpected go-trials. This difference is expressed in the number of standard deviations of MRTexpected-go (MRTexpected-go – MRTunexpected-go)/SDRTexpected-go. After testing for normality (Shapiro-Wilk test) and homogeneity of variances (Levene's test), analysis of covariance (ANCOVA) was conducted with diagnosis as factor. If age or IQ significantly covaried with a measure of task performance, analyses were run, reported and interpreted both with and without the covariate for additional insight. If they did not, the covariates were left out of the final model. Where group differences were found, we performed post-hoc testing using Fisher's least significant difference (LSD). Moreover, we followed up with dimensional analyses by testing for an effect of attention problems (i.e. SWAN-inattention subscores) or hyperactivity/impulsivity (i.e. SWAN-hyperactivity/impulsivity subscores) on these performance measures, within the combined clinical group and the control group separately. Where no group differences were found, correlational analyses were run on the entire sample. Results were corrected for multiple comparisons using False Discovery Rate (FDR) correction on the separate ANCOVA results (per task performance measure) using the Benjamini-Hoghberg method (Benjamini & Hochberg, 1995).

Statistical analyses – fMRI

Statistical analyses of fMRI data were performed in a two-level procedure within the framework of the general linear model. First, for each subject, we modeled the blood oxygenation level dependent (BOLD) activation invoked by task cues as conditions of interest, and realignment parameters as potential confounders (condition of no interest). Four cues were modeled as conditions of interest: expected go-trials, unexpected go-trials, expected nogo-trials and unexpected nogo-trials. Regressors were created by convolving delta functions coding for cue onset with a canonical hemodynamic response function (as implemented in SPM8) for each cueing category separately. The estimated regression coefficients for the different cues were then contrasted, resulting in two first-level contrast images for each subject: go versus nogo-trials and expected versus unexpected trials. Data were high-pass filtered using discrete cosine basis functions with a 128 second cut-off. The analysis focused on average activity in a-priori specified regions of interests (ROIs). We used regions that are considered part of fronto-striato-cerebellar loops involved in motor control and, more specifically, in response inhibition and temporal processing (Hart et al., 2012; McCarthy et al., 2014). ROIs were created using different atlases provided in the FSL software package (the Harvard-Oxford cortical and subcortical structural atlases, the Probabilistic cerebellar atlas and the Subthalamic nucleus atlas). Six fronto-striatal regions putatively involved in response inhibition or motor timing were selected per hemisphere: anterior cingulate, inferior frontal gyrus, putamen, pallidum, supramarginal gyrus and subthalamic nucleus. In addition, a cerebellar vermis ROI was created, adding up to a total of 13 ROIs. If results were found in a given ROI, a supplementary figure of the map is provided, see Online Resource 1, supplementary Figures S1 and S2. Average activity per ROI was operationalized as average □-values of the contrast image and extracted using Marsbar (http://marsbar.sourceforge.net/). Main effects of expectancy and inhibition were analyzed in typically developing children using a single-factor analysis of variance (ANOVA). To test for group differences in brain activity we conducted an ANCOVA with diagnosis as factor. Where age and IQ significantly covaried with activity in an ROI, analyses were run, reported and interpreted both with and without the covariate for additional insight. If not, the covariates were left out of the final model. Where group differences were found we performed post-hoc testing using Fisher's least significant difference (LSD) to compare the three groups. In a follow-up analysis, nogo accuracy and RTbenefit were included as an additional performance-related covariate. In further follow-up analyses, we tested for effects of ADHD-symptoms (i.e. scores on two separate SWAN subscales) on brain activity (using ANCOVA) within the combined clinical group and control group separately. If group differences were not found, correlational analyses were run on the entire sample. Results were corrected for multiple comparisons using

False Discovery Rate (FDR) correction on the separate ANCOVA results (per ROI) using the Benjamini-Hoghberg method (Benjamini & Hochberg, 1995).

Results

Questionnaires

ANOVA showed group differences on the inattention scale of the SWAN and the hyperactivity/impulsivity scale of the SWAN (see Table 1). Post-hoc testing indicated that both clinical groups had lower scores on the two SWAN subscales than typically developing children, corresponding to more symptoms of ADHD. No differences were found between children with ADHD and children with ASD and ADHD symptoms.

Task performance

ANOVA showed between-group differences on mean response times (MRTexpectedgo), standard deviation of response times (SDRTexpectedgo), percentage of correct go-trials (Accuracygo) and response time benefit (RTbenefit) (see Table 2). No effects of age or IQ were found, and accordingly, we left those out of the final model. As SDRTexpectedgo and Accuracygo were not normally distributed, we confirmed these results using a Kruskal-Wallis test (SDRTexpectedgo: $H(2) = 13.23$, $p = 0.001$; Accuracygo: $H(2) = 8.73$, $p = 0.13$). Post-hoc testing showed that compared to typically developing children, both clinical groups had longer response times (high MRTexpectedgo); higher variability of response times (SDRTexpectedgo) and lower go-trial accuracy (Accuracygo). Furthermore, children with combined ASD and ADHD symptoms benefitted less on predictable trials than controls and children with ADHD (lower RTbenefit).

Brain activity

Typically developing children showed a main effect of temporal expectancy in all ROIs except cerebellar vermis and right inferior frontal gyrus, (for details of main effects see Online Resource 1, supplementary Table S1a and S1b). A main effect of stimulus type was found in bilateral supramarginal gyrus, bilateral anterior cingulate, bilateral vermis and right pallidum. We found between-group differences in brain activation related to temporal expectancy in left STN ($F(2,73) = 5.72$, $p = 0.005$) and left pallidum ($F(2,73) = 5.36$, $p = 0.007$) (see Figure 1, for activation in all ROI's see Online Resource 1, supplementary Table S2a and S2b). We found no effects of age or IQ and accordingly they were left out of the final model. Post-hoc analyses showed that in left STN, both clinical groups (ADHD: $M = -0.23$, $SD = 0.81$; ASD: $M = 0.06$, $SD = 0.76$) had less activation than typically developing children ($M = 0.49$, $SD = 0.69$). Notably, in

left pallidum, we found a dissociation between the clinical groups, with children with ADHD showing less activation (M = 0.04, SD = 0.72) than both typically developing children (M = 0.65, SD = 0.81) and children with ASD and ADHD symptoms (M = 0.56, SD = 0.59). We found no associations between any of the questionnaire measures and any of the brain activity measures. In a follow-up analysis we found that task performance (i.e. RTbenefit) significantly covaried with activity in left pallidum and left putamen (see Online Resource 1, supplementary Table S3). We found that with RTbenefit as covariate in the model, between-group differences in left STN and left pallidum retained significance and an additional between-group difference was found in left putamen (F(2,73) = 5.67, p = 0.005).

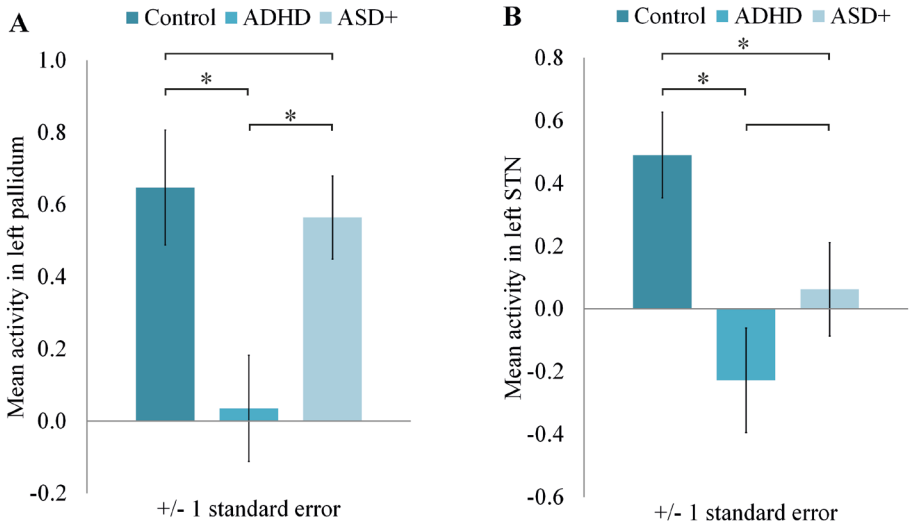
Table 2. Task performance measures per group

	Control (SD)	ADHD (SD)	ASD (SD)	F-value	p-value
MRTexpgo	433.0 (38.0)	471.3 (48.1)	470.0 (55.1)	(2,73) 5.37	0.007*
SDRTexpgo	96.9 (23.0)	128.6 (44.3)	122.9 (47.7)	(2,73) 4.61	0.013*
Goaccuracy	94.4 (6.5)	86.2 (11.3)	89.1 (9.6)	(2,73) 5.04	0.009*
Nogoaccuracy	48.8 (15.1)	52.7 (16.4)	45.7 (18.1)	(2,73) 1.13	0.329
RTbenefit	0.84 (0.36)	0.77 (0.40)	0.51 (0.31)	(2,73) 5.94	0.004*

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SD, standard deviation; MRTexpgo, mean response time on go trials with expected timing; SDRTexpgo standard deviation of response times on go trials with expected timing; Goaccuracy, percentage of correct go trials; Nogoaccuracy, percentage of correct nogo trials; RTbenefit, response time benefit.

* Significant group difference.

Figure 1. Timing-related brain activity in left pallidum and left subthalamic nucleus



STN, Subthalamic Nucleus; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD+, Autism Spectrum Disorder and symptoms of ADHD.

Note. Timing-related brain activity per group is shown for two regions of interest: left pallidum (panel a) and left subthalamic nucleus (panel b). For both regions of interest, ANOVA results were significant after FDR correction for multiple comparisons.

* Significant post-hoc group difference

Discussion

We used task-based fMRI to investigate how children with symptoms of ADHD predict what events will occur (cognitive control) and when events will occur (timing). We found two brain regions in children with ADHD that showed hypo-activity related to the timing of events. Children with ADHD and children with ASD and ADHD symptoms both showed timing-related hypo-activity in the left subthalamic nucleus. However timing-related hypo-activity in left pallidum was only found in children with a primary diagnosis of ADHD. In their task performance, children with ASD and ADHD symptoms had reduced benefit in terms of response time on trials with predictable timing, compared to typically developing children and children with ADHD. We found no between-group differences in brain activity or task performance related to predicting what events will occur.

Nigg and Casey hypothesized that children with ADHD may show a context-dependent deficit in generating or monitoring predictions (Nigg & Casey, 2005). Indeed, we found that children with ADHD showed reduced brain activity related to the temporal predictability of events. This timing-related hypo-activity was found in left subthalamic nucleus and left pallidum, in line with studies that have proposed a role for the basal ganglia in timing deficits in ADHD (Noreika et al., 2013; Toplak et al., 2006; Valera et al., 2010), but contradicting meta-analytical findings (Hart et al., 2012). However, Hart and colleagues (2012) noted that a further differentiation of results in separate timing domains could prove pivotal to find specific temporal processing deficits in ADHD. Remarkably, both subthalamic nucleus and pallidum have a prominent role in the striatal beat frequency theory of interval timing in which these structures act as a coincidence detector, signaling patterns of oscillatory activity matching a previously learned time-interval (Allman & Meck, 2012; Buhusi & Meck, 2005). As such, the subthalamic nucleus and pallidum are considered key areas in the temporal monitoring of predictive models. Our finding of timing-related striatal hypo-activity links the striatal beat frequency theory (Buhusi & Meck, 2005) with theories on dopamine signaling in ADHD (e.g. Tripp & Wickens, 2008), as in both theories reduced striatal dopamine signaling leads to reduced anticipatory brain activity.

We hypothesized that any deficits found would not be specific to children with ADHD, but would be apparent in both groups of children with ADHD symptoms. Indeed, we found subthalamic hypo-activity in children with ASD and ADHD symptoms and in children with ADHD. However, hypo-activity in left putamen was only found in children with a primary diagnosis of ADHD. We did not expect to find such a clear

categorical difference in brain activity between two groups with similar levels of ADHD symptoms. Notably, this finding is in line with reasoning that was made explicit in DSM-IV, where it states that, although symptoms of inattention, hyperactivity and impulsivity may appear alike in children with ADHD and children with ASD, they stem from different neuropsychological problems and should thus be approached differentially. In addition, similar hypo-activity in subthalamic nucleus in children with ADHD and in children with ASD and ADHD symptoms could not be explained in a trans-diagnostic way (i.e. by ADHD symptoms alone) and was not reflected in task performance. This suggests that the mechanisms underlying subthalamic hypo-activity might differ between children with ASD and children with ADHD. Deficient temporal processing in ASD has been found in several studies (e.g. McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; Szelag, Kowalska, Galkowski, & Pöppel, 2004) and has been related to atypical sensory processing (Brock, Brown, Boucher, & Rippon, 2002; Stevenson et al., 2015). Reduced benefit on response times to predictable trials could be related to enhanced sensory processing of less relevant stimuli (Marco, Hinkley, Hill, & Nagarajan, 2011). This way, in children with ASD, cues with expected and unexpected timing may be judged equally relevant and processed equally fast.

We did not find differences in task performance or brain activity related to the 'what' component of expectancy in children with ADHD symptoms (i.e., cognitive control). This is unexpected, as several meta-analyses have reported hypo-activity during response inhibition tasks in children with ADHD (Cortese et al., 2012; Hart et al., 2013; McCarthy et al., 2014). Our task had a relatively low even rate (four second inter-trial interval), and as such it is possible that it overtaxed attentional control, especially in this age-range. This explanation is supported by lower go-accuracy (86%) and slower response times (471ms) for children with ADHD than for typically developing children (respectively: 94%, 433ms). Both metrics have been linked to attentional lapses (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Weissman, Roberts, Visscher, & Woldorff, 2006) and could explain why we did not find differences in cognitive control.

Ultimately, the neurobiological changes found in children with ADHD symptoms might relate to a failure to build or monitor predictive models of the environment, which in turn hinders their efficient interaction with it. Problems with the predicting environmental events have high face validity for children with ADHD symptoms, as they would be expected to lead to behavior that is inappropriate only given a certain context, similar to what is seen in the disorder.

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Ethical standards

The study and its procedures were approved by the institutional review board of the UMCU. After study procedures had been explained, all parents and adolescents (aged 12) gave full written consent, while children provided verbal assent. All procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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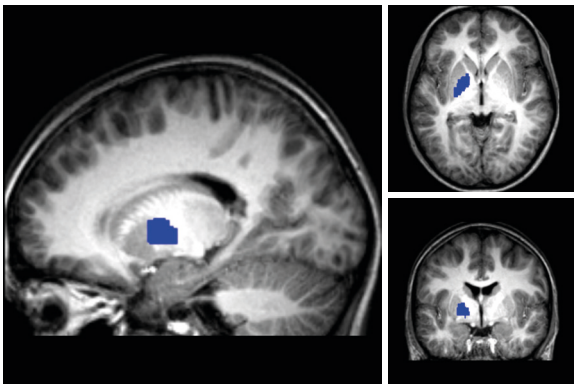
Supplementary information

Supplementary Text S1. Screening of data quality

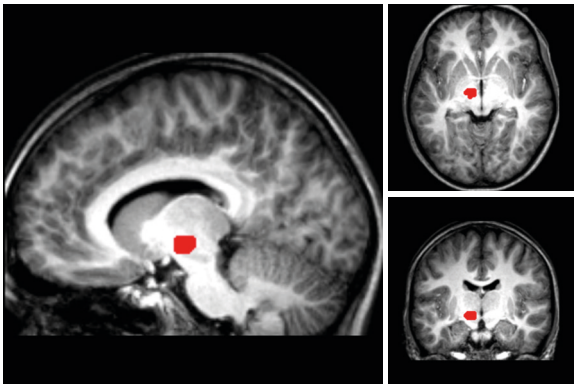
All T1-weighted scans were assessed by an expert radiologist. Following this step, three participants were excluded on the basis of anatomical abnormalities (in all cases an arachnoid cyst). Scan-to-scan movement was assessed using ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009). Scans with more than 1.0 mm scan-to-scan movement and scans with a more than 1.5% deviation from the average global signal, were replaced using a linear interpolation of the values of neighboring scans. Recordings from task levels with more than 30% corrected scans were excluded from further analyses. Subsequently, participants with less than three levels of sufficient data quality were excluded. 29 Participants (4 typically developing children, 14 children with ADHD and 11 children with ASD) were excluded on the basis of this criterion.

Supplementary Figure S1. Region of interest map for the left pallidum



Note. Supplementary Figure 1 shows three views (sagittal, axial and coronal) of the atlas-based left pallidum map that was used for the region of interest analyses. The sections were placed at MNI-coordinates (x, y, z respectively): -17 -4 -3.

Supplementary Figure S1. Region of interest map for the left subthalamic nucleus



Note. Supplementary Figure 2 shows three views (sagittal, axial and coronal) of the atlas-based left subthalamic nucleus map that was used for the region of interest analyses. The sections were placed at MNI-coordinates (x, y, z respectively): -10 -15 -7.

Supplementary Table S1a. Main effect of expectancy

ROI	Control (SD)	F-value (1,25)	p-value
l-smg	0.92 (1.04)	20.19	<0.001*
r-smg	0.69 (1.51)	5.30	0.030*
l-ifg	1.00 (1.46)	12.26	0.002*
r-ifg	0.64 (1.85)	3.13	0.089
l-pal	0.65 (0.81)	16.50	<0.001*
r-pal	0.60 (0.88)	12.16	0.002*
l-acg	0.71 (0.86)	17.88	<0.001*
r-acg	0.85 (1.17)	13.87	0.001*
l-stn	0.49 (0.69)	12.93	0.001*
r-stn	0.49 (0.97)	6.73	0.016*
b-ver	0.52 (1.32)	3.97	0.057
l-put	1.04 (1.07)	24.66	<0.001*
r-put	1.06 (1.18)	20.95	<0.001*

ROI, region of interest; SD, standard deviation; l, left; r, right; smg, supramarginal gyrus; ifg, inferior frontal gyrus; pal, pallidum; acg, anterior cingulate gyrus; stn,

subthalamic nucleus; ver, vermis; put, putamen.

* Significant group difference.

Supplementary Table S1b. Main effect of inhibition

ROI	Control (SD)	F-value (1,25)	p-value
l-smg	-0.74 (0.78)	23.24	<0.001*
r-smg	-0.91 (0.92)	24.10	<0.001*
l-ifg	0.06 (1.06)	0.08	0.783
r-ifg	-0.39 (0.98)	4.02	0.056
l-pal	-0.06 (0.52)	0.30	0.588
r-pal	-0.20 (0.33)	9.47	0.005*
l-acg	-0.55 (0.61)	20.67	<0.001*
r-acg	-0.65 (0.76)	18.94	<0.001*
l-stn	0.02 (0.48)	12.93	0.001*
r-stn	-0.17 (0.47)	3.50	0.073
b-ver	0.48 (0.91)	7.24	0.013*
l-put	-0.12 (0.73)	0.05	0.822
r-put	-0.23 (0.66)	3.17	0.087

ROI, region of interest; SD, standard deviation; l, left; r, right; smg, supramarginal gyrus; ifg, inferior frontal gyrus; pal, pallidum; acg, anterior cingulate gyrus; stn, subthalamic nucleus; ver, vermis; put, putamen.

* Significant group difference.

Supplementary Table S2a. Timing related activity per region of interest

ROI	Control (SD)	ADHD (SD)	ASD (SD)	F-value (2,73)	p-value
l-smg	0.92 (1.04)	0.41 (1.27)	0.35 (1.54)	1.49	0.232
r-smg	0.69 (1.51)	0.29 (1.41)	0.23 (1.43)	0.74	0.481
l-ifg	1.00 (1.46)	0.06 (1.71)	0.48 (1.11)	2.68	0.075
r-ifg	0.64 (1.85)	-0.03 (1.47)	0.35 (1.39)	1.11	0.337
l-pal	0.65 (0.81)	0.04 (0.72)	0.56 (0.59)	5.36	0.007*
r-pal	0.60 (0.88)	0.08 (0.80)	0.34 (0.64)	2.82	0.066
l-acg	0.71 (0.86)	0.25 (0.78)	0.33 (0.74)	2.51	0.089
r-acg	0.85 (1.17)	0.18 (0.94)	0.36 (1.00)	2.85	0.064
l-stn	0.49 (0.69)	-0.23 (0.81)	0.06 (0.76)	5.72	0.005*
r-stn	0.49 (0.97)	-0.05 (0.88)	0.14 (0.69)	2.62	0.080
b-ver	0.52 (1.32)	0.60 (0.90)	0.08 (1.27)	1.38	0.259
l-put	1.04 (1.07)	0.33 (0.89)	0.97 (0.77)	5.54	0.014
r-put	1.06 (1.18)	0.36 (0.96)	0.73 (1.04)	2.69	0.080

ROI, region of interest; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SD, standard deviation; l, left; r, right; smg, supramarginal gyrus; ifg, inferior frontal gyrus; pal, pallidum; acg, anterior cingulate gyrus; stn, subthalamic nucleus; ver, vermis; put, putamen.

* Significant group difference.

Supplementary Table S2b. Inhibition related activity per region of interest

ROI	Control (SD)	ADHD (SD)	ASD (SD)	F-value (2,73)	p-value
l-smg	-0.74 (0.78)	-0.07 (1.14)	-0.33 (0.99)	3.03	0.054
r-smg	-0.91 (0.92)	-0.39 (1.32)	-0.59 (1.26)	1.18	0.313
l-ifg	0.06 (1.06)	0.27 (2.21)	-0.15 (1.33)	0.44	0.649
r-ifg	-0.39 (0.98)	-0.17 (1.68)	-0.55 (1.17)	0.55	0.580
l-pal	-0.06 (0.52)	0.12 (0.83)	0.12 (0.50)	0.67	0.516
r-pal	-0.20 (0.33)	0.12 (0.61)	-0.07 (0.56)	2.38	0.099
l-acg	-0.55 (0.61)	-0.16 (0.96)	-0.20 (0.64)	2.13	0.126
r-acg	-0.65 (0.76)	-0.23 (1.05)	-0.30 (0.82)	1.66	0.197
l-stn	0.02 (0.48)	0.05 (0.82)	-0.17 (0.44)	1.01	0.369
r-stn	-0.17 (0.47)	-0.06 (0.73)	-0.15 (0.77)	0.21	0.809
b-ver	0.48 (0.91)	0.56 (1.64)	0.55 (1.27)	0.03	0.971
l-put	-0.12 (0.73)	0.02 (1.11)	0.18 (0.71)	0.74	0.480
r-put	-0.23 (0.66)	-0.00 (1.00)	-0.08 (0.67)	0.56	0.576

ROI, region of interest; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SD, standard deviation; l, left; r, right; smg, supramarginal gyrus; ifg, inferior frontal gyrus; pal, pallidum; acg, anterior cingulate gyrus; stn, subthalamic nucleus; ver, vermis; put, putamen.

Supplementary Table S3. Activation differences with performance covariates

ROI	Factor	B	F-value	p-value
l-pal	RTbenefit	0.80	13.64	<0.001*
	Group		8.03	0.001*
l-put	RTbenefit	0.68	5.35	0.024*
	Group		5.67	0.005*
l-stn	RTbenefit	0.06	0.06	0.810
	Group		5.47	0.006*

ROI, region of interest; l, left; r, right; pal, pallidum; put, putamen; stn, subthalamic nucleus; RTbenefit, response time benefit.

* Significant group difference.

4

Reward anticipation in ventral striatum and individual sensitivity to reward: A pilot study of a child-friendly fMRI task

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Abstract

Reward processing has been implicated in developmental disorders. However, the classic task to probe reward anticipation, the monetary incentive delay task, has an abstract coding of reward and no storyline and may therefore be less appropriate for use with developmental populations. We modified the task to create a version appropriate for use with children. We investigated whether this child-friendly version could elicit ventral striatal activation during reward anticipation in typically developing children and young adolescents (aged 9.5-14.5). In addition, we tested whether our performance-based measure of reward sensitivity was associated with anticipatory activity in ventral striatum. Reward anticipation was related to activity in bilateral ventral striatum. Moreover, we found an association between individual reward sensitivity and activity in ventral striatum. We conclude that this task assesses ventral striatal activity in a child-friendly paradigm. The combination with a performance-based measure of reward sensitivity potentially makes the task a powerful tool for developmental imaging studies of reward processing.

Introduction

Reward processing, and reward anticipation in particular, have been implicated in child and adolescent disorders such as attention-deficit/hyperactivity disorder (ADHD) (Plichta & Scheres, 2014), oppositional defiant disorder (ODD) (Matthys, Vanderschuren, & Schutter, 2013) and depression (Stringaris et al., 2015). Functional magnetic resonance imaging (fMRI) studies have addressed reward anticipation using the monetary incentive delay (MID) paradigm (Knutson, Adams, Fong, & Hommer, 2001). In this paradigm, a cue is presented at the beginning of each trial, signaling the amount of monetary reward that can be won (or lost) on the upcoming trial. By contrasting trials with different monetary cues, brain activation related to reward anticipation can be assessed (Knutson et al., 2001). In adults, the MID paradigm has been shown to reliably activate ventral striatum in anticipation of reward (e.g. Knutson, Fong, Bennett, Adams, & Hommer, 2003a; Plichta et al., 2012). Yet the symbols used in the task are highly abstract and there is no storyline. Accordingly, it has not often been used successfully with younger children and in particular those with developmental disorders.

