Fachbereich Erziehungswissenschaft und Psychologie

der Freien Universität Berlin

„Cool and Hot Executive Functions in Attention Deficit Hyperactivity Disorder"

Dissertation

zur Erlangung des akademischen Grades

Doktorin der Philosophie

(Dr. phil.)

vorgelegt von

Dipl.-Psych.

Viola Kappel

Berlin, 2014

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Tag der Disputation:	26.01.2015

Acknowledgement

I would like to express my special appreciation to all the people who supported me in the last couple of years and contributed to the completion of this thesis. Without your help this thesis would not be here.

First of all, I thank PD Dr. Harriet Salbach-Andrae for the remarkable drive and energy with which she established the scientific framework in which I pursued my PhD. Next, I wish to thank Prof. Ulrike Lehmkuhl and Dr. Ernst Pfeiffer for giving me the opportunity and support to start and finish this thesis in their clinic. I want to express my gratitude to Prof. Dr. Babette Renneberg for critically reviewing this work and offering me her professional advice during the course of this thesis. I wish to thank Prof. Dr. Christine Knaevelsrud, Prof. Dr. Hauke Heekeren, and Dr. Lars Schulze who kindly agreed to be part of the doctoral thesis committee.

I am very grateful to the members of *Emotional Neuroscience* for their support in the fMRI section of my thesis. My deepest gratitude goes to Dr. Anne Beck, who supervised my project and always found helpful answers to many questions. Thank you for your guidance, reliable support and professional input. I deeply appreciate our collaboration on this project and always enjoyed our discussions. I thank Robert Lorenz for his invaluable support and patience during the analyses of functional imaging data. Without you, the red puzzles MATLAB came up with would be unsolved.

I also thank my colleagues in the child and adolescent research group. Thank you Helena Rohlf, Charlotte Jaite, Martina Streifling, Monika Jacker, and Anne Koch for extremely good teamwork and your invaluable support in the

ADHD team. I thank Charlotte Jaite, Betteke van Noort and Daniel Führer for the motivation and scientific feedback during our PhD journey and for proof reading my first drafts. Our fruitful meetings at the Grimm Zentrum and the coffee breaks will always be remembered. Thank you Lindsey Otten for language editing. A special thank you goes to all the participants and their parents for their time, trust and support of this work.

At all times, I will be grateful to my hard working parents and grandparents who taught me the personal skills to finish this dissertation project. I thank my husband Jörg who always supports my work and who reminds me to take breaks. Your humor and positive energy helped me change perspectives more than once. I am very much looking forward to every day with you and our little son to be. Danke!

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Theoretical Background

Chapter 1

The introduction of this thesis will start with an outline of the symptomatology and epidemiology of attention deficit hyperactivity disorder (ADHD). Next, a theoretical model for cool and hot executive functions (EF) is described. This model provides a greater framework for the difficulties in executive functioning seen in individuals with ADHD, i.e. set shifting, working memory and reward anticipation. In particular, it will be discussed that the difficulties these patients experience in everyday life might be a result of disturbed cool and hot executive functioning. Furthermore, the neural representation of reward anticipation will be examined. Subsequently, recent empirical evidence for alterations in cool EF, specifically set shifting and working memory, and hot EF, in particular reward anticipation processing in individuals with ADHD, will be summarized. Finally, the research questions of this thesis will be outlined.

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder is a chronic childhood onset neuropsychiatric disorder characterized by developmentally inappropriate inattentiveness, impulsivity and hyperactivity, impairing multiple areas of life (Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, APA, 2000). Worldwide ADHD affects up to 5.3% of children and 4.7% of the adult population (Biederman & Faraone, 2005; Döpfner et al., 2008; Huss, Hölling, Kurth & Schlack, 2008; Polanczyk, de Lima, Horta, Biederman & Rohde, 2007). The DSM-IV-TR[1] (APA, 2000) distinguishes three ADHD subtypes: 1) predominantly hyperactive-impulsive, 2) predominantly inattentive, and 3) combined hyperactive-impulsive and inattentive type (ADHD-CT). Longitudinal studies suggest that in 60 to 70% of cases childhood ADHD persists into adulthood either as a full syndrome (15% in young adults) or in partial remission. In most cases, hyperactivity symptoms remit over time while attention deficits and impulsivity persist (Faraone, Biederman & Mick, 2006; Kessler et al., 2005). Community-based studies suggest a male:female ratio of 2.3:1 (Ramtekkar, Reiersen, Todorov & Todd, 2010). Most individuals with ADHD display disturbed EF that compromise self-regulation and multiple tasks of daily life (Biederman et al., 2004; Kasper, Alderson & Hudec, 2012, see below). The adverse outcomes of ADHD include poor academic and occupational performance (de Graaf et al., 2008; Loe &

[1] During the course of this thesis, the APA guidelines DSM-V (APA, 2013) published a few changes in diagnostic ADHD criteria. However, this thesis was conducted according to DSM-IV-criteria. Implications regarding DSM-V can be found in the discussion section of this thesis.

Feldmann, 2007), drug abuse (Lee, Humphreys, Flory, Liu & Glass, 2011), sexual risk taking and partner violence (Fang, Massetti, Ouyang, Grosse & Mercy, 2010), risky driving (Barkley & Cox, 2007), and other disadvantageous behavior (de Zwaan et al., 2012). In addition, childhood ADHD is associated with high co-morbidity rates of up to 90%, including oppositional defiant and conduct disorders, emotional disorders, specific learning disorders, and tic disorders in childhood (Gillberg et al., 2004), as well as mood disorders, anxiety, substance use disorders, and antisocial and borderline personality disorders in adulthood (Barkley & Brown, 2008; Cumyn, French & Hechtman, 2009). Together, this demonstrates that ADHD is a common psychiatric disorder in the population and in clinical settings and is accompanied by severe psychosocial impairments. As a result, ADHD is associated with increasing direct and indirect costs within the health care system and other economic areas (Asherson et al., 2012). Taking into account that only 25% of individuals with ADHD get treatment, the total direct costs in Europe have been estimated at €2546 million per year (Olesen et al., 2012).

From a biological perspective, ADHD appears to be one of the most heritable psychiatric disorders. Twin studies show substantial heritability with genetic factors contributing 60 to 75% of the phenotypic variance in the population (Wood, Buitelaar, Rijsdijk, Asherson & Kuntsi, 2010; Faraone & Mick, 2010). Additionally, findings from structural and functional neuroimaging studies suggest the involvement of abnormally developed brain networks related to cognition, attention, motivation, emotion and sensorimotor functions (Dickstein, Bannon, Castellanos & Milham, 2006; Nakao, Radua, Rubia & Mataix-Cols, 2011; Shaw & Rabin, 2009, see following section). At the neurotransmitter level,

the interplay of alterations in several systems, including the dopaminergic, adrenergic, serotoninergic and cholinergic pathways, has been linked to ADHD (Perlov et al., 2009; Prince, 2008). Taken together, ADHD is considered to be a brain disorder (Olesen et al., 2012).

The substantial societal burden, high prevalence and severe impairments of children and adults with ADHD not only highlight the importance of providing sufficient treatment options, but also stress the need for a better understanding of biological factors associated with this severe mental disorder in order to advance current treatment approaches.

A Framework of Cool and Hot Executive Functions

Attention deficit hyperactivity disorder has long been conceptualized as a neuropsychiatric disorder with deficits in EF. However, the ADHD phenotype is highly heterogeneous and therefore multiple etiological pathways are likely. The dual-pathway model of ADHD attempts to explain this heterogeneity by the involvement of two etiological pathways, a) the dorsal executive pathway, and b) the ventral reward pathway (Sonuga-Barke, 2003). While the dorsal executive pathway is linked to executive deficits, such as attention, working memory and response inhibition, the reward pathway is linked to altered reward processing and hyperactivity.

The dual-pathway model supports the distinction between cool and hot EF in ADHD (Cubillo, Halari, Giampietro, Taylor & Rubia, 2011; Zelazo & Müller, 2002). Cool EF refer to purely top-down cognitive processes, which are typically elicited by abstract, decontextualized abilities, such as attention, working memory, planning, inhibition, and set shifting. Cool EF are grouped into three domains: 1) inhibition, 2) mental set shifting, and 3) working memory (Miyrake et al., 2000). In contrast, hot EF refer to both top-down and bottom-up cognitive processes that have affective, motivational, or reward components, like reward anticipation, delay aversion, and reward-related decision making. Due to their affective component, bottom-up processes are supposed to have more impact on hot EF than top-down processes. Indeed, ADHD involves disturbances that compromise cool and hot EF, in particular disturbances in attention span, self-regulation, activity level, impulse control, and an inability to consider consequences of behavior (cool EF) next to delay aversion and deprived

motivation (hot EF). These disturbances may lead to poor social adjustment, low academic achievement and ineffective behavior.

Current empirical evidence supports this framework by demonstrating structural and functional abnormalities in shared but separable functional networks underlying the observed deficits in ADHD. Cool EF deficits are closely linked to dysfunctions in the fronto-striatal pathway, which is critically involved in cognitive control and composed of the dorsolateral prefrontal cortex (DLPFC), the ventrolateral PFC (VLPFC), and dorsal regions of the caudate and putamen. Hot EF deficits are linked to dysfunctions in the ventral-striatal pathway, which includes the lateral orbitofrontal cortex (LOFC) and ventromedial prefrontal regions (VMPFC) and their associated ventral-striatal and limbic areas (Cubillo et al., 2012). Figure 1.1 summarizes the framework explained above.

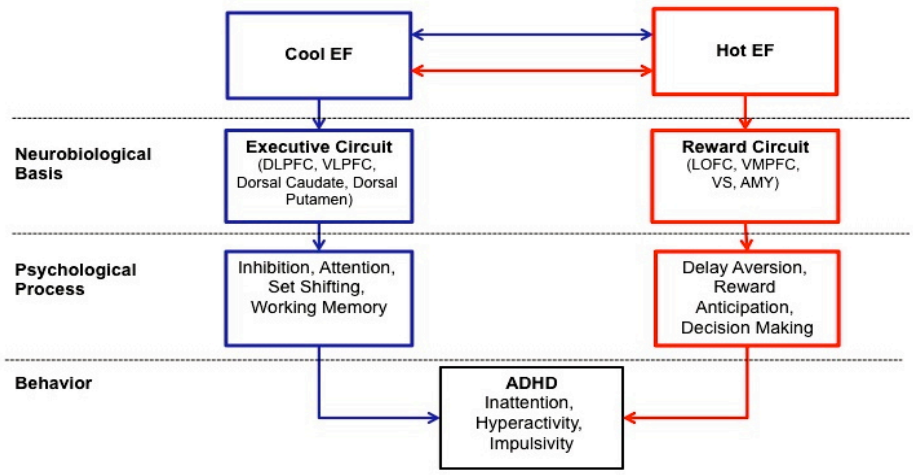

Figure 1.1. **A framework of cool and hot executive functions in ADHD.** (reproduced from Sonuga-Barke, 2003, p. 594; modified according to Cubillo, Halari, Smith, Taylor & Rubia, 2012, p. 208)

Abbreviations. AMY, amygdala; DLPFC, dorsolateral prefrontal cortex; EF, executive functions; LOFC, lateral orbitofrontal cortex; OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; VS, ventral striatum.

Empirical Support for Disturbed Set Shifting and Working Memory in ADHD (Cool EF)

The dual-pathway model assumes disturbances in cool EF as one potential etiopathological pathway in ADHD (Sonuga-Barke, 2003). At the same time, clinicians consider the difficulties of individuals with ADHD, such as focusing their attention and using working memory effectively, as primarily driven by a developmental impairment of EF (Brown, 2008). Following these theoretical and clinical considerations, the role of disturbed cool EF was extensively investigated via neuropsychological tests. Several studies and meta-analyses illustrated that children with ADHD commonly show deficits in a wide range of cool EF, including working memory, set shifting, inhibition, sustained attention, verbal fluency, and executive processing speed (e.g. Biederman et al., 2004; Kasper, Alderson & Hudec, 2012; Martinussen, Hayden, Hogg-Johnson & Tannock, 2005; Pennington & Ozonoff, 1996; Seidman, 2006; Willcutt, Doyle, Nigg, Faraone & Pennington, 2005). These functions facilitate self-regulation and play an important role in managing the multiple tasks of daily life. Deficits in cool EF are associated with poor academic outcome in children with ADHD, i.e. a decrease in academic achievement, grade retention, and an increased risk for placement in special classes (Biederman et al., 2004, Bull, Espy & Wiebe, 2008). Moreover, EF deficits appear to be stable over time. Specifically, cool EF in children and adolescents with ADHD (e.g. set shifting and working memory) were found to predict EF performance in adulthood (Biederman et al., 2007). Thus, deficits in EF represent a potential source of impairment in ADHD.

Most studies on cool EF have been conducted in children with ADHD; findings in adults are limited. EF in adults with ADHD warrant examination due to the lifelong trajectory of ADHD symptoms and associated outcomes (see Chapter 1). Adults with ADHD are at greater risk of lower socioeconomic status, decreased levels of education and professional employment; they experience more frequent job changes and difficulties at work (Shaw et al., 2012). The examination of a rather large cohort of adults with ADHD and healthy controls via self-ratings of EF and neuropsychological tests of EF demonstrated that EF deficits contribute to the impairments in occupational functioning in adults with ADHD (Barkley & Murphy, 2010).

Meta-analytic reviews on neuropsychology in adults with ADHD revealed notable impairments in attention, behavioral inhibition, and memory (Hervey, Epstein & Curry, 2004; Schoechlin & Engel, 2005). However, these meta-analyses are constrained by the limitations that were inherent in the published study data. One problematic aspect is the number and variety of included studies. While only 33 studies were included by Schoechlin & Engel (2005), and only 24 studies by Hervey et al. (2004), these studies used various designs with different approaches to diagnosis and a variety of neuropsychological instruments.

To date, most studies suggest that adult ADHD is characterized by weak inhibition functions (Boonstra, Kooij, Oosterlaan, Sergeant & Buitelaar, 2010; Fischer, Barkley, Smallish & Fletcher, 2005; Halperin, Trambush, Miller, Marks & Newcorn, 2008; Murphy, Barkley & Bush, 2001), while a few studies do not support such deficits (Halleland, Haavik & Lundervold, 2012; Marchetta, Hurks, Krabbendam & Jolles, 2008). However, other cool EF, such as set shifting and

working memory have not been adequately examined. This is surprising, because particularly impairments in set shifting and working memory are associated with academic problems (Biederman et al., 2004; Bull & Scerif, 2001). Set shifting is defined as the ability to flexibly switch back and forth between mental sets or multiple tasks (Monsell, 1996). Common neuropsychological tests for set shifting are the Trail Making Test, Part B (Reitan, 1986a, 1986b) and the Wisconsin Card Sorting Test (Grant & Berg, 1948, see 1.2). Working memory is analogous to a mental "clipboard" that holds information on line for short periods of time, usually seconds. Specifically, working memory refers to a temporally limited storage mechanism in which task-relevant information is monitored and manipulated in order to enable complex behavior (Ullsperger & von Cramon, 2006). Working memory is commonly investigated via the Digit Span Test (von Aster et al., 2006, see Figure 1.2).

Poor set shifting and working memory limit the ability to think flexibly and multitask. Both EF are important components to compliantly adapt to environmental changes (e.g. occupational responsibilities). They facilitate self-management in a wide variety of daily tasks that are difficult for individuals with ADHD, e.g. organizing and prioritizing tasks, shifting focus to tasks, completing tasks on time, and short term memory (Brown, 2008). Thus, the assessment of set shifting and working memory in adults with ADHD would provide valuable information, e.g. for the development of targeted interventions to improve academic and work performance.

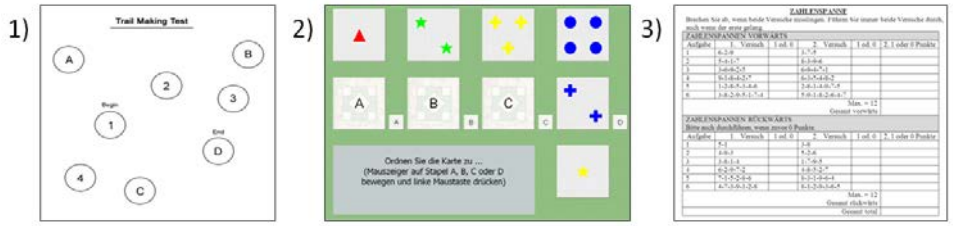

Figure 1.2. **Neuropsychological measures for set shifting and working memory**: 1) Trail Making Test, Part B (TMT-B, Reitan, 1986a). Participants have to connect numbers and letters as fast as possible, while alternating flexibly between numbers (Set 1) and letters (Set 2). 2) Wisconsin Card Sorting Test (original developed by Grant & Berg, 1948; modified computerized German version by Drühe-Wienholt & Wienholt, 2004). Four stimulus cards with different shapes are presented; they differ in color, number, and form of the shapes. The participant is asked to sort a fifth card onto these stimulus cards without being told what stimulus dimension should be used. After each match, the computer gives feedback if this particular match is correct. Sorting rules change during the test and the participant must discover the new sorting rule in order to be successful. 3) Digit Span Test (subtest of the Wechsler adult intelligence scale; German version: Wechsler Intelligenztest für Erwachsene; von Aster, Neubauer & Horn (2006). Participants are asked to repeat a series of digits read aloud by the examiner; first, in the same order as presented, second, backwards. The difficulty increases by the presentation of increasingly longer series. The backward condition requires working memory.

The few studies investigating set shifting and working memory in adults with ADHD revealed inconsistent results. While some studies demonstrated weak set shifting (Biederman et al., 2007; Halleland, Haavik & Lundervold, 2012)

and working memory (Gropper & Tannok, 2009; Hervey et al., 2004; Walker, Shores, Trollor, Lee & Sachdev, 2000) in adults with ADHD, others found no differences in set shifting (Rapport, Van Voorhis, Tzelepis & Friedmann, 2001; Stavro, Ettenhofer & Nigg, 2007) and working memory (Murphy et al., 2001; Walker et al., 2000) compared to healthy controls.

The majority of these studies, however, did not control for certain potentially confounding variables and this may have skewed results. Among the most critical of these variables are ADHD subtype, comorbidities, and the influence of basic cognitive functions (i.e. attention span, information processing speed). Individuals with different ADHD subtypes show different degrees of EF impairment. Individuals with ADHD-CT show worse performance in most EF areas than individuals with the predominantly inattentive type (Hinshaw, Carte, Sami, Treuting & Zupan, 2002; Nigg, Blaskey, Huang-Pollok & Rappley, 2002), whereas processing speed seems to be more impaired in the predominantly inattentive type (Goth-Owens, Martinez-Torteya, Martel & Nigg, 2010; Solanto et al., 2007). Thus, future studies should investigate samples with homogeneous subtypes. Moreover, ADHD typically co-occurs with other psychiatric disorders, such as mood disorders, substance use disorder, and anxiety disorders (see Chapter 1). These comorbidities are in themselves associated with EF deficits (for reviews see Fernández-Serrano, Pérez-García & Verdejo-García, 2011; Ferreri, Lapp & Peretti, 2011; Lee, Hermens, Porter & Redoblado-Hodge, 2012) and may therefore impact the performance on set shifting and working memory tasks. Consequently, comorbidities represent a potential confounding factor and should be controlled for. Furthermore, task performance in set shifting and working memory may be influenced by basic cognitive functions, such as

attention span and information processing speed, both compromised in adults with ADHD (Boonstra, Oosterlann, Sergeant & Buitelaar, 2005; Müller et al., 2007). Accordingly, control measures should be applied to analyze set shifting and working memory isolated from other cognitive abilities. In sum, future studies of executive functioning in ADHD should control for ADHD subtype, the influence of other neuropsychological abilities, and comorbidities.

Taken together, these findings demonstrate that cool EF are highly relevant in order to understand the daily challenges faced by individuals with ADHD. While a large amount of knowledge derives from studies in children, recent findings illustrate that adults with ADHD also show disturbances in cool EF that affect multiple areas of life, especially academic and occupational performance. To date, most studies in adults explored inhibition and studies on set shifting and working memory are scarce. The resulting research questions for this dissertation will be discussed at the end of the introduction.

The Ventral Striatum – A Key Region of Reward Processing (Hot EF)

As outlined above, a key region critically involved in reward processing is the ventral striatum**.** This chapter summarizes anatomic localization and function of the ventral striatum including animal studies and knowledge derived from human imaging studies.

The striatum is part of the basal ganglia. It consists of the dorsal caudate nucleus and putamen, and the ventral striatum, including the nucleus accumbens (NAc). Particularly involved in reward processing is the mesolimbic reward system, a pathway from the ventral tegmental area (VTA) to the NAc that uses the neurotransmitter dopamine (Schultz, 1986, 2002). The NAc receives input from the OFC, dopaminergic projections from the VTA and glutamatergic projections from the amygdala (Herrero, Barcia & Navarro, 2002).

There is considerable evidence from animal studies that the ventral striatum, including the NAc, plays a central role in reward processing. In rats, electrical stimulation of the NAc induced dopamine release and repetitive self-stimulating behavior (Milner, 1989). Based on this evidence, dopamine release in mesolimbic regions, including the NAc, was hypothesized to signal reward (Wise & Rompre, 1989). Single neuron recordings from dopamine neurons in monkeys during behavioral tasks with rewarding liquids strongly support this (Schultz, Dayan & Montague, 1997). Specifically, neurons in the striatum show activity related to the expectation and detection of reward. Likewise, other neurons in the striatum are activated in relation to the preparation, initiation and

execution of movements to achieve a reward, and this depends on the predictability of the reward expected at trial end (Schultz, Apicella, Scarnati & Ljungberg, 1992). Overall, these findings suggest that reward anticipation elicits dopamine release in the NAc and induces striatal activity related to the behavior to achieve these rewards (Schultz, Tremblay & Hollerman, 2000).

Functional magnet resonance imaging (fMRI) experiments indicate that blood oxygen level dependent (BOLD) signal changes in the ventral striatum most likely also possess these characteristics (McClure, Berns & Montague, 2003; O'Doherty, Dayan, Friston, Critchley & Dolan, 2003). An initial study on cocaine addicts found that cocaine injection increased BOLD signal in mesolimbic regions, including the VTA, the NAc, and the mesial PFC (Breiter et al., 1997). Consistently, pharmacological MRI studies indicated that dopamine release (via agonism of postsynaptic D1 receptors) correlated with increased BOLD signal in the NAc of anesthetized rats (Febo et al., 2004; Marota et al., 2000). Together, these findings show that reward anticipation elicited by rewarding cues increases local BOLD signal in the NAc. Psychological predictions can also be derived from these findings; increases in NAc BOLD signal might index an affective state marked by increased positive arousal (e.g. excitement, motivation), which typically occurs during reward anticipation (Knutson, Adams, Fong & Hommer 2001). Consistently, human studies using positron emission tomography (PET) have demonstrated positive correlations between stimulant-induced dopamine release in the ventral striatum and ratings of euphoria (Drevets et al. 2001). Therefore, reward cues may increase NAc BOLD signal by stimulating endogenous dopamine release. The association between NAc BOLD activity and increased ratings of happiness may at least

partly be accounted for by dopamine release in the ventral striatum. This implies that fMRI may be used to explore dopaminergic reward anticipation processing in humans. During fMRI, phasic changes in dopamine release are reflected in BOLD signal changes in the ventral striatum (Knutson & Gibbs, 2007). In line with animal research, fMRI research in healthy participants has identified distinct stages of neural reward processing (see Figure 1.3).

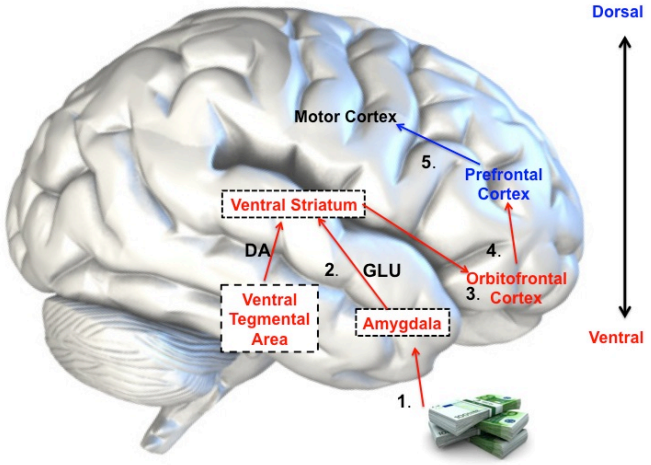

Figure 1.3. **Neural reward processing.** 1. The presence of a salient reinforcing stimulus activates the amygdala, which then 2. generates a learning signal in the ventral striatum that may provoke better predictability of the reward in the future. While dopaminergic neurons (DA) of the ventral tegmental area activate the ventral striatum, including the nucleus accumbens, glutamatergic neurons (GLU) activate the amygdala (Herrero, Barcia & Navarro, 2002). 3. Next, the orbitofrontal cortex assesses the value of the reward, to be 4. used by the prefrontal cortex in order to decide 5. a course of action consistent with current goals that may initiate movement (Schultz, Apicella, Scarnati & Ljungberg, 1992; McClure, Laibson, Loewenstein & Cohen, 2004).

Based on previous work described above, Knutson, Adams et al. (2001) developed the monetary incentive delay (MID) task to explore human reward processing via fMRI. The MID task is a well-established task for investigating neurobiological correlates of reward anticipation processes as well as reward feedback response. During this task, participants see cues that indicate monetary win or loss, then they wait for a variable anticipatory delay period, and finally respond to a rapidly presented target with a single button press to either win or avoid losing money (see Figure 1.4). The MID task provokes phasic ventral-striatal responses by the presentation of instruction (cue) and trigger (target) stimuli that have gained a predictive value for the future occurrence of monetary reward through the past experience of the participant (during a practice trial). The timing of the BOLD signal increases alternates between the delivery of reward (Elliot, Friston & Dolan, 2000) and reward anticipation (Knutson, Fong et al., 2001; O'Doherty et al., 2002). Whereas responses during reward activation were predominantly found in the ventral striatum, responses following rewarding feedback were mainly found in the OFC. BOLD activity in the ventral striatum reflects a learning signal important for acquiring stimulus-reward contingencies (Berns, McClure, Pagnoni & Montague, 2001, see Figure 1.3). In line with knowledge derived from animal studies, activations following the trigger stimulus are understood to enable movement initiation and execution to obtain a reward. FMRI studies using the MID task in healthy participants consistently show ventral striatal BOLD signal changes that vary with reward amplitude (e.g. Knutson, Adams et al., 2001). Moreover, anticipation of rewards elicited both self-reported happiness and NAc activation (Knutson, Westdorp, Kaiser & Hommer, 2000).

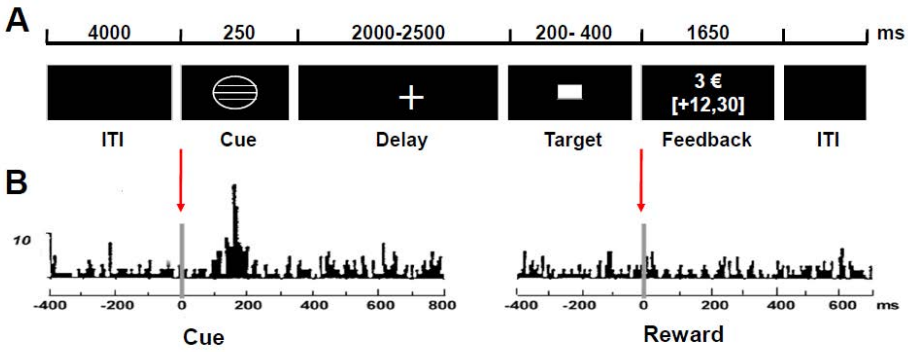

Figure 1.4. **A Monetary Incentive Delay Task (Knutson, Adams, Fong & Hommer, 2001), B Single neuron recordings in primates during reward processing (Schultz, Apicella & Ljungberg, 1993)**

In sum, dopamine inputs to the NAc are involved in the evaluation of rewarding outcomes, the selection and preparation of various ways of reacting, and the action of addictive substances. Reward anticipation facilitates goal-directed behavior, increases the frequency and intensity of behavior leading to attainment of rewards and thus enables behavior control, approach behavior, and reward-related learning. Deficiencies in neural reward processing would lead to slowed, inaccurate or redundant learning. Previous findings raise the possibility that BOLD signal in the NAc may show more irregularities in people with disorders involving symptoms that respond to dopaminergic medications. Therefore, fMRI is used to explore symptoms related to NAc dopaminergic dysregulation in psychiatric disorders. Indeed, the VS plays a crucial role in different psychiatric conditions involving impulsivity, such as drug dependence (nicotine, alcohol, cocaine), borderline personality disorder, and ADHD (Blum et al., 2000). The following chapter focuses on the neurobiological correlates underlying reward anticipation processing in ADHD.

Empirical Support for Disturbed Reward Anticipation Processing in ADHD (Hot EF)

The dual pathway model (Sonuga-Barke, 2003) assumes that hypofunctioning in the mesolimbic reward circuitry contributes to the pathophysiology of ADHD. Both, behavioral and functional neuroimaging findings reinforce this assumption.

Behavioral studies in children and adults with ADHD demonstrate a diminished ability to tolerate reward delay ("delay aversion") that leads to impulsive choices (Marx et al., 2010; Scheres, Tontsch, Thoeny & Kaczkurkin, 2010; Sonuga-Barke, Sergeant, Nigg & Willcutt, 2008). In detail, individuals with ADHD prefer small immediate rewards rather than larger but delayed rewards (Marco et al., 2009; Marx et al., 2010), and need higher reinforcers to modify their behavior (Kollins, Shapiro, Newland & Abramowitz, 1998). When directly rewarded, individuals with ADHD improve in several cognitive functions. For example, incentives stimulate children with ADHD to learn faster (Kollins et al., 1998) and improve working memory (Strand et al., 2012), while adults with ADHD show adequately longer reaction times, fewer impulsivity errors, as well as longer smoking abstinence (Kollins, McClernon & Van Voorhees, 2010; Marx, Höpcke, Berger, Wandschneider & Herpertz, 2013). This is important knowledge for clinicians as well as teachers, parents and colleagues of individuals with ADHD because delay aversion compromises motivational skills and thus may impede learning abilities and work performance. If individuals with ADHD depend on external reinforcement to perform optimally, their cognitive and behavioral difficulties may be partly explained by an altered sensitivity to reward. Altered reward sensitivity contributes to impulsive behavior that can trigger

adverse and dangerous life events. Understanding the factors that mediate altered reward processing may be crucial for the prevention of symptom onset and treatment of its effects on learning, motivation, and overall functioning.

Driven by the literature mentioned above, researchers investigate neural reward sensitivity in individuals with ADHD by using different methodological approaches. A main focus of interest is the dopaminergic processing of reward anticipation in the ventral striatum (see section above). To date, studies focus on adolescents and adults with ADHD, while no studies exist in children. Studies using PET revealed that adult ADHD is strongly associated with decreased function in the brain dopamine reward pathway. This diminished function is accompanied by motivation deficits, which may contribute to attention deficits and supports the use of therapeutic interventions to enhance motivation (Volkow et al., 2007, 2011). In detail, adults (Volkow et al., 2007) and adolescents (Rosa-Neto et al., 2005) with ADHD showed reduced dopamine receptor availability in the dorsal (caudate) and ventral striatum, including the NAc. Consistently, methylphenidate (MPH), the first choice medication for ADHD treatment, increases dopamine availability in the ventral striatum and prefrontal and temporal cortices, and is accompanied by clinical improvement of inattention and impulsivity (Rosa-Neto et al., 2005; Volkow et al., 2011).

In line with these findings, fMRI studies in ADHD samples suggest the involvement of developmentally abnormal brain networks related to reward processing and delay aversion. The first study on reward processing in ADHD was conducted in eleven adolescents with ADHD in comparison to healthy controls by using the MID task (see chapter above, Scheres, Milham, Knutson & Castellanos, 2007). The preliminary results demonstrated decreased brain

responses in the ventral striatum in adolescents with ADHD and this was inversely correlated with hyperactive symptoms. The authors hypothesize that this neural lack of positive arousal and motivation may encourage hyperactive attempts to seek environmental stimulation. To date, a decent amount of fMRI studies also suggest altered reward anticipation processing in adults with ADHD. Most studies demonstrate hyporesponsiveness in the ventral striatum, including the NAc (Carmona et al., 2012; Hoogman et al., 2011; Plichta et al., 2009; Ströhle et al., 2008). Additionally, a dimensional approach in young healthy students with varying levels of self-reported ADHD related behavior (i.e. subclinical inattention, impulsivity, hyperactivity), demonstrates that even non-clinical ADHD related behavior is associated with diminished brain activation in the reward system (Stark et al., 2011). In line with results in individuals diagnosed with ADHD, NAc activation was negatively correlated with ADHD related behavior.

It has to be noted that some behavioral (Sjöwall, Roth, Lindquvist & Thorell, 2013; Solanto et al., 2007) and fMRI studies reveal no differences between ADHD and control groups during reward anticipation processing (Edel et al., 2013; Paloyelis, Mehta, Faraone, Asherson & Kuntsi, 2012; Stoy et al., 2011). However, most fMRI-studies included adults with different ADHD subtypes and psychopharmacological status in one sample. Additionally, psychiatric drugs, such as MPH, influence dopamine and this may have pronounced effects on changes in the NAc BOLD signal. In fact, oral doses of MPH normalize fronto-striatal activation in children and adults with ADHD (for a review see Spencer et al., 2013). Thus, studies with homogenous samples,

including participants with equal ADHD subtype and medication status, may reveal a clearer picture of neural reward anticipation in ADHD.

Another factor that hinders direct comparisons of different fMRI studies is the use of diverse fMRI paradigms. For example, Paloyelis and colleagues (2012) used a variant of the MID task, the Motivational Incidental Learning task, which may trigger different brain responses than the MID task. For direct comparisons it is important to use equal or very similar tasks. Moreover, the classical MID task is a rather abstract task and it requires the ability to calculate numbers. Therefore, younger participants may have trouble understanding the task which may have contributed to the lack of similar studies in children with ADHD. Although ADHD is most prevalent in childhood, no comparable studies on reward anticipation processing exist in children with ADHD. Results in adolescents and adults cannot be used for interpretation in children as fMRI studies indicate that reward related brain function changes with puberty (Forbes et al., 2010).

Moreover, longitudinal MRI studies demonstrate delayed brain maturation in children with ADHD, even in mesolimbic brain regions of the reward system (Shaw et al., 2007, 2012). Interestingly, these changes diminish from childhood to adulthood (for meta-analysis see Frodl & Skokauskas, 2012). Treatment with psychostimulants is associated with normalization of cortical structural deficits (Nakao, Radua, Rubia & Mataix-Cols, 2011) and should therefore be controlled for in related studies. Although the link between brain structure and function is still unclear, these structural alterations may compromise brain function especially in children with ADHD. Together, these

findings highlight the crucial relevance of studies on reward anticipation in drug-naive children with ADHD.

So far, two alternative tasks exist to study reward anticipation in children (Gotlib et al., 2010; Helfinstein et al., 2013). Helfinstein et al. (2013) introduced a colorful cartoon-style reward task, the piñata task. Although its stimuli are likely to be more engaging for younger children than the abstract stimuli of the MID task, the context of a game represents a very different and emotionally engaging set of stimuli that may distract participants and therefore attenuate neural activation (Vuilleumier, 2005). Furthermore, the piñata task does not include ‘‘loss’’ trials while the MID task includes neutral and rewarding stimuli intermixed with loss conditions, and this may change the way participants respond to the reward trials (Reyna & Brainerd, 2011). Thus, direct comparisons seem to be tentative. In contrast, Gotlib et al. (2010) presented the ‘‘kids monetary incentive delay (KIDMID) task’’ for children. In order to use an age appropriate incentive, the feedback condition was modified for children older than 10 years of age. Still, this task is not applicable in children younger than 10 years of age. To date, no comparable MID task exists for children aged eight years and younger.

In sum, these results suggest decreased ventral striatal BOLD signal in adults with ADHD during reward anticipation, while no studies with comparable fMRI tasks investigated drug-naïve children with ADHD. Information on reward anticipation processing in drug-free children and adults with ADHD-CT will complement previous results.

Research Questions

Before outlining the research questions, I will integrate the current state of research on ADHD with the available knowledge about cool and hot EF. The combination of both research foci may be fruitful to further refine concepts of executive functioning in ADHD in order to obtain a more specific picture of different ADHD subtypes with potentially different etiopathological pathways.

As stated above, EF are important for the understanding of ADHD and disturbed EF and their underlying brain networks are suggested as potential etiopathological pathways. Disturbed EF seem to underlie core symptoms of ADHD, in particular inattention, impulsivity and hyperactivity. Executive functions are divided into cool and hot EF, whereby cool executive functions are grouped into three domains: 1) inhibition, 2) mental set shifting, and 3) working memory (Miyrake et al., 2000). Although many studies investigated cool EF in children with ADHD, only few studies exist with adults. Especially scarce are studies investigating working memory and set shifting in adults with ADHD. Clinically, individuals with ADHD are described as unable to organize and complete activities. These problems may partly be due to deficits in set shifting, which may reduce the ability to make decisions based on multiple information sources, to organize complex activities, and modify plans when they turn out to be inefficient. In addition, working memory disturbances can have important clinical implications, since low working memory capacities are associated with the DSM-IV criteria for ADHD: “is forgetful in daily activities” and “does not follow through on instructions and fails to finish school-work, chores, or duties in the workplace”

(p. 88, APA, 2000; Hervey et al., 2004). Both abilities are especially relevant for adults as childhood daily activities are more guided by parents and teachers. In sum, deficits in set shifting and working memory are important neuropsychological components of ADHD and will therefore be investigated in Study I.

More recently, the construct of hot EF has been proposed. Hot EF reflect abilities mediated by mesolimbic pathways, in particular reward processing. Dysfunctional reward processing is strongly related to impulsivity in other psychiatric disorders, such as alcohol dependency (e.g. Beck et al., 2009), and may also be attributable to impulsivity in ADHD. Disturbed reward anticipation hinders successful motivational learning and therefore may, in combination with disturbed cool EF, cause adverse academic outcomes in individuals with ADHD. Although a fair amount of recent studies investigated reward processing in adults with ADHD, no comparable studies exist in children with ADHD. Moreover, the inclusion of participants with different ADHD subtypes and different pharmacotherapeutical status within one sample may have skewed results of previous studies. Since ADHD is a very heterogeneous syndrome and since medication may influence reward anticipation processing, these factors need to be controlled for. Accordingly, studies II and III deal with reward anticipation processing.

Consequently, the following studies aimed to clarify the raised questions about cool EF (in particular set shifting and working memory) in adults with ADHD, and hot EF (in particular reward anticipation processing) in children and adults with ADHD combined subtype.

Study I investigated set shifting and working memory in adults with ADHD. Participants completed two measures for set shifting and one measure for working memory. Additionally, the ADHD group was divided into two subgroups: adults with pure ADHD (ADHD-) and adults with at least one comorbid disorder (ADHD+).

In **Study II**, a modified incentive delay task for children was evaluated in a healthy sample of children and adults via fMRI. The child-friendly incentive delay (CID) task aims to assess reward processing in children who are too young to sufficiently understand the classical MID task as developed by Knutson, Adams et al. (2001). By using the CID task, I aimed to improve comparability of results in adults and children.

With the help of the task evaluated in Study II, I conducted **Study III** to investigate reward anticipation processing in drug-naïve children and drug-free adults with ADHD combined subtype (ADHD-CT) in comparison to age- and gender-matched healthy control participants.

Study I: Set shifting and Working Memory in Adults with Attention Deficit Hyperactivity Disorder

Chapter 2

This chapter has been published as 'Rohlf, H., Jucksch, V., Gawrilow C., Huss, M., Hein, J., Lehmkuhl U. & Salbach-Andrae, H. 2012. Set shifting and working memory in adults with attention-deficit/hyperactivity disorder. *Journal of Neural Transmission, 119, 95-106*.'

DOI: http://dx.doi.org/10.1007/s00702-011-0660-3

The reader is referred to the appendix for the published article.

Study II: CID: A Valid Incentive Delay Paradigm for Children

Chapter 3

This chapter has been published as 'Kappel, V., Koch A., Lorenz, R. C., Brühl, R., Renneberg, B., Lehmkuhl, U., Salbach-Andrae, H., Beck, A. 2013. CID: a valid incentive delay paradigm for children. *Journal of Neural Transmission*, *120(8), 1259-1270*.'

DOI: http://dx.doi.org/10.1007/s00702-012-0962-0

The reader is referred to the appendix for this published article.

Study III: Effect of Brain Structure and Function on Reward Anticipation in Children and Adults with Attention Deficit Hyperactivity Disorder Combined Subtype (ADHD-CT)

Chapter 4

Abstract

Background: ADHD is associated with decreased ventral-striatal (VS) responsiveness during reward anticipation. However, previous research mostly focused on adults with heterogeneous ADHD subtype and divers drug treatment status while studies in children with ADHD are sparse. Moreover, it remains unclear to what degree ADHD is characterized by a delay of normal brain structure or function maturation. We therefore attempt to determine whether results from structural and functional magnetic resonance imaging are associated with childhood and adult ADHD-CT.

Methods: This study used functional Magnetic Resonance Imaging (fMRI) to compare VS structure and function of 30 participants with ADHD-CT (16 adults, 14 children) and 30 healthy participants (20 adults, 10 children), using a monetary incentive delay (MID) task. Joint analyses of structural and functional imaging data were conducted with Biological Parametric Mapping.

Results: Reward anticipation elicited decreased VS responsiveness in adults but not in children with ADHD-CT. Children and adults with ADHD showed

reduced volume in the VS. Taking these differences in grey matter (GM) into account, the results remained the same.

Conclusions: These results suggest that decreased VS responsiveness during reward anticipation is present in adults but not in children with ADHD-CT, irrespective of structural characteristics. Therefore, the question arises whether VS hypoactivity is an ADHD correlate that develops during the course of illness.

Introduction

Attention deficit hyperactivity disorder is a heterogeneous childhood onset, neurodevelopmental disorder that affects up to 5.3% of children and 4.7% of adults worldwide (Biederman & Faraone, 2005; Döpfner et al., 2008; Huss, Hölling et al., 2008; Polanczyk et al., 2007). A hallmark characteristic of ADHD is the diminished ability to tolerate delayed reward. For example, compared with healthy controls, children, adolescents and adults with ADHD show altered responses to reinforcement by having very strong preferences for immediate small rewards rather than larger delayed rewards (Marx et al., 2010; Scheres et al., 2010; Sonuga-Barke et al., 2008). They require higher reinforcers to modify their behavior and learn faster when behavior is reinforced directly (Bitsakou et al., 2009; Marco et al., 2009; Solanto et al., 2001). This contributes to impulsive behavior and serious motivational and learning difficulties that negatively affect occupational performance. Understanding the factors that mediate altered reward processing may be essential for the prevention of symptom onset and treatment of its effects on learning, motivation, and overall functioning.

At the neural level, the mesolimbic dopaminergic system plays a central role in reward processing (e.g. Haber & Knutson, 2010; Schulz et al., 1997). Key components of this network are the ventral striatum (VS), the ventral pallidum, the anterior cingulate cortex, the orbitofrontal cortex, and the dopaminergic midbrain. The dual-pathway model of ADHD by Sonuga-Barke (2003) assumes an underlying hypofunctioning of the mesolimbic reward circuitry that contributes to the pathophysiology of ADHD. Functional neuroimaging findings reinforce this assumption and describe the involvement of developmentally abnormal brain

networks related to reward processing and delay aversion (Dickstein et al., 2006; Nakao et al., 2011; Shaw & Rabin, 2009). However, other studies did not find a relation between delay aversion and ADHD (Sjöwall et al., 2013; Solanto et al., 2007) and therefore multiple pathways are likely. Next to the reward pathway, the dual-pathway model includes an executive pathway assuming executive deficits, such as inhibition and working memory, in a subgroup of patients with ADHD (Sonuga-Barke, 2002). It has to be noted that delay aversion is an important characteristic of some, but not all, patients with ADHD. Because the executive pathway is very well explored, this study focuses on the reward pathway.

Neurobiological correlates of reward processing can be investigated with the MID task in combination with fMRI (Knutson, Adams et al., 2001; Knutson, Fong et al., 2001; Ströhle et al., 2008). Alterations of brain activity during reward anticipation are supposed to be associated with abnormalities within the dopaminergic reward system. Furthermore, previous studies suggest VS hyporesponsiveness during reward anticipation in adolescents (Scheres et al., 2007) and adults with ADHD (Carmona et al., 2012; Hoogman et al., 2011; Plichta et al., 2009; Ströhle et al., 2008) that increases with the severity of hyperactivity and impulsivity. However, other studies did not replicate VS-hypoactivity in ADHD adults (Stoy et al., 2011) and adolescents (Paloyelis et al., 2012). The latter group used a variant of the MID task, which may have contributed to these inconsistent results. Moreover, the inclusion of mixed ADHD subtypes and medication status make direct comparisons difficult. Only one study investigated VS activation in homogeneous samples of drug-naïve adults with ADHD using the MID task (Edel et al., 2013). Interestingly, the group with

predominantly inattentive ADHD, and not the group with ADHD combined subtype (ADHD-CT), exhibited VS hypoactivation. Moreover, a recent study in a population-based sample of adolescent boys revealed that the association between ADHD symptoms and VS activity varied by monoamine oxidase A (MAOA) genotype. Only in participants with lower MAOA levels, ADHD symptoms were associated with VS hypoactivation, whereas in participants with higher levels of MAOA, ADHD symptoms were associated with increased VS activation during the MID task (Nymberg et al., 2013). To date, it remains unclear, how these contrasting findings can be integrated and therefore further research on homogeneous samples is necessary.

Although ADHD is defined as a childhood onset disorder, it remains unclear whether alterations in the processing of reward anticipation are present in children with ADHD. Given the importance of brain development prior to adulthood, the exploration of reward anticipation in children is crucial to identify and analyze critical periods during early development when mesolimbic dysfunction might create a predisposition to neurodevelopmental disorders such as ADHD. To date, no study has examined processing of reward anticipation in children with ADHD with the MID task. The examination of children with ADHD during reward anticipation may help to determine whether VS hypoactivity during reward anticipation is present at disease onset or if it is a correlate that appears later in the course of ADHD.

Brain function in patients with ADHD may be partly affected by altered brain maturation processes. Lesion studies as well as MRI-studies suggest that brain structure is at least partly related to brain functioning. For example there is strong evidence that hippocampal-formation size is positively associated with

memory (Kaup et al., 2011; Visser et al., 1999). There is also evidence that the strength of blood oxygenation level-dependent (BOLD) activation is related to structural characteristics such as brain volume (e.g. Venkatraman et al., 2010). Moreover, developmental and age-related structural changes (such as pruning, synaptic formation, and myelinization in children) are likely to be correlated to functional changes. Further, altered cortical development is likely to lead to changes in the configurations of brain networks (cerebral plasticity). It has to be noted, that developmental cortical malformations may provoke a functional reorganization through alternative anatomical pathways, which may result in restoration or compensation of functions (Rykhlevskaia et al., 2008; Wieshmann et al., 2001). To date, the exact interplay between brain structure and function is far from known and therefore it is important to analyze possible connections. Very little is known about how structural and functional abnormalities are related in ADHD. In structural magnetic resonance imaging (MRI), children with ADHD have shown consistent abnormalities in late developing fronto-striatal networks. These networks mediate reward processing and associated cognitive functions (delay discounting, motivation, inhibition) that are impaired in ADHD. Longitudinal MRI studies demonstrated that structural discrepancies in frontal, striatal, parietal and cerebellar regions of children with ADHD, may be due to a delay in structural maturation (Castellanos et al., 2002; Shaw et al., 2007). A meta-analytic approach revealed that these changes diminish from childhood to adulthood (Frodl & Skokauskas, 2012). There is evidence that children with ADHD, whose developmental trajectory of cortical thickness is more similar to that of typically developing children, have better clinical outcomes than children with persistent thickness reductions (Shaw et al., 2006). Based on these

findings, we also performed a new statistical approach using a local voxel-wise correction for GM alterations as additional information. To the best of our knowledge, there is no imaging study in ADHD patients using this additional information of potentially altered brain structure as a voxel-wise covariate, although this most likely interferes with brain function.

The aim of the present study is to determine whether results from structural and functional MRI are associated with ADHD-CT in drug-naïve children and unmedicated adults. Drawing on findings obtained by previous neuroimaging studies, we hypothesized 1) decreased VS GM volume in children but not in adults with ADHD-CT, and 2) decreased VS brain response during reward anticipation in children and adults with ADHD-CT. Moreover, we will compare standard functional imaging analyses (to ensure methodological consistency with previous studies) with a new statistical approach using a local voxel-wise correction for GM alterations as additional information.

Methods

Participants

Twenty unmedicated adults with ADHD-CT (and with the same confirmed childhood diagnosis), 16 drug-naïve children with ADHD-CT, and 30 healthy controls (HC, 20 adults, 10 children) participated in the study. Adults with ADHD-CT were recruited via a longitudinal sample of former patients with childhood ADHD-CT (Huss, Poustka et al., 2008). Children with ADHD-CT were recruited via our inpatient and outpatient unit. Current ADHD-CT was diagnosed according to DSM-IV-TR criteria (APA, 2000) by clinical experts using the ADHD-Diagnostic Checklist (Rösler et al., 2004). In adults, *childhood* ADHD-CT was diagnosed as part of a longitudinal study according to DSM-III-R or DSM-IV diagnostic criteria by experienced psychiatrists at our clinic. To exclude other Axis I and Axis II psychiatric disorders in patients and to ensure mental health in controls, a standardized diagnostic assessment was conducted prior to the MRI data acquisition. The assessment in adults included the German version of the structured clinical interview for DSM–IV diagnoses (SCID I & II, Wittchen & Zaudig, 1997). Due to its high comorbidity rates and its relevant association with reward processing (Beck et al., 2009), addiction was examined via the Composite International Diagnostic Interview, module addiction (CIDI/DIA-X, Wittchen & Pfister, 1997). None of the adults with ADHD-CT fulfilled lifetime or current criteria for drug addiction (excluding nicotine), two fulfilled the criteria for alcohol abuse during the past 12 months, and one fulfilled the criteria of multiple drug use abuse > 12 months ago. Psychiatric examination in children included the diagnostic interview Schedule for Affective Disorders and Schizophrenia for

School-Age Children – Present and Lifetime Version (Kiddie-SADS-PL, Kaufmann et al., 1997; German translation: Delmo et al., 2001). The severity of ADHD was assessed using the German version of the Conners' adult ADHD rating scale (CAARS, Connors et al., 1999) in adults, and the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version in children (DuPaul et al., 1998). The socioeconomic status was measured with the Hollingshead Index of Social Position (Hollingshead, 1975). IQ was assessed using the short form of the Culture Fair Intelligence Test (CFT-20-R, Weiß, 2006). Handedness was examined with the Edinburgh Handedness Inventory (Oldfield, 1971).

Due to technical problems or excessive head motion (translation larger than 3 mm and/or rotation larger than 2° in any direction), respectively, 4 ADHD adults and 2 ADHD children had to be excluded from further analyses. Thus, data of 16 young adults with ADHD-CT (1 female) between 19 and 31 years of age (M = 23.5, SD = 4.1), and 14 drug-naïve children with ADHD-CT (4 female) between 8 and 12 years of age (M = 9.8, SD = 1.3) were finally analyzed. Because distribution of males and females was skewed, we reanalyzed the sample with only male participants. All subanalyses with only male participants revealed comparable results. Of the final sample, 13 ADHD adults had been treated with methylphenidate (MPH) in childhood, while 3 were drug-naïve. Adults with ADHD were free of medication for at least 2 weeks before imaging procedures.

Control participants were recruited from the local community through advertisements and 1. were right-handed, 2. had no psychiatric diagnosis according to ICD-10 or Axis I and II of the DSM-IV, 3. had no history of

dependence on illicit drugs and alcohol, 4. had no first-degree relatives with a neurological or psychiatric disorder, 5. were currently not taking any psychotropic medication, and 6. had no sensory-motor deficits or other neurological disorders.

Behavioral and clinical data were analyzed with IBM SPSS 21 (Statistical Package for the Social Sciences, Stanford, USA) and reported at $p < .05$ using 2-sample *t*-tests with exceptions for group differences in self-reported motivation (1 x 3 Analysis of Variance, ANOVA), Hollingshead Index of Social Position (Mann-Whitney-*U*-test) and gender (χ^2-test). Demographic characteristics are presented in Table 4.1.

Approval for the study was obtained from the responsible Ethics Committee of the Charité-Universitätsmedizin Berlin and the German Psychological Society, and informed written consent was obtained from all participants and, in the case of children, from a legal guardian.

Table 4.1

Sample characteristics

	HC adults *n*=20		ADHD adults *n*=16		*p*-value	HC children *n*=10		ADHD children *n*=14		*p*-value	Adults vs. Children[d]
	M	*SD*	*M*	*SD*		*M*	*SD*	*M*	*SD*		
Age[a]	23.7	3.4	23.5	4.1	*t*(34)=.2, *p*=.87	11.0	1.3	9.8	1.3	*t*(22)=2.3, *p*=.03	*F=269.3, p <.001*
Gender (m/ f)[b]	20/0		15/1		$\chi^2(1)=1.3$, *p*=.26	8/2		10/4		$\chi^2(1)=0.2$, *p*=.63	$\chi^2(1)=6.9$, *p*=.013
SES[c]	5.6	1.4	4.4	0.9	*p*=.02	5.9	0.7	4.5	1.7	*p*=.04	*F=0.3, p=.564*
Education in years[a]	12.1	1.41	9.69	1.89	*t*(34)=0.4, *p*<.001	5.1	1.3	3.8	1.3	*t*(22)=2.3, *p*=.03	*F=225.0, p<.001*
CFT-IQ [a]	108.5	11.3	97.8	12.9	*t*(34)=2.6, *p*=.01	111.9	16.2	104.6	15.5	*t*(22)=1.1, *p*=.28	*F=2.0, p=.164*
Edinburgh Handedness Inventory[a]	95.8	8.7	71.3	67.2	*t*(15.4)=1.5, *p*=.17	75.8	47.3	90.5	26.3	*t*(22)=-1.0, *p*=.34	*F=50.3, p<.001*
ADHD total score[a]	9.0	5.2	23.6	10.0	*t*(21.5)=-5.3, *p*<.001	8.4	2.8	40.2	5.8	*t*(19.8)= -17.8, *p*<.001	n.a.

ADHD Inattention[a]	4.6	3.7	12.6	6.2	$t(21.2)=-5.2$, $p<.001$	5.2	3.4	23.0	4.4	$t(22)= -10.7$, $p<.001$	n.a.
ADHD Hyperactivity/ Impulsivity[a]	4.5	2.4	11.0	4.6	$t(21.2)= -5.2$, $p<.001$	3.0	3.0	21.4	8.9	$t(22)= -6.3$, $p<.001$	n.a.
Cigarettes per day[b]	1.9 (n=6)	3.8	6.3 (n=8)	7.8	$\chi^2(11)=11.3$, $p=.42$	0	0	0	0		n.a.
Alcohol grams/month[a]	304.3	284.2	310.2	400.9	$t(34)=-0.1$, $p=.96$	0	0	0	0		n.a.

Note. Adult ADHD scores via Conner's adult ADHD Rating Scale, children ADHD scores via ADHD Rating Scale; CFT, Culture Fair Intelligence Test; f, female; HC, healthy controls; m, male; SES, Socioeconomic status. [a] Student's *t*-test, [b] χ^2-test, [c] Mann-Whitney-U-Test, [d] 2x2 ANOVA

Magnetic resonance imaging

MID

Adults completed a MID task according to Knutson, Adams et al. (2001), while children completed a child-friendly version (CID, Kappel et al., 2013). The child-friendly version was chosen to provide a less abstract feedback and to assure a clear and prompt comprehension even for younger children. Therefore, the original MID was modified by inserting a feedback phase that used points (instead of numbers) as a rewarding stimulus. Apart from the modified feedback condition, MID and CID did not differ and were conducted in the exact same way. Both tasks are event-related fMRI designs that consist of two sessions of 72 trials, yielding a total of 144 trials per task with the same delay intervals. Each run lasted about 11 min. Before entering the scanner, all participants completed a short practice version to minimize later learning effects and to ensure that they had completely understood the task. After scanning, participants retrospectively rated their own exertion in response to each of the three cues on a visual analog scale (VAS effort). Adults and children received monetary rewards. While adults were paid directly, children received a voucher for a toy store. Details and evidence for the validity of the CID task are presented elsewhere (Kappel et al., 2013).

MRI Data acquisition and analysis

Scanning was conducted on a 3T GE Signa Scanner with an 8 channel head coil.

Data processing and analysis were performed with the Statistical Parametric Mapping 8 (SPM8) software package

(http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Imaging Neuroscience, London, Great Britain), the ArtRepair software (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html, Stanford, USA, Mazaika et al., 2005), the voxel-based morphometry toolbox for SPM 8 (VBM8) developed by Gaser and colleagues (http://dbm.neuro.uni-jena.de/vbm8/), and the Biological Parametric Mapping (BPM) toolbox (http://fmri.wfubmc.edu/cms/software, Casanova et al., 2007). Corresponding brain regions were identified with reference to the Anatomy Toolbox for SPM (version 1.8, http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomy Toolbox _node.html, Jülich, Germany, Eickhoff et al., 2007).

Voxel-based morphometry was conducted using standard procedures as implemented in the VBM8 toolbox. For investigating the children's data, the low-dimensional SPM8 normalization approach combined with customized Tissue Probability Maps from the Template-O-Matic (TOM) toolbox (Wilke et al., 2008) (http://dbm.neuro.uni-jena.de/software/tom/, Jena, Germany) was used. Statistical analysis for the smoothed GM segments was carried out by means of whole brain comparison of GM volume between ADHD and HC groups. Age and sex were entered as covariates of no interest. To correct for multiple comparisons Monte Carlo simulation based cluster size correction was applied (as provided in REST toolbox, Song et al., 2011). 1000 Monte Carlo simulations revealed an alpha error probability of $p < .05$, when using a minimum clustersize of 75 voxels (adults) or 78 voxels (children) with a significance level of $p < .001$. For further quantification, each subject's ventral-striatal mean GM volumes were extracted in terms of the first eigenvariate using a priori regions of interest (ROI).

The ROI was created by combining anatomical hypotheses with functional findings as reported in the literature of comparable experimental designs for the left and right ventral striatum. The resulting mean GM values (extracted mean ROI GM) were used for further statistical analysis (two-sample *t*-test) in SPSS 21 to compare ventral-striatal mean GM volumes in children (ADHD, HC) and adults (ADHD, HC).

BOLD fMRI: On the first level, the three different cue conditions (anticipation of gain, anticipation of loss, and anticipation of neutral outcome), and five feedback conditions (successful gain, non-successful gain, successful loss avoidance, non-successful loss avoidance, and neutral outcome) were modeled as events of interest. Movement parameters and the target were modeled as events of no interest and convolved with the canonical hemodynamic response function. On the second level, one-sample *t*-tests were performed to determine activations within groups using the individual contrast images “anticipation of gain > anticipation of neutral outcome”. Two-sample *t*-tests were then used to compare these contrasts between HC and ADHD groups. Age and IQ were entered as covariates of no interest.

A Monte Carlo simulation based cluster size correction was used for correction of multiple comparisons (Song et al., 2011). Therefore, 1000 Monte Carlo simulations were computed and revealed a minimum cluster size of 25 voxels for children and adults with a statistical threshold of $p < .005$ to correct with an alpha error probability of $p < .05$. Only results were reported surviving this multiple comparison corrected threshold. Due to a priori hypothesis of VS activation, we additionally performed a small volume correction (SVC) with the same literature based ROI as mentioned for VBM mean value extraction analysis. SPM’s SVC

was performed with a significance level set at $p < .05$ (familywise error-corrected) for the contrast images “anticipation of gain > anticipation of neutral outcome”.

In order to explore ventral-striatal activation while controlling for the influence of local GM volume differences, we used the Biological Parametric Mapping toolbox (BPM, Casanova et al., 2007) in which the voxel-wise GM volume maps of each subject were used as a covariate. The resulting maps were thresholded to 10 voxels and $p < .05$ for ROI-based analyses and for whole brain analyses Monte Carlo based cluster size correction was conducted as described in the fMRI-section above. For detailed information on data acquisition and analysis please view Supplementary Material (see Appendix, Supplement 1, Supplement 6).

Results

Behavioral data

1) Adult sample: Reaction times were analyzed using a three-factorial ANOVA for repeated measures with the between subject factor group (HC vs. ADHD) and the within subject factor condition (gain, loss, neutral). ANOVA revealed a significant main effect of condition [$F(1, 34) = 7.52$; $p = .009$]. There was no significant main effect of group [$F(1, 34) = 0.82$; $p = .37$] and no significant interaction [$F(1, 34) = 0.31$; $p = .59$] between the factors group and condition. Post hoc within group paired *t*-tests revealed faster responses during gain and loss trials compared to neutral trials in the ADHD group, and a trend in HC (see Appendix, Supplement 2).

2) Children sample: The same 2 x 3 ANOVA as conducted for the adult sample revealed a significant main effect of condition [$F(1.5, 22) = 14.45$; $p < .001$]. There was no significant main effect of group [$F(1, 22) = 0.93$; $p = .35$] and no significant interaction [$F(1.5, 22) = 1.06$; $p = .34$] between the factors group and condition. Post hoc within group paired *t*-tests revealed faster responses during gain and loss trials compared to neutral trials in the ADHD and HC groups (see Appendix, Supplement 2).

Neuroimaging results

Voxel based morphometry

1) Adult sample: The two-sample *t*-test, with the extracted mean GM volume per participant within the VS ROIs, revealed significantly decreased volumes in the ADHD group compared to the HC group in the bilateral VS (left T = 5.69, $p <$

.001; right T = 4.07, $p < .001$). Exploratory whole brain analyses (AlphaSim correction $p < .05$) revealed significantly less GM volume in ADHD in the right supramarginal gyrus, right precuneus, right hippocampus, left orbital frontal gyrus, and left rectal gyrus. No significant differences appeared for ADHD > HC.

2) Children sample: The two-sample *t*-test for the extracted ROI data revealed significantly decreased volumes in the ADHD group compared to the HC group in the left ventral striatum (T = 4.77, $p < .001$) but not in the right VS (T = 1.72, $p = .10$). Exploratory whole brain analyses (AlphaSim correction $p < .05$) revealed significantly less GM volume in ADHD in the right superior temporal gyrus, right heschls gyrus, and right rolandic operculum and significantly increased GM volume in the ADHD group compared with HC in the left paracentral lobule, bilateral middle orbital gyrus, right fusiform gyrus, and left rectal gyrus (see Appendix, Supplement 3).

Neural activity between groups during gain anticipation

1) Adult sample: The two-sample *t*-test revealed significant hypoactivity in the ADHD group compared to the HC group in the left VS (SVC analysis FWE-corrected

T = 3.02, $p = .047$, x = -5, y = 7, z = -4) but not in the right ventral striatum (T = 2.40, $p = .14$). Exploratory whole brain analyses (AlphaSim correction $p < .05$) revealed significant hypoactivation in the ADHD group compared to the HC group in the left caudate head and putamen and significant hyperactivation in the right superior medial and frontal gyrus, right middle and superior temporal gyrus, right insula and right precuneus and left superior medial gyrus, and left middle frontal gyrus (see Appendix, Supplement 4).

2) Children sample: During gain anticipation, the two-sample *t*-test revealed no significant differences in ventral-striatal activation between ADHD and HC (SVC analysis FWE-corrected $p > .05$). Exploratory whole brain analyses (AlphaSim correction $p < .05$) revealed significant hypoactivation in ADHD compared with HC in the left inferior parietal lobule, left angular gyrus, and left occipital gyrus. No significant differences appeared for ADHD > HC (see Appendix, Supplement 4).

Biological Parametric Mapping: Ventral-striatal activity during reward anticipation with voxel-wise grey matter covariation

1) Adult sample: Between-group analysis revealed the following findings: During gain anticipation, the two-sample *t*-test revealed significant hypoactivity in the ADHD group compared to the HC group in the left VS (peak coordinate in MNI space: -5, 7, -4; T = 3.27, $p = .04$ SVC FWE-corrected) but not in the right VS (T = 2.41, $p = .35$). Exploratory whole brain analyses (AlphaSim correction $p < .05$) revealed significant hypoactivation in ADHD compared with HC in the left caudate head and pallidum, left precuneus, left middle temporal gyrus, and left superior occipital gyrus and significant hyperactivation in the left superior medial gyrus, left middle temporal gyrus, left cingulate gyrus, bilateral middle temporal gyrus, bilateral superior temporal gyrus, left supramarginal gyrus, right medial and superior frontal gyrus, right insula, and right middle frontal gyrus (see Appendix, Supplement 5).

2) Children sample: During gain anticipation, the two-sample *t*-test revealed no significant differences in ventral-striatal activation between ADHD and HC (SVC analysis FWE $p > .05$). Exploratory whole brain analyses (AlphaSim correction *p*

< .05) revealed no significant differences between HC and ADHD (see Appendix, Supplement 5).

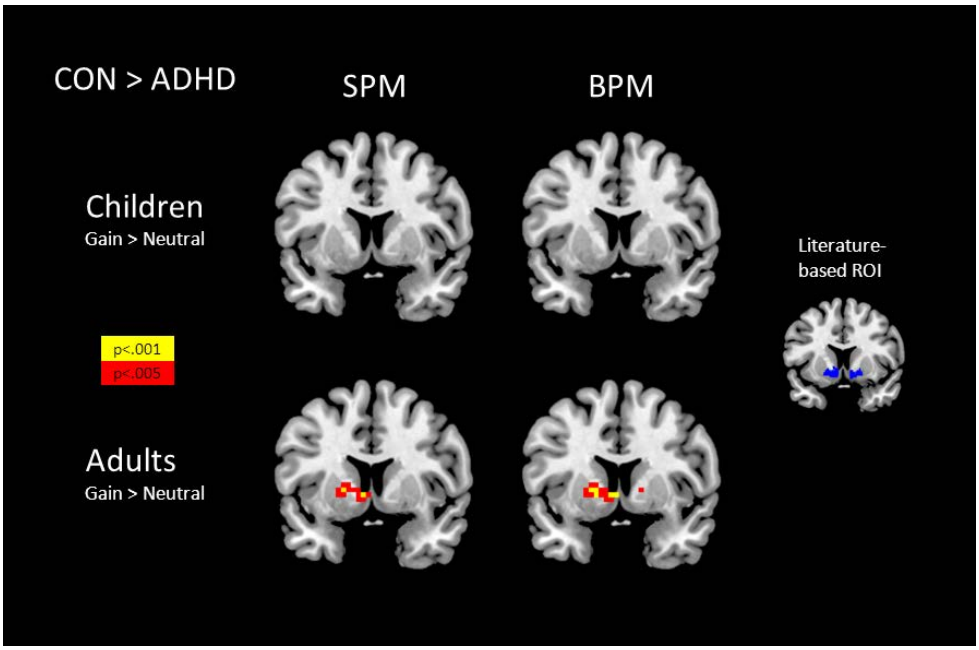

Figure 4.1. **Region-of-interest (ROI) analyses of the ventral striatum. SPM (left panels):** Increase in ventral striatal activation during gain anticipation in healthy adults compared to adults with ADHD, but not in children comparing HC > ADHD, displayed at MNI coordinate y = 7. **BPM (middle panels)**: Increase in ventral striatal activation during gain anticipation in healthy adults compared to adults with ADHD, but not in children comparing HC > ADHD as revealed by Biological Parametric Mapping analysis, displayed at MNI coordinate y = 7. **Literature-based ROI (right panel)**: A priori-defined, literature-based probabilistic ROI, volumes: left ventral striatum 1130mm³ (center of gravity: x = -13, y = 9, z = -8), right ventral striatum 1133mm³ (center of gravity: x = 14, y = 11, z = -9). The overlays were mapped on the standard MNI template as

provided by MRIcroN (http://www.mccauslandcenter.sc.edu/mricro/mricron/; McCausland Center for Brain Imaging, Columbia, South Carolina, USA). For illustrative purposes all results are shown at $p < .005$ (red) and $p < .001$ (yellow), uncorrected. CON, control group; MNI, Montreal Neurological Institute.

Discussion

The findings suggest that decreased VS responsiveness during reward anticipation processing is present in unmedicated adults but not in drug-naïve children with ADHD-CT. VS responsiveness seems to be independent of morphometric VS differences because results remained stable after controlling for VS GM differences in children and adults with ADHD-CT compared with healthy controls.

The findings in adults are in line with previous studies showing decreased VS responsiveness in adolescents and adults with ADHD (Carmona et al., 2012; Hoogman et al., 2011; Plichta et al., 2009; Scheres et al., 2007; Ströhle et al., 2008). Our data add several aspects to the existing literature. Previous studies explored heterogeneous samples with different ADHD subtypes and medication history so that direct comparisons and interpretation were difficult. Only one study explored reward anticipation in drug-naïve homogeneous ADHD samples (Edel et al., 2013) demonstrating VS hypoactivity in patients with ADHD predominantly inattentive subtype, whereas the ADHD-CT group did not differ from healthy controls. Our results contradict this. This difference may be attributable to different sample characteristics, such as symptom and medication history. While Edel et al. (2013) recruited adult outpatients, we explored former ADHD patients of our clinic with both confirmed childhood diagnosis and present diagnosis of ADHD-CT. Therefore, symptom load and duration of illness may differ between study samples and this may have impacted results. Further, Edel et al. (2013) examined drug-naïve adult patients, while most of our ADHD-CT adults had been treated with MPH in childhood.

MPH blocks the reuptake of dopamine in the striatum (Volkow et al., 2001) and may enhance the saliency of rewarding stimuli (Volkow et al., 2004). Although adults of our sample were unmedicated for at least 2 weeks before the MRI examination, it may still be possible that medication during childhood influenced VS reward responsiveness in adulthood (Shiels et al., 2009; Volkow et al., 2012). To date, the long-term effects of MPH on reward responsiveness, even after the medication phase, remain unclear and prospective studies on long-term effects in subtype homogeneous ADHD groups are needed (Stoy et al., 2011).

To our knowledge, this is the first study examining VS responsiveness during reward anticipation in drug-naïve children with ADHD-CT via the MID task. In contrast to our hypotheses, children with ADHD-CT did not show VS hypoactivity during reward anticipation, which is consistent with behavioral results indicating no differences in reaction times between patients and healthy controls (while within groups, children with ADHD and healthy children reacted faster during gain and loss trials compared to neutral trails). Therefore, children and adults with ADHD seem to differ with respect to reward anticipation processing and the question arises whether VS hypoactivity is an ADHD correlate that develops during the course of illness. Structural and functional brain imaging studies aim to establish how much ADHD interferes with normal trajectories of brain changes. During normal development, child and adult brains differ highly regarding volumetric and neurotransmitter development; therefore, different brain structures may mediate reward processing in children compared with adults. A recent review supports this assumption. While reward-based learning impairments in children seem to be due to premature prefrontal structures involved in executive control, impairments in adults seem to be

associated with deficits in the integration of reward information. These deficits may reflect reduced dopaminergic input from the midbrain via the ventral striatum to the VMPFC (Hämmerer & Eppinger, 2012). Furthermore, the hormonal changes that occur during puberty may play an important role in the development of the ventral striatum. Stress during puberty and adolescence may also affect brain development and vulnerability to psychopathologies. In ADHD the manifold developmental changes during adolescence might interact with the disease not only in the domain of reward processing but also in various other disease and non-disease related domains. Thus, more research, especially with a longitudinal sample, is needed.

Our morphometric analyses revealed VS GM reductions in both children and adults with ADHD. This is only partly in line with previous studies. Whereas VS GM reduction seems to be a typical correlate in children with ADHD, this has not been shown in adults with ADHD (Frodl & Skokauskas, 2012). Hence, in contrast to previous studies, we followed a hypothesis driven ROI based approach and focused only on the VS. The functional BPM analysis (which takes individual differences in brain volumes into account in a voxel-by-voxel manner) revealed a decreased VS BOLD response during reward anticipation processing in adults but not in children with ADHD combined subtype compared with healthy controls. To the best of our knowledge, this is the first study examining the impact of structural VS alterations on functional VS brain response in children and adults with ADHD. We consider this as highly relevant because Shaw et al. (2007) reported delayed brain maturation in a large sample of children with ADHD compared with healthy controls. Therefore, differences in brain response might partly be mediated by structural discrepancies between

ADHD patients and healthy controls. Our results strengthen the association of adult ADHD with VS hypoactivity during reward anticipation. However, the influence of structural changes on functional activity is far from clear. Therefore, longitudinal studies with larger samples should clarify the association between VS structure and functioning in children with ADHD.

One possible limitation of the findings of our study is the relatively small sample size, especially of the children groups. Here, results may be biased possibly due to large variance. To address this, we reported only whole brain results that survived clustersize based multiple comparison correction. Second, results may potentially be skewed when comparing ADHD-CT adults on medication washout versus ADHD-CT drug-naïve children. While acute MPH doses normalized fronto-striatal activation in children with ADHD (Rubia et al., 2009), it remains unclear whether MPH influences brain functioning, even after medication washout. Although a comparison between drug-naïve and MPH-treated adults with ADHD revealed no differences in their ventral striatal activations (Stoy et al., 2011), more studies are needed to clarify this. Third, it has to be noted that children in the control group were slightly older than the ADHD group; therefore, we included age as a covariate of no interest.

In summary, we observed decreased VS brain response during reward anticipation in unmedicated adults but not in drug-naïve children with ADHD-CT in comparison to healthy controls. This association was still present after controlling for VS GM differences. Decreased brain response during reward anticipation may thus be perceived as an ADHD correlate that develops during the course of illness. To date, there are very mixed findings regarding reward processing in patients with ADHD. Studies with larger sample sizes are essential

to verify our results. Next to reward processing, future studies should explore executive functioning and consider other factors that might discriminate between subgroups of patients with ADHD. Our results may sensitize clinicians to consider motivational characteristics of patients with ADHD with respect to diagnostic and therapeutic approaches, such as performing contingency management and validating motivational fluctuations, next to treatment of executive functioning deficits. To avoid potential brain alterations, it may be important to prevent dysfunctional reward anticipation processing via psychological interventions.

General Discussion

Chapter 5

Disturbed cool and hot EF are proposed to be characteristic features of individuals with ADHD and are related to many difficulties that patients experience in their everyday life. The studies presented above investigated both, cool EF, in particular set shifting and working memory in adults with ADHD, and hot EF, in particular reward anticipation processing in drug-naïve children and drug-free adults with ADHD-CT. Implications for the understanding of the neuropsychological and neurofunctional basis of ADHD will be discussed in the following sections. The final part of this chapter will provide a discussion of study limitations and an outlook on future research.

Cool and Hot EF in ADHD

The studies composing this thesis derived from a theoretical framework of cool and hot EF in ADHD to further differentiate neuropsychological and neurofunctional aspects contributing to cognitive and behavioral difficulties in individuals with ADHD. The implications of the presented findings will be summarized below. Further implications for theoretical models of ADHD will be addressed in a later section. Thus here I will focus on cool and hot EF in ADHD.

The dual-pathway model of ADHD highlights the role of 1) deficits in cool EF resulting from disturbances in the frontodorsal-striatal circuit and associated mesocortical dopaminergic branches, and 2) deficits in hot EF, in particular impaired signaling of reward anticipation involving frontoventral-striatal circuits and mesolimbic branches terminating in the ventral striatum, particularly the NAc (see Chapter 1). The results of Study I and III partly support the dual-pathway model of ADHD and underline the involvement of disturbed cool and hot EF (Sonuga-Barke, 2002).

Cool EF in ADHD

Children with ADHD show distinct alterations in working memory, set shifting, response inhibition, and planning abilities that compromise their daily functioning (for a review see Rubia, 2011). Although in 50 to 60% of cases ADHD symptoms continue into adulthood (Barkley et al., 2002) knowledge on cool EF in adults with ADHD is limited. Yet, cool EF, in particular set shifting and working memory, are even more relevant for adults than for children, as in childhood daily activities are more guided by parents and teachers. Furthermore, although up to 90% of individuals with ADHD suffer from psychiatric comorbidities, the impact of comorbidities on cool EF is unclear.

The findings of **Study I** address this gap and support the assumption that alterations in set shifting and working memory are also present in adults with ADHD. Adults with ADHD-CT performed more poorly than their typically developing peers on both measures for set shifting, indicating ADHD-related difficulties in concept shifting and advanced planning. The inability to organize and complete complex activities is a core feature of ADHD. Deficits in set shifting are likely to contribute to these difficulties and reduce the ability to organize daily activities, to modify plans when they turn out to be inefficient, and to make decisions based on multiple information. In line with previous studies, the ADHD-CT group also showed working memory deficits (Gropper & Tannock, 2009; Hervey et al., 2004). Low working memory capacities are associated with core DSM-IV criteria for ADHD ("is forgetful in daily activities", "does not follow through on instructions and fails to finish homework, chores, or duties in the workplace", APA, 2000, p. 88). The subgroup comparison of patients with comorbidities (ADHD+) and patients without comorbidities (ADHD-) revealed no

significant differences between these groups. Consistent with previous findings, these results suggest that the observed deficits are attributable to ADHD-CT rather than to comorbidity (Seidman, 2006). Therefore, disturbed cool EF represent a significant component of ADHD-CT, not only in children (as confirmed by previous results, see above), but also in adults with ADHD-CT.

The results of Study I suggest that, next to the clinical diagnosis of core symptoms of ADHD, the evaluation of distinct cool EF may stimulate tailored interventions to improve executive dysfunctions related to real world impairments (Biederman et al., 2004). Neuropsychological assessment may especially serve the needs of adults with ADHD, most of whom live independently from their parents and may be in occupational education, university or employed. Here, the clinician has less access to information typically provided by teachers and parents. As demands for flexibility and management increase with age, adults with ADHD may benefit from training programs aimed to improve organization skills by using environmental feedback. Working memory training programs may help adults with ADHD to hold information until a plan is realized, especially in situations with multiple distracting stimuli.

However, the large performance variance in our ADHD sample shows, in line with previous studies, that cool EF impairments are characteristic for many but not all individuals with ADHD. Although most individuals with ADHD display neuropsychological weaknesses in cool EF, only 30 to 50% of them score within the clinically impaired range (Biederman et al., 2007; Nigg et al., 2005; Seidmann, 2006; Sjöwall et al., 2013). However, studies with questionnaires (e.g. Behavior Rating Inventory of Executive Function; Guy,

Isquith & Gioia, 2004) reveal very high rates (89 – 98%) of cool EF deficits in children and adults with ADHD (e.g. Barkley & Murphy, 2010; Biederman et al., 2011). For example, adults with ADHD reported significant impairment on a behavioral rating of EF, in particular on the working memory scale (Biederman et al., 2011). Moreover, significant correlations were found between EF ratings and quality of life of adults with ADHD (Stern, Pollak, Bonne, Malik & Maeir, 2013). These results strengthen the idea that deficits in cool EF have real-world implications for individuals with ADHD. Thus, further work on cool EF in ADHD should implicate neuropsychological tests as well as behavior ratings of EF to ensure clinical validity.

Taken together, **Study I** reveals deficits in set shifting and working memory in adults with ADHD-CT that are not an effect of comorbidity. Overall, these findings support the dual-pathway model of ADHD assuming that cool EF are an important neuropsychological component of ADHD, although they are neither necessary nor sufficient to cause symptoms of ADHD.

Hot EF in ADHD

In addition to a predominantly cognitive pathway (cool EF), the dual-pathway model of ADHD suggests a pathway of dysregulated reward mechanisms (hot EF) leading to ADHD symptoms (Sonuga-Barke, 2002, see Chapter 1). Individuals with ADHD prefer immediate, small rewards in favor of larger but delayed rewards and need higher reinforcers to modify their behavior (Kollins et al., 1998; Marx et al., 2010). Accordingly, neuroimaging studies show diminished reward anticipation processing in adolescents (Scheres et al., 2007) and adults with ADHD (e.g. Ströhle et al., 2008; Carmona et al., 2012). However, some studies suggest no deficits in reward anticipation processing in adults with ADHD (Paloyelis et al., 2012; Stoy et al., 2011). Highly heterogenic study designs may have contributed to these contradicting results, as previous studies use different fMRI paradigms and include participants with different ADHD subtypes and medication history. Importantly, although ADHD is a childhood onset disorder, no fMRI studies investigated reward anticipation processing in children with ADHD. Clinically this topic is highly relevant because diminished reward sensitivity impedes motivation and learning and contributes to impulsive behavior that can trigger adverse life events. Consequently, disturbances in reward processing compromise school performance, quality of life, and overall functioning of children with ADHD.

The lack of research in children may partly result from a shortage of fMRI paradigms suitable for this age group. Therefore, **Study II** aimed to validate a child-friendly incentive delay (CID) task. As with the original MID task (Knutson, Adams et al., 2001), the CID task elicited significant ventral striatal activity in healthy adults during reward anticipation. Accordingly, no behavioral

differences appeared between the two tasks (i.e. reaction times, accuracy rates or the total amount of gain). Moreover, the CID task elicited significant ventral striatal activity in healthy children. These findings clearly demonstrate evidence for the validity of the CID task wich can thus be recommended for the application in studies in reward anticipation processing in children and adults. To the best of my knowledge, this is the first study providing evidence for the validity of a child-friendly incentive delay fMRI paradigm for children aged 8 to 12 years. Based on these findings, the CID task was used in Study III.

Study III is the first to investigate reward anticipation processing in drug-naïve children with ADHD-CT next to drug-free adults with ADHD-CT. The results suggest that, irrespective of structural differences, decreased reward anticipation processing is present in adults but not in children with ADHD-CT. This study provided new, important findings. First, the study controlled for ADHD subtype and medication status and was able to show that decreased reward sensitivity is present in a group of drug-free adults with ADHD-CT. This underlines the motivational path of the dual-pathway model of ADHD (Sonuga-Barke, 2002). Information on reward anticipation abilities in adults with ADHD may be relevant for treatment. Primarily driven by the clinical phenotype and behavioral studies of ADHD, current psychotherapeutical approaches for children already use incentive-based treatments, e.g. token economy, in parent-child training (e.g. Döpfner, Schürman & Frölich, 2007). The neuropsychological and neurofunctional results discussed in this thesis strongly support this approach. The results of Study III further emphasize the notion that incentive-based treatments may also be helpful for adults with ADHD. In particular, the addition of rewarding incentives may increase motivation and stimulate adults

with ADHD to put more effort into concentrating or achieving academic goals while reducing the perceived cost of the task. In the long run, increased experience of reward may lead to a better mood and a more adjusted behavior. However, a recent fMRI study questions the hypothesis of altered reward sensitivity in adults with ADHD-CT, showing no significant alterations in a homogeneous group of adults with ADHD-CT (Edel et al., 2013). Given that most studies investigated heterogeneous ADHD samples, more studies with homogeneous subgroups are needed to draw firm conclusions.

Second, this is the first study investigating reward anticipation processing in drug-naïve children with ADHD-CT via a valid, child-friendly version of the MID task. The results suggest that drug-naïve children with ADHD-CT show no alterations in ventral striatal responsiveness during reward anticipation. This is in line with recent behavioral results demonstrating no significant impairment in reward anticipation in children with ADHD (70% ADHD-CT, Sjöwall et al., 2013). Our findings in children extend the dual-pathway model of ADHD and generate the hypothesis that deficient reward sensitivity develops during the course of the illness. However, longitudinal research with larger samples is needed before a solid conclusion can be drawn.

Third, this is the first ADHD study that takes structural brain alterations into account for brain function. This is important because children with ADHD show delayed brain maturation that diminishes from childhood to adulthood (for meta-analysis see Frodl & Skokauskas, 2012). The results remained stable, even after controlling for structural differences between participants with ADHD and healthy controls. Although the direct link between brain structure and brain function remains unclear; this is a first indication that alterations in brain

structure in ADHD may not directly impact functional reward anticipation processing.

Taken together, the findings of Study III only partly underline alterations in hot EF in ADHD. Specifically, the results implicate altered reward anticipation processing in adults but not in children with ADHD-CT. These results emphasize a more age-related, developmental perspective on EF in ADHD. Overall, the current empirical evidence on cool and hot EF in ADHD somewhat parallels the clinical representation of ADHD as a heterogeneous neuropsychiatric disorder. It is very likely that multiple pathways contribute to different ADHD symptom representations.

Implications for Models of EF in ADHD

The findings of this thesis only partly support the dual-pathway model of ADHD. Theoretical models of ADHD should aim to better explain the clinical and neuropsychological heterogeneity associated with ADHD. The implications of the presented findings for theoretical models of neurodevelopmental pathways in ADHD will be summarized below.

The core symptoms of ADHD are related to the EF of the PFC, which provides "top-down" regulation of attention, cognitive control of behavior, motivation and emotion through connections with posterior cortical and subcortical structures (for review see Arnsten & Rubia, 2012). This network is also known as the executive control circuit, as it underpins goal-directed executive processes and provides flexibility to configure information processing in response to changing environmental demands. While the DLPFC and inferior PFC regulate attention and cognitive control, the OFC and VMPFC regulate motivation and affect. Individuals with ADHD show abnormalities in the inferior PFC and its connections to striatal, cerebellar, and parietal regions. Cool EF deficits are closely linked to dysfunctions in the fronto-striatal pathway, which is critically involved in cognitive control and composed of the DLPFC, the VLPFC, and dorsal regions of the caudate and putamen. More specifically, the DLPFC and VLPFC are hypoactivated in various tasks (e.g. working memory, Vaidya & Stollsdorff, 2008). The findings of Study III underline that hot EF deficits are linked to dysfunctions in the ventral-striatal pathway, which includes the LOFC and VMPFC and their associated ventral striatal and limbic areas (Cubillo et al.,

2011). Thus, prefrontal-striatal circuits are likely to underpin executive dysfunction in ADHD. However, the findings of this thesis implicate that alterations in cool and hot EF are unlikely to be exhaustive or equally relevant for all individuals with ADHD. There are groups of patients who are impaired in either cool or hot EF with only some of them having overlapping deficits. Given that a number of patients with ADHD are not impaired with regard to cool and hot EF (Nigg et al., 2005), other factors should be considered to fully understand the impairments associated with ADHD.

In combination with previous literature, the results of Study I and Study III suggest the possibility of different neuropsychological subtypes of ADHD. Given the heterogeneity in cool and hot EF, it seems likely that specific deficits in cool and hot EF may discriminate between subgroups of patients with ADHD. This is highly relevant, as the DSM subtypes of ADHD are empirically not well supported. During the course of life, children with one ADHD subtype are often diagnosed with a different subtype later on (e.g. Willcutt, 2005). Looking at the low discriminatory rates of EF (e.g. Sjöwall et al., 2013), one can conclude that these are too low to regard deficits in cool and hot EF as a viable replacement for the behavioral symptoms assessed in the current version of the DSM. However, although they may be irrelevant for diagnosis, knowledge on neuropsychological abilities of patients with ADHD is clinically relevant and enables tailored treatment approaches (see above). Although the dual-pathway model of cool and hot EF in ADHD offers a valuable framework to investigate multiple etiological pathways, the distinction of dorsal and ventral pathways is somewhat simplistic. Given the heterogeneous results, complex behavior is likely to require a combination of cool and hot EF. Moreover, dysfunctional

interactions between cognitive and motivational processes are likely. Cool and hot EF may interact, for example disturbed cool EF (i.e. inattention, deficits in working memory and set shifting) may compromise hot EF abilities to achieve rewards. Cool EF deficits demand a greater cognitive effort in order to gain rewards associated with cognitive achievement. Likewise, deficits in reward processing may aggravate cool EF because these tasks are perceived as less rewarding and therefore less worthwhile to put effort in. This leads to unfinished tasks and lower levels of achievement. Thus, cool EF deficits in combination with diminished reward sensitivity may highly affect the life course of individuals with ADHD. ADHD is associated with severe negative outcomes that accumulate with age, in particular, poor school and work performance (see Chapter 1). It seems likely, that individuals with ADHD and associated deficits in cool and hot EF show a higher level of overall impairment than individuals who do not show deficits in these domains. Consistent with a severity model, children with ADHD-CT perform worse in cool EF domains than children with the predominantly inattentive subtype of ADHD. Additionally, cool EF (e.g. working memory) provide uniquely statistical prediction of distinct symptom dimensions and ADHD subtype presentation (Nikolas & Nigg, 2013). Therefore, the symptomatology of ADHD is likely to depend on the severity of executive deficits as well as on their relative balance. Consequently, the difficulties experienced by individuals with ADHD show different degrees of impairment, reflecting primarily cognitive dysfunction, primarily motivational dysfunction, or a combination of both. Given that specific cool and hot EF discriminate between different clinical ADHD groups, models of ADHD should implicate potential EF subtypes and consider the combination of cool and hot EF processes.

The dual-pathway model integrates only two distinct pathways that may contribute to the development of ADHD (Sonuga-Barke, 2002). Given that some patients are not impaired in cool or hot EF, other deficits might constitute further dissociable neuropsychological components of ADHD. In particular, current evidence suggests including temporal processing deficits (Sonuga-Barke, Bitsakou & Thompson, 2010), reaction time variability (Castellanos et al., 2005), and emotional functioning (Sjöwall et al., 2013). The strongest evidence is available for temporal processing deficits, since evidence for the validity of neuropsychological subgroupings and domain-specific patterns of familial co-segregation regarding inhibition, delay-related deficits, and temporal processing has been found (Sonuga-Barke et al., 2010). Furthermore, evidence of familial correlation and co-segregation was shown for altered cool EF (e.g. Rommelse et al., 2008), hot EF (Marco et al., 2009) and for temporal processing deficits (Himpel et al., 2009). However, reward anticipation processing involves time anticipation and this is associated with temporal processing. Therefore, further investigation is required to establish reward anticipation and temporal processing as separate components. In the future much larger studies using measures from multiple EF domains are required. The presented conceptualization of ADHD also largely ignores the involvement of other brain circuits. Given the number of findings in other candidate neural systems of ADHD, e.g. occipital and temporal structures (Proal et al., 2011), the prefrontal-striatal model should be extended to other circuits and their interrelationships to formulate a more inclusive brain model of ADHD. Including results from other methods may add more information to our understanding of brain-behavior relationships in ADHD, e.g. findings from resting state studies or functional

connectivity analysis (Yeo et al., 2011). Taken together, cool and hot EF deficits are important characteristics of some, but not all, individuals with ADHD. Future theoretical models should encompass other disease-relevant factors to explain heterogeneity in ADHD.

Importantly, the findings of Study III implicate potentially age-related alterations in brain function in ADHD and suggest the need for a more developmental perspective. Age is a very important dimension of ADHD, not only with regard to the clinical representation, as defined more clearly in the current version of the DSM (DSM-5, APA, 2013), but also with regard to more general neuropsychological and neurofunctional components that may contribute to clinical symptoms. In line with this age-specific conceptualization of ADHD symptoms, Study III found no significant alterations in reward anticipation processing in children with ADHD-CT. This extends the dual-pathway model of ADHD (Sonuga-Barke, 2002) and adds a developmental perspective. Previous findings support this age-related perspective. Longitudinal MRI studies show maturational delays in several brain structures that correlate with clinical and functional outcome. ADHD is strongly associated with delayed brain maturation in childhood (Shaw et al., 2007), including significantly smaller volumes in the DLPFC, and regions that project to the PFC including the caudate, pallidum, anterior cingulate, and cerebellum (Seidmann, Valera & Makris, 2005). Functional brain abnormalities have also consistently implicated these structures (for a review see Rubia, 2011). Interestingly, structural changes diminish from childhood to adulthood (for meta-analysis see Frodl & Skokauskas, 2012). It therefore seems likely that the ADHD phenotype is strongly connected with age-related brain development. As described in Chapter 1, both frontal and non-

frontal brain regions are involved in cool and hot EF. As the PFC matures until young adulthood, associated EF also develop with age and are usually at their peak in young adulthood (Spencer-Smith & Anderson, 2009). In adults with ADHD, EF impairments are consistently observed in attention, behavioral inhibition, and memory. The persistent picture of disturbed EF in children and adults with ADHD and the presence of age-related structural brain abnormalities (Castellanos et al., 2002) support the assumption that brain structure, brain function and EF functions are interrelated. In detail, recent findings have proposed links between main symptom dimensions of ADHD and impairments in specific brain circuits. Significant correlations between EF and distinct anatomical brain areas were found in children with ADHD, in particular in the PFC and caudate nuclei (Casey et al., 1997; Semrud-Clikeman et al., 2000). Significant relationships have also been reported between EF, brain structures and externalizing behavior (Semrud-Clikeman et al., 2000). Functional neuroimaging studies in adults provide evidence that working memory performance is associated with dysfunctions of the PFC (Schweitzer et al., 2000).

To integrate these findings, future ADHD models should aim to map EF onto different brain structures and further differentiate between different age groups. Given the behavioral, neuropsychological and neurofunctional inconsistency, future ADHD models should relate clinical measures to distinct brain networks and neuropsychological profiles. Mapping neuropsychological results and core symptoms of ADHD combined with current brain imaging results may provide a more differentiated framework for understanding ADHD. Together, there is a crucial correspondence between anatomical circuitry

mediating compromised functions and patterns of structural and functional brain changes over the developmental trajectory of ADHD. It therefore seems likely that interactions among distinct functional networks will form distinguishable neurobiological patterns that can provide the basis for meaningful subtyping of this heterogeneous disorder. In sum, models of ADHD should aim to establish age-related neurobiological subtypes of ADHD on the basis of neural network profiles (see Figure 5.1).

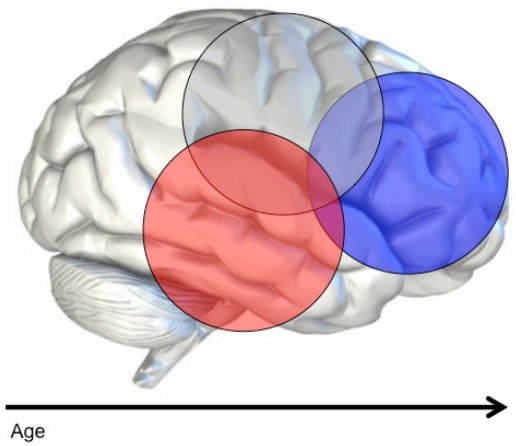

Figure 5.1. **Executive Functions in ADHD.** Disturbances in cool (blue) and hot (red) EF are described in individuals with ADHD and are proposed to derive from neural alterations. Empirical evidence for alterations in distinct cool and hot EF is presented throughout this thesis. Future models of ADHD should include a more age-related perspective and encompass other neuropsychological components (grey) to further explain heterogeneity in ADHD.

Limitations and Future Directions

The presented findings hold some limitations that will be addressed in the following section.

First, small sample sizes may have impacted the ability to find significant effects in Study I (ADHD+ vs. ADHD-) and Study III (children with ADHD vs. healthy controls). Nevertheless, results of Study I are in line with previous findings supporting cool EF deficits in ADHD, irrespective of comorbidity. Study III aimed to include a larger sample of children and adults with ADHD-CT, but this was hindered because the MRI scanner was sold before data collection was completed (see appendix). To deal with the small sample sizes, Study III reported results that were corrected for multiple comparisons according to AlphaSim. Given that this correction was developed especially for fMRI studies with small sample sizes, our results seem trustworthy. However, this is the first fMRI-study on reward anticipation in drug-naïve children with ADHD-CT and further research with larger sample sizes is needed to investigate this topic.

Second, as there is much to learn from different age groups of individuals with ADHD, cross-sectional studies remain correlational and unable to inform causal mechanisms. Given the cross-sectional design of the presented studies, developmental conclusions remain hypothetical. A full understanding of ADHD requires research from a life span perspective. Future studies should therefore characterize brain behavior relationships across the life span. Longitudinal designs are warranted to directly investigate age-related developments of distinct EF and associated symptoms of ADHD. In particular, future studies should determine whether the clinically observed, age-related

modifications in core symptoms of ADHD relate to developmental alterations in brain structure and function. Studies should focus on both the role of the frontal lobes as well as subcortical areas (in particular the ventral striatum) in EF impairments. It would be very informative to evaluate a child sample longitudinally to determine whether neuropsychological, structural and functional brain abnormalities change throughout life. Including children at risk for ADHD may provide information on whether brain alterations are primary or compensatory. Additionally, imaging pre- and post-treatment can reveal biomarkers linked to causal pathways. For example, stimulant medications primarily target dopaminergic and noradrenergic pathways that seem to be altered in ADHD (Rubia et al., 2011). Future studies should aim to link cognitive dysfunctions of ADHD and their underlying neurochemistry in order to further improve cognitive function with pharmacological treatments. Using PET and fMRI, the regional changes in dopamine activity could be correlated with tests of cool and hot EF and with changes in core symptom severity. These approaches may inform us whether distinct brain networks are useful to track pharmacological and behavioral treatment response and may reveal information on causes of a lack of treatment. Future studies should therefore evaluate whether medication and psychotherapeutical treatments optimize brain structure and function.

Third, given the implication of multiple etiological pathways of ADHD, it is important to combine neuropsychological and neuroimaging approaches on homogeneous groups of individuals with ADHD. The combined investigation of diverse etiological pathways via different methodological approaches may add important knowledge to potential independent or shared effects of EF in ADHD.

Moreover, knowledge about brain circuits in ADHD mainly derives from between-group differences in task-based fMRI activations or anatomic volumetric differences. Their generalizability is limited to the specific construct of interest, the population sampled, and by idiosyncratic methodological factors. Future studies should focus on the interrelationships among executive control and limbic-motivational networks. Adding neuropsychological assessments may be useful for the identification of executive dysfunction leading to implications regarding the presence, type, and etiology of brain dysfunction in ADHD. Therefore, further analysis of structural and functional correlates of ADHD and their relation to specific measures of cool and hot EF is warranted. Furthermore, the association between cool and hot EF with behavioral impairments of individuals with ADHD should be investigated.

Fourth, cool and hot EF deficits are common in many psychiatric disorders and therefore not specific to ADHD (Sergeant, Geurts & Oosterlaan, 2002). For example, there is a strong link between oppositional defiant disorder (ODD) and conduct disorder (CD) and disturbances in cool and hot EF as well as hyposensitivity to reward (Matthys, Vanderschuren & Schutter, 2013). In ODD and CD, the lack of reward may cause adverse effects on mood resulting in a negative attitude and potentially triggering oppositional behavior. It has been shown that antisocial or aggressive behavior can be rewarding, as these behaviors are associated with limbic dopamine release in the NAc in the ventral striatum (Buckholtz et al., 2010). This increased reward salience of aggressive behavior would increase motivation for such reward-seeking behavior. Neuroimaging findings suggest that EF impairments in ADHD depend on comorbid CD. While pure ADHD shows strong associations with cool EF deficits,

patients with comorbid CD show greater impairments in motivational control and reward-based learning (Rubia, 2011). It is therefore assumed, that individuals with ADHD and comorbid CD have greater impairments in both cool and hot EF domains compared to those with ADHD alone. In fact, ADHD with comorbid disruptive behavior disorders is associated with greater EF deficits than ADHD alone (Dolan & Lennox, 2013; Hummer et al., 2011). Given these significant correlations between externalizing behavior and performance in cool and hot EF, a cross-diagnostic dimensional approach seems to offer more insight into brain-behavior relationships. The variability in current findings may partly be due to the degree of symptom overlap between different clinical groups. Future research should add a cross-diagnostic approach to determine which EF impairments are shared by what kind of mental disorders. Focus should be given to mapping neuropsychological findings on EF deficits in a variety of clinical disorders relevant to these neurobiological substrates. Given concerns over diagnostic co morbidity between disorders, future investigations should examine relationships between indices of relevant psychopathology and neurocognitive profiles across different psychiatric cohorts to explore dimensional relationships that may better inform the field. Overlapping phenomena with other neuropsychiatric disorders should be recognized and theoretically integrated into dimensional models of psychiatric disorders. These models should combine both phenotypic symptom dimensions and current neurocognitive aspects, as proposed by the US National Institute of Mental Health Research Domains Criteria project (Insel, 2014). Combined information on brain networks, genes and behavior represent an opportunity to formulate hypotheses linking these multiple levels. This approach may improve the understanding of the common and distinctive neurocognitive

underpinnings of psychiatric disorders and lead to a better understanding of endophenotypes in disorders that are frequently comorbid.

In conclusion, the findings of this thesis have provided important knowledge that refines theoretical and clinical conceptualizations of ADHD. In sum, cool and hot EF deficits are implicated in ADHD, although neither is necessary for ADHD nor specific to it. Both constructs are separable from one another so that each may represent an idiosyncratic feature associated with an ADHD subsample. Currently, neither cool EF deficits nor deficits in reward anticipation are diagnostic criteria of ADHD, but both constructs may be helpful to separate heterogeneity in ADHD, leading to a refinement of ADHD nosology and treatment. Further research is needed to integrate different EF and clinical impairments associated with ADHD with a more dimensional approach. The results of this thesis emphasize the need to include not only cool and hot EF in future theoretical models and clinical conceptualizations of ADHD but also consider other factors and age specific representations of ADHD.

Summary

Chapter 6

Attention deficit hyperactivity disorder is a chronic childhood onset neuropsychiatric disorder characterized by developmentally inappropriate inattentiveness, impulsivity and hyperactivity, impairing multiple areas of life. Distinct deficits in cool and hot EF were proposed to represent a source of impairment in ADHD and shown to relate to the core symptoms of ADHD. In particular, deficits in cool EF, including set shifting and working memory, were proposed to compromise self-regulation, managing multiple tasks of daily life, and academic and occupational outcome. Deficits in hot EF, including reward anticipation processing, represent a second pathway of impairment in ADHD and were shown to compromise motivation and may thus impede learning abilities and work performance. Diminished reward anticipation processing was shown to contribute to impulsive behavior that can trigger adverse and dangerous life events typically experienced by individuals with ADHD. The central role of cool and hot EF in ADHD was the starting point of the studies presented in this thesis with the aim to address limitations of previous findings in children and adults with ADHD.

Three cross-sectional studies investigating individuals with ADHD-CT were conducted. To address limitations of the previous literature, distinct age groups were chosen to investigate cool EF (Study I) and hot EF (Study II and III) in drug-free individuals with ADHD-CT.

Study I investigated cool EF, in particular set shifting and working memory in adults with ADHD-CT. Compared to healthy controls, adults with ADHD showed significant alterations in both attributes. Subgroup comparisons between patients with pure ADHD and patients with ADHD plus comorbidity revealed no significant differences. These results suggest that alterations in set shifting and working memory are rather related to ADHD than to comorbidity.

Study II evaluated a child-friendly incentive delay (CID) task in comparison to the MID task by Knutson, Adams et al. (2001). In line with my hypothesis, both tasks elicited significant ventral striatal activity in healthy adults during reward anticipation. Accordingly, no differential behavioral task effects appeared (i.e. reaction times, accuracy rates or the total amount of gain). Moreover, the CID task elicited significant ventral striatal activity in healthy children. Taken together, these findings demonstrate evidence for the validity of the CID task. Thus, the CID task can be recommended for the application in future studies in reward anticipation processing in children and adults.

Study III investigated reward anticipation processing in children and adults with ADHD using the MID and the CID task. Reward anticipation elicited decreased ventral striatal responsiveness in adults but not in children with ADHD-CT. Moreover, children and adults with ADHD showed reduced ventral striatal grey matter volumes. Taking these grey matter differences into account, the results remained stable. These results suggest that decreased ventral striatal responsiveness during reward anticipation is present in adults but not in children with ADHD-CT, irrespective of structural characteristics. Longitudinal studies should therefore examine whether ventral striatal hypoactivity is an ADHD correlate that develops during the course of illness.

Taken together, the presented findings support the view of ADHD as a heterogeneous disorder related to cool and hot EF deficits. In particular, the results suggest cool EF impairments in set shifting and working memory in adults with ADHD-CT, irrespective of comorbidity. Findings in hot EF, in particular reward anticipation processing, suggest diminished reward sensitivity in adults with ADHD-CT, whereas no significant differences emerged between children with ADHD-CT and healthy controls. To the best of my knowledge, this is the first study on reward anticipation in drug-naïve children with ADHD-CT that also considers potential effects of brain structure. The cross-sectional results of this thesis facilitate hypothesis driven longitudinal studies that combine investigations of cool and hot EF in individuals with ADHD-CT.

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Zusammenfassung

Die Aufmerksamkeitsdefizit-Hyperaktivitätsstörung (ADHS) ist eine chronische neuropsychiatrische Erkrankung mit Beginn im Kindesalter, die durch entwicklungsunangemessene Unaufmerksamkeit, Impulsivität und Hyperaktivität charakterisiert ist. Eine potentielle Quelle der Beeinträchtigungen bei ADHS stellen spezifische Defizite sogenannter kalter und heißer exekutiver Funktionen (EF) dar, die zudem in Verbindung mit Kernsymptomen des ADHS gebracht werden. Im Fokus stehen Defizite kalter EF, insbesondere Set Shifting und Arbeitsgedächtnis, die zu Einschränkungen in der Selbstregulation führen sowie die Organisation multipler Aufgaben des täglichen Lebens und die akademische und berufliche Performanz beeinträchtigen. Einen zweiten Pfad der Beeinträchtigungen bei ADHS stellen Defizite heißer EF dar, die sich vor allem auf die Verarbeitung belohnungsanzeigender Stimuli (Belohnungsantizipation) beziehen. Es wurde gezeigt, dass Defizite der Belohnungsantizipation mit einer beeinträchtigten Motivation einhergehen und infolge Lernen und Arbeitsperformanz einschränken.

Mithilfe von drei querschnittlichen Studien werden spezifische kalte und heiße EF untersucht. Entsprechend der Limitationen bisheriger Studien werden homogene Stichproben (Alter, ADHS Subtyp, Medikationsstatus) einbezogen um kalte (Studie I) und heiße (Studie II und III) EF bei unmedizierten Personen mit ADHS-CT zu untersuchen.

Studie I untersucht ausgewählte kalte EF (Set Shifting, Arbeitsgedächtnis) bei Erwachsenen mit ADHS-CT. Im Vergleich zu gesunden Kontrollprobanden zeigt die Patientengruppe signifikante Beeinträchtigungen im

Set Shifting und im Arbeitsgedächtnis. Subgruppenvergleiche zwischen Patienten mit purem ADHS und Patienten mit psychischen Komorbiditäten zeigen keine signifikanten Unterschiede. Diese Ergebnisse weisen darauf hin, dass Beeinträchtigungen im Set Shifting und Arbeitsgedächtnis eher mit der ADHS als mit Komorbiditäten in Verdingung stehen.

Studie II evaluiert eine altersadäquate Version des MID Paradigmas von Knutson, Adams et al. (2001) für Kinder (CID) im Vergleich zur Originalversion. Entsprechend der Erwartungen induzieren beide Paradigmen während der Belohnungsantizipation bei gesunden Erwachsenen signifikante ventral-striatale Aktivierungen. Damit übereinstimmend zeigen sich keine behavioralen Task-Effekte (Reaktionszeiten, Fehlerraten, Gesamtgewinn). Darüberhinaus zeigen sich unter Verwendung der CID Ausgabe bei gesunden Kindern signifikante ventral-striatale Aktivierungen. Insgesamt bestätigen diese Ergebnisse die Validität des CID Paradigmas. Schlussfolgernd kann das CID Paradigma für die Untersuchung der Belohnungsantizipation bei Kindern und Erwachsenen empfohlen werden.

Unter Zuhilfenahme des MID- und des CID-Paradigmas untersucht **Studie III** die neuronale Belohnungsantizipation bei Kindern und Erwachsenen mit ADHS-CT. Während der Belohnungserwartung zeigen sich bei Erwachsenen, aber nicht bei Kindern mit ADHS-CT verminderte ventral-striatale Aktivierungen. Darüberhinaus zeigen Kinder und Erwachsene mit ADHS-CT verminderte ventral-striatale Volumina der Grauen Substanz. Auch unter Einbezug dieser strukturellen Unterschiede bleiben die funktionellen Ergebnisse bestehen. Diese Befunde weisen auf strukturunabhängige verminderte ventral-striatale Aktivierungen bei unmedizierten Erwachsenen mit ADHS-CT hin,

während medikamenten-naive Kinder mit ADHS-CT keine Unterschiede zu gesunden Probanden zeigen. Längsschnittstudien sollten ermitteln, inwiefern ventral-striatale Hypoaktivität während der Belohnungsantizipation ein Korrelat der ADHS darstellt, das sich im Verlauf der Erkrankung entwickelt.

Insgesamt unterstreichen die dargestellten Befunde die Sicht auf ADHS als heterogenes Störungsbild, das mit Defiziten kalter und heißer EF in Verbindung steht.

Curriculum Vitae

For reasons of data protection the curriculum vitae is not available in the online version of this thesis.

Publications

Kappel, V., van Noort, B., Ritschel, F., Seidel, M., & Ehrlich, S. (2014). [Anorexia nervosa - from a neuroscience perspective]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 42*(1), 39-48; quiz 49-50.

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Selbstständigkeitserklärung

Ich erkläre an Eides Statt, dass ich diese Dissertation selbständig und ohne fremde Hilfe verfasst, andere als die angegebenen Quellen nicht benutzt und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe. Mir ist bekannt: Bei Verwendung von Inhalten aus dem Internet habe ich diese zu kennzeichnen und mit Datum sowie der Internet-Adresse (URL) ins Literaturverzeichnis aufzunehmen.

Diese Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

Appendix

Publication – Set shifting and working memory in adults with attention-deficit/hyperactivity disorder.

The appendix has been published as 'Rohlf, H., Jucksch, V., Gawrilow C., Huss, M., Hein, J., Lehmkuhl U. & Salbach-Andrae, H. 2012. Set shifting and working memory in adults with attention-deficit/hyperactivity disorder. *Journal of Neural Transmission, 119, 95-106*.'

DOI: http://dx.doi.org/10.1007/s00702-011-0660-3

Publication – CID: A valid incentive delay paradigm for children.

The appendix has been published as 'Kappel, V., Koch A., Lorenz, R. C., Brühl, R., Renneberg, B., Lehmkuhl, U., Salbach-Andrae, H., Beck, A. 2013. CID: a valid incentive delay paradigm for children. *Journal of Neural Transmission*, *120(8), 1259-1270*.'

DOI: http://dx.doi.org/10.1007/s00702-012-0962-0