NEUROCOGNITIVE PROCESSES
OF DECISION-MAKING IN ADULTS WITH ADHD

Deficits in behaviour and functional brain processing,
and the effects of methylphenidate

Athanasia Monika Mowinckel

Department of Psychology
Faculty of Social Sciences
University of Oslo
2016
ACKNOWLEDGEMENTS

I would like to thank my main supervisor Guido Biele for the encouragement, advice, all the great discussions and laughs along the way, and for constantly pushing the boundaries of what I thought I was capable of.

To my second supervisor, Tor Endestad, who was always optimistic, provided endless scan hours, and never shied away from any task I asked for help with.

My colleagues, fellow fellows, and constant companions in this research endeavour, Mads Lund Pedersen and Sigurd Ziegler: Not only did we have innumerable great academic discussions together, but the companionship, laughter, and shared periodic stress, made this collective journey more enjoyable by far. It would not have been the same without you.

Our data collection would not have been possible if not for Mats Fredriksen and his team at Vestfold Hospital Trust in Tønsberg. Dr. Fredriksen and his team have been a vital part of the project and I am so grateful for their assistance and friendliness.

I would also like to thank the team at NORMENT, especially Dag Alnæs, for the collaboration on the last exploratory paper in this dissertation. Your high spirits and quick wits made all the hard work enjoyable and inspiring. Simpe group, enough said.

I want to give special thanks to Cecilie Skaftnes and Alexandra Tzircoti for reading through this thesis and providing valuable feedback. I am also particularly thankful for all the support and advice from my good friends and colleagues, Anine Riege and Unni Sulutvedt. You always make me feel better, and always make me laugh.

To my parents and brother: thank you for always being there for me, for always encouraging me, and never letting me think there was something I could not accomplish.

Last, but far from least, I want to thank my partner, Inger Tolleskoven. You always keep my spirits up and my head grounded, you force me to make checklists, and always support me fully. You are my compass and my zen.

To all my friends: Thank you for your patience, I’m back now.
# Table of Contents

General summary ........................................................................................................ iii

List of articles .............................................................................................................. vii

List of abbreviations ................................................................................................... viii

Introduction ................................................................................................................ 1

  Attention deficit-hyperactivity disorder ................................................................. 1

  The dopamine system .............................................................................................. 7

  Reward based decision-making .............................................................................. 12

Main research objectives ......................................................................................... 17

Methodological considerations ............................................................................... 21

  Experimental design and hierarchical models ...................................................... 21

  Event-related functional MRI ............................................................................... 23

  Participants ............................................................................................................. 26

Summary of articles .................................................................................................. 33

  Article I ............................................................................................................... 33

  Article II .............................................................................................................. 34

  Article III ............................................................................................................ 35

General Discussion .................................................................................................. 37

  Behavioural deficits in decision-making .............................................................. 38

  Irregular brain functioning .................................................................................. 39

  The effects of methylphenidate ........................................................................... 43

Concluding remarks ................................................................................................. 47

References .................................................................................................................. 49

Articles I-III ............................................................................................................... 71
GENERAL SUMMARY

The work discussed herein is centred on questions regarding possible decision-making deficits in adults with attention-deficit hyperactivity disorder (ADHD), and on how methylphenidate potentially remediates dysfunctional neurocognitive processes of decision-making. Extracellular availability of dopamine has been consistently implicated as crucial for decision-making. Observations from animal and human studies repeatedly report improvements in decision choices by dopamine agonists, and decision-making deficits in patients with pathologies related to dopamine deficiency, like ADHD. The first-line pharmacological treatment for ADHD, methylphenidate, is a known dopamine (and noradrenaline) agonist, and it is thus reasonable to assume improvement in possible decision-making deficits by methylphenidate.

While ADHD is largely studied in paediatric and adolescent samples, research on adults with ADHD has only recently become of interest. The emergent research interest has also become of clinical importance, now that the newly revised Diagnostic and Statistical Manual – fifth edition also includes diagnostic instructions for adults with childhood-onset ADHD. Some researchers have even called for an adult-onset ADHD diagnosis, arguing that ADHD is not a purely developmental phenomenon persisting into adulthood, but might also arise in adult age. The possibility of adult-onset ADHD increases the importance of studying ADHD in adulthood, as research on children with ADHD cannot be readily applied to this group.