We designed a child-friendly version of the task to be compatible with an fMRI environment (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012). We focused on making the task more engaging, as sustained attention is not yet fully developed at school age, and can be particularly challenging for children with developmental disorders. Furthermore, we used response times to develop a measure of performance that captures individual reward sensitivity, but does so in a manner that is independent of intra-individual variability in response times. This is important as intra-individual variability in response times is often increased in developmental disorders and can confound statistical inferences (De Zeeuw et al., 2012; van Hulst, de Zeeuw, & Durston, 2015). The inclusion of a performance measure of reward sensitivity is essential to the interpretation of changes in activity of ventral striatum and can aid the generalization of results to a real life construct of reward sensitivity. Other studies that successfully modified the MID task to be more suitable for use with children have reported on task performance, but have not considered the relationship between task performance and brain activation in the interpretation of their results (Helfinstein et al., 2012; Kappel et al., 2013).

In the MID task, faster reaction times signify better performance, as participants are instructed to press a button as fast as possible following a cue. Accordingly, the anticipation of greater reward may elicit faster reaction times (Mir et al., 2011). Nevertheless, the effect of performance on brain activation has rarely been studied

in the context of this task. This is likely related to the typical implementation of a staircase procedure in this task, designed to keep accuracy constant at a predetermined level (usually 60-70%) for all participants. Task performance then appears equal across participants. However, within individual participants, task performance (as expressed by mean reaction times, accuracy scores or both) may still differ across incentive conditions. Such a difference across incentive conditions may vary between participants and could therefore be operationalized as a behavioral measure of individual reward sensitivity. Following this rationale, we devised our measure of individual reward sensitivity by comparing rank-ordered reaction times across incentive conditions (De Zeeuw et al., 2012). In previous studies, we have used our child-friendly version of the MID-task to show that participants with ADHD had lower behavioral sensitivity to reward compared to typically developing controls (De Zeeuw et al., 2012; van Hulst et al., 2015).

In this pilot-study, we set out to validate our child-friendly, modified MID task for use as a developmental fMRI paradigm. First, we tested whether it could elicit ventral striatal activation during the anticipation of reward in typically developing children and young adolescents. Second, we hypothesized that our individual measure of reward sensitivity should be associated with activity in ventral striatum. If so, future studies could use such a performance measure in the interpretation of their neuroimaging results.

Methods

Participants

A total of 18 right-handed children and young adolescents were recruited through schools in the wider Utrecht area. After screening for data quality (for details see supplementary Text S1) two participants were excluded from further analyses due to anatomical abnormalities and three participants were excluded due to excessive motion during acquisition of the fMRI data. Data from six male and seven female participants, with an average age of 12.2 years (range: 9.5-14.5) and average IQ of 116, were available for fMRI analyses (see Table 1). The parents of participants reported no psychiatric diagnoses on the DISC-IV interview (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). After the study procedures had been explained, all parents and adolescents (aged 12 and older) gave full written consent, while children provided verbal assent. The study and its procedures were approved by the medical ethical review board of the University Medical Center Utrecht (approval number: 08-081).

Table 1. Characteristics of the 13 subjects included in the fMRI analyses.

	Mean (SD)
Age	12.2 (1.62)
Gender (m/f)	6/7
IQ	116 (11.8)
MRT 0ct	424ms (63.2)
MRT 5ct	408ms (57.8)
MRT 15ct	405ms (63.7)
B0vs15ct	0.89 (0.31)

SD, standard deviation; m, male; f, female; MRT, mean reaction time, ms, milliseconds; ct, cents; B0vs15ct, shift in reaction time distribution between high reward and no reward trials.

Monetary incentive delay paradigm

We used a modified version of the monetary incentive delay task (De Zeeuw et al., 2012) in a rapid event-related fMRI design. The task was made more engaging for use in children by adding a two-choice response selection aspect to the task. Trial sequence was as follows: first, the cue, a picture of a wallet with 0, 5 or 15 cents was shown (2000 ms), indicating the amount of money that could be won on the upcoming trial. Next, pictures of two popular cartoon figures (SpongeBob and Patrick Star from the SpongeBob TV-series) were shown (750 ms) and participants were to guess which cartoon figure was hiding the wallet by pressing either the left or the right response button. They were instructed to respond as fast as possible. Subsequently, a black screen was shown (500 ms) and finally, a thumbs-up or a thumbs-down picture, indicating a correct or incorrect choice, was shown (750 ms) along with the total amount of money won so far. The task was rigged in such a way that outcome of each trial was fixed; the choices made did not affect reward outcome. If participants did not respond within a 1250 milliseconds timeframe after the appearance of SpongeBob and Patrick Star, the feedback text "too late!" was presented. The task consisted of 240 four-second trials (80 trials per cue) divided evenly into four blocks and consequently took four minutes per block to complete. Each block had a fixed reward frequency of either 20% (low reward) or 80% (high reward). Participants were randomly presented with one out of two counterbalanced reward sequences ('high-low-high-low' or 'low-high-low-high'), so that average reward frequency totaled 50% for the full task. For a schematic overview of task design see S2S1 Fig.

Performance measures

The primary neuropsychological outcome measure was the shift in reaction time distribution between rewarded and unrewarded trials. This was quantified using linear regression of the rank ordered reaction times to high rewarded trials (15 cents) on the rank ordered reaction times to unrewarded trials (0 cents), as described previously (De Zeeuw et al., 2012). We chose this measure as it is minimally influenced by differences in reaction-time variability, which is an important consideration in studying developmental disorders such as ADHD, where intra-individual variability in reaction times is greater than in typical development (Klein, Wendling, Huettner, Ruder, & Peper, 2006). A regression coefficient smaller than one indicates faster responses time on rewarded then on unrewarded trials.

fMRI acquisition

The study was run on a 3.0 T Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) using an eight-channel sensitivity-encoding (SENSE) parallel imaging head coil. For anatomical reference, a whole-brain three-dimensional fast field echo T1-weighted scan (200 slices; repetition time = 10 ms; echo time = 4.6 ms; flip angle = 8°; field of view, 240 x 240 x 160 mm; voxel size: 0.75 x 0.8 x 0.75 mm isotropic) was acquired. Whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast (4 sessions; 126 volumes per session; 33 slices per volume; interleaved acquisition; TR = 2.00 s; TE = 35 ms; field of view = 240 × 240 × 116 mm; flip angle = 70°; voxel size = 3.0 × 3.0 × 3.5mm) oriented in a transverse plane were acquired. We acquired six dummy scans to allow for T1 equilibration effects.

Preprocessing of fMRI data

FMRI data were analyzed using SPM8 (r4290) (http://www.fil.ion.ucl.ac.uk/ spm/ software/spm8) as implemented in Matlab 7.12 (Mathworks Inc., Natick, MA, USA). To correct for between-scan head motion, all images were realigned to the first volume using rigid body transformations, and subsequently resliced. Next, the data were temporally interpolated to the middle slice to adjust for time differences due to multislice image acquisition (i.e., slice time correction). The anatomical image was co-registered to the first fMRI image using the mutual information criteria method and subsequently normalized to Montreal Neurological Institute (MNI) space using unified segmentation, finally the image was resliced at a voxel size of 1.0 x 1.0 x 1.0mm. Functional images were normalized using the normalization parameters generated in this step, the images were resliced at a voxel size of 3.0 x 3.0 x 3.0mm. Finally, the fMRI images were spatially smoothed with a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm. In addition, scan-to-scan movement was assessed using

ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009). Scans with more than 0.5 mm scan-to-scan movement or more than 1.5% deviation from the average global signal, were replaced using a linear interpolation of the values of neighboring scans. Participants with more than 15% corrected scans were excluded from further analyses (for details, see S1 Text).

Statistical analyses - performance

After testing for normality (Shapiro-Wilk test) and sphericity (Mauchly's test), a repeated measures analysis of variance (ANOVA) was conducted to test for the effect of incentive magnitude on mean reaction time. Next, we tested for an effect of age on the shift in reaction time distribution using single-factor ANCOVA.

Statistical analyses - fMRI

Statistical analyses were performed within the framework of the general linear model following a two-level procedure (Friston et al., 1995). First level analysis involved the modeling of blood oxygenation level dependent (BOLD) activation invoked by 0, 5 and 15 cents cues as conditions of interest, and realignment parameters as potential confounders (condition of no interest) for each subject. Regressors were created by convolving delta functions coding for cue onset with a canonical hemodynamic response function (as implemented in SPM8) for each cueing category separately. The estimated regression coefficients for the 0, 5 and 15 cents condition were then contrasted resulting in three first-level contrast images for each subject: 0 versus 5, 0 versus 15 and 5 versus 15 cents. Data were high-pass filtered using discrete cosine basis functions with a 128 second cut-off. At the group level we conducted two analyses. First, we tested for brain activation related to the anticipation of reward by conducting one-sample t-tests on the contrast images of the three different contrasts separately. We corrected for multiple comparisons using a family wise error (FWE) correction on a predefined volume of interest (VOI) (i.e., small volume correction). This VOI was generated by combining the bilateral nucleus accumbens masks provided by the WFU PickAtlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) and dilating the resulting mask by one voxel in all dimensions (size of VOI: 151 voxels, 4077 mm3). Next, we tested for associations between reward-related brain activation and both task performance and age. We conducted six separate single-factor ANCOVAs, using the three first-level contrasts as dependent variables and the measure of task performance (the regression coefficient of rank ordered reaction times for the greatest contrast, 0 versus 15 cents; B0vs15ct), and age as separate continuous predictors (i.e., covariate of interest). Again we applied FWE correction for multiple comparisons restricted to the bilateral ventral striatum. When anticipatory

ventral striatal activity was found, we additionally tested for an effect of reward frequency on brain activation by contrasting activity in blocks with high (80%) and low (20%) reward frequency (for the contrast in question). This was done using a one-sample t-test on a newly created contrast image, again we corrected for multiple comparisons using FWE in the same VOI.

Results

Task tolerability

18 Subjects participated in an fMRI session and performed the task without problem. Data for five subjects had to be excluded from the analyses due to anatomical abnormalities on the T1-weighted scan or motion during fMRI-scanning. They did not differ in terms of age, gender or IQ from the 13 subjects for whom fMRI data were available for analysis.

Behavioral data

There was an effect of reward magnitude on mean reaction times ($F(2,24)=4.41, p=0.023$). Average reaction times were 424 ms, 408 ms and 405 ms across respectively no reward, low reward and high reward conditions. The mean B0vs15ct (the shift in reaction time distribution between high reward and no reward) was 0.89 (SD 0.31), indicating faster responses on high reward then on no reward trials. There was no effect of age on the shift in reaction time distribution.

fMRI data

The first analysis aimed to test whether the MID task would elicit ventral striatal activation during reward anticipation. We contrasted the anticipation of 0 versus 5 cents, 5 versus 15 cents, and 0 versus 15 cents, separately. We found reward-related activation in the bilateral ventral striatum for the 0 versus 5 cents contrast (see Table 2), but not for the two other contrasts (5 versus 15 cents and 0 versus 15 cents). Next, we tested for a relationship between task performance and reward-related activity in ventral striatum by conducting a single-factor ANCOVA with the shift in reaction time distribution between high reward and no reward trials (B0vs15ct) as a continuous predictor. We found an association in bilateral ventral striatum for both the 5 versus 15 and the 0 versus 15 cents contrast (see Fig. 1), but not for the 0 versus 5 cents contrast. We found no effect of reward frequency or age on anticipatory activity in ventral striatum.

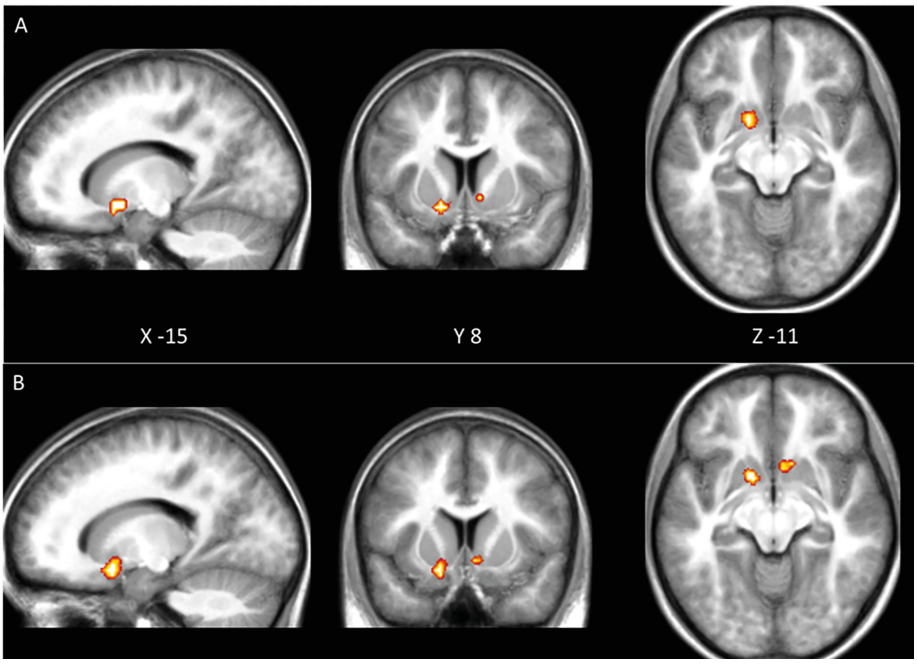
Table 2. Activity in ventral striatum during the anticipation of reward.

	L/R	P-value cluster	Cluster size	P-value peak	T-value peak	MNI-coordinates
0ct vs 5ct	L	0.016	7	0.041	4.29	-18, 5, -11
0ct vs 5ct	R	0.021	5	0.024	4.69	15, 14, -8
5ct vs 15ct	L	0.008	14	0.025	4.76	-15, 5, -8
5ct vs 15ct	R	0.034	2	0.019	5.01	9, 5, -5
0ct vs 15ct	L	0.003	25	0.019	4.90	-15, 5, -8
0ct vs 15ct	R	0.017	7	0.006	5.91	6, 11, -8

L, left; R, right; MNI, Montreal Neurological Institute; ct, cents.

All reported p-values were FWE corrected for multiple comparisons.

Figure 1. Ventral striatal activity is related to task performance.



There was a positive correlation between activation in ventral striatum and the shift in reaction time distribution (B0vs15ct) (FWE corrected for multiple comparisons). Both panels display the T-map of a single-factor ANCOVA with B0vs15ct as continuous predictor variable. Panel A shows the effect of task performance on the activation difference between low and high reward conditions. Panel B shows the effect of task performance on the activation difference between no reward and high reward conditions.

Discussion

We set out to validate our child-friendly, modified MID paradigm as a task appropriate for use in developmental fMRI studies. The task successfully elicited activity in ventral striatum during the anticipation of reward. Furthermore, our task-based measure of reward sensitivity was associated with striatal activity during reward anticipation. The task was well tolerated by all subjects. In all, we conclude that this task has potential as a tool for assessing reward anticipation in developmental populations.

We found that the task was well tolerated by all subjects: children and young adolescents, ranging in age from nine to fourteen years, were able to comprehend and complete the modified MID-task in a scanner environment. In previous studies we have shown that children as young as six years old were able to comprehend and complete the task outside of the scanner (De Zeeuw et al., 2012; van Hulst et al., 2015). The task successfully elicited activity in ventral striatum during the anticipation of reward. Furthermore, we found that a task-based measure of reward sensitivity correlated positively with striatal activation during reward anticipation. This suggests that anticipatory activity in striatum may be interpreted as a neurobiological measure of reward sensitivity in the context of this task. Such a direct interpretation of results is likely to be crucial in linking fMRI findings to real-world reward sensitivity, as assessed by differences in approach behavior. To date, results from studies reporting response-time differences across incentive conditions have been mixed (Helfinstein et al., 2012; Hoogman et al., 2011; Knutson et al., 2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003b; Scheres, Milham, Knutson, & Castellanos, 2007; Vaidya, Knutson, O'Leary, Block, & Magnotta, 2013) and when found, their relationship to brain activation has not previously been explored (Hoogman et al., 2011; Knutson et al., 2003b; Vaidya et al., 2013. A study by Lamm and colleagues did report a relationship between task performance and brain activation in an MID paradigm, yet they only included performance as a nuisance variable (Lamm et al., 2014). In this way the potential value of task performance in the interpretation of fMRI results is left unexploited.

As in previous studies with adults (Knutson et al., 2003a; Plichta et al., 2012), we found ventral striatal activation when contrasting no reward cues to low reward cues. However, we found no differences in activation when contrasting low reward cues to high reward cues. Stoppel and colleagues (Stoppel et al., 2011) have suggested that the effect of contrasting low reward to high reward is smaller than that between no reward and low reward, as the former contrast only probes reward magnitude and not reward itself. In addition, developmental studies using overlapping age-ranges (12-18 years) have reported reduced striatal engagement (Lamm et al., 2014; Vaidya et al.,

2013) and decreased discrimination between reward magnitudes (Lamm et al., 2014) . As such, the difference between the anticipation of low and high reward may have been too subtle to elicit significant differences in brain activity, particularly given our relatively modest sample size. Likewise, the absence of an effect of age on anticipatory ventral striatal activity may be a result of limited power.

Furthermore, we only found an association between reward sensitivity and activity in ventral striatum for the contrast of high versus either low or no reward, but not for the contrast of low versus no reward. This may be related to increased inter-individual variability in striatal activation in high reward conditions, associated with individual differences in overall task performance. This increased variability may explain the lack of activation in the 0 versus 15 cents contrasts. Following this rationale, anticipatory striatal activation is more likely to be linked to a neuropsychological construct of reward sensitivity under high reward, than under low reward conditions.

To conclude, we show that a child-friendly version of the MID-task elicited activity in ventral striatum during the anticipation of reward in children and young adolescents. Furthermore, this striatal activation was related to inter-individual differences in a task-based measure of reward sensitivity. In all, this task assesses ventral striatal activity in a child-friendly manner. The combination with an individual task-based measure of reward sensitivity makes the task a potentially powerful tool for developmental imaging studies of reward processing.

Limitations

First, the sample size of this pilot study was modest. This was in part caused by the exclusion of five datasets due to high subject motion or anatomical abnormalities (for details see supplementary Text S1). As a result, any negative findings in this study should be interpreted with caution. In particular, tests to be expected to have a modest effect size (e.g. the manipulation of reward frequency) would be vulnerable to type II errors. Second, an important distinction between this version of the task and the classical MID is that participants had no control over their results (although they would be expected to have experienced control). This could have affected our results, as a recent study by Lorenz and colleagues (Lorenz et al., 2015) showed that subjective lack of control can attenuate ventral striatal activity. Third, it should be mentioned that the task was set up to have optimal statistical power with as many as 80 trials per condition. However, this led to a total time-on-task of 16 minutes, which may also have taxed sustained attention. Finally, the participants in our sample had above average IQ, necessitating prudence when interpolating findings to participants

with an average IQ.

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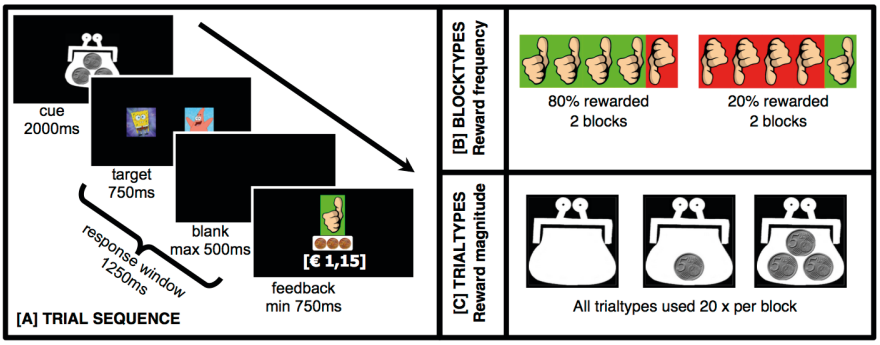
Supplementary information

Supplementary Text S1. Screening of data quality.

All T1-weighted scans were assessed by an expert radiologist. Following this step, two participants were excluded on the basis of anatomical abnormalities (one arachnoid cyst, one enlarged ventricular system). Scan-to-scan movement was assessed using ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009). Scans with more than 0.5 mm scan-to-scan movement and scans with a more than 1.5% deviation from the average global signal, were replaced using a linear interpolation of the values of neighboring scans. Participants with more than 15% corrected scans were excluded from further analyses. One participant was excluded on the basis of this criterion. In addition, global quality was assessed with ArtRepair. Subjects were defined as outliers according to the 1.5 IQR criterion on the basis of their global mean (average contrast estimate across all voxels) and average residual error. Two subjects were excluded based on this criterion.

Supplementary Figure S1. Task design.



A schematic overview of task design is shown. Panel A shows the time course of a single trial. Panel B shows the two different reward frequency blocks. Panel C shows three different reward magnitudes that were used as trial types and contrasted for further analyses. Reprinted with permission from "Deficits in Cognitive Control, Timing and Reward Sensitivity Appear to be Dissociable in ADHD" by De Zeeuw et al, 2012, PLoS One. Jan;7(12):e51416.

5

Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward irrespective of ADHD diagnosis

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Abstract

Changes in reward processing are thought to be involved in the etiology of ADHD, as well as of other developmental disorders. In addition, different forms of therapy for ADHD rely on reward processing. As such, improved understanding of reward processing in ADHD could eventually lead to more effective treatment options. However, differences in reward processing may not be specific to ADHD, but may be a trans-diagnostic feature of disorders that involve ADHD-like symptoms. Methods In this event-related fMRI study, we used a child friendly version of the monetary incentive delay task to assess brain activity during reward anticipation. Data from 76 school-aged children were available for final analyses: 27 typically developing children and 49 children with ADHD symptoms. We found decreased activity in ventral striatum during anticipation of reward in children with ADHD symptoms, both for children with ADHD as their primary diagnosis and in children with autism spectrum disorder and ADHD symptoms. We found that higher parent-rated sensitivity to reward was associated with greater anticipatory activity in ventral striatum for children with ADHD symptoms. In contrast, there was no relationship between the degree of ADHD symptoms and activity in ventral striatum. We provide evidence of combined biological and behavioral differences in reward sensitivity in children with ADHD symptoms, regardless of their primary diagnosis. Ultimately, a dimensional brain-behavior model of reward sensitivity in children with symptoms of ADHD may be useful to refine treatment options dependent on reward processing.

Introduction

Changes in reward processing are suggested to be involved in the etiology of Attention-deficit/hyperactivity disorder (ADHD). Indeed, various forms of therapy for ADHD are dependent on reward processing: behavior therapy and parent training programs often use reinforcement contingencies to promote desired behavior (Fabiano et al., 2009). Psychostimulants, commonly used to treat ADHD, increase dopamine availability in the synapse, thereby affecting reward processing (Frank, Santamaria, O'Reilly, & Willcutt, 2006; Pelham, Milich, & Walker, 1986; Wilkison, Kircher, McMahon, & Sloane, 1995). However, children with ADHD differ in the extent with which they respond to treatment and individual differences in reward processing may relate to differences in treatment response. Furthermore, it is an open question whether differences in reward processing are specific to ADHD or whether they are related to disorders in a more general, trans-diagnostic way. Changes in brain activation related to reward processing have also been reported in autism, schizophrenia and major depressive disorder (G. S. Dichter et al., 2010; Gabriel S Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Juckel et al., 2006; Kohls et al., 2014; Smoski et al., 2009).

On average, children with ADHD show atypical behavioral responses to reward (Luman, Oosterlaan, & Sergeant, 2005). They tend to favor smaller, immediate rewards over larger, delayed ones (e.g. Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). Furthermore, the improvement in task performance following reward is greater for children with ADHD than for typically developing children (Luman et al., 2005; Luman, Tripp, & Scheres, 2010). As a result, some models of ADHD have focused on changes in reward processing: Sagvolden and colleagues suggested that ADHD may be associated with a general hypo-dopaminergic state, where deficits in dopamine signaling lead to a strong preference for immediate reward (Sagvolden, Johansen, Aase, & Russell, 2005). In contrast, Tripp and Wickens suggested that there may be a more specific problem with dopamine signaling in ADHD. They suggest that not the processing of a rewarding event itself is affected, but rather that the transfer of signal from rewarding events to the cues that predict them is attenuated; this would result in atypical reward learning (Tripp & Wickens, 2008, 2009). Both theories make explicit predictions about dopamine activity in anticipation of reward in ADHD. Activity in ventral striatum (VS) as assessed by fMRI can be used as a proxy for such dopamine activity (Knutson & Gibbs, 2007). fMRI studies of reward processing have shown anticipatory hypoactivity of VS in adults and adolescents with ADHD (Plichta & Scheres, 2014). However, to date only limited data on younger participants exists and a first study on children with ADHD (Kappel et al., 2015) found no between-group differences.

In this study, we set out to investigate changes in brain activity during the anticipation of reward in children with ADHD symptoms, irrespective of a primary diagnosis of ADHD. We included typically developing children, children with ADHD and children with similar levels of parent-rated ADHD symptoms but a different primary diagnosis. For this last group, we chose to include children with an autism spectrum disorder (ASD) as this is the next primary diagnosis with the highest prevalence of ADHD symptoms. We hypothesized that (1) Children with ADHD would show hypoactivity in ventral striatum during reward anticipation, similar to adults and adolescents with ADHD. We also investigated other regions in fronto-striatal reward circuitry to assess the topological specificity of this hypoactivity. We further hypothesized that (2) this hypoactivity would not be specific to ADHD, but rather would also be found in children with ASD and ADHD symptoms; (3) ADHD symptoms would drive this effect, where a trans-diagnostic dimensional measure of ADHD symptoms would explain additional variance in addition to any effect of diagnosis; (4) anticipatory activity in VS would be positively associated with reward sensitivity in daily life. The inclusion of two groups of subjects with ADHD symptoms allowed us to address the latter two hypotheses by facilitating dimensional analyses across diagnostic groups. Such analyses have been suggested to be more powerful than categorical ones, as they more closely resemble the dimensional nature of the underlying neurobiology (Robbins, Gillan, Smith, de Wit, & Ersche, 2012).

Methods and Materials

Participants

A total of 108 right-handed boys, aged 8-12 years were included in the study: 33 typically developing boys and 75 boys with ADHD symptoms. The children with ADHD symptoms included 38 boys with a primary diagnosis of ADHD and 37 with a primary diagnosis of autism spectrum disorder (ASD). Typically developing children were recruited through schools in the wider Utrecht area. Children with ADHD symptoms were recruited through the outpatient clinic for developmental disorders of the University Medical Center Utrecht (UMCU) and schools for special education. Only children using no medication or short-acting psychostimulants (e.g. methylphenidate) were included; 71% of children with ADHD and 68% of children with ASD and symptoms of ADHD were using short-acting psychostimulants. All parents were instructed not to administer medication in the 24 hours prior to testing. All children completed a modified monetary incentive delay (MID) paradigm in the context of a functional MRI scan (van Hulst, de Zeeuw, Lupas, et al., 2015). After screening data quality, 27 participants were excluded on the basis of excessive head motion, three participants were excluded due to anatomical abnormalities and two participants had to be excluded as a result of an incorrectly placed field of view (for details see

supplementary text S1). Data from 76 participants were available for final analyses. Notably, these 76 children did not differ from the children that were excluded from the final analyses on their level of ADHD symptoms (independent samples t-test per group: control: t(31) = 0.36, p = 0.724; ADHD: t(33) = 0.30, p = 0.764; ASD: t(34) = 0.43, p = 0.674). Participants were matched at a group level for age and IQ. Demographics are provided in Table 1.

Table 1. Demographics and questionnaire data per clinical group

	Control (SD)	ADHD (SD)	ASD (SD)	F-value	p-value
N (76)	27	24	25		
Age	10.5 (1.0)	11.2 (1.0)	10.8 (1.4)	(2,73) 2.59	0.082
IQ	116.9 (18.3)	108.2 (16.0)	107.4 (19.1)	(2,73) 2.27	0.110
SWAN-hyp	0.42 (0.73)	-1.09 (0.65)	-0.90 (0.70)	(2,70) 34.84	<0.001*
SWAN-att	0.39 (0.62)	-1.34 (0.65)	-1.46 (0.46)	(2,70) 81.27	<0.001*
SPSRQ-C	2.70 (0.39)	3.26 (0.33)	2.97 (0.63)	(2,70) 8.53	<0.001*

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SD, standard deviation; SWAN-hyp, hyperactivity/impulsivity subscale of the Strengths and Weaknesses of ADHD and Normal Behavior Rating Scale; SWAN-att, inattention subscale of the Strengths and Weaknesses of ADHD and Normal Behavior Rating Scale; SPSRQ-C, reward sensitivity subscale of the Sensitivity to Punishment and Sensitivity to Reward Questionnaire for Children.

* Significant group difference.

In- and exclusion criteria

The Diagnostic Interview Schedule for Children (DISC-IV, parent version) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was administrated to parents of all participants. In addition, children participated in a four-subtest short-form of the WISC-III in order to estimate full-scale IQ. If intelligence testing using WISC-III had been performed in the past two years, it was not repeated and that score was used. Inclusion criteria for typically developing children were: no psychiatric diagnoses on the DISC-IV interview (except for specific phobia and enuresis) and no scores in the clinical range on any scale of the Child Behavior Checklist (CBCL), as reported by (one of) the parents. Inclusion criteria for children with ADHD symptoms included either a clinical DSM-IV diagnosis of ADHD, established by an expert clinician as part of routine clinical care and supported by the Diagnostic Interview Schedule for Children (DISC); or a DSM-IV autism spectrum diagnosis established by an expert clinician as

part of routine clinical care and a score in the (sub)clinical range of the CBCL subscale of Attention Problems. For all participants, major illness, present or past neurological illness, IQ lower than 70 and the presence of interfering metal objects in or around the body were grounds for exclusion. After study procedures had been explained, all parents and adolescents (aged 12) gave full written consent, while children provided verbal assent. The study and its procedures were approved by the institutional review board of the University Medical Center Utrecht.

Questionnaires

Apart from the CBCL, parents completed two questionnaires: The Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) questionnaire (Lakes, Swanson, & Riggs, 2012). We chose this questionnaire as it assesses symptoms listed in the DSM-IV definition of ADHD across the complete spectrum of functioning (both behavior below and behavior above that of typically developing peers). Also, parents completed the Sensitivity to Punishment and Sensitivity to Reward Questionnaire for children (SPSRQ-c) (Luman, van Meel, Oosterlaan, & Geurts, 2012), a questionnaire designed to assess sensitivity to reinforcement in children.

Monetary incentive delay paradigm

We used a child friendly version of the monetary incentive delay task (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; van Hulst, de Zeeuw, Lupas, et al., 2015) to assess brain activity during reward anticipation. Children were instructed that they could win real money during the task and were paid afterwards using gift certificates. The trial sequence was as follows: first, a picture of a wallet with 0, 5 or 15 cents was shown (2000 ms), indicating the amount of money that could be won on the upcoming trial. Next, pictures of two cartoon figures (SpongeBob and Patrick Star from the SpongeBob TV-series) were shown (750 ms) and participants were asked to guess which cartoon figure was hiding the wallet by pressing the left or right response button as fast as possible. Then, a black screen was shown (500 ms) and finally, a thumbs-up or a thumbs-down picture, indicating a correct or incorrect choice, was shown (750 ms) along with the total amount of money won so far. However, the task was rigged in such a way that trial outcome was fixed; the choices made did not affect reward outcome. 240 Trials (80 trials per cue type) were divided evenly into four blocks. Each block had a fixed reward frequency of either 20% (low reward) or 80% (high reward). Participants were randomly presented with one out of two counterbalanced reward sequences ('high-low-high-low' or 'low-high-low-high'), so that average reward frequency was 50% for the full task. The task design is described in detail elsewhere (De Zeeuw et al., 2012). The primary neuropsychological outcome

measure was the speeding-up of response times in reaction to the anticipation of reward (cue of filled wallet); as compared to response times when no monetary reward was anticipated (cue with empty wallet). This was quantified using linear regression of the rank ordered response times to high rewarded trials (15 cents) on the rank ordered response times to unrewarded trials (0 cents), as described previously (De Zeeuw et al., 2012). We chose this measure as it is minimally influenced by differences in response-time variability, as intra-individual variability in response times is greater in ADHD than in typical development (Klein, Wendling, Huettner, Ruder, & Peper, 2006). A regression coefficient smaller than one indicates faster responses on rewarded than on unrewarded trials.

fMRI acquisition

The study was run on a 3.0 T Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) using an eight-channel sensitivity-encoding (SENSE) parallel imaging head coil. For anatomical reference, a whole-brain three-dimensional fast field echo T1-weighted scan (200 slices; repetition time = 10 ms; echo time = 4.6 ms; flip angle = 8°; field of view, 240 x 240 x 160 mm; voxel size: 0.75 x 0.8 x 0.75 mm isotropic) was acquired. Whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast (4 sessions; 122 volumes per session; 36 slices per volume; interleaved acquisition; TR = 2.02 s; TE = 35 ms; field of view = 232 × 123 × 256 mm; flip angle = 70°; voxel size = 2.67 × 2.67 × 3.43mm) oriented in a transverse plane were acquired. Six dummy scans were acquired to allow for T1 equilibration effects.

Preprocessing of fMRI data

FMRI data were analyzed using SPM8 (r4290) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) as implemented in Matlab 7.12 (Mathworks Inc., Natick, MA, USA). To correct for between-scan head motion, all images were realigned to the first volume using rigid body transformations. Next, the anatomical image was co-registered to the first fMRI image using the mutual information criteria method and subsequently normalized to Montreal Neurological Institute (MNI) space using unified segmentation. The image was then resliced at a voxel size of 1.0 x 1.0 x 1.0mm. Functional images were normalized using the normalization parameters generated in this step, the images were resliced at a voxel size of 3.0 x 3.0 x 3.0mm. Finally, the fMRI images were spatially smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm. In addition, scan-to-scan movement was assessed using ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009). Scans with more than 1.0 mm scan-to-scan movement or where the average signal deviated more than 1.5% from the average global signal over scans, were replaced using a linear interpolation of

the values of neighboring scans (i.e. the scan before and after the discarded scan). Participants with more than 30% replaced scans were excluded from further analyses (for details, see supplementary text S1).

Statistical analyses - task performance

We tested for an effect of ADHD symptoms (categorically and dimensionally) on three performance measures: baseline (no reward condition) mean response times (MRT), baseline standard deviation of response times (SDRT) and the shift in response time distribution between high reward and no reward (B0vs15). After testing for normality (Shapiro-Wilk test) and homogeneity of variances (Levene's test), analysis of covariance (ANCOVA) was conducted with diagnosis as a factor. If age or IQ co-varied with a measure of task performance, analyses were run both with and without the covariate. If not, the covariates were left out of the final model. If between-group differences were found, we performed post-hoc testing using Fisher's least significant difference (LSD) to compare the three groups. We followed up with trans-diagnostic, dimensional analyses: here, we tested for an effect of ADHD symptoms (i.e. SWAN-inattention and SWAN-hyperactivity/impulsivity subscores (Lakes et al., 2012)) and parent-rated reward sensitivity (i.e. SPSRQ-c reward subscores (Luman et al., 2012)) on the three different performance measures, within the combined clinical group and the control group separately. If there were no between-group differences, we ran correlational analyses on the entire sample. Results were corrected for multiple comparisons using False Discovery Rate (FDR) correction on the separate ANCOVA results (per performance measure) using the Benjamini-Hoghberg method (Benjamini & Hochberg, 1995).

Statistical analyses - fMRI

Statistical analyses of fMRI data were performed in a two-level procedure within the framework of the general linear model. First, for each subject, we modeled the blood oxygenation level dependent (BOLD) activation invoked by task cues as conditions of interest, and realignment parameters as potential confounders (condition of no interest). Three cues were modeled as conditions of interest: anticipation of respectively 0, 5 and 15 cents reward. Regressors were created by convolving delta functions coding for cue onset with a canonical hemodynamic response function (as implemented in SPM8) for each cueing category separately. The estimated regression coefficients for the different cues were then contrasted resulting in first-level contrast images for each subject. The contrast between 0 and 15 cent was used for the main analyses. If effects were found, post-hoc analyses were conducted on the two underlying contrasts (0 versus 5 cents and 5 versus 15 cents) in order

to dissociate reward valence and reward magnitude. Our task was only designed to detect differences in anticipatory activity, and as a consequence of collinearity we could not analyze reward outcome separately. Data were high-pass filtered using discrete cosine basis functions with a 128 second cut-off. At the group level, the analysis focused on average activity in a-priori specified regions of interests (ROIs). Our main hypotheses focused on the bilateral ventral striatum. However we included a number of additional regions in the ventral fronto-striatal loop to assess whether any results were specific to the ventral striatum or a more widespread feature of neural reward circuitry. ROIs were created using different atlases provided in the FSL software package (the Harvard-Oxford cortical and subcortical structural atlases and the Oxford thalamic connectivity atlas). Four fronto-striatal regions putatively involved in reward anticipation were selected per hemisphere: ventral striatum (VS), anterior cingulate, pallidum (combined internal and external segment) and thalamus, resulting in a total of eight ROIs. Average activity per ROI was operationalized as average □-values of the contrast image and extracted using Marsbar (http://marsbar.sourceforge.net/). Main effects of reward anticipation on brain activity were analyzed in typically developing children using a single-factor analysis of variance (ANOVA). To test for group differences in brain activity, we conducted an ANCOVA with diagnosis as factor. If age and IQ co-varied with activity in an ROI, analyses were run both with and without the covariate. If not, the covariates were left out of the final model.

If there were between-group differences, we performed a series of follow-up analyses. First, we conducted post-hoc testing using Fisher's least significant difference (LSD) to compare the three groups. Also, we included the shift in response time distribution between rewarded and unrewarded trials as an additional performance-related covariate. Next, we performed trans-diagnostic, dimensional analyses: Using ANCOVA, we tested for an effect of ADHD symptoms (i.e. scores on two separate SWAN subscales) and parent-rated reward sensitivity (i.e. scores on the SPSRQ-C reward subscale) on anticipatory brain activity, within the combined clinical group and control group separately. If there were no between-group differences, we ran correlational analyses on the entire sample. Results were corrected for multiple comparisons using False Discovery Rate (FDR) correction on the separate ANCOVA results (per ROI) using the Benjamini-Hoghberg method (Benjamini & Hochberg, 1995).

Exploratory analysis

As a group, children with symptoms of ADHD showed more parent-rated reward sensitivity and less ventral striatum activity compared to typically developing children (see Results section for details). However, within the group of children with ADHD

symptoms, increased parent-reward sensitivity was related to increased ventral striatum activity. In order to get more insight in this counterintuitive relation between behavior and ventral striatum activity, we performed a post-hoc, exploratory analysis. We used a median split on SPSRQ-c scores and on response time speeding (i.e. B0vs15), for typically developing children and children with ADHD symptoms separately. Next, we performed a 2x2 factorial ANOVA with group and reward sensitivity (low versus high) as factors; and a 2x2 factorial ANOVA with group and response time speeding (low versus high) as factors.

Results

Questionnaires

ANOVA showed between-group differences on the reward sensitivity scale of the SPSRQ-c, the inattention scale of the SWAN and the hyperactivity/impulsivity scale of the SWAN (see Table 1). Post-hoc testing indicated that both groups of children with ADHD symptoms had lower scores (i.e. more symptoms of ADHD) on the two SWAN subscales than typically developing children. SPSRQ-c scores differed between all three groups, with parents reporting lowest reward sensitivity for typically developing children, highest reward sensitivity for children with ADHD and intermediate scores children with ASD and ADHD symptoms.

Table 2. Task performance per clinical group

	Control (SD)	ADHD (SD)	ASD (SD)	F-value	p-value
MRT	422.18 (65.74)	465.49 (60.54)	444.80 (80.75)	(2,73) 2.47	0.091
SDRT	137.75 (33.79)	170.81 (43.88)	144.31 (42.24)	(2,73) 4.77	0.011*
B0vs15	0.85 (0.25)	0.76 (0.26)	0.83 (0.30)	(2,73) 0.82	0.447

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SD, standard deviation; MRT, mean response time in no reward condition; SDRT, standard deviation of response times in no reward condition; B0vs15, shift in response time distribution between high reward and no reward.

* Significant group difference.

Task performance

AN(C)OVA showed group differences in the standard deviation of response times on baseline trials (SDRT) (see Table 2). There was no effect of age or IQ. Post-hoc testing showed that children with ADHD had higher SDRT than typically developing children and children with ASD and ADHD symptoms. There were no other group

differences or associations with dimensional measures.

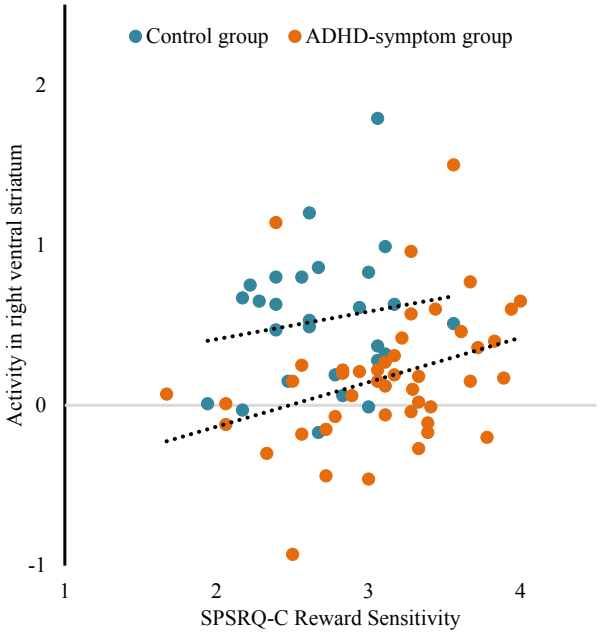
Brain activity

In typically developing children, there was a main effect of reward anticipation on brain activity in all ROIs. Furthermore, there was a between-group difference in anticipatory activity in right ventral striatum (VS) ($F(2,73) = 6.38$, $p = 0.003$). Age and IQ were left out of the model, as we found no associations between brain activity and age or IQ. Both clinical groups (ADHD: $M = 0.26$, $SD = 0.42$; ASD: $M = 0.12$, $SD = 0.42$) showed less anticipatory activity in right ventral striatum than typically developing children ($M = 0.52$, $SD = 0.45$). Task performance (i.e. B0vs15) co-varied with activity in bilateral ventral striatum. Specifically, increased speeding of response times when reward was at stake, was associated with increased activity of ventral striatum. When we added task performance as a covariate to the model, we found between-group differences in ventral striatum activity bilaterally (for detailed results, see Table 3). Reward sensitivity as reported by parents (SPSRQ-c) was positively associated with anticipatory activity in right VS for the combined clinical group ($F(1,44) = 5.85$, $p = 0.020$) (see Figure 1): This indicates that more parent-rated reward sensitivity was associated with more VS activity during reward anticipation. We found no association between activity in VS and any of the SWAN subscales, within either (clinical or control) group. Post-hoc testing indicated that neither the 0 versus 5 cents contrast nor the 5 versus 15 cents contrast by itself could explain the group difference in VS activity.

Exploratory analysis

A 2x2 factorial ANOVA on activity in right VS yielded no interaction between diagnosis (TDC vs ADHD symptoms) and parent-rated reward sensitivity (upper versus lower 50%). However, children with ADHD symptoms and low SPSRQ-c scores showed no anticipatory VS activity (one-sample t-test: $t (21) = 0.40$, $p = 0.694$), whereas the three other groups (comparison group with low SPSRQ-c, comparison group with high SPSRQ-c, clinical group with high SPSRQ-c) did show anticipatory VS activity (see supplementary Figure 1.). A 2x2 factorial ANOVA on task performance (B0vs15) yielded no interaction between clinical status and parent-rated reward sensitivity (upper versus lower 50%). However, children with ADHD symptoms and low SPSRQ-c scores did show less reward sensitive task performance (B0vs15) than children with ADHD symptoms and high SPSRQ-c ($t (44) = 2.59$, $p = 0.013$) (see supplementary Figure 2).

Figure 1. Ventral striatal activity and parent-rated reward sensitivity



Note. Figure 1 shows the relationship between activity in right ventral striatum during reward anticipation and reward sensitivity in daily life (as assessed by one of the parents using the SPSRQ-C questionnaire). For the group of children with ADHD symptoms and for the group as a whole there was a positive correlation between the two.

Table 3. Differences in activity in ventral striatum with task performance as covariate

	Factor	B	F-value	p-value
Left	B0vs15	-0.47	9.25	0.003*
	Group		5.40	0.006**
Right	B0vs15	-0.48	9.29	0.003*
	Group		9.82	<0.001**

B0vs15 , shift in response time distribution between high reward and no reward.

* Significant covariate.

** Significant group difference.

Discussion

We studied reward processing in children with ADHD symptoms, as this neuropsychological domain holds strong relevance for clinical practice. We found that children with ADHD symptoms had decreased activity in ventral striatum during the anticipation of reward, and increased sensitivity to reward, as rated by their parents. This was apparent for children with ADHD, as well as for children with a primary diagnosis of ASD and ADHD symptoms. In addition, we found that for children with ADHD symptoms, parent-rated reward sensitivity was positively correlated with anticipatory activity in ventral striatum.

We found reduced activity in ventral striatum during the anticipation of reward in childhood ADHD, confirming our first hypothesis. Previous studies have reported anticipatory hypoactivity in adolescent or adult ADHD populations (Plichta & Scheres, 2014), but a first study on children with ADHD (Kappel et al., 2015) found no group differences. Accordingly, the authors suggested that this hypo-activation might be an epiphenomenon of ADHD that emerges at a later developmental stage. In contrast, we found evidence for anticipatory hypoactivity as early as eight years of age. Our finding is in line with theories of reward processing in ADHD that suggest changes in mesolimbic reward processing are a core etiological factor in the development of the behavioral symptoms (Sagvolden et al., 2005; Tripp & Wickens, 2008).

Our second hypothesis was that anticipatory hypoactivity in ventral striatum would be found in children with ADHD symptoms irrespective of whether their primary diagnosis was ADHD. In order to test this we included a third group of children with similar levels of parent-rated ADHD symptoms, but a different primary diagnosis (ASD). Both groups showed comparable hypoactivity in the ventral striatum, in line with our hypothesis as well as with previous findings on reward processing in ASD (G. S. Dichter et al., 2010; Gabriel S Dichter et al., 2012; Kohls et al., 2014). Our third hypothesis was that ADHD symptoms would drive this anticipatory hypoactivity. Notably, we found no association between ADHD symptoms and anticipatory brain activity within the combined clinical group or within the group of typically developing children. Consequently, the hypoactivity in ventral striatum in children with ADHD symptoms may be related to distinct traits in both groups, as was suggested by a recent paper by Van Dongen and colleagues (van Dongen et al., 2015). Another explanation is that the linear relationship does not hold for the extreme ends of the distribution, as represented by both clinical groups and as might be represented by the sample of (hyper) control children. Environmental and neurobiological factors might have a differential effect on the expression of symptoms across the ADHD continuum A third

explanation could be neurobiological heterogeneity (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2002), where only a subgroup of participants might show this effect, making it hard to detect in the group as a whole. Techniques to model and quantify this heterogeneity are needed to allow for differential relationship within one clinical group (e.g. Fair, Bathula, Nikolas, & Nigg, 2012; van Hulst, de Zeeuw, & Durston, 2015).

Reward sensitivity in children was assessed at three different levels: behavior in daily life (SPSRQ-C reward subscale), neuropsychological task performance (B0vs15), and activity in ventral striatum. Within the combined group of children with ADHD symptoms, anticipatory ventral striatum activity was positively correlated with parent-rated reward sensitivity. In addition, higher anticipatory activity was related to better task performance, replicating our previous finding (van Hulst, de Zeeuw, Lupas, et al., 2015) and challenging the assumption of performance independent brain activity during an MID task (Knutson, Adams, Fong, & Hommer, 2001). In all, children with ADHD symptoms and higher parent-rated reward sensitivity showed more reward-sensitive task performance and higher anticipatory activity than children with ADHD symptoms and lower parent-rated reward sensitivity. As a whole, the combined clinical group showed higher parent-rated reward sensitivity than typically developing children. Such a strong drive towards rewarding situations in children with ADHD symptoms might be a consequence of low VS activity in anticipation of reward. This ties in with the vigilance regulation model of ADHD, where individuals with ADHD seek sensation as an autoregulatory attempt to stabilize arousal (Geissler, Romanos, Hegerl, & Hensch, 2014; Zentall & Zentall, 1983). These children might deploy behavior that is heavily focused on short-term reward as a mechanism to normalize dopaminergic neurotransmission. If the characteristic inattentive, hyperactive and impulsive behavior can be seen as a compensatory mechanism for an understimulated brain, arousal levels could even be considered a direct target for treatment (for an example see: Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010).

We found that as a group, children with ADHD symptoms had decreased brain activity during reward processing and increased reward sensitivity in daily life. However, within the group of children with ADHD symptoms, these measures of neurobiology and behavior were positively related to each other. The delineation of such a trans-diagnostic deficit in reward processing, both at a behavioral and a biological level, is a promising step towards a dimensional brain-behavior model of reward sensitivity in children with symptoms of ADHD. Ultimately, such a model might be used to refine treatment options that are dependent on reward processing.

Limitations

We had to exclude 30% of our participants, primarily due to head motion. In our experience, this is not an unusual percentage for children in this age range. When hyperactivity is part of the phenotype, exclusion on the basis of head motion conveys the risk of confounding results. However, the children we excluded did not differ from children included in the analyses in the level of their ADHD symptoms. Furthermore, our task was designed to detect differences in anticipatory activity rather than reward processing, and as a result of collinearity we could not analyze brain activity related to the latter separately. Studies combining reward anticipation and reward receipt are needed to discriminate between models on dopamine signaling in ADHD (e.g. Furukawa et al., 2014).

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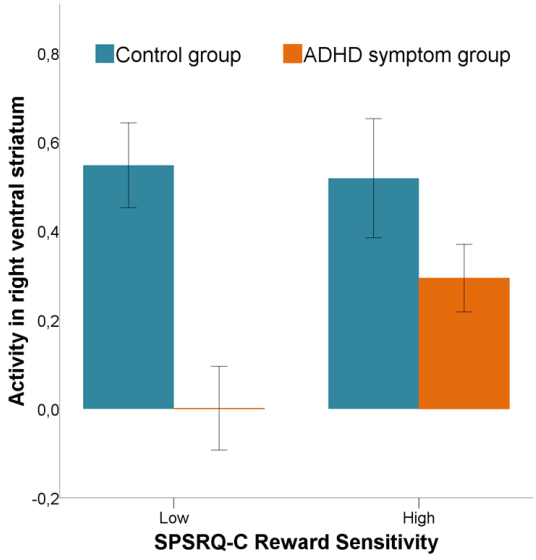
Supplementary Text S1. Screening of data quality

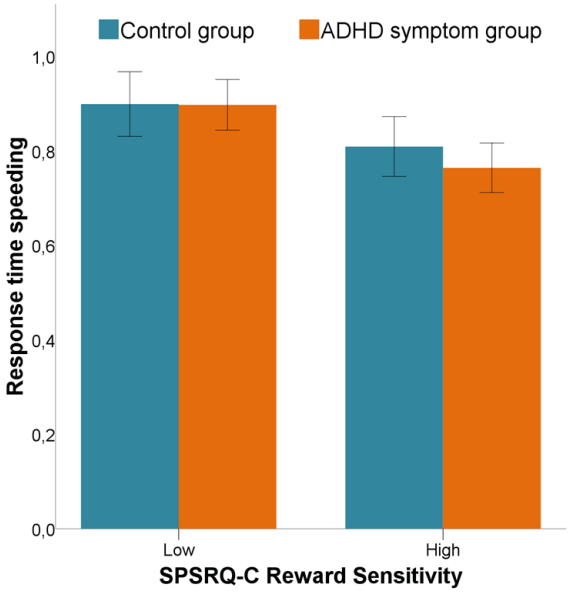
All T1-weighted scans were assessed by an expert radiologist. Following this step, three participants were excluded on the basis of anatomical abnormalities (in all cases an arachnoid cyst). Scan-to-scan movement was assessed using ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009). Scans with more than 1.0 mm scan-to-scan movement and scans with a more than 1.5% deviation from the average global signal, were replaced using a linear interpolation of the values of neighboring scans. Recordings from task levels with more than 30% corrected scans were excluded from further analyses. Subsequently, participants with less than three levels of sufficient data quality were excluded. 27 Participants (2 typically developing children, 14 children with ADHD and 11 children with ASD) were excluded on the basis of this criterion. An additional two participants (one typically developing child and one child with ASD) had to be excluded as a consequence of an incorrectly placed field of view.

Supplementary Figure 1. Parent-rated reward sensitivity versus anticipatory activation



Note. This figure shows mean activity in right ventral striatum for four groups of children: Typically developing children with low SPSRQ-C scores, children with ADHD symptoms and low SPSRQ-C scores, typically developing children with high SPSRQ-C scores and children with ADHD symptoms and high SPSRQ-C scores.

Supplementary Figure 2. Parent-rated reward sensitivity versus task performance



Note. This figure shows mean response time speeding (i.e. B0vs15) for four groups of children: Typically developing children with low SPSRQ-C scores, children with ADHD symptoms and low SPSRQ-C scores, typically developing children with high SPSRQ-C scores and children with ADHD symptoms and high SPSRQ-C scores.

6

Distinct neuropsychological profiles within ADHD: A latent class analysis of cognitive control, reward sensitivity and timing

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Abstract

Multiple pathway models of ADHD suggest that this disorder is the behavioral expression of dysfunction in one of several separable brain systems. One such model focuses on the brain systems underlying cognitive control, timing and reward sensitivity. It predicts separable subgroups among individuals with ADHD, with performance deficits in only one of these domains. We used Latent Class Analysis (LCA) to identify subgroups of individuals with ADHD based on their overall pattern of neuropsychological performance, rather than grouping them based on cut-off criteria. We hypothesized that we would find separable subgroups with deficits in cognitive control, timing and reward sensitivity respectively. 96 Subjects with ADHD (of any subtype) and 121 typically developing controls performed a battery assessing cognitive control, timing and reward sensitivity. LCA was used to identify subgroups of individuals with ADHD with a distinct neuropsychological profile. A similar analysis was performed for controls. Three subgroups represented 87% of subjects with ADHD. Two of our three hypothesized subgroups were identified, with poor cognitive control and timing. Two of the ADHD subgroups had similar profiles to control subgroups, whereas one subgroup had no equivalent in controls. Our findings support multiple pathway models of ADHD, as we were able to define separable subgroups with differing cognitive profiles. Furthermore, we found both quantitative and qualitative differences from controls, suggesting that ADHD may represent both categorical and dimensional differences. These results show that by addressing heterogeneity in ADHD, we can identify more homogeneous subsets of individuals to further investigate.

Introduction

Attention problems, impulsiveness and hyperactivity are the defining symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) (American Psychiatric Association, 2013). However, the way these symptoms are expressed and experienced in everyday life varies widely between children, resulting in a highly diverse clinical group. This diversity is also reflected in the neuropsychology of ADHD, where neuropsychological impairments vary greatly between affected individuals. It is this neuropsychological heterogeneity that has led a number of authors to suggest a paradigm shift from hypothesizing one core dysfunction in ADHD, to describing multiple neuropsychological domains that may be independently affected (Castellanos & Tannock, 2002; Nigg & Casey, 2005; Sonuga-Barke, 2002). These domains may even reflect separable etiological pathways at the neurobiological level, where changes in separable brain systems may independently give rise to the behavioral phenotype (Durston, van Belle, & de Zeeuw, 2011; Nigg & Casey, 2005; Sonuga-Barke, 2005). This ties in with a recent meta-analysis of 55 fMRI studies (Cortese et al., 2012) that found a wide variety of brain systems to be involved in ADHD.

Two neuropsychological domains studied extensively in ADHD are cognitive control (Barkley 1997; Alderson et al. 2007), which can be defined as 'the ability to override an inappropriate response in favor of another' (Casey et al., 2005, p.106); and sensitivity to reward. Here, we define reward sensitivity within the framework of the 'dopamine transfer deficit' theory, which focuses on the anticipatory firing of dopamine cells (Tripp & Wickens, 2009). We therefore focus on the anticipation of reward, as opposed to the evaluation of reward outcome (for an comprehensive review see: Luman et al. 2010).

At a group level, deficits in both domains have been found in children with ADHD. Nonetheless a substantial proportion of children with ADHD performs within the normal range on such tasks (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). This underlines the notion that no single neuropsychological deficit can explain the behavioral phenotype. Building on a multiple-pathway hypothesis, recent studies have found several subgroups with varying neuropsychological profiles in ADHD (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Fair, Bathula, Nikolas, & Nigg, 2012; Sonuga-Barke, Bitsakou, & Thompson, 2010). In addition to deficits in cognitive control and reward sensitivity, deficits in motor and perceptual timing have been reported (Noreika, Falter, & Rubia, 2013; Toplak, Dockstader, & Tannock, 2006).

In this study, we aimed to analyze heterogeneity in task performance across

a battery of neuropsychological tasks in ADHD. Rather than averaging out inter-individual differences in performance, we used Latent Class Analysis (LCA), a statistical method that classifies individuals into subgroups (latent classes) based on their task performance. This technique models the variance within ADHD by constructing subgroups of children who show a similar pattern of performance. Note that this approach differs from more widely used factor analytical techniques, which classify variables as opposed to individuals. In order to compare the resulting classification of ADHD patients with typically developing controls, we performed two separate analyses: One on a sample of 96 subjects with ADHD and one on a sample of 121 typically developing control subjects.

We used two neuropsychological tasks to test for differences in cognitive control, timing and reward sensitivity. The first task was an adaptation of a go-nogo paradigm where the timing of events was manipulated to create expected and unexpected events (Durston et al., 2007). This manipulation was chosen as we hypothesized that timing deficits in ADHD are a consequence of an attenuated build-up and monitoring of temporal expectations (Nigg & Casey, 2005). In previous work, we have shown that the manipulation of stimuli in this paradigm is associated with frontostriatal hypoactivation in ADHD (Durston et al., 2007; Mulder et al., 2008), whereas the manipulation of timing is associated with cortico-cerebellar hypoactivation in ADHD (Durston et al., 2007; Mulder et al., 2008; Mulder, van Belle, van Engeland, & Durston, 2011). The second task was a reward anticipation paradigm, adapted from the monetary incentive delay task (MID) (Knutson, Adams, Fong, & Hommer, 2001) to be suitable for children (De Zeeuw et al., 2012). Previous studies using a MID paradigm (Scheres, Milham, Knutson, & Castellanos, 2007; Ströhle et al., 2008) have shown hypo-activation of the ventral striatum in ADHD during reward anticipation. We hypothesized that we would be able to identify three separate subgroups among individuals with ADHD, each with a deficit in one of the three domains of cognitive control, timing and reward sensitivity.

Methods

Participants

The institutional review board of the University Medical Center Utrecht approved the study and its procedures. Participants with ADHD were recruited from our outpatient clinic for developmental disorders. All subjects with ADHD were diagnosed by an expert child and adolescent psychiatrist according to DSM-IV TR criteria (American Psychiatric Association, 2000). Typically developing controls were recruited through schools in the wider Utrecht area. The groups were matched for

age and gender at the group level. A total of 217 subjects aged 6-25 were included in this study: 96 subjects with ADHD and 121 typically developing controls. Only subjects with ADHD using no medication or on short-working medication were included (e.g., methylphenidate). Seventy-three participants (76%) with ADHD were using some form of methylphenidate at the time of inclusion. All participants were requested not to take any medication on the day of testing. Table 1 gives demographic information.

Table 1. Demographic characteristics

	ADHD (SD)	Control (SD)	t-value/ Chi2	p-value
Age	12.9 (4.18)	13.6 (4.26)	1.26	0.21
Gender (m/f)	76/20	89/32	0.93	0.34
IQ	104 (16.4)	111 (14.9)	3.25	0.001*

ADHD, Attention-Deficit/Hyperactivity Disorder; SD, standard deviation.

* Significant group difference.

Written informed consent was obtained from both parents for subjects under eighteen years of age. Children provided verbal assent. Participants over eighteen years of age signed for their own informed consent. The Diagnostic Interview Schedule for Children (DISC-IV, parent version) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was administered to parents of subjects aged 6 to 18 years. Participants aged 18 years or older participated in the MINI-plus abbreviated psychiatric interview (Sheehan et al., 1998). Results from these two interviews were used to exclude psychiatric comorbidity in typically developing controls. Furthermore, the DISC-IV was used to specify the subtype of ADHD according to DSM-IV criteria. As the MINI-plus interview does not provide subtype specification, we only have subtype information on 89 out of 96 participants with ADHD. Of these participants 49% met criteria for the ADHD combined subtype, 10% met criteria for the predominantly hyperactive-impulsive subtype, 29% met criteria for the predominantly inattentive subtype and 11% did not meet DISC-IV criteria for current ADHD. These 10 children did not meet criteria as a direct consequence of successful symptomatic control using ADHD medication (e.g. methylphenidate), according to their parents. Participants with ADHD were excluded from the study if they met diagnostic criteria for a comorbid psychiatric disorder other than ODD/CD, based on the diagnostic interview. Exclusion criteria for all participants were major physical or neurological illness. Parents completed the Swanson, Nolan and Pelham-IV (SNAP-

IV) rating scale, a 26-item questionnaire assessing all symptoms of ADHD listed in the DSM-IV-TR definition (Swanson 1992), and the Child Behavior Checklist (CBCL) , a 120-item questionnaire assessing behavioral and emotional problems (Verhulst et al. 1996). Subjects participated in two computerized neuropsychological tasks and a four-subtest shortened WISC-III or WAIS-III, as age-appropriate, in order to estimate full-scale IQ.

Cognitive control/ timing task

The first task was a timing-manipulated go-nogo task (Durston et al., 2007). Participants were instructed to aid a mouse in its search for cheese. A little door was shown that opened regularly. Behind it was either a piece of cheese (go; 82% of 264 trials) or a cat (nogo; 18% of 264 trials). The subjects were asked to press a button as fast as possible when a piece of cheese was shown and to withhold their response when a cat was shown. Timing of trials was manipulated, with the majority of trials presented with an interstimulus interval (ISI) of 4 seconds (expected timing), and a minority (18%) with a 2 second ISI (unexpected timing). This created four types of trials: go-trials with expected timing, go-trials with unexpected timing, nogo-trials with expected timing and nogo-trials with unexpected timing. There were eight outcome measures for this task: percentage of correct nogo-trials (both expected and unexpected: accuracyexpected-nogo and accuracyunexpected-nogo), reaction time benefit (RTbenefit, explained below), MRT on the go-trials (i.e., MRTexpected-go and MRTunexpected-go), ICV on expected go-trials (ICVexpected-go), and the percentage of correct go-trials (both expected and unexpected: accuracyexpected-go and accuracyunexpected-go). RTbenefit denotes the difference in MRT between the expected and unexpected go-trials. In other words, how much faster subjects respond on expected versus unexpected go-trials. This difference is expressed in the number of standard deviations of MRTexpected-go (MRTexpected-go – MRTunexpected-go)/ SDRTexpected-go.

Reward sensitivity task

The second task we used was a modified version of the MID-task (Knutson et al., 2001), composed of four blocks of 60 trials, with an intertrial interval of 4 seconds (De Zeeuw et al., 2012). Participants were asked to guess which of two cartoon figures (SpongeBob and Patrick Star) was hiding a wallet. First, a picture of a wallet (cue) with 0, 5 or 15 cents was presented. The participant was told that this was the amount of money that could be won during the upcoming trial. Second, a screen appeared where a picture of SpongeBob (always on the left) and Patrick (always on the right) was shown, and the subject was asked to guess who was hiding the wallet by pressing

the appropriate key as quickly as possible (the left arrow key for SpongeBob and the right arrow key for Patrick). The task was rigged so that the result was unrelated to the participant's response. On 50 percent of all trials, participants were shown a screen showing a thumbs-up picture, stating a "correct guess" and the cued reward amount was added to their total. On the other half of the trials, a thumbs-down picture was shown, denoting an "incorrect guess" with no reward added to their total. The primary outcome measure of this task is the shift in reaction time distribution between rewarded and unrewarded trials. This was quantified using linear regression of the rank ordered reaction times of the rewarded condition on the rank ordered reaction times of the non-rewarded condition, as described previously (De Zeeuw et al., 2012). Any regression coefficient below 1 represents a faster response time on rewarded then on unrewarded trials. Other variables used in the LCA were mean response time (MRT) on the non-rewarded trials and the intra-individual coefficient of variation (ICV: SD of RTs divided by MRT) on the non-rewarded trials. In total, we had 12 outcome variables from these tasks, eight derived from the go-nogo task and four from the MID task (see Table 2). We tested for the effect of IQ on all variables.

Statistical analyses

Basic analyses on demographic data and (sub)group comparisons were conducted in SPSS version 20.0 (SPSS Inc, Chicago). In order to ensure data quality across ADHD and control groups, the data were screened for signs of off-task behavior. We only excluded subjects for off-task behavior based on go-accuracy in the go-nogo task or the percentage of trials without a response in the MID task. Participants who scored more than three interquartile ranges above the third quartile (data from both groups combined) were considered extreme outliers and excluded from further analyses. Four subjects with ADHD and one typically developing control were excluded on the basis of this criterion. Group differences in baseline demographics between children with ADHD and typically developing controls were tested using independent sample t-test or chi-squared test as appropriate (see Table 1).

The latent class analysis (LCA) was performed in Latent Gold (Vermunt & Magidson, 2005). A Latent Class model refers to any statistical model where unobserved subgroups are identified based on their scores on observed (task) measures. (Magidson & Vermunt, 2004). As such, the analysis uses quantified data (measures of task performance in this case) to assess the presence of qualitatively different subgroups across these variables. This contrasts with factor analytical approaches that do not directly classify individuals into subgroups, but first classify variables into factors. Factor analytical approaches assume that the correlation between variables is equal

for the entire group, whereas LCA makes no such assumption. As we reasoned that ADHD subgroups may differ from subgroups in typically developing controls in both qualitative and quantitative ways, we conducted two separate analyses: the primary analysis was based on data from participants with ADHD only. A second LCA used the data from typically developing controls.

Twelve variables (Table 2) were entered into a latent class model. As latent class models need a fixed number of classes to determine the best model fit, eight preliminary models were constructed, with between 1 and 8 latent classes, allowing us to compare model fit across the range of estimated classes. For each model, an estimation of fit was calculated to convey the likelihood that the model was an accurate reflection of the performance differences. For this particular analysis, the Bayesian Information Criterion (BIC) was used, which takes parsimony of the model (i.e. the simplest possible model) into account by penalizing additional parameters. From the eight preliminary models, the model with the lowest BIC was chosen for further analysis (Vermunt & Magidson, 2005).

Basic latent class modeling relies on the assumption that within one latent class, all variables are independent of one another. To allow for association between pairs of variables within latent classes, direct effects can be added. First, we tested for direct effects of age on all included variables using Wald's statistic. Any significant age-effects were included in the analysis. Second, we added a direct effect for the pair of variables with the highest within-subgroup correlation. This step was then repeated adding one pair of variables at a time, as described by Magidson & Vermunt (2004). After every step, the model fit was evaluated using the BIC-value. At the point where adding one more direct effect did not lead to a lower BIC value, we concluded the current model was the best fit. We visualized the results by plotting the performance profiles for the subgroups. Performance was expressed in z-values, reflecting the number of standard deviations a value was above or below the mean of the group. The subgroups derived from the separate analyses (on ADHD subjects and on control subjects) were compared in both a quantitative and a qualitative manner, similar to the approach of Fair and colleagues (Fair et al. 2012). To facilitate a visual, qualitative comparison of the shapes of the profiles between the ADHD and control groups, we adjusted the Z-scores for baseline between-group differences. The Z-scores used in this comparison were calculated on the performance data for the whole group (ADHD and control combined). Second, a between-subjects MANOVA was conducted to compare the ADHD and control subgroups on all performance measures for any pair of subgroups that showed similarity on visual inspection.

Exploratory analyses

In a final step, we tested for behavioral differences between the ADHD subgroups found in the LCA. Exploratory analyses were performed using data from behavioral rating scales. For this purpose, we used the Internalizing and Externalizing Problems subscales of the CBCL, and the Inattentive, Hyperactive/Impulsive and Oppositional Defiant Disorder subscales of the SNAP-IV (parent version). A one-way, between-subjects ANOVA was conducted to test for the effect of LCA subgroup on CBCL-scores. As the SNAP-IV data were not normally distributed, we used the non-parametric Kruskal-Wallis test to test for differences between subgroups on these data. Due to considerable floor effects in the control data, any analysis of between group behavioral differences in controls would have been uninformative.

Results

Task performance

Descriptive statistics of task performance for both groups are shown in Table 2. Performance on the go-nogo task differed between groups for all outcome measures, except for accuracy on unexpected go-trials (p=0.052). On the MID-task, there was a between group difference in the shift of the reaction time distribution between high and non-rewarded conditions: both controls and subjects with ADHD showed faster reaction times when they anticipated high reward, but controls showed a bigger difference. None of the task variables correlated with IQ.

Latent Class model construction

In the ADHD group, a five-class solution (of the eight preliminary models) provided the best fit for the data, as indicated by the lowest BIC value (BIC=2467, LL=-1060, npar=76). This model was carried forward. Age contributed significantly to 7 of the 12 indicators of the model (see Supplementary Material Table s1). Accordingly, we added direct effects between these indicators and age to the model. Next, we added any bivariate interactions that were not accounted for by the model so far (see Methods), by adding additional direct effects. After the addition of four direct effects (between RTbenefit and MRTunexpGO, between MRTexpGO and MRTunexpGO, between ICVexpGO and MRTunexpGO and between RegB_5ct and RegB_15ct; see Table s1), an optimal model fit was achieved. We constructed a model for controls, using an analogous procedure. Again, a model with five latent classes provided best fit (BIC=2831, LL=-1233, npar=76). Direct effects for this model are shown in Table s2.

Latent Classes ADHD

Table 2. Task performance: timing-manipulated go-nogo task and monetary incentive delay task

Go nogo task

Measure	Type of trial	ADHD (SD)	Control SD)	t-value	p-value	df	Cohens D
MRT	Expected Go	440 (74.5)	410 (56.9)	3.32	0.001*	174**	0.46
MRT	Unexpected Go	511 (99.4)	477 (67.7)	2.92	0.004*	160**	0.41
ICV	Expected Go	0.28 (0.085)	0.22 (0.071)	4.80	< 0.001*	184**	0.64
Correct	Expected Go	94% (4.8)	95% (4.8)	2.39	0.018*	215	0.32
Correct	Unexpected Go	89% (9.2)	91% (7.0)	1.95	0.052	215	0.27
Correct	Expected NoGo	48% (18.3)	57% (23.1)	3.24	0.001*	215	0.42
Correct	Unexp NoGo	61% (21.3)	74% (19.7)	4.75	< 0.001*	215	0.62
RT benefit	Exp VS Unexp Go	0.61 (0.361)	0.80 (0.422)	3.42	0.001*	215	0.46

Monetary incentive delay task

Measure	Type of trial	ADHD (SD)	Control SD)	t-value	p-value	df	Cohens D
Regr. coeff	0 cents VS 5 cents	0.94 (0.327)	0.92 (0.338)	0.41	0.680	215	0.06
Regr. coeff.	0 cents VS 15 cents	0.90 (0.301)	0.81 (0.255)	2.46	0.015*	215	0.33
ICV	0 cent trials	0.41 (0.105)	0.39 (0.102)	0.93	0.355	215	0.13
MRT	0 cent trials	407 (76.3)	389 (79.6)	1.46	0.147	215	0.20

MRT, mean reaction time; ICV, intra-individual coefficient of variation; RT, reaction time; VS, versus; ADHD, Attention-Deficit/Hyperactivity Disorder; SD, standard deviation; df, degrees of freedom.

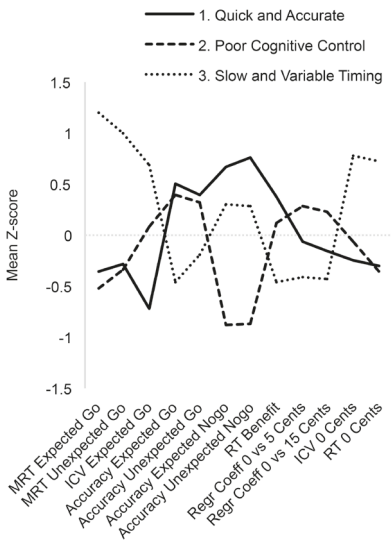
* Significant group difference.

** Equal variances not assumed.

As indicated above, a five-class solution gave the best fit for the ADHD group. This can be conceptualized as five subgroups of participants with ADHD, with similar performance within each subgroup across all tasks and measures. In the ADHD group, three larger and two smaller subgroups were found (consisting of 36.7%, 30.6%, 19.7%, 9.6% and 3.3% of the participants). The subgroups were numbered 1 through 5 according to their size, where subgroup 1 was the largest and subgroup

5 the smallest. Mean age within the subgroups ranged between 9.9 and 13.6 (13.3, 13.6, 11.8, 12.4 and 9.9 respectively). Out of all participants with ADHD, 87% fit one of the three larger neuropsychological profiles. The latter two subgroups were too small (n < 10) to interpret the performance profiles. The performance profiles of the three largest subgroups are shown in Figure 1. Subgroup 1 showed a profile with short reaction times and above average go and nogo-accuracy, and was named the 'quick and accurate' subgroup. Subgroup 2 had poor nogo accuracy (for both expected and unexpected nogo trials) and hence was named the 'poor cognitive control' subgroup. Subgroup 3 showed slow and variable reaction times, and a low benefit in reaction time to predictable trials (RTbenefit), and was thus named the 'slow and variable timing' subgroup. Note that these names serve merely as a label, and represent our subjective interpretation of the data.

Figure 1. Subgroups of individuals with ADHD, based on latent class analysis of their individual performance profiles



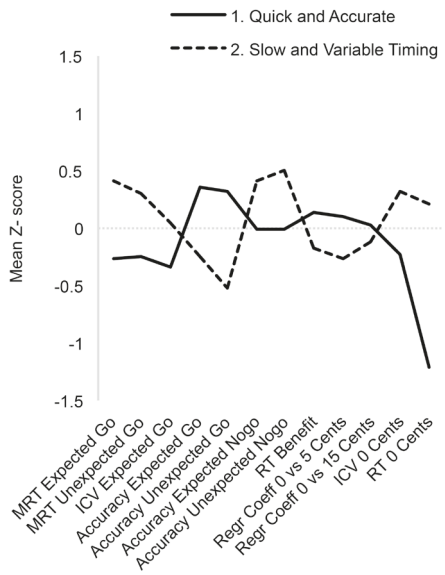
MRT, mean reaction time; ICV, intra-individual coefficient of variation; RT, reaction time; Regr Coeff, regression coefficient.

Note. The figure shows the average z-values for the 12 input variables, per latent subgroup within the ADHD group. Only the three largest latent subgroups are displayed.

Controls

For the typically developing controls, a five-class solution also fit the data best. Two larger and three smaller subgroups were found (consisting of 62.1%, 23.5%, 5.9%, 5.8% and 2.6% of participants). The mean age of these subgroups varied between 9.0 and 15.8 (13.2, 15.8, 11.3, 12.3 and 9.0). 86% of control subjects fit one of the two larger neuropsychological profiles. The latter three subgroups were too small (n < 10) to interpret the performance profiles. The performance profiles of the two largest subgroups are shown in Figure 2. The first subgroup had fast reaction times with limited variability and high go-accuracy, and was named the 'quick and accurate' control subgroup. The second subgroup had slow and variable reaction times and a low benefit in reaction time to predictable trials (RTbenefit), and was named the 'slow and variable timing' control subgroup.

Figure 2. Subgroups of typically developing controls, based on latent class analysis of their individual performance profiles



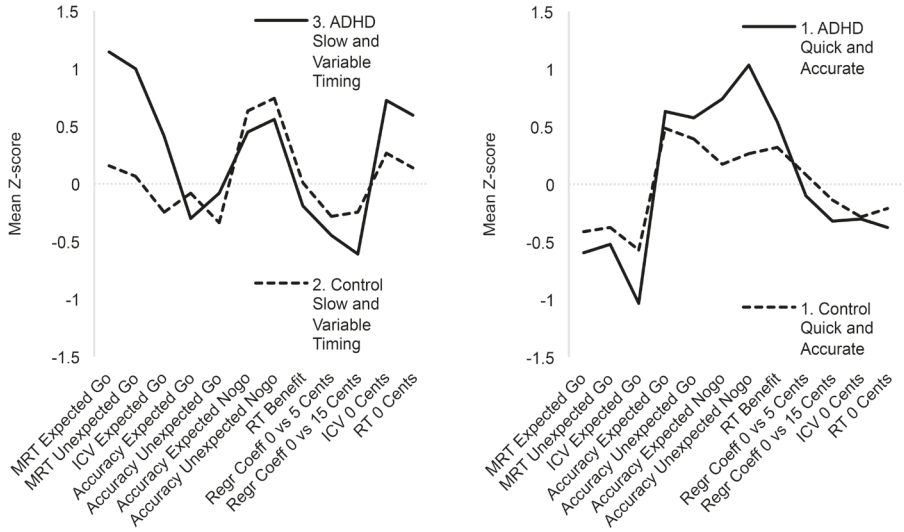
MRT, mean reaction time; ICV, intra-individual coefficient of variation; RT, reaction time; Regr Coeff, regression coefficient.

Note. The figure shows the average z-values for the 12 input variables, per latent subgroup within typically developing controls. Only the two largest subgroups are displayed.

Comparison of Latent Class profiles between ADHD and controls

Figures 3a and 3b show the profiles of two ADHD and control subgroups in a single graph. Upon visual inspection it is clear that the profile of the 'quick and accurate' subgroup in ADHD strongly resembles the first subgroup in controls (see Figure 3a). The 'slow and variable timing' subgroup in ADHD resembles the second subgroup in controls. Therefore, these ADHD subgroups have performance patterns that are qualitatively similar to control subgroups. However, we should bear in mind that these figures display the adjusted Z-scores and as such disregard any quantitative differences. To address this, we investigated whether the subgroups showing similar profiles differed quantitatively. We found an effect of diagnosis on performance measures for the two 'slow and variable timing' subgroups (ADHD and control), $F(12, 33) = 5.39$, $p < 0.001$. By contrast, we found no performance differences between the two 'quick and accurate' subgroups (ADHD and control), $F(12, 100) = 1.29$, $p = 0.237$. For the third ADHD subgroup with poor cognitive control, there was no equivalent subgroup among controls.

Figure 3. The 'slow and variable timing' and the 'quick and accurate' subgroups of individuals with ADHD show a similar pattern of performance to comparable subgroups among control subjects.



MRT, mean reaction time; ICV, intra-individual coefficient of variation; RT, reaction time; Regr Coeff, regression coefficient.

Note. The figure shows the average z-values per latent subgroup for the 12 input variables. Z-values of the ADHD group are adjusted to correct for baseline group differences.

Questionnaire data

Exploratory analyses were performed to test for differences between the three ADHD subgroups in parent-rated SNAP-IV (n = 71) and CBCL (n = 63) measures of behavioral problems. There was a significant effect of LCA subgroup on the internalizing problems subscale of the CBCL, $F(2, 52) = 3.72$, $p = 0.031$. Subjects from the ADHD subgroup with poor cognitive control showed the most internalizing problems. Post-hoc comparisons (Bonferroni-corrected) indicated that the mean score of the subgroup with poor cognitive control (M = 11.58, SD = 6.69) differed from the 'slow and variable timing' subgroup (M = 6.80, SD = 4.65), but not from the 'quick and accurate' subgroup (M = 8.29, SD = 4.23). For the SNAP-IV data, there were no effects of subgroup on any of the subscales.

Discussion

Building on multiple pathway models of ADHD, we aimed to investigate heterogeneity in neuropsychological task performance. We used Latent Class Analysis to classify individuals into subgroups based on their overall task performance. This type of analysis differs from traditional analyses of performance, where mean values are compared between groups, as it specifically addresses within-group heterogeneity in performance. Moreover, LCA uses a more direct approach than factor analytical techniques, as they first reduce variables into factors and then classify individuals using a performance cut-off, and as such make the assumption that the translation from variables to factors is homogeneous across the whole group (De Zeeuw et al., 2012; Sonuga-Barke et al., 2010). Previous studies have used LCA to define subgroups of individuals with ADHD at the symptom level, and have subsequently analyzed between subgroup differences in neuropsychological performance (van der Meer et al., 2012) or genotype (Li & Lee, 2012). We built more directly on multiple pathway models of ADHD (Durston et al., 2011; Nigg et al., 2005; Sonuga-Barke, 2005), as we applied an inter-individual approach to analyzing neuropsychological performance data: we defined subgroups at the neuropsychological level and carried these groups forward to study differences at the symptom level.

Dividing subjects with ADHD into subgroups based solely on their neuropsychological performance, resulted in five subgroups, two of which were too small to investigate further. We had hypothesized that we would find subgroups with poor cognitive control, poor sensitivity to reward and poor temporal processing in ADHD. We found evidence of a subgroup with poor cognitive control (the 'poor cognitive control' subgroup) and poor temporal processing (the 'slow and variable timing' subgroup), but not of a group with poor sensitivity to reward. Although there was an overall

group difference in sensitivity to reward between ADHD and control subjects, we did not find a subgroup related to reward sensitivity. This might reflect a lack of inter-individual variance in reward sensitivity within ADHD, but could also be an effect of the emphasis on parsimony in the model we used.

The 'poor cognitive control' subgroup had a profile that distinguished itself by low accuracy on the nogo-trials (Figure 1). The performance of this subgroup is in keeping with models that place poor cognitive control at the core of neuropsychological dysfunction in ADHD (e.g. Barkley, 1997). However, this subgroup represented only 31% of the subjects with ADHD in our sample. The 'slow and variable timing' subgroup represented 20% of all participants with ADHD and had a profile with slow and variable reaction times, and a low benefit in reaction time on predictable trials. This reduced benefit of trials being predictable in time, suggests there may be a role for deficient motor or perceptual timing in this subgroup of subjects with ADHD. However, slow and variable reaction times may also reflect fluctuations in sustained attention and/or concurrent attentional lapses. This particular performance profile is in keeping with models that emphasize bottom-up intrusions of the default mode network into task-specific processing in ADHD (Sonuga-Barke & Castellanos, 2007) and with models of top-down deficits in state-regulation in ADHD (Sergeant, 2005). Finally, the last subgroup, which represented 37% of all participants with ADHD, was characterized by quick and accurate performance.

There were clear similarities between two of the ADHD subgroups and subgroups from the control analysis: the 'quick and accurate' ADHD subgroup and the 'slow and variable timing' ADHD subgroup both had counterparts amongst controls. However, when analyzed in a traditional way, the 'slow and variable timing' subgroup in ADHD had poorer task performance than its counterpart subgroup in controls. This is in line with findings by Fair and colleagues (Fair et al. 2012), who concluded that some of the heterogeneity in ADHD might be 'nested' in the normal variation. By contrast, there were no performance differences between the two 'quick and accurate' subgroups, indicating that a fairly large proportion of participants with ADHD performed as well as the best performing subgroup of control participants. We did not find a control counterpart for our ADHD subgroup with poorer cognitive control. This could be taken to suggest that this pattern of performance in ADHD is qualitatively different from the distribution of performance in controls. Such dissociation between extremes of normal variation on one side and categorical differences on the other is particularly interesting in the light of the ongoing debate about dimensionalizing psychiatric disorders. Our results support the notion that both categorical and dimensional approaches are valuable in child and adolescent psychology, as was stressed in a

recent review by Coghill and Sonuga-Barke (Coghill & Sonuga-Barke, 2012).

Classifying individuals with ADHD into neuropsychologically defined subgroups is one way to address the heterogeneity in ADHD. Additional insights at the neuropsychological level may then be used to inform us on heterogeneity at the behavioral (symptom) level or even, in longitudinal studies, on outcome. In order to test the principle of studying behavioral heterogeneity from a neuropsychologically informed perspective, this study tested for cross-sectional associations between ADHD neuropsychological subgroup and symptoms. Parents of participants in the 'poor cognitive control' subgroup reported more internalizing problems than the other groups. Various studies have described elevated levels of internalizing problems in ADHD (Daviss, 2008; Faraone, Biederman, Weber, & Russell, 1998; Franke et al., 2011; Williams et al., 2008). However, in our data, internalizing problems were more prevalent in one particular subgroup. This could signal that this subgroup distinguished itself not only in neuropsychological performance, but also in terms of behavior. As this was an exploratory part of our study and we had limited power to investigate subgroup differences in behavior, this finding could also represent a more general increase in behavior problems that only reached significance for the internalizing subscale. It could also represent a chance finding altogether.

This study illustrates how using a data-driven approach in the context of a theoretical framework can be applied to neuropsychological heterogeneity in ADHD to parse affected individuals into more homogeneous subgroups, defined by similar neuropsychological profiles. This represents an operationalization of the traditional endophenotype approach (Gottesman & Gould, 2003), where defining subgroups – particularly on neurobiologically plausible basis – can be used to investigate other levels, either behavioral (as was done here), or neurobiological (Durston, 2010).

In sum, we used an alternative approach to data reduction to define subgroups of individuals with ADHD with different patterns of neuropsychological task performance, in keeping with predictions from multiple-pathway hypotheses of ADHD. Of three identified subgroups, two had patterns of task performance with separable deficits in domains predicted by such models: cognitive control and timing. Two of the subgroups of individuals with ADHD had performance patterns that were similar to subgroups of typically developing controls: in both ADHD and controls, we found a subgroup with good task performance, and a subgroup with variable timing. A third subgroup of individuals with poor cognitive control was identified among subjects with ADHD, with no equivalent among controls. This combination

of quantitative and qualitative differences in performance patterns between subjects with ADHD and controls suggests that there may be both categorical and dimensional differences that distinguish subjects with ADHD from typically developing individuals; and that for some subjects categorical differences may be more relevant than dimensional ones. This is relevant to ongoing discussions on dimensionalizing psychiatric disorders. Finally, perhaps the most important contribution of this study is that it demonstrates the added value of investigating within-group differences in ADHD. We have shown that by formally addressing neuropsychological heterogeneity in ADHD, more homogeneous subsets of individuals can be identified. Analyses based on differences between neurobiologically defined subgroups have great potential for studying biological heterogeneity in psychiatric disorders.

Limitations

This study used only two tasks. As a result, the neuropsychological constructs addressed here relied on one task per construct. We recommend that future studies use multiple tasks per neuropsychological domain. Furthermore, we included a broad age range (6-25 years). We took this into account in the modeling of latent classes. In addition, there were no significant age differences between the LCA subgroups. However, given the considerable, non-linear neurodevelopmental changes in ADHD, future studies are recommended to investigate to which extent these results are generalizable in an equivalent way for all age groups.

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Supplementary information

Supplementary Table S1. Age and Direct Effects for subjects with ADHD

Age effects	Wald statistic	p-value	Direct effects	BIC-value
MRTexpGO	110.8	6.4e-26	No direct effects	2467
MRTunexpGO	64.3	1.1e-15	Only age effects	2413
ICVexpGO	20.5	6.0e-6	RTbenefit <-> MRTunexpGO	2361
PcorrExpGO	54.5	1.6e-13	MRTexpGO <-> MRTunexpGO	2229
PcorrUnGO	2.4	0.12*	ICVexpGO <-> MRTunexpGO	2178
PcorrExpNOGO	8.0	0.0046	RegB_5ct <-> RegB_15ct	2159**
PcorrUnNOGO	4.9	0.027	ICV_0ct <-> RegB_5ct	2169
RTbenefit	1.5	0.22*		
RegB_5ct	4.7	0.031*		
RegB_15ct	2.2	0.14*		
MRT_0ct	54.2	1.8e-13		
ICV_0ct	5.0	0.026*		

MRTexpGO, mean reaction time expected go-trials; MRTunexpGO, mean reaction time unexpected go-trials; ICVexpGO, Intraindividual coefficient of variation; PcorrExpGO, percentage correct expected go-trials; PcorrUnGO, percentage correct unexpected go-trials; PcorrExpNOGO, percentage correct expected nogo-trials; PcorrUnNOGO, percentage correct unexpected nogo-trials; RTbenefit, reaction time benefit; RegB_5ct, regression coefficient 0 versus 5 cents condition; RegB_15ct, regression coefficient 0 versus 15 cents condition; MRT_0ct, mean reaction time in the 0 cents condition; ICV_0ct, intraindividual coefficient of variation in the 0 cents condition; BIC, Bayesian inference criterion.

Note. This table shows all direct effects that were added to the model for the ADHD group. First, age effects were added if they affected the parameter values of the predictors according to the Wald statistic. Second, bivariate interactions were added recursively, starting with the bivariate interaction with the largest residual variance. This process was repeated until the BIC-value no longer decreased by adding another interaction.

* Non-significant age effects not included in the model

** Lowest BIC value when recursively adding direct effects

Supplementary Table S2. Age and Direct Effects for controls

Age effects	Wald stat.	p-value	Direct effects	BIC value
MRTexpGO	229.6	7.3e-52	No direct effects	2831
MRTunexpGO	174.4	8.3e-40	Only age effects	2668
ICVexpGO	85.0	3.0e-20	RTbenefit <-> MRTunexpGO	2614
PcorrExpGO	89.2	3.6e-21	MRTexpGO <-> MRTunexpGO	2475
PcorrUnGO	53.1	3.1e-13	PcorrExpNOGO <-> PcorrUnexpNOGO	2429
PcorrExpNOGO	103.2	3.0e-24	RTbenefit <-> ICVexpGO	2398
PcorrUnNOGO	65.5	5.8e-16	RegB_5ct <-> RegB_15ct	2388
RTbenefit	18.4	1.8e-5	ICV_0ct <-> RegB_15ct	2350**
RegB_5ct	3.3	0.068*	PcorrExpGO <-> PcorrUnexpGO	2359
RegB_15ct	0.4	0.52*		
MRT_0ct	85.9	1.9e-20		
ICV_0ct	2.7	0.098*		

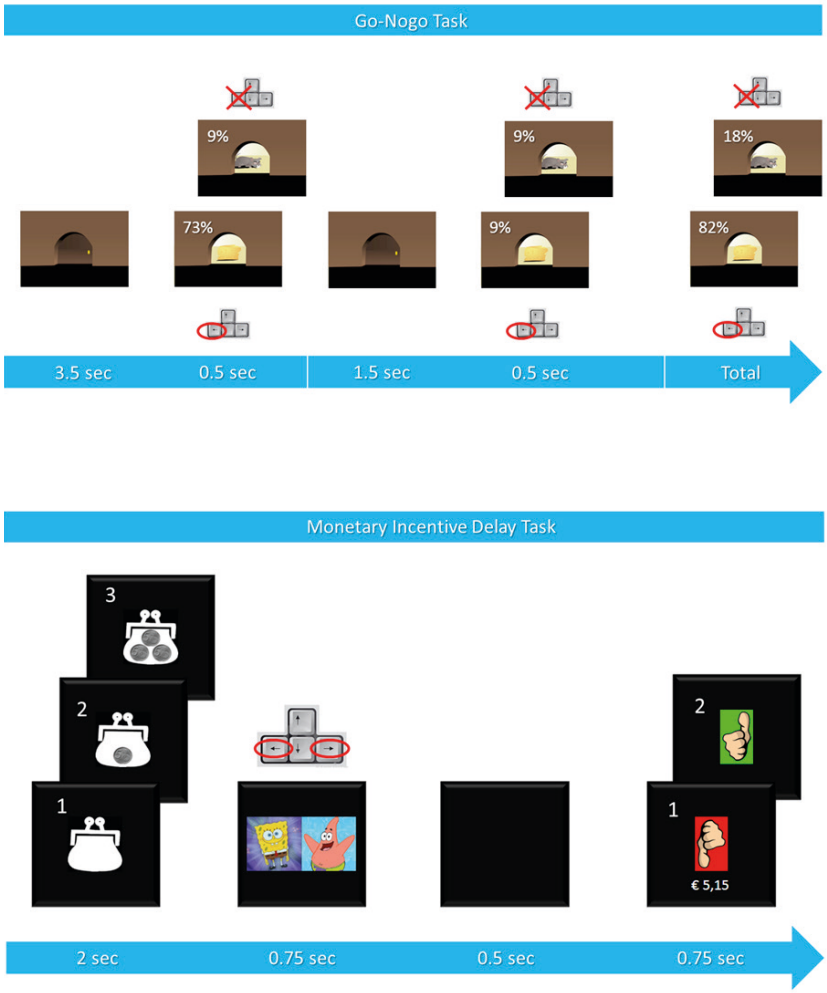
MRTexpGO, mean reaction time expected go-trials; MRTunexpGO, mean reaction time unexpected go-trials; ICVexpGO, Intraindividual coefficient of variation; PcorrExpGO, percentage correct expected go-trials; PcorrUnGO, percentage correct unexpected go-trials; PcorrExpNOGO, percentage correct expected nogo-trials; PcorrUnNOGO, percentage correct unexpected nogo-trials; RTbenefit, reaction time benefit; RegB_5ct, regression coefficient 0 versus 5 cents condition; RegB_15ct, regression coefficient 0 versus 15 cents condition; MRT_0ct, mean reaction time in the 0 cents condition; ICV_0ct, intraindividual coefficient of variation in the 0 cents condition; BIC, Bayesian inference criterion.

Note. This table shows all direct effects that were added to the model for the control group. First, age effects were added if they affected the parameter values of the predictors according to the Wald statistic. Second, bivariate interactions were added recursively starting with the bivariate interaction with the largest residual variance. This process was repeated until the BIC-value no longer decreased by adding another interaction.

* Non-significant age effects not included in the model

** Lowest BIC value when recursively adding direct effects

Supplementary Figure S1. Task design



Note. The two tasks included in the neuropsychological assessment of cognitive control, timing and reward sensitivity. The time course of a single trial is indicated by the blue band. Different trial types are displayed as partly overlapping squares. The red circles indicate which buttons subjects were instructed to use. A red cross indicates that a subject should withhold a button press on that particular trial type.

7

Can we use neuroimaging data to identify distinct subgroups among children with ADHD symptoms: a proof of concept study using latent class analysis of brain activity

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Submitted for publication

Abstract

Multiple pathway models of ADHD suggest that multiple, separable biological pathways may lead to symptoms of ADHD. If this is the case, it should be possible to identify subgroups of children with ADHD based on distinct patterns of brain activity. Previous studies have used latent class analysis (LCA) to define subgroups at the behavioral and cognitive level. In this proof of concept study, we took the opposite approach of using LCA on functional imaging data to explore whether we could identify neurobiological subgroups of children with ADHD symptoms. Fifty-six children with symptoms of ADHD (27 children with ADHD and 29 children with ASD and ADHD symptoms) and 31 typically developing children performed two neuropsychological tasks assessing reward sensitivity and temporal expectancy during functional magnetic resonance imaging. LCA was used to identify subgroups with homogeneous patterns of brain activity separately for children with ADHD-symptoms and typically developing children. Neurobiological, cognitive and behavioral differences between subgroups were then investigated. Results. For typically developing children we found a single homogeneous group, whereas for children with ADHD-symptoms we found two subgroups. The first ADHD subgroup showed attenuated brain activity compared to the second subgroup and typically developing children. Notably, the second subgroup had more behavioral problems in everyday life. In this proof of concept study, we showed that we could identify distinct subgroups of children with ADHD-symptoms based on their brain activity profiles. Ultimately, such subtle neurobiological differences may inform individually tailored treatment and indicate long-term developmental risks.

Introduction

Much of what is known about ADHD comes from studies that have compared groups of children with ADHD to groups of typically developing children, without accounting for within-group heterogeneity (Costa Dias et al., 2013). However, multiple pathway theories argue that changes in multiple, separable neurobiological pathways could lead to symptoms of ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2005). If neurobiological pathways to ADHD are truly separable, then it should be possible to identify subgroups of children with ADHD-symptoms based on distinct neurobiological profiles. Moreover, these subgroups will likely not be apparent based on symptoms alone (or we would long have identified them). The present study aims to provide a proof of concept by exploring whether subgroups of children with ADHD-symptoms can be identified on the basis of their brain activity profiles. We focused on two neuropsychological domains: reward sensitivity and temporal expectancy.

As a group, children with ADHD show changes in reward processing: they respond more impulsively to reward in that they often favor smaller immediate rewards over larger delayed rewards. Furthermore, they have been shown to show greater improvement in task performance following reward than typically developing children (Luman, Oosterlaan, & Sergeant, 2005). Both, the dynamic developmental theory (DDT) and dopamine transfer deficit theory (DTD) propose that such sensitivity to reward may be the result of changes in dopamine signaling (Sagvolden, Aase, Johansen, & Russell, 2005; Tripp & Wickens, 2008). Activity in ventral striatum as assessed with fMRI can be used as proxy for local dopamine activity (Delgado, Miller, Inati, & Phelps, 2005; Knutson & Gibbs, 2007). In addition to changes in reward processing, changes in temporal expectancy have been suggested in children with ADHD (Durston et al., 2007; Nigg & Casey, 2005; Rubia, Smith, Brammer, & Taylor, 2003). Attenuated temporal expectancy may be a result of reduced anticipatory brain activity in fronto-striatal networks (e.g. Durston et al., 2007; Ghajar & Ivry, 2009; McClure, Berns, & Montague, 2003), which in turn may be related to reduced dopamine signaling (Tripp & Wickens, 2008, 2009).

In this proof of concept study, we used latent class analysis (LCA) to identify subgroups of individuals with ADHD-symptoms based on their individual patterns of brain activity, instead of grouping them together based on predefined criteria of symptomatic or cognitive markers. To do so, we included data from two earlier fMRI-studies (Van Hulst et al., submitted for publication-a; Van Hulst et al., submitted for publication-b). We included children with a primary diagnosis of ADHD, as well as children with a primary diagnosis of autism spectrum disorder and symptoms of

ADHD (ASD+).

Methods

Sample

We included 87 right-handed boys in this study, 56 boys with symptoms of ADHD (27 with a primary diagnosis of ADHD and 29 with a primary diagnosis of ASD and ADHD symptoms (ASD+), Mage = 10.94, SD = 1.24) and 31 typically developing children (Mage = 10.28, SD = 1.07). 19 Children with ADHD and 19 with ASD+ were using short-acting psychostimulants (e.g. methylphenidate). All participants were asked not to take medication 24 hours prior to testing (Van Hulst et al. submitted for publication-a; Van Hulst et al. submitted for publication-b). Inclusion criteria for children with ADHD symptoms included a diagnosis of ADHD or ASD based on DSM-IV-TR criteria (APA, 2000). The diagnosis ADHD was confirmed using the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer, Fisher, Lucas, Dulcan & Schwab-Stone, 2000). An additional inclusion criterion for children with ASD was a (sub-)clinical score on the Child Behavior Checklist subscale for attention problems (CBCL; Verhulst, van der Ende, & Koot, 1996). Inclusion criteria for typically developing children included the absence of psychiatric disorders based on the DISC-IV (except for specific phobia and enuresis). General exclusion criteria included IQ lower than 70 as assessed using a four-subtest shortened Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), major illness of the cardiovascular, endocrine, pulmonary or gastrointestinal system, the presence of interfering metal object in or around the body, and a history of or present neurological disorder.

Procedure

The study and its procedures were approved by the institutional review board of the UMC Utrecht. Children with ADHD symptoms were recruited through the UMCU outpatient clinic for developmental disorders and schools for special education. Typically developing children were recruited through local schools. After the purpose and procedure of the study had been explained, informed consent was obtained from parents and verbal assent was obtained from children. Data was collected during two visits. During the first visit, the DISC-IV (Shaffer et al., 2000) was administered to one or both parents while children participated in a shortened WISC-III (Wechsler, 1991) IQ assessment. Afterwards, children participated in a mock-scanner session to prepare for the fMRI scan. Prior to the visit, parents completed the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ-C; Luman, van Meel, Oosterlaan, & Geurts, 2012), and the Strengths and Weaknesses of Attention Deficit/Hyperactivity Disorder Symptoms and Normal Behavioral Scale (SWAN; Swanson et

al., 2001) at home. Three composite scales were computed: SWAN-attention, SWAN-hyperactivity, SPSRQC-reward. During the second visit, the mock-scanner session was repeated. Afterwards, the fMRI session was run in two parts with a break in the middle. During the fMRI scan children performed two neurocognitive tasks, a child-friendly version of the monetary incentive delay (MID) task and a timing manipulated go/nogo task. A detailed description of the tasks can be found in the supplementary text and previously published papers (e.g. de Zeeuw et al., 2012). Task order was randomized across subjects.

Task performance measures

A child-friendly MID task was used to assess reward anticipation. The primary performance measure was the shift in reaction time (RT) distribution between rewarded and unrewarded trials. This was quantified using linear regression of individual rank-ordered reaction times in the high-reward condition (i.e. 15 cents) on the individual rank-ordered reaction times in the non-rewarded conditions (RegB), as described previously (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012). A regression coefficient smaller than one indicates faster RT on rewarded than on unrewarded trials. A timing manipulated go/nogo task was used to measure temporal expectancy. The primary performance measure was the difference score between mean response times on go-trials with expected timing (i.e. RTexpectedgo) and mean response times on go-trials with unexpected timing (i.e. RTunexpectedgo) divided by the standard deviation of response times. This measure indicates whether participants' responses on expected trials were faster than on unexpected trials.

Neuroimaging measures

We used average brain activity in four regions of interest (ROIs) as input for our latent class analysis (LCA). The choice of ROIs was based on between-group differences found in earlier analyses on this dataset (Van Hulst et al. submitted for publication-a; Van Hulst et al. submitted for publication-b). These studies compared children with symptoms of ADHD with typically developing children and found between-group differences in left subthalamic nucleus and left pallidum related to temporal expectancy, and bilateral nucleus accumbens related to reward anticipation. Average activity in these four ROIs (two per task) was used as input for the LCA.

Analytic strategy

The analysis consisted of three steps: (1) identifying homogenous subgroups of children with ADHD symptoms based on patterns of brain activity during reward anticipation and temporal expectancy; (2) assessing neurobiological, neurocognitive

and behavioral differences between these subgroups; (3) comparing neurobiological and cognitive measures of these subgroups to those of (subgroups of) typically developing children.

First, we performed an LCA on mean activity in the four ROIs to explore possible homogenous subgroup models (using Mplus, Version 7.3 (Muthén & Muthén, 1998-2012)). Full information maximum likelihood (FIML) was used to deal with missing data. We determined the number of classes on the basis of the Bayesian information criterion (BIC). Better fitting models have a lower BIC. Since activity in bilateral nucleus accumbens was highly correlated ($r > .70$), we added this correlation to the overall model. Subsequently, we examined models for conditional independence by inspecting the modification index. The modification index approximates the increase in chi-square of the overall model fit by freeing a parameter. By introducing possible local dependences between residuals, a more parsimonious model fit can be found compared to adding more classes (Magidson & Vermunt, 2000). Lastly, Wald tests were performed to test for differences in brain activity between subgroups. In the second step, we analyzed the relation between the latent classes and continuous outcome variables (i.e. RegB, RTbenefit-SD, SWAN-attention, SWAN-hyperactivity, SPSRQC-R, age, TIQ) using the Bolck, Croon and Hagenaars (BCH) method in Mplus (Bolck, Croon, & Hagenaars, 2004). BCH is a new method for 3-step mixture modeling with continuous outcomes. It uses weighted multiple group analysis in which the subgroups correspond to the latent classes. In doing so, the subgroups are known and not susceptible to changes (Bakk & Vermunt, 2015). Categorical outcome variables (i.e. DSM-IV-TR and DISC-IV diagnosis) were analyzed using DCAT in Mplus. In the third step, we tested for differences on the distal outcome variables between the ADHD-symptom subgroups and control subgroups using MANOVA in SPSS.

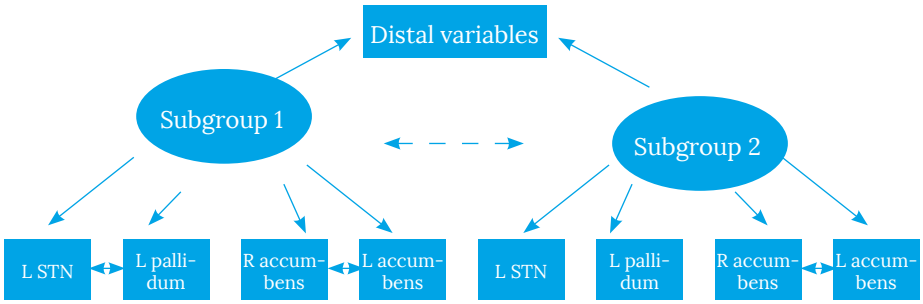
Results

LCA - ADHD

Global maximum was achieved in all models. The lowest BIC was found for the three class model. However, the three and four class models included a subgroup with only two participants. There, we carried forward the two-class model that had a better model fit (BIC) than the single class model. Within the ADHD-symptom group, the correlation between activity in left and right nucleus accumbens was high ($r = .87$) and was thus included in the overall model. Conditional independence testing indicated an improvement in model fit after including the correlation between left subthalamic nucleus and left pallidum within subgroup 1. This resulted in a final model as depicted in Figure 1, with model fit statistics provided in Table 1. We found an overall difference

between subgroups, with higher ROI activity in ADHD subgroup 2 (ADHD-2, n = 7) than in ADHD subgroup 1 (ADHD-1, n = 49) (Wald (3) = 144.141, p <.001). However, univariate tests of individual ROIs did not reach significance ((WaldleftPalidum (1) = 2.124, p = .145), (WaldLeSTN (1) = 0.021, p = .883), (WaldReNacc (1) = 3.343, p = .067), (WaldlEnACC (1) = 0.087, p = .768).). As the effect sizes were medium to large for some of the univariate tests (e.g. left pallidum d = 0.52, right nucleus accumbens d = 0.77), this may reflect limited statistical power.

Figure 1. Final LCA model for children with ADHD-symptoms



L, left; R, right; STN, subthalamic nucleus.

Note. The final model includes the correlation between left and right nucleus accumbens and a correlation between left subthalamic nucleus and left pallidum within subgroup ADHD-1.

LCA – typically developing children

For the typically developing children, we selected a one-class model, as adding more classes resulted in a subgroup with only one participant. Again the correlation between left and right nucleus accumbens was high (r = .87) and was included in the overall model. Conditional independence testing indicated no residual correlations. Model fit statistics are provided in Table 2. Figure 2 shows mean activation for all four ROIs for the two ADHD subgroups and the control group.

Differences in demographics, task performance and behavior between ADHD subgroups

To assess whether subgroups ADHD-1 and ADHD-2 differed in demographics, task performance or behavior, we compared the subgroups using the BCH method. Subgroup ADHD-2 showed more parent-rated reward sensitivity and more parent-rated attention problems than subgroup ADHD-1 (see Figure 3 and supplementary Table 1).

Table 1. Model fit statistics for the one to four class models of LCA within the ADHD-symptom group

	1-Class		2-Class		3-Class		4-Class	
	BIC	Entropy	BIC	Entropy	BIC	Entropy	BIC	Entropy
Without correlation	364.0	1.00	352.6	.88	339.5	.86	339.7	.88
Overall correlation			302.7	.72				
Correlation in subgroup ADHD-1			287.2	.85				

BIC, bayesian information criterion; LCA, latent class analysis.
Note. Table 1 shows the different steps taken in fitting the LCA model. First, the number of latent classes was determined based on BIC-values. The 3-class model had the lowest BIC-values but included a subgroup with only two participants. In view of parsimony and interpretability, the 2-class model was carried forward. In subsequent steps, we included direct effects were included in the model: first, the overall correlation between left and right nucleus accumbens; then the correlation between left pallidum and left subthalamic nucleus for subgroup ADHD-1.

Table 2. Model fit statistics for the one to four class models of LCA within typically developing controls.

	1-Class		2-Class		3-Class		4-Class	
	BIC	Entropy	BIC	Entropy	BIC	Entropy	BIC	Entropy
Without correlation	204.3	1.00	194.5	.98	194.2	.80	199.3	.80
Overall correlation	172.6	1.00						

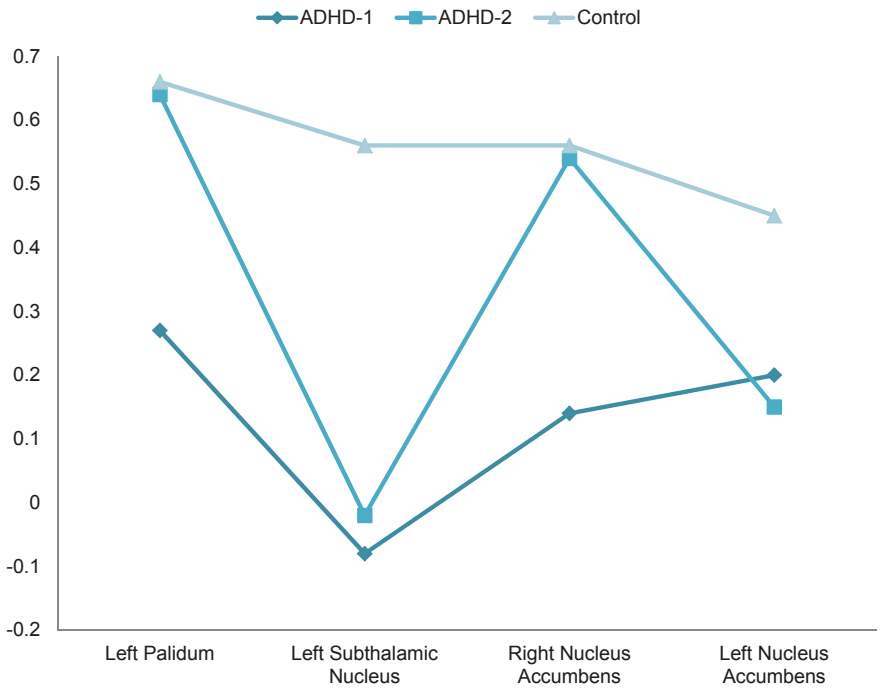
BIC, bayesian information criterion; LCA, latent class analysis.

Note. Table 2 shows the different steps in fitting the LCA model for the group of typically developing children. First, the number of latent classes was determined based on BIC-values. The 2 and 3-class models had the lowest BIC-values but both included a subgroup with only one participant. Therefore the 1-class model was carried forward.

Differences in demographics, task performance and behavior from typically developing children

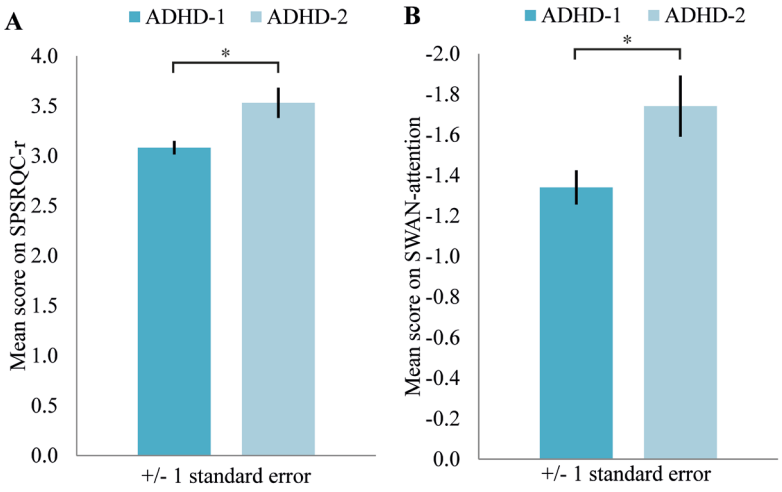
We compared the two subgroups of children with ADHD symptoms to the typically developing group on the same measures and found differences at the neurobiological level (see Figure 2). Subgroup ADHD-1 had lower activation than typically developing children in left subthalamic nucleus and right nucleus accumbens (see supplementary Table 1). At the descriptive level (see Figure 2), all four ROIs appeared less active in subgroup ADHD-1, but not subgroup ADHD-2, compared to the typically developing group. As expected, both subgroups of children with ADHD showed more parent-rated reward sensitivity, attention problems and hyperactivity in everyday live than typically developing children. There were no differences in task performance.

Figure 2. Mean activity in the four regions of interest



Note. Figure 2 shows mean activity per ROI for the two ADHD-symptom subgroups (ADHD-1 and ADHD-2) and typically developing children.

Figure 3. Behavioral differences between neurobiological ADHD subgroups



Note. Figure 3 shows differences in behavior between the two ADHD subgroups as reported by parents. Panel A shows reward sensitivity and panel B shows attention problems.

* Significant group difference at $p < 0.05$

Discussion

The goal of this proof of concept study was to explore whether we could identify latent neurobiological subgroups among children with symptoms of ADHD, based on their brain activity. Previous studies have used latent class analysis (LCA) to define subgroups at the behavioral and cognitive level and have subsequently investigated neurobiological differences between these subgroups. We took the opposite approach and used LCA to directly identify neurobiological subgroups on their functional imaging data. Two subgroups of children with ADHD-symptoms were identified. The largest ADHD subgroup (ADHD-1) had lower brain activity than the other subgroup (ADHD-2). However, subgroup ADHD-2 exhibited more ADHD-related symptoms as reported by the parents.

Children in this study were classified based on their brain activity in left pallidum, left subthalamic nucleus and bilateral nucleus accumbens. This permitted us to identify two subgroups of children with ADHD symptoms: subgroup ADHD-1 was characterized by attenuated brain activity across the four ROIs compared to subgroup ADHD-2. In part, this is in keeping with the multiple pathway hypothesis that proposes that children with ADHD can be distinguished by separable brain activity profiles while exhibiting the same, or similar, behavioral problems (Sonuga-Barke, 2005). On the other hand, multiple pathway models could be taken to suggest a more differentiated profile, where one subgroup might be affected in reward sensitivity but not timing and another subgroup vice versa (De Zeeuw et al., 2012; Sonuga-Barke, Bitsakou, & Thompson, 2010).

As a group, typically developing children showed a more homogenous pattern of brain activity and the 1-class model gave the most parsimonious fit. Interestingly, brain activity of subgroup ADHD-2 resembled that of typically developing children more than subgroup ADHD-1, but subgroup ADHD-2 simultaneously exhibited more symptoms of ADHD.

We also investigated whether neurobiologically defined (sub-) groups differed at the cognitive and behavioral levels. No differences between the two ADHD subgroups were found on task performance measures. There were no differences between the ADHD subgroups on DSM-IV-TR (sub-)diagnosis, which is consistent with previous studies that have reported that multiple etiological pathways to ADHD do not appear to correspond to DSM-IVs behavioral subtypes (Castellanos & Tannock, 2002; Durston et al., 2003). However, at the behavioral level, the subgroups differed from each other on measures of attention problems and reward sensitivity: the parents of children

in subgroup ADHD-2 reported more attention problems and more reward sensitive behavior in everyday life. One explanation could be that the children in subgroup ADHD-2 seek more external stimulation to compensate for reduced brain activity. This fits with existing theories that propose an organism will work to maintain optimal levels of arousal (Geissler, Romanos, Hegerl, & Hensch, 2014; Zentall & Zentall, 1983). According to this theory, impulsive and reward seeking behavior represent autoregulatory mechanisms to attain more optimal levels of brain activity (Geissler et al., 2014). If this is true, it suggests that forms of therapy that directly target arousal levels may be effective. Indeed, some studies have shown that introducing environmental noise can improve ADHD symptoms for some children (e.g. Stansfeld et al., 2005; Söderlund, Sikström, & Smart, 2007). Furthermore, one interpretation for the mechanism by which stimulants are effective is that they increase dopamine levels and may therefore lead to more optimal levels of arousal, and thus ameliorate behavior (Bresnahan, Barry, Clarke, & Johnstone, 2006).

Limitations and future directions

While the sample size of the current study is typical for fMRI studies, especially ones including young children with behavioral disorders, it also borders on the minimum for LCA. As such, complex models such as the ones presented here should not be generalized to the population at large. However, the sample size was sufficient for a proof of concept, which was the goal of this study. A second limitation is that our regions of interest were chosen a priori, based on between-group differences. Accordingly, we cannot be sure that we did not miss subgroups in our analysis that might have been more apparent had other ROIs been included.

Conclusion

In the present proof of concept study we explored whether we could use neuroimaging data to identify neurobiological homogeneous subgroups within a group of children with ADHD symptoms. We found that we could. This study should be taken as an incentive for other initiatives to empirically address neurobiological heterogeneity in ADHD. The present findings suggest that underlying neurobiological differences between children with symptoms of ADHD may go undetected if we continue to diagnose and group subjects for studies based solely on behavioral or cognitive symptoms. In the future, subtle neurobiological differences may also inform treatment selections and indicate long-term developmental risks (Reuter et al., 2005). As such, neurobiological subtyping is an important next step in investigating the biology of ADHD.

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Supplementary information

Supplementary Text S1

Neuropsychological measures – monetary incentive delay task

We assessed reward sensitivity using a child-friendly modification of the Monetary Incentive Delay Task (MID-task; de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012) in a rapid event-related fMRI design. The task sequence started with a picture of a wallet that contained 0, 5 or 15 cents (i.e. manipulation of reward magnitude; 2000 ms). This was followed by a picture of two cartoon characters (i.e. Sponge Bob always on the left, Patrick Star always on the right; 750 ms). The participants were instructed to guess which cartoon character was hiding the wallet and to respond by pressing the left or right response button. This was followed by a black screen (500 ms). Participants were encouraged to guess even if no reward was available in the wallet (i.e. 0 cent) and instructed to respond as fast as possible. If they did not respond within 1250 ms after the appearance of the cartoon characters, they received the feedback "too late!" Finally, a picture of a thumbs-up or thumbs-down was presented (750 ms) indicating a correct or incorrect guess. This was accompanied by the total amount of money earned so far. The task was manipulated in such a way that the outcome of each trial was predetermined; the choices the participants made did not affect reward outcome. A total of 240 trials (i.e. 80 rewarded and 80 unrewarded trials) were divided into four blocks of 60 trials (total duration 16.96 min). Two blocks with an 80% reward frequency (high reward) and two with a 20% reward frequency (low reward). These reward sequences were counterbalanced ("high-low-high-low" or "low-high-low-high") and participants were randomly assigned. The primary outcome measure of this task was the shift in response time (RT) distribution between rewarded and unrewarded trials. This was quantified using linear regression of individual rank-ordered response times in the high-reward condition (i.e. 15 cents) on the individual rank-ordered response times in the non-rewarded conditions, as described previously (de Zeeuw et al., 2012). A regression coefficient smaller than one can be interpreted as faster RT on rewarded compared to unrewarded trials.

Neuropsychological measures – timing manipulated go/nogo task

We assessed temporal expectancy using a timing-manipulated go/no-go task where temporal predictability of events was manipulated. The participants were presented with a picture of a mouse hole on a computer screen in the form of a closed door, and instructed to press a response button each time a piece of cheese appeared behind the door (go-trial) in order to help the mouse in its search for food. If the door opened and a cat appeared (no-go trial) they were instructed to

suppress their response and not press the button. Go-trials occurred the majority of times (82% of 264 trials) and no-go trials the minority of times (12% of 264 trials). In total there were four blocks of 66 trials (total duration 18.20 min). The stimuli were presented for 500 ms, in random order, and with an expected interstimulus interval (ISI) of 3500 ms (82%) or unexpected ISI of 1500 ms (18%). This led to four conditions: 1) go trials at expected time (73%; expected go trials) 2) no-go trials at expected time (9%; expected no-go trials), 3) go trials at unexpected time (9%; unexpected go trials), 4) no-go trials at unexpected time (9%; unexpected no-go trial). The primary outcome measure of this task (i.e., RTbenefitSD) was computed by subtracting RTexpectedgo from RTunexpectedgo and subsequently dividing that number by RTSD. This response speed benefit for expected trials indicated whether participants' responses on predictable trials were faster than on unpredictable trials.

fMRI acquisition

All fMRI data was collected in the context of two previously published fMRI studies (Van Hulst et al. submitted for publication-a; Van Hulst et al. submitted for publication-b). In these studies we used a 3.0 T Achieva MRI scanner (Philips Medical System, Best, the Netherlands) with an eight-channel sensitivity-encoding (SENSE) parallel imaging head coil. A whole-brain three-dimensional fast field echo T1-weighted scan (200 slices; repetition time = 10 ms; echo time = 4.6 ms; flip angle = 8°; field of view, 240 x 240 x 160 mm; voxel size: 0.75 x 0.8 x 0.75 mm isotropic) was acquired for purposes of anatomical reference. Whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast oriented in a transverse plane were acquired (4 sessions; 135 volumes per session for expectancy; 126 volumes per session for reward anticipation; 36 slices per volume; interleaved acquisition; TR = 2.02 sec.; TE = 35 ms; field of view = 240 × 240 × 116 mm; flip angle = 70°; voxel size = 3.0 × 3.5 × 3.0). To allow for T1 equilibration effects the first six images were discarded.

fMRI data pre-processing

FMRI data were analyzed using SPM8 as implemented in Matlab 7.12 (Mathworks Inc., Natick, MA, USA). All images were realigned, corrected for between-scan head motion, co-registered, normalized and smoothed using a Gaussian kernel. ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009) was used to assess scan-to-scan movement. Linear interpolation of values of the neighboring scans were used to replace the scans with more than 1.0 mm scan-to-scan movement or more than 1.5% deviation from the average global signal. Participants with more than 30% corrected scans

were excluded from further analyses (as is described in detail in: Van Hulst et al. submitted for publication-a; Van Hulst et al. submitted for publication-b). Based on these criteria, data of 29 participants from the go/no-go task (4 typically developing children, 13 children with ADHD and 11 with ASD+) and of 27 participants from the MID task (2 typically developing children, 14 children with ADHD and 11 with ASD+) were excluded. Additionally, three typically developing children were excluded because of an arachnoid cyst, and one typically developing child and one child with ASD and ADHD symptoms as a consequence of an incorrectly placed field of view.

Individual and group level fMRI analysis

The individual level analysis involved modeling blood oxygenation level dependent (BOLD) activity for the different conditions per task within the framework of the general linear model. A detailed description can be found in Van Hulst et al. (submitted for publication-a). The group level analysis involved assessing mean activity in Regions of Interest (ROIs) on the group level. The ROIs were specified using the Subcortical Structural Atlas and the Subthalamic Nucleus Atlas, as provided in the FSL software package. We chose four ROIs on the basis of group differences in brain activity between children with ADHD symptoms and typically developing children. These between-group differences were found in previous analyses of the current dataset (Van Hulst et al. submitted for publication-a; Van Hulst et al. submitted for publication-b). For reward anticipation, the left and right nucleus accumbens were selected. For temporal expectancy the left subthalamic nucleus and left pallidum were selected (Supplementary Figures 1 and 2). For these ROIs, we computed average activity per participant using MarsBar (http://marsbar.sourceforge.net/).

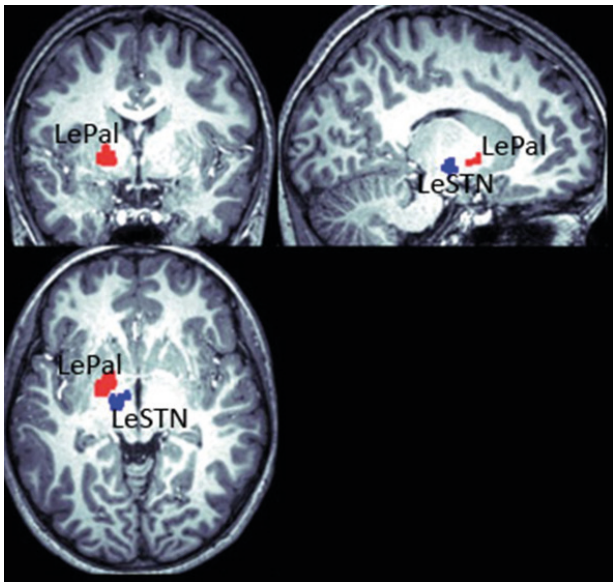
Supplementary Table 1. Neurobiological, neurocognitive and behavioral differences between ADHD subgroups and typically developing children

	M1 (SD1)	M2 (SD2)	F (df)	p
Left pallidum				
ADHD-1 vs control		0.65 (.80)	5.586 (1)	.021
ADHD-2 vs control			0.012 (1)	.914
ADHD vs control	0.31 (.70)		2.564 (1)	.113
Left subthalamic nucleus				
ADHD-1 vs control		0.50 (.68)	12.345	.001
ADHD-2 vs control			1.880 (1)	.180
ADHD vs control	-0.08 (.80)		10.749 (1)	.002
Right nucleus accumbens				
ADHD-1 vs control		0.55 (.44)	18.291	<.001
ADHD-2 vs control			0.000 (1)	.989
ADHD vs control	0.19 (.42)		13.325 (1)	<.001
Left nucleus accumbens				
ADHD-1 vs control		0.45(.40)	5.640	.021
ADHD-2 vs control			2.140 (1)	.154
ADHD vs control	0.21 (.43)		6.416 (1)	.013
RegB				
ADHD-1 vs ADHD-2	0.81 (.24)	0.80 (.42)	0.002	.965
ADHD-1 vs control	0.83 (.26)	0.89 (.29)		.901
ADHD-2 vs control	0.80 (.41)			1.00
ADHD vs control	0.80 (.29)		2.108 (1)	.150
RTbenefit				
ADHD-1 vs ADHD-2	0.66 (.36)	0.45 (.43)	1.517	.218
ADHD-1 vs controls	0.64 (.33)	0.82 (.37)		.100
ADHD-2 vs controls	0.76 (.40)			.061
ADHD vs conrol	0.63 (.36)		5.096 (1)	.027
SPSRQC-R				
ADHD-1 vs ADHD-2	3.07 (.48)	3.57 (.40)	8.282	.004
ADHD-1 vs controls	3.01 (.49)	2.70 (.42)		.007
ADHD-2 vs controls	3.55 (.40)			<.001
ADHD vs control	3.14 (.47)		17.737 (1)	<.001
SWAN-att				

ADHD-1 vs ADHD-2	-1.33 (.60)	-1.77 (.40)	6.059	.014
ADHD-1 vs controls	-1.35 (.57)	0.37 (.89)		<.001
ADHD-2 vs controls	-1.74 (.40)			<.001
ADHD vs control	-1.39 (.56)		183.03 (1)	<.001
SWAN-hyp				
ADHD-1 vs ADHD-2	-1.05 (.69)	-0.91 (.63)	0.296	.587
ADHD-1 vs controls	-1.08 (.64)	0.39 (.70)		<.001
ADHD-2 vs controls	-0.92 (.62)			<.001
ADHD vs control	-1.03 (.65)		88.583 (1)	<.001

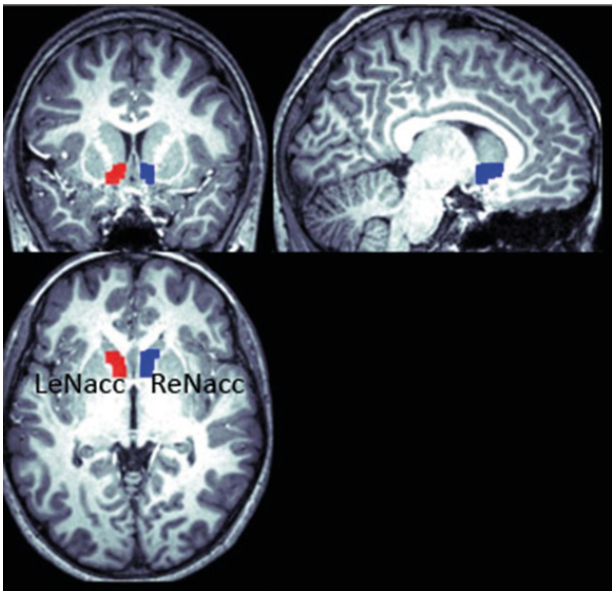
Note. Supplementary Table 1 shows differences in mean scores between ADHD-1, ADHD-2, ADHD (as a whole group) compared to typically developing children (control). ANOVAS were conducted to compare the groups on neurobiological, neurocognitive and behavioral measures. When comparing subgroup ADHD-1 and subgroup ADHD-2 sample sizes are nADHD-1=49, nADHD2=7. When comparing both ADHD subgroups to controls on activity in ROIs, sample sizes were nADHD-1 = 38, nADHD-2 = 5, ncontrol = 27. When comparing the ADHD subgroups to the control group on neuropsychological and behavioral measures, sample sizes were nADHD-1 = 38, nADHD-2 = 5, ncontrol = 28.

Supplementary Figure 1. Mask of left pallidum and left subthalamic nucleus



LePal, left pallidum; LeSTN, left STN.

Supplementary Figure 2. Mask of right and left nucleus accumbens



LeNacc, left nucleus accumbens; ReNacc, right nucleus accumbens

8

Summary and general discussion

Summary and general discussion

On a daily basis, clinicians bridge the gap between scientific knowledge of a diagnostic category on one side; and valuable anecdotal knowledge of a single child and all its distinctive characteristics on the other. Combining these sources of information is the backbone of clinical decision making. If neurobiological models of ADHD manage to incorporate individual differences among children with the same diagnosis, such models might be used to help guide clinical practice. So far, most of our knowledge on the neurobiology of ADHD comes from studies that have focused on group differences. In this thesis, we have tried to expand this knowledge by exploring possible pitfalls of this between-group approach. These pitfalls can be summarized in the following three questions:

- Are neurobiological differences specific to the diagnosis ADHD, or a more general feature of children with similar problems? (chapters 2, 3 and 5)
- Do neurobiological differences scale with ADHD symptom levels in a trans-diagnostic way? (chapters 2, 3 and 5)
- Are multiple, separable neurobiological pathways involved in ADHD? (chapters 6 and 7)

Summary

In Chapter 2 we disentangled different aspects of response inhibition: a neuropsychological function that is consistently found to be affected in studies of ADHD. We used a modified stop-signal task (a stop-signal anticipation task) to dissociate reactive inhibition (outright stopping) from proactive inhibition (anticipatory response slowing). We replicated the well-documented finding of attenuated reactive inhibition in children with ADHD. In addition, we found a similar deficit in children with ASD and a similar level of ADHD symptoms. In contrast, we found no evidence for deficits in proactive inhibition in either clinical group. These findings re-emphasize the role of reactive inhibition as a separable neuropsychological function that is affected in children with ADHD.

In Chapter 3 we focused on neurobiological functions related to predictions about what (cognitive control) and when (timing) events will happen. Both functions are involved in monitoring the environment, and altering behavior if predictions are violated. Accordingly, we analyzed cognitive control and timing in concert, in a

single child-friendly fMRI paradigm: a timing manipulated go/nogo task. We found group differences in brain activity related to predictions about when, but not what events will occur. Specifically, we found timing-related hypo-activity that was in part unique to children with a primary diagnosis of ADHD (left pallidum) and in part shared by children with similar levels of ADHD symptoms and a primary diagnosis of ASD (left subthalamic nucleus). Moreover, we found reduced task performance related to temporal expectancy, but only in children with ASD and symptoms of ADHD. Ultimately, such neurobiological changes in children with ADHD (symptoms) may relate to a failure to build or monitor predictive models and thereby hinder their efficient interaction with the environment.

Chapter 4 addresses an important intermediate step in this thesis. In order to test reward processing in children with ADHD, we first needed a child-friendly task to do so. We piloted a child-friendly modification of the monetary incentive delay (MID) task, a classical task to probe reward anticipation, in a group of typically developing children. To make the task better suited for children, we introduced a story line and a less abstract coding of reward magnitude. We found activity in bilateral ventral striatum during the anticipation of reward. In addition, we found an association between activity in ventral striatum and a task-based measure of individual reward sensitivity. We concluded that this child-friendly task probes ventral striatal activity and that it provides an additional measure of individual reward sensitivity that relates to this ventral striatal activity.

In chapter 5 we used this child-friendly MID task to assess brain activity during reward anticipation in children with ADHD. It was already established that adolescents and adults with ADHD show ventral striatum hypoactivity during reward anticipation. We found similar hypoactivity in ventral striatum in children (aged 8 to 12) with ADHD and in children with ASD and a similar level of ADHD symptoms. In addition, we found that activity in ventral striatum was positively associated with parent-rated reward sensitivity in daily life. This way, we provided evidence that neurobiological differences in reward processing are already present during childhood. Moreover, we showed that neurobiological differences were present in children with symptoms of ADHD, regardless of whether ADHD was the primary diagnosis.

In chapter 6 we aimed to identify different subgroups of children with ADHD, each with a distinct pattern of performance on neuropsychological tasks. We tested children and adolescents with ADHD on tasks of cognitive control, timing and reward sensitivity. Next, we used latent class analysis (LCA) to find subgroups on the basis of

task performance. We identified separable subgroups with distinct cognitive profiles. The largest subgroup we found (37% of participants) showed performance that was just as quick and accurate as typically developing controls. The second largest subgroup (31% of participants) showed an isolated inhibitory deficit. The third subgroup (20% of participants) showed slow and variable response times and had limited response time benefit on temporally predictable trials. In a post-hoc analysis we found that children in the second subgroup showed more internalizing problems than children in the other two subgroups. In all, we showed that by formally addressing heterogeneity in ADHD, we could identify more homogeneous subsets of individuals to further investigate.

In chapter 7 we took the opposite approach of using LCA on functional imaging data to explore whether we could identify neurobiological subgroups of children with ADHD symptoms. In this proof of concept study, children with symptoms of ADHD and typically developing children performed two neuropsychological tasks assessing reward sensitivity and temporal expectancy during fMRI. LCA was used to identify subgroups with homogeneous patterns of brain activity separately for children with ADHD-symptoms and typically developing children. Neurobiological, cognitive and behavioral differences between subgroups were then investigated. For typically developing children we found a single homogeneous group, whereas for children with ADHD-symptoms we found two subgroups. The first ADHD subgroup showed attenuated brain activity compared to the second subgroup and typically developing children. Notably, the second subgroup had more behavioral problems in everyday life. We showed that we could identify distinct subgroups of children with ADHD-symptoms based on their brain activity profiles. Ultimately, such subtle neurobiological differences may inform individually tailored treatment and indicate long-term developmental risks.

General discussion

Are neurobiological differences specific to the diagnosis ADHD or a more general feature of children with similar problems?

In three different studies included in this thesis, we addressed this question by adding a third group of children: Children with a primary diagnosis of ASD and parent-rated symptom levels of ADHD were included in addition to children with ADHD and typically developing children. This was done to achieve a more trans-diagnostic approach of the underlying neurobiology. At a group level, differences in brain structure, brain function and neuropsychological performance have consistently been found in ADHD (Alderson, Rapport, & Kofler, 2007; Cortese et al., 2012; Dickstein,

Bannon, Castellanos, & Milham, 2006; Hart, Radua, Mataix-Cols, & Rubia, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Huang-Pollock, Karalunas, Tam, & Moore, 2012; Lipszyc & Schachar, 2010; McCarthy, Skokauskas, & Frodl, 2014; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Noreika, Falter, & Rubia, 2013; Plichta & Scheres, 2014; Toplak, Dockstader, & Tannock, 2006; Valera, Faraone, Murray, & Seidman, 2007; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). However, it is uncertain if these neurobiological differences are specifically related to the diagnostic category of ADHD. Neurobiological differences could likewise be related to ADHD symptom levels across different diagnoses, rather than to an ADHD diagnosis per se (Coghill & Sonuga-Barke, 2012; Etkin & Cuthbert, 2014; Insel et al., 2010). As such, the following question can be asked: is it the assignment into diagnostic categories itself that accounts for the high association between ADHD and neurobiological changes? Or is it because ADHD is a trans-diagnostic, dimensional trait that is associated with the diagnosis and with neurobiological changes? In the latter case, group differences would be a result of the logical association between symptom levels and the diagnosis of ADHD. To answer our initial research question: no, most neurobiological differences in response inhibition, timing and reward processing were not specific to children with ADHD. Overall, a group of children with ASD and similar levels of ADHD symptoms showed a similar neurobiological and neuropsychological profile. The only exception we found was timing-related hypoactivity in left pallidum. When reviewing the literature on the neurobiology of psychiatric disorders in general, numerous trans-diagnostics deficits can be found (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). As an example, hypoactivity during reward anticipation is found in various psychiatric conditions including: schizophrenia, autism, major depressive disorder, ADHD and substance use disorder (Balodis & Potenza, 2015; G. S. Dichter et al., 2010; Gabriel S Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Juckel et al., 2006; Kohls et al., 2014; Smoski et al., 2009). It is tempting to assume specificity when a diagnostic group shows a neurobiological deficit. However, neurobiological deficits could likewise be an expression of a more general, trans-diagnostic form of dysfunction. In that case, a promising future direction is to explore which dimensions of this general dysfunction are associated with neurobiology across disorders. As such, our findings are in line with the recent push of the National Institute of Mental Health towards trans-diagnostic models of neurobiology, as is being facilitated by the Research Domain Criteria (Insel et al., 2010).

One could argue that if these children with a primary diagnosis of ASD, indeed have similar symptom levels of ADHD, they also fulfill criteria for ADHD. In that case we would not be looking at a group with a different diagnosis, but a group with a comorbid diagnosis of ASD. We would argue that as these children have a different primary

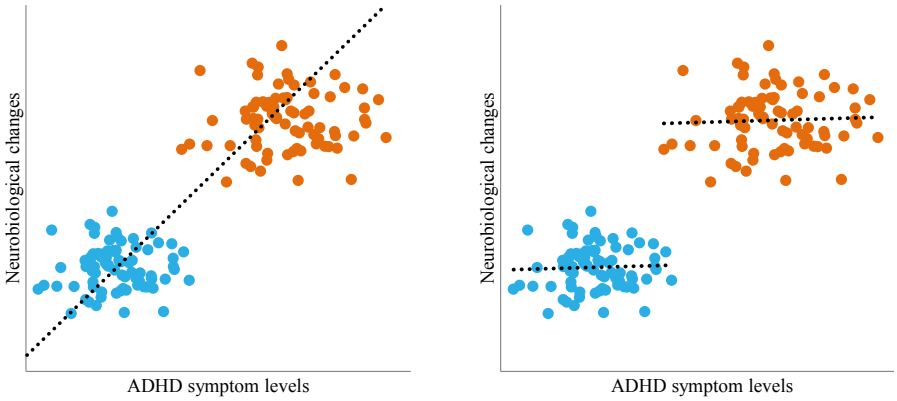
diagnosis and are treated as a qualitatively different group in clinical practice, these studies provide an important first step for studying trans-diagnostic mechanisms. However, to extend this line of reasoning, future studies could include diagnoses where the symptoms are qualitatively different from those of ADHD. An example would be to investigate a group of adolescents with major depressive disorder and similar levels of attention problems and to compare them to adolescents with ADHD.

Do neurobiological differences scale with ADHD symptom levels in a trans-diagnostic way?

This question can in part be seen as an extension of the previous one, as it addresses the association between a dimensional trait and neurobiology. We tested whether a higher level of ADHD symptoms coincides with greater neurobiological change. First, we tested this in the combined clinical group: children with symptoms of ADHD and a diagnosis of either ADHD or ASD (chapters 2, 3 and 5). Here, we found no evidence for a within-group correlation between parent-rated ADHD symptom levels and neurobiological measures of inhibition, timing and reward anticipation, respectively. Next, we tested this in typically developing children and again we found no within-group association. As such, the short answer appears to be: no, neurobiological differences do not linearly scale with ADHD symptom levels. However, an important limitation is that we did not test this across the entire population. Instead, we sampled three different groups at two extremes of the distribution. Children with ADHD and children with ASD were selected on the basis of high levels of ADHD symptoms. So, by definition, they represent the right-end tail of the population distribution of ADHD symptoms. Typically developing children were selected to show absolutely no behavior problems and thus may have represented the left-end tail of the distribution of ADHD symptoms, as opposed to the entire normal distribution.

The best way to assess a dimensional relationship is to conduct population studies. These type of studies across the entire distribution of ADHD symptoms have shown a positive correlation between levels of inhibitory control and symptom levels of ADHD (Crosbie et al., 2013; Tillman, Thorell, Brocki, & Bohlin, 2007). However, we could not replicate this when we assessed it in a patient group only (REF SSAT). Even when an association between a trait and neurobiology is found across the population, it may be worthwhile to separately test this association in a patient group. That is the only way that neuroscientists can inform clinicians by saying: in this patient group, a more severely affected phenotype is associated with a more severely affected neurobiology. Studies that try to find dimensional associations often test across a combined patient and control group. This way, a strict categorical difference can be interpreted as a

Figure 1. A spurious dimensional relation between neurobiology and ADHD symptom levels



The left panel shows an example image of the relation between neurobiology and ADHD symptom levels when tested across a combined clinical and typically developing group. The right panel shows the same example data, but now tested separately within both groups. Note that the initial dimensional relationship between neurobiology and ADHD symptoms disappears when both groups are assessed separately.

dimensional one (see figure 1). As an example, the negative correlation between brain activity during reward anticipation and trait impulsivity that was found for children with ADHD (Plichta & Scheres, 2014) is in part based on these type of spurious dimensional associations (e.g. Carmona et al., 2012; Scheres, Milham, Knutson, & Castellanos, 2007).

In addition, different models of behavior by biology interactions may account for the lack of a dimensional association between ADHD symptom levels and neurobiology (Breakspear & Terry, 2002). For example, if the relation between neurobiology and ADHD symptom levels is a non-linear one, especially if the relation is non-linear at the ends of the distribution, we would have had very limited power to detect this association (Breakspear & Terry, 2002; Breakspear, 2006). Another explanation for the absence of such a linear relation may be that at the end of the distribution (e.g. in the clinical groups) there is an increased influence of environmental factors on the expression of ADHD symptoms. This would fit the diathesis-stress and differential susceptibility models of nature-nurture interactions (Belsky, Bakermans-kranenburg,

& Van IJzendoorn, 2007; Belsky & Pluess, 2009; Monroe & Simons, 1991; Nuechterlein & Dawson, 1984). In these theories, biological factors determine if individuals are resilient or vulnerable/malleable to environmental factors. For example, a diathesis-stress model of the relation between neurobiology and ADHD symptoms could describe an innate neurobiology that puts children at risk for developing ADHD symptoms, while ultimately environmental factors determine the degree of ADHD symptomatology. Future studies could assess whether this null-finding is a result of an increased within-group influence of environment in children with a diagnosis of ADHD as compared to the influence of environment in a population based sample.

In the end, phenotypical heterogeneity in ADHD in itself is not a reason to discard categorical models of developmental disorders (Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010). Well known medical conditions such as influenza clearly show the possibility of a homogeneous etiology with a heterogeneous clinical expression. Moreover, dimensional models of (dys)functioning necessitate equally stringent validation as categorical ones (Lawrie et al., 2010; Pickles & Angold, 2003). So far, no sufficient evidence has been accumulated to justify a definite preference for a continuum (or multiple continua) to define ADHD over the current categorical definition.

Can multiple, separable neurobiological pathways be involved in ADHD?

There has been a recent surge of theories that suggest that multiple, separable neurobiological pathways can lead to ADHD (Durston, van Belle, & de Zeeuw, 2011; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2002, 2003, 2005). In response to this, different studies have tried to empirically confirm this heterogeneity (e.g. De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Fair, Bathula, Nikolas, & Nigg, 2012; Sonuga-Barke, Bitsakou, & Thompson, 2010; van Hulst, de Zeeuw, & Durston, 2015). Early studies showed that for every neuropsychological domain, only a minority of children with ADHD can be considered to be deficient (Nigg et al., 2005). Other studies tested different neuropsychological domains and concluded that both were affected in ADHD, but not correlated with each other (Solanto et al., 2001). Following on this, studies tried to cluster neuropsychological measures into separable domains and then judge which percentage was affected in each domain (De Zeeuw et al., 2012; Sonuga-Barke et al., 2010). To judge which percentage was affected an arbitrary cut-off was determined on the basis of scores from typically developing children. These authors concluded that if a child is affected in one domain, the chance that it is affected in the other is not above chance-level (De Zeeuw et al., 2012; Sonuga-Barke et al., 2010).

While these results all tend to favor the multiple pathway hypothesis, none of them is a direct answer to the question: are there separable neurobiological subgroups among children with ADHD? In the two last chapters of this thesis, we tried to answer exactly that question. In both studies, we found subgroups of children with ADHD with a distinct neurobiological profile. In the first study, these subgroups were based on neuropsychological performance measures; in the second study, subgroups were based on brain activity levels during task performance. The subgroups that were found using this data-driven approach were tested for differences in other domains, such as parent-rated behavior scales. In this thesis, we have shown that neurobiological subgroup identification is a valuable way to generate new hypotheses. First and foremost this should be seen as a proof of principle: we show a direct way of testing whether neurobiological subgroups exist within a diagnostic group. It is important to mention that before any definite interpretation can be given to these subgroups, the stability of subgroups over time should be assessed. In all, the technique is far from making any claims about the etiology or biological validity of these subtypes. Longitudinal studies using subgroup identification techniques will be particularly valuable in this regard, as they can directly address their predictive value. This way, neurobiologically defined subgroups might eventually improve predictions about developmental trajectories of children; or even improve predictions about treatment response (Fair et al., 2012).

Clinical implications

There are multiple ways in which clinical practice could potentially benefit from neurobiological knowledge. A very restricted way is by designing neurobiological tests with clinical implications (e.g. Kambeitz et al., 2015). For example, MRI techniques could potentially be used to confirm a diagnosis and determine a treatment plan based on this. However, so far, no proven method to do so exists (Borgwardt, Radua, Mechelli, & Fusar-Poli, 2012; Weinberger & Radulescu, 2015). Other, indirect ways of translating neurobiological findings to clinical practice might be more promising. An intermediate form can be found in a detailed neurobiological validation of neuropsychological tests. Children could perform out-of-scanner neuropsychological testing and, if the relationship with brain activity is studied extensively beforehand, statements could be made about neurobiological functioning. An example of this can be found in chapter 5, where we found an association between the speeding of response times when reward is at stake, and brain activity during the anticipation of reward. Yet sensitivity and specificity of this relationship should be well validated, before such a direct neurobiological interpretation of task performance can be implemented in clinical practice (Borgwardt et al., 2012). There is a third way in which clinical practice could benefit from neurobiological knowledge. Insight into

neurobiological mechanisms that lead to behavior could improve our understanding of that behavior. As an example: if we know that a subgroup of children with ADHD has a reduced release of dopamine in anticipation of reward and we also know how anticipatory dopamine release relates to behavior, we might be able to identify these children on the basis of behavior alone. Our judgement of behavior would then be informed by neurobiological knowledge, without the need to first scan every child. Ultimately, this could lead to improved treatment options, tailored to the needs of the individual child. For this approach to work, it is not only important to establish the relationship between a diagnosis and neurobiology, but also the relationship between individual behavioral measures and neurobiology. The positive association we found between reward drive and brain activity in anticipation of reward, might be a first step towards such a neurobiologically informed assessment of behavior. We found that during reward anticipation, children with ADHD who show a brain activity profile similar to that of typically developing children actually have more severe attention problems. One interpretation of this finding is that children actually exhibit ADHD-related behavior as an auto-regulatory mechanism to compensate for a lack of arousal (Geissler, Romanos, Hegerl, & Hensch, 2014; Zentall & Zentall, 1983). These children might deploy behavior that is heavily focused on short-term reward as a mechanism to normalize dopaminergic neurotransmission. If the characteristic inattentive, hyperactive and impulsive behavior can be interpreted as a compensatory mechanism for an understimulated brain, arousal levels may be considered a direct target for treatment (for an example see: Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010). Of course, this finding has to be replicated, preferably in a longitudinal design. Moreover, more direct tests of this hypo-arousal theory should be designed. Still, the finding shows how neurobiological knowledge can provide a different perspective on behavior and eventually via behavior, on clinical practice.

To conclude

In this thesis, we have explored different options to move away from solely studying between-group differences and towards neurobiological models of ADHD that incorporate individual differences. In the end, studying developmental disorders at this point in time is not about constructing a perfect biophysical model that explains all psychological functioning. It is about choosing models of underlying biology that work best; that help us understand behavior a little better, and in turn help improve our predictions of what will and what will not work for an individual child.

By addressing individual differences in the neurobiology of children with ADHD and more generally, in the neurobiology of children with symptoms of ADHD, we

showed the following:

- As a group, children with ADHD are affected in multiple neuro-psychological domains: reward sensitivity, timing and cognitive control (chapters 2, 3, 5 and 6).
- The deficit in response inhibition that is consistently found in children with ADHD is a deficit of reactive inhibition; we found no evidence for a deficit of proactive inhibition (chapter 2).
- Neurobiological deficits studied in this thesis are mostly not specific to ADHD, but are shared with children with ASD and similar levels of parent-rated ADHD symptoms (chapters 2, 3 and 5).
- Within a trans-diagnostic group of children with ADHD symptoms, there is no clear-cut linear association between higher levels of ADHD related behavior and reduced brain activity or impaired task performance (chapters 2, 3 and 5).
- Within the trans-diagnostic group of children with ADHD symptoms, reward sensitivity in daily life is positively associated with brain activity during reward anticipation (chapter 5).
- Within a group of children with (symptoms of) ADHD, different subgroups of children can be identified on the basis of distinct neuropsychological and neurobiological profiles (chapters 6 and 7).

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NL

Nederlandstalige samenvatting

Samenvatting

Iedere dag weer combineren clinici informatie over een individueel kind met ADHD, met wetenschappelijke kennis over ADHD op groepsniveau. Aan de ene kant is het duidelijk dat kinderen met eenzelfde diagnose toch uniek zijn en op vele manieren van elkaar verschillen. Aan de andere kant heeft de wetenschap ons geleerd om individuen in groepen in te delen zodat we betere, generaliseerbare uitspraken kunnen doen. Het maken van zulke diagnostische groepen is altijd arbitrair, zeker wanneer het onderliggende werkingsmechanisme van een stoornis niet duidelijk is. Je zou kunnen zeggen dat een diagnostische categorie zo sterk is als zijn voorspellende waarde, en dat de grenzen van een diagnose aan die voorspellende waarde kunnen worden aangepast. Tot op heden is een volledig gedragsmatige definitie van ADHD van waarde geweest voor kinderen met een combinatie van aandachtsproblemen, hyperactiviteit en impulsiviteit. Een veelbelovende volgende stap is om deze gedragsmatige definitie te verrijken met informatie vanuit neurobiologische studies en wel op zo'n manier dat er rekening wordt gehouden met individuele verschillen tussen kinderen met ADHD. Kort gezegd is de reden om de individuele verschillen in de neurobiologie van kinderen met ADHD te bestuderen, dat deze verschillen een voorspellende waarde kunnen hebben. Neurobiologische profielen zouden kunnen helpen om te voorspellen hoe een kind zich zal ontwikkelen of bij welke behandeling een kind het meest gebaat zou zijn. Dit proefschrift gaat in op meerdere aspecten van deze interindividuele verschillen: trans-diagnostische mechanismen, dimensionaliteit en heterogeniteit.

Het zou voor de klinische praktijk bijvoorbeeld effectief kunnen zijn om ADHD-gedrag te modelleren als een dimensionele eigenschap die diagnostische categorieën overstijgt (Coghill & Sonuga-Barke, 2012). Als de onderliggende neurobiologie inderdaad beter overeenkomt met een dimensionele ADHD-score dan met een ADHD-categorie, dan zouden zulke scores een model van ADHD kunnen vormen dat beter rekening houdt met individuele verschillen. In dit proefschrift hebben we getoetst of een hogere mate van ADHD-gedrag, samenhangt met een hogere mate van neurobiologische verstoring, los van welke diagnose is gesteld. Om dit te testen hebben we, naast een groep kinderen met ADHD en een groep kinderen zonder diagnose, een groep kinderen meegenomen met een diagnose in het autisme spectrum én symptomen van ADHD. Verder hebben we de kinderen getest op verschillende neurobiologische domeinen. We onderzochten of er meerdere, deel onafhankelijke neurobiologische paden, naar hetzelfde ADHD-gedrag konden leiden. Zulke oorzakelijke heterogeniteit zou grote gevolgen kunnen hebben voor de klinische toepasbaarheid van resultaten van neurobiologische studies naar ADHD. Als de oorzaken van ADHD inderdaad verschillen van kind tot kind, dan zouden voorspellingen op basis van één enkele neurobiologische theorie er altijd naast zitten voor een subgroep van kinderen met

ADHD. Deze vragen rondom interindividuele verschillen in de neurobiologie van ADHD leidden uiteindelijk tot de volgende onderzoeksvragen:

- Zijn neurobiologische verschillen specifiek voor de diagnose ADHD of zijn zij een algemene eigenschap van kinderen met vergelijkbare problemen? (hoofdstuk 2, 3 en 5)
- Hangt de grootte van de neurobiologische verschillen samen met de hoeveelheid ADHD-symptomen op een manier die diagnostische categorieën overstijgt? (hoofdstuk 2, 3 en 5)
- Zijn er meerdere, deels onafhankelijke neurobiologische paden die tot ADHD kunnen leiden? (hoofdstuk 6 en 7)

Zijn neurobiologische verschillen specifiek voor de diagnose ADHD of zijn zij een algemene eigenschap van kinderen met vergelijkbare problemen?

In drie verschillende hoofdstukken van dit proefschrift zijn we op deze vraag ingegaan. Een belangrijke stap om dit te onderzoeken was het meenemen van een derde groep kinderen: naast kinderen met ADHD en kinderen zonder diagnose, onderzochten wij een groep kinderen met een autisme spectrum diagnose én symptomen van ADHD. Dit hebben we gedaan om naar ADHD-symptomen te kijken, zonder alleen naar ADHD als diagnose te kijken.

Op groepsniveau worden consistent verschillen gevonden in hersenstructuur, hersenfunctie en neuropsychologie bij mensen met ADHD (Alderson, Rapport, & Kofler, 2007; Cortese et al., 2012; Dickstein, Bannon, Castellanos, & Milham, 2006; Hart, Radua, Mataix-Cols, & Rubia, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Huang-Pollock, Karalunas, Tam, & Moore, 2012; Lipszyc & Schachar, 2010; McCarthy, Skokauskas, & Frodl, 2014; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Noreika, Falter, & Rubia, 2013; Toplak, Dockstader, & Tannock, 2006; Valera, Faraone, Murray, & Seidman, 2007; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). Toch is het nog onzeker of deze neurobiologische verschillen specifiek zijn voor de diagnose ADHD. Een andere mogelijkheid is dat deze verschillen gerelateerd zijn aan symptomen die veel voorkomen bij ADHD, onafhankelijk van welke diagnose is gesteld (Coghill & Sonuga-Barke, 2012; Etkin & Cuthbert, 2014; Insel et al., 2010). In dat tweede geval zouden er uiteraard nog steeds groepsverschillen worden gevonden. Om een direct antwoord te geven op onze onderzoeksvraag: nee, de meeste neurobiologische verschillen (verschillen in respons inhibitie, beloningsgevoeligheid en in het verwerken van tijdsgebonden stimuli) waren niet specifiek voor de groep kinderen met ADHD. Alleen verminderde activiteit in de linker globus pallidus tijdens het verwerken van temporele informatie, was specifiek voor kinderen met een diagnose ADHD. In het algemeen werd bij kinderen met autisme en eenzelfde mate van ADHD-symptomen, eenzelfde neurobiologisch en neuropsychologisch profiel gevonden. Wanneer je naar de wetenschappelijke literatuur kijkt, kom je vaker zulk soort trans-diagnostische eigenschappen tegen (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). De verminderde activiteit tijdens het anticiperen op beloning wordt bijvoorbeeld gevonden bij verscheidene psychiatrische aandoeningen zoals schizofrenie, autisme, depressie, ADHD en middelenmisbruik (Balodis & Potenza, 2015; Dichter & Adolphs, 2012; Dichter et al., 2010; Juckel et al., 2006; Kohls et al., 2014; Smoski et al., 2009). Wanneer een onderzoeker een neurobiologische dysfunctie identificeert, is het verleidelijk om ervan uit te gaan dat de dysfunctie specifiek is voor de diagnose die op dat moment wordt onderzocht. Toch kan een gevonden neurobiologische dysfunctie net zo goed samenhangen met een eigenschap die bij verschillende diagnoses

past. Een veelbelovende stap om dit verder te onderzoeken is om na te gaan welke gedragseigenschap van een bepaalde diagnose precies samenhangt met de gevonden neurobiologie.

Men zou kunnen betogen dat kinderen met een autisme spectrum stoornis en dezelfde mate van ADHD-symptomen, zoals wij die hebben geïncludeerd, ook gewoon aan de diagnose ADHD voldoen. In dat geval zou onze derde groep niet puur een groep kinderen met een andere diagnose zijn, maar eerder een groep met een extra diagnose. Wij betogen dat, aangezien deze kinderen een andere hoofddiagnose hebben en in de klinische praktijk als een kwalitatief andere groep worden behandeld, deze studie een belangrijke eerste stap zet in het onderzoeken van trans-diagnostische mechanismen. Om deze manier van denken verder te onderzoeken zouden toekomstige studies een groep kunnen meenemen waarbij de symptomen kwalitatief nog verder verschillen van de symptomen bij ADHD. Een voorbeeld hiervan is een groep adolescenten met een depressie, maar met precies dezelfde mate van aandachtsproblemen als adolescenten met ADHD.

Hangt de grootte van de neurobiologische verschillen samen met de hoeveelheid ADHD-symptomen op een manier die diagnostische categorieën overstijgt?

Deze vraag ligt in het verlengde van de voorgaande, aangezien het gaat over het verband tussen een dimensionele eigenschap en neurobiologie. Wij onderzochten of een hogere mate van ADHD-symptomen, samengaat met een groter verschil in neurobiologie. Als eerste onderzochten wij dit in de gecombineerde klinische groep (kinderen met ADHD én kinderen met autisme en symptomen van ADHD). Binnen deze groep vonden we geen bewijs voor een verband tussen de mate van ADHD-symptomen en de mate van neurobiologische verschillen in inhibitie, de anticipatie van beloning of het verwerken van tijdsgebonden stimuli. Vervolgens onderzochten wij dit binnen de groep kinderen zonder diagnose, ook hier vonden we geen dergelijk verband. Het korte antwoord lijkt dus te zijn: nee, neurobiologische verschillen schalen niet met ADHD-symptomen.

Een belangrijke beperking van deze studie is dat we dit niet hebben onderzocht in de algemene bevolking. In plaats daarvan hebben we groepen geselecteerd aan twee uiteindes van de normale verdeling. Kinderen met ADHD en kinderen met autisme werden geselecteerd op basis van hun hoge mate van ADHD-symptomen. Deze kinderen vertegenwoordigen dus per definitie het uiteinde van de verdeling van ADHD-symptomen in de bevolking. De kinderen zonder diagnose daarentegen, waren geselecteerd op basis van het feit dat zij helemaal geen gedragsproblemen

lieten zien en vertegenwoordigen dus mogelijk het andere uiterste van het spectrum. De beste manier om een volledig dimensionele relatie te vinden is met behulp van een populatiestudie in de algemene bevolking. Dit type studie heeft eerder een verband laten zien tussen inhibitie en ADHD-symptomen (Crosbie et al., 2013; Tillman, Thorell, Brocki, & Bohlin, 2007). Wij vonden het waardevol om ook los binnen één of meerdere diagnostische categorieën naar dit verband te kijken. Dit is de enige manier waarop neurowetenschappers tot een uitspraak zouden kunnen komen als: "binnen deze patiëntengroep is ernstiger aangedaan gedrag geassocieerd met een ernstiger aangedane neurobiologie". Een uitspraak die voor clinici zeer relevant zou zijn. In onze studies lukte het niet om dit verband te vinden binnen de groep van kinderen met een diagnose (hoofdstuk 3).

Het ontbreken van een dergelijk dimensioneel verband zou ook verklaard kunnen worden door de manier waarop gedrag en biologie interacteren (Breakspear & Terry, 2002). Als dit verband er wel is, maar bijvoorbeeld op een sterk non-lineaire wijze, dan zouden we ten onrechte kunnen concluderen dat er geen verband is (Breakspear & Terry, 2002; Breakspear, 2006). Een interessante aanvullende verklaring voor het ontbreken van een dergelijk verband in deze studies, is dat aan het einde van normale verdeling (dus in de klinische groepen) de invloed van omgevingsfactoren op het voorkomen van ADHD-symptomen vergroot zou kunnen zijn. Dit zou kunnen passen bij de differential susceptibility hypothese (Belsky, Bakermans-kranenburg, & Van IJzendoorn, 2007; Belsky & Pluess, 2009; Monroe & Simons, 1991; Nuechterlein & Dawson, 1984). Volgens die theorie kunnen biologische factoren bepalen in hoeverre individuen vatbaar zijn voor omgevingsinvloeden. Een voorbeeld hiervan zou zijn dat een bepaalde aangeboren neurobiologie kinderen vatbaar maakt voor de ontwikkeling van ADHD, maar dat omgevingsinvloeden uiteindelijk bepalen in welke mate ADHD-symptomatologie tot ontwikkeling komt. Interessant in dit opzicht zouden toekomstige studies zijn waarbij wordt gekeken of de invloed van omgeving op ADHD-symptomatologie binnen de hele populatie kleiner is dan binnen de groep kinderen met de diagnose ADHD.

Uiteindelijk is het feit dat kinderen met ADHD erg van elkaar verschillen op zichzelf geen reden om de diagnose ADHD te verwerpen (Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010). Een veelvoorkomende medische aandoening zoals de griep laat duidelijk zien hoe een homogene etiologie kan leiden tot een heterogeen klinisch beeld. Bovendien, voor dimensionele modellen van psychisch functioneren is net zo'n stringente validatie nodig als voor categorische diagnoses (Lawrie et al., 2010; Pickles & Angold, 2003). Op dit moment is er nog geen overtuigend bewijs om een voorkeur voor een strikt dimensionele definitie van ADHD, boven de huidige categorische

definitie, te rechtvaardigen.

Zijn er meerdere, deels onafhankelijke neurobiologische paden die tot ADHD kunnen leiden?

In de afgelopen decennia is de aandacht voor theorieën waarin meerdere, deels onafhankelijke neurobiologische paden tot ADHD kunnen leiden, toegenomen (Durston, van Belle, & de Zeeuw, 2011; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2002, 2003, 2005). Als reactie hierop hebben verschillende studies deze heterogeniteit in een testsituatie willen bevestigen (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Fair, Bathula, Nikolas, & Nigg, 2012; Sonuga-Barke, Bitsakou, & Thompson, 2010; van Hulst, de Zeeuw, & Durston, 2015). Vroege studies hierover lieten zien dat binnen elk neuropsychologisch domein, slechts een minderheid van de kinderen met ADHD is aangedaan (Nigg et al., 2005). Andere studies lieten zien dat kinderen met ADHD wel aangedaan zijn op verschillende domeinen, maar dat in hoeverre iemand is aangedaan op het ene domein niet samenhangt met de prestaties in het andere domein (Solanto et al., 2001). Hierop volgend hebben studies geprobeerd verschillende neuropsychologische maten te clusteren in onafhankelijke domeinen, om vervolgens te berekenen welk percentage van de kinderen was aangedaan binnen ieder domein (De Zeeuw et al., 2012; Sonuga-Barke et al., 2010). Om dit percentage te bepalen werd gebruikt gemaakt van arbitraire cutoff criteria, gebaseerd op de prestaties van kinderen zonder diagnose. De auteurs concludeerden dat als een kind is aangedaan op het ene neuropsychologische domein, de kans dat hij of zij ook aangedaan is op het andere domein niet boven het kans-niveau ligt: een aanwijzing voor meerdere onafhankelijke paden die tot ADHD kunnen leiden (De Zeeuw et al., 2012; Sonuga-Barke et al., 2010).

Hoewel deze resultaten allemaal in de richting wijze van de multiple pathway hypothese, geeft geen van deze studies een direct antwoord op de vraag: zijn er verschillende neurobiologische subgroepen onder kinderen met ADHD? In de laatste twee hoofdstukken van dit proefschrift probeerden we een antwoord te vinden op precies deze vraag. In beide studies vonden we subgroepen van kinderen met ADHD met een specifiek neuropsychologisch of neurobiologisch profiel. In de eerste studie zijn de subgroepen gebaseerd op scores op neuropsychologische testen; in de tweede studie zijn de subgroepen gebaseerd op hersenactiviteit tijdens het uitvoeren van verschillende taken. We hebben de subgroepen die werden gevonden met deze data-gedreven aanpak, vervolgens getoetst op verschillen andere terreinen, zoals gedrag in het dagelijks leven. In deze studies hebben we laten zien dat het identificeren van subgroepen op basis van neuropsychologie of neurobiologie, een waardevolle manier

is om nieuwe hypotheses te genereren. Bovenal zien wij dit als een proof of principle: we laten zien dat er een directe manier is om de aanwezigheid van neurobiologische subgroepen te toetsen. Het is belangrijk om hier te melden dat, voordat we al te veel interpretatie aan de subgroepen geven, de stabiliteit en validiteit van deze subgroepen eerst moet worden onderzocht, bij voorkeur in longitudinale studies. Uiteindelijk zouden neurobiologische subgroepen gebruikt kunnen worden om voorspellingen over het ontwikkelingstraject van kinderen, of over welke behandeling het beste werkt, te verbeteren (Fair et al., 2012).

Klinische toepasbaarheid

De klinische praktijk kan op verschillende manieren baat hebben bij neurobiologisch onderzoek. Een veel genoemde, maar beperkte manier om hier naar te kijken, is door te kijken naar neurobiologische testen met klinische implicaties (voor een voorbeeld zie: Kambeitz et al., 2015). De suggestie is dat MRI-technieken gebruikt zouden kunnen worden om een diagnose te bevestigen en een behandelplan op te stellen. Een dergelijke toepassing van neurobiologische kennis binnen de psychiatrie bestaat op dit moment niet (Borgwardt, Radua, Mechelli, & Fusar-Poli, 2012; Weinberger & Radulescu, 2015). Andere, meer indirecte manieren om neurobiologisch onderzoek te vertalen naar de klinische praktijk zijn allicht vruchtbaarder. Een groter inzicht in neurobiologische mechanismen die ten grondslag liggen aan gedrag, kan ons begrip van dat gedrag vergroten. Om een voorbeeld te noemen: wanneer we weten dat een subgroep van kinderen met ADHD een verminderde dopamine-afgifte heeft tijdens de anticipatie van beloning en we weten ook hoe de anticipatoire dopamine-afgifte samenhangt met gedrag, dan zouden we deze kinderen op de basis van gedrag alleen kunnen identificeren. Onze beoordeling van gedrag zou dan deels gestuurd worden door neurobiologische kennis, zonder dat we eerst ieder kind hoeven te scannen. Uiteindelijk kan dit leiden tot verbeterde behandelmogelijkheden toegespitst op de behoefte van het individuele kind. Dit kan alleen als we het verband tussen diagnose en neurobiologie én het verband tussen gedragsmaten en neurobiologie duidelijk in kaart hebben. De samenhang tussen beloningsgevoeligheid in het dagelijks leven en hersenactiviteit tijdens de anticipatie van beloning kan zo'n eerste stap zijn richting een door de neurobiologie geïnformeerde kijk op gedrag. Wij vonden dat bij kinderen met ADHD waarbij de hersenactiviteit tijdens beloningsanticipatie het meest leek op de hersenactiviteit van kinderen zonder diagnose, de aandachtsproblemen juist het meest uitgesproken waren. Een mogelijke verklaring hiervoor is dat ADHD-gedrag een compensatiemechanisme is voor een gebrek aan neurobiologische activiteit (Geissler, Romanos, Hegerl, & Hensch, 2014; Zentall & Zentall, 1983). Kinderen zouden dan gedrag laten zien dat sterk gericht is op beloning op de korte termijn, om daarmee hun dopaminerge hersenactivatie te normaliseren. Als het karakteristieke

aandachtsgestoorde, hyperactieve en impulsieve gedrag inderdaad kan worden gezien als een compensatiemechanisme voor een onder-gestimuleerd brein, dan zou de behandeling zich daar direct op kunnen richten (voor een voorbeeld hiervan zie de studie van Söderlund en collega's (2010)). Uiteraard zal onze bevinding eerst moeten worden gerepliceerd, liefst in longitudinale studies, en zou deze theorie vervolgens meer direct getoetst moeten worden. Toch laat deze bevinding goed zien hoe neurobiologische kennis ons perspectief op gedrag en daarmee uiteindelijk ons perspectief op de klinische praktijk, kan veranderen.

Conclusies

- Als groep zijn kinderen met ADHD aangedaan op verschillende neuropsychologische domeinen: beloningsgevoeligheid, timing en inhibitie.

- De gebrekkige respons inhibitie die herhaaldelijk is gevonden bij kinderen met ADHD lijkt een gebrek aan reactieve inhibitie; we vonden geen bewijs voor een gebrek aan proactieve inhibitie.

- Neurobiologische bevindingen in dit proefschrift waren grotendeels niet specifiek voor ADHD, maar werden ook gevonden in kinderen met autisme en een vergelijkbare hoeveelheid ADHD-gedrag.

- Binnen de hele groep van kinderen met symptomen van ADHD is er geen duidelijk lineair verband tussen ADHD-gedrag en hersenactivatie of taakprestaties.

- Binnen de hele groep van kinderen met symptomen van ADHD is meer beloningsgevoeligheid in het dagelijks leven, geassocieerd met meer hersenactiviteit tijdens de anticipatie van beloning.

- Binnen de hele groep van kinderen met symptomen van ADHD kunnen we verschillende subgroepen identificeren op basis van verschillende neuropsychologische en neurobiologische profielen.

Concluderend

In dit proefschrift hebben we verkend hoe bij het onderzoek naar ADHD rekening kan worden gehouden met individuele verschillen, in tegenstelling tot onderzoek op basis van groepsverschillen alleen. Uiteindelijk gaat het bij het bestuderen van ontwikkelingsstoornissen niet over het uitwerken van een perfect biofysisch model dat al het psychologisch functioneren kan verklaren. Het gaat over het kiezen van die

biologische modellen die ons helpen gedrag net iets beter te begrijpen; modellen die helpen om onze voorspellingen te verbeteren over wat wel en wat niet zal werken bij een individueel kind.

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De adoptiestagiaries. Het gaat wat ver om iedereen hier apart te benoemen, maar sommige van mijn adoptiestagiaires kan ik toch echt niet onbenoemd laten: het was leuk om jullie vanaf de zijlijn te zien groeien binnen Niche. **Julia**, de beloningsschema's om aan het werk te blijven zal ik niet snel vergeten. Al zijn we door ons arbeidsethos

nooit echt ver gekomen met Jungle Book. **Hanne**, het is ook zo wat om jou te reduceren tot hofleverancier van babydierenfilmpjes, maar goed waren ze zeker.

Afdeling Psychiatrie. En dan de grote club, daar zitten ook nog wel een aantal mensen waar ik een hartig dankwoordje mee wil spreken. **Pascal**: 'Gedaan! de muis voelt zich weer helemaal'. **Nikita**, als er iemand een trouw pleitbezorger was voor meer gezelligheid, dan was jij het. Met als hoogtepunt de borrel met kerstverhaal. **Marc**, dit is bij uitstek de plek om een grap te maken of een anekdote op te halen, maar ik ga het niet doen. Jij bent een van die mensen die net een stapje verder waren en die ik af en toe als voorbeeld heb genomen. Dank daarvoor. **Martijn**, het schept een band om samen een geheim te delen over het goedhouden van een relatie. Ok, ik heb mij stellig voorgenomen om niet een lijst met namen te maken die ik dan allemaal bedank, maar daardoor vallen er hier een hoop mensen af waarmee ik een goede tijd heb gehad. Sorry, maar jullie weten toch ook zonder dat ik jullie noem, dat ik jullie heel hoog heb zitten? Toch **Lucija? Annabel? Maya? Marscha? Sanne's?**

Oud Niche. Marieke, was het symbolisch dat ik het eerste jaar op jouw fiets door Utrecht fietste? **Janna**, het was een eer om zo nu en dan te mogen opereren als vertaler van het Janna-iaans naar gewone mensentaal (lees: mensen zonder synesthesie). Man, wat denk jij snel en veel en divergent. **Tamar**, je drukte mij altijd op het hard om van Amsterdam te genieten zolang ik er nog zou wonen. Ik volg je advies nog elke dag op. **Sanne de Wit**, het organisatorisch powerhouse. **Juliette**, de oermoeder van alle onderzoeksassistentes, de grote vriendelijke probleemoplosser. **Fenny**, de startloper van de 531 estafette. **Lizanne**, de onderwijsvernieuwer. **Tilman**, der kleine General. **Kelli**, our American polyglot and **Szilvia**, with whom I learned to walk in the wonderfull place that is Matlab. Allemaal bedankt.

De Tippelaars. Geestesvaders van het nivellerende hardlopen. Niets boven een goede woensdagavondtippel om de werkweek door midden te zagen. Wat ik van jullie en van een monsterlijk grote schaal Tzatziki heb geleerd: 'als niemand wil, dan moeten we met z'n allen'.

De Kolchoz. Mannen. Het zal jullie niet verbazen dat een groot deel van het fundament voor dit wetenschappelijk werk al bijzonder vroeg is gelegd. Geheel volgens de Kolchoz-filosofie is dit boekje dan ook geen individueel werk, maar een product van ons allen. De relevantie van de uitspraak 'ook hadden we plexiglas over het doolhof kunnen leggen, alleen hadden we niet zoveel plexiglas' kan haast niet worden overschat. Eenmaal hierop gewezen zie je overal in de wetenschap parallellen.

En ja, **Ivo**, ook de fototaxis van vliegenmaden was een belangrijke leidraad. Het was allebei belangrijk. Dus dat het een combinatie is. Het is jullie verder vast ook niet ontgaan dat het Kolchoz motto 'gutes Qualität und billige Preisen' ook bij het drukken van dit proefschrift voorop heeft gestaan.

De Van Lennep. Zonder jullie buitenproportionele hoeveelheden eten had ik hier überhaupt niet meer gezeten. Maar vooral de gratis gezelligheid die ik met jullie altijd om me heen heb verdient een eervolle vermelding.

Teun en José. Het was bij vlagen confronterend om te zien hoe weinig woorden ik schreef in de tijd dat jullie een heel appartement verbouwden. Daar stond dan weer tegenover dat ik altijd één trap verwijderd was van een goede koffiepauze/lunch met bijbehorende goede gesprekken.

Mams. Aan het begin van de middelbare school heb je mij een keer uitgelegd dat je na een studie nóg langer door kan gaan met school, namelijk door te promoveren. Mijn reactie was toen iets in de trant van: 'ja daahag, dat ga ik dus echt nooit doen'. Maar jij weet als geen ander hoe je een idee in mijn hoofd kan planten. Was jij het niet ook, die mij een aantal jaar daarvoor uitlegde wat een psychiater was… Het blijft een beetje een vreemde plek om je moeder te bedanken, die dank voert wel wat verder dan alleen zo'n proefschrift. Maar toch, als iemand mij altijd onvoorwaardelijk heeft gesteund, ben jij het wel. Ook hierin. Bedankt voor alles.

Sytske. Jaaha! Daar sta je dan. Een prima plekje in het dankwoord. Achter elke sterke vrouw staat een sterke man en ik ben blij dat ik dat mag zijn. Ook hier is bedanken een beetje gek. Het is gewoon fijn om thuis te komen bij iemand waar je stiekem fan van bent. Waarmee je zonder uitzondering nog elke avond aan het lachen bent. Uiteindelijk kan ik het niet beter zeggen dan de hamsters van de supermarkt: 'ze krijgen ons niet klein, omdat we dat al zijn'.

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Publications

Journal articles

Van Hulst, B. M., de Zeeuw, P., Vlaskamp C., Rijks, Y., Zandbelt, B.B., & Durston, S. Children with ADHD symptoms show deficits in reactive but not proactive inhibition, irrespective of their formal diagnosis. Manuscript submitted.

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Abstracts

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Van Hulst, B. M., de Zeeuw, P., Lupas, K., Neggers, S. F. W., & Durston, S. (2015). A developmentally appropriate version of the MID task can elicit striatal activity. Poster presentation on the 2015 Annual Meeting of the Organization for Human Brain Mapping, Honolulu, United States. Poster presentation on the 2015 Eunethydis Network Meeting, Stockholm, Sweden.

Van Houdt, C.A., **Van Hulst, B.M.,** De Zeeuw, P., & Durston, S. (2014). Timing in ADHD: A pilot study of motor timing, perceptual timing and temporal expectancy violations. Poster presentation on the 2014 Eunethydis International ADHD Conference, Istanbul, Turkey.

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CV

Curriculum Vitae

Curriculum Vitae

Branko Mark van Hulst was born on October 9th, 1985 in Heemskerk, The Netherlands. In 2003 he graduated from Bonhoeffer College in Castricum (A-levels) and started his studies in Medicine at the VU University. He completed his medical training in August 2010 and in January 2011 he started working as a medical doctor at De Bascule, an academic center for child and adolescent psychiatry. Here he worked at an inpatient clinic for children with behavioral disorders. In September 2011, Branko started his PhD-project at the NICHE neuroimaging lab, part of the Brain Center Rudolf Magnus, UMC Utrecht. In 2013 and 2014 he was involved in the medical curriculum, coordinating a bachelor course on developmental disorders of the brain. In April 2016 he finished his PhD-project and started his clinical training in psychiatry.

Branko Mark van Hulst is geboren op 9 oktober 1985 in Heemskerk. In 2003 haalde hij zijn gymnasium diploma aan het Bonhoeffer College in Castricum en begon hij zijn studie geneeskunde aan de Vrije Universiteit. Hij voltooide zijn studie geneeskunde in augustus 2010 en werkte vanaf januari 2011 bij De Bascule, een academisch centrum voor kinder- en jeugdpsychiatrie. Hier werkte hij op een opname-afdeling voor kinderen met gedragsstoornissen. In september 2011 begon Branko zijn PhD-project bij het NICHE neuroimaging lab, deel van het Hersencentrum Rudolf Magnus, UMC Utrecht. In 2013 en 2014 was hij betrokken bij het onderwijs van het geneeskunde curriculum als coördinator van een bachelorvak over ontwikkelingsstoornissen van de hersenen. In april 2016 voltooide hij zijn proefschrift en begon hij zijn opleiding tot psychiater.