In article I, we sought to quantify current knowledge on decision-making in adult ADHD. To synthesize the current understanding of decision-making deficits in ADHD, we conducted meta-analyses on data from studies comparing adults with ADHD to healthy peers during different decision-making paradigms. In order to assess the importance of possible decision-making deficits in adult ADHD, we used established attention deficits in ADHD as benchmarks for comparison. The results demonstrate decision-making deficits of similar magnitude as attention deficits in adults with ADHD. The analyses thus revealed that decision-making and attention deficits persist into adulthood in ADHD, and that decision-making deficits might be more central in the ADHD pathophysiology than previously thought. The article highlights the importance of studying decision-making in ADHD, while also revealing the scarcity of studies on this subject in adults with ADHD.
The two last papers were based on the functional magnetic resonance (fMRI) data collected in a double-blinded, placebo-controlled, crossover trial of methylphenidate, and sought to further understand the neurocognitive origins of decision-making deficits in ADHD. The main aim of **article II** was to use an established neurocognitive model of value-based decision-making in order to investigate three stages of decision-making and identify where decision-making deficits occur in ADHD. Behaviourally, patients when unmedicated made less advantageous choices than the controls, and while performance improved through methylphenidate, the patients still made worse choices than controls. The fMRI results provided evidence of attenuated subcortical representation of reward in adult ADHD, which was alleviated with methylphenidate medication. The study thus suggests that deficits in value-based decision-making in adult ADHD are likely to arise already in the basic coding of stimulus values. Moreover, under the influence of methylphenidate, severely affected patients more strongly recruited the dorsomedial prefrontal cortex during value comparisons. This indicates that the dorsomedial prefrontal cortex might serve as a support structure for decision-making in ADHD, and that methylphenidate particularly strengthens the support function of this region in adults severely affected by ADHD symptoms.

While article II focused on disentangling the role of sub-processes of decision-making in the occurrence of decision-making deficits in ADHD, **article III** was more concerned with the dynamics of intrinsic functional brain networks during decision-making. Functional brain networks can be defined as spatially distant brain regions with temporally correlated activity, and such networks have been found to differentiate during development into several independent functional networks that show consistency during rest and cognitive engagement. In the current literature on functional networks in ADHD, the *default mode network* (DMN) has been repeatedly implicated as aberrant. By exploring the dynamics and connectivity within and between established functional brain networks, not just the DMN, we describe disturbances in functional networks in our own sample, and provide additional information about the effect of methylphenidate on these disruptions in adults with ADHD. The results from this exploratory investigation indicate that adults with ADHD have difficulties in sustaining DMN suppression during prolonged cognitive engagement, necessitating re-suppression of the DMN at each choice, and that this
increased frequency of suppression is negatively associated with task performance. Furthermore, while the study replicates observations of methylphenidate reducing precuneus connectivity in the DMN during cognitive engagement, the effects of methylphenidate on network dynamics were weak.

In sum, the research described in this thesis contributes to the further understanding of neurocognitive processes of decision-making in adult ADHD in several ways. In article I, we found the current literature to clearly implicate aberrant decision-making as an important cognitive dysfunction in adult ADHD. The use of a neurocognitive model of value-based decision-making in article II suggested that reduced performance in value-based decision-making might arise from reduced striatal reward coding in ADHD, a deficit methylphenidate alleviated. The data-driven, multifaceted analysis approach in article III allowed us to find converging evidence of deficits in sustaining DMN suppression in adult ADHD, which was furthermore associated with reduced performance and was not alleviated by methylphenidate medication. The main results from each of the articles presented continue to implicate reduced striatal activation in response to rewards and excessive activity of the DMN to now established deficits in decision-making in adult ADHD.
LIST OF ARTICLES


II. Mowinckel, A. M., Pedersen, M., Ziegler, S., Fredriksen, M., Bjørnerud, A., Endestad, T. & Biele, G., Aberrant reward processing is alleviated by methylphenidate in adults with ADHD: A randomized, placebo-controlled trial. *(Submitted)*

**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Attention deficit-hyperactivity disorder</td>
</tr>
<tr>
<td>ASRS</td>
<td>Adult ADHD self report scale</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood oxygen level dependency</td>
</tr>
<tr>
<td>CPT</td>
<td>Continuous performance task</td>
</tr>
<tr>
<td>DAT</td>
<td>Dopamine transporter</td>
</tr>
<tr>
<td>DDT</td>
<td>Dynamic developmental theory</td>
</tr>
<tr>
<td>DMN</td>
<td>Default mode network</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and statistical manual of mental disorders</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GLM</td>
<td>General linear model</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome wide association studies</td>
</tr>
<tr>
<td>HRF</td>
<td>Haemodynamic response function</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent component analysis</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of diseases</td>
</tr>
<tr>
<td>MCMC</td>
<td>Markov chain Monte Carlo</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized clinical trial</td>
</tr>
<tr>
<td>SHR</td>
<td>Spontaneously hypertensive rat</td>
</tr>
<tr>
<td>SNC</td>
<td>Substantia nigra pars compacta</td>
</tr>
<tr>
<td>VTA</td>
<td>Ventral tegmental area</td>
</tr>
<tr>
<td>WURS</td>
<td>Wender-Utah rating scale</td>
</tr>
</tbody>
</table>
INTRODUCTION

This thesis will endeavour to elucidate the current understanding of decision-making deficits in adults with attention-deficit hyperactivity disorder (ADHD), and the ways in which methylphenidate might improve decision-making in this patient population. This first introductory section will present key concepts for discussing decision-making in ADHD. In the second section, brief descriptions of the main research questions are presented. Aspects regarding the sample of participants and methods used to study decision-making in the current clinical-trial will be discussed following this, before the summaries of the three articles are presented. Lastly, the results from the various studies are compared and discussed in the last section. The published or submitted manuscripts of the three empirical articles are printed in full after the general discussion.

Attention deficit-hyperactivity disorder

Attention deficit-hyperactivity disorder (ADHD), or Hyperkinetic disorder, is characterized by age-inappropriate levels of hyperactivity, impulsivity, and inattention (Biederman & Faraone, 2005; Thapar & Cooper, 2015), and is commonly treated with central stimulants like methylphenidate (Fredriksen & Peleikis, 2015; Thapar & Cooper, 2015). While the description of ADHD, and its treatment, have gone through several changes since they first emerged, the basic concepts remain the same: motoric hyperactivity and inattention as core symptoms (Salum et al., 2014), and stimulant medication reducing these symptoms (Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). Twin studies indicate high heritability of ADHD, with estimates ranging between 60-90% (Faraone et al., 2005; Hawi et al., 2015; Larsson, Chang, D’Onofrio, & Lichtenstein, 2013), while genome wide association studies show that typically less than 5% of the variance in ADHD symptoms is explained by genes (Hawi et al., 2015). However, these studies do suggest that there are biological components to the pathophysiology of ADHD. As a developmental disorder, ADHD has been studied quite extensively (Coghill et al., 2014; Huang-Pollock, Karalunas, Tam, & Moore, 2012; Rubia, Alegria, & Brinson, 2014; Van der Oord et al., 2008), but it has been less studied as a disorder persisting into adulthood.
The clinical assessment of ADHD is a process of multi-stage interviews and inventories, which map the extent of manifested ADHD symptoms, how long they have been present, in which situations they occur, and whether other diagnoses might better explain the symptom constellation (Haavik, Halmøy, Lundervold, & Fasmer, 2014). To obtain an ADHD diagnosis as an adult (i.e. above 18 years of age) at least five (in stead of the paediatric six) symptoms in either the hyperactive-impulsive or the inattentive symptom categories must have been present for the last six months and must retrospectively have been present before the age of 12 (American Psychiatric Association, 2013). ADHD is divided into three sub-diagnoses, depending on whether the primary manifested symptoms are within the inattentive, hyperactive-impulsive, or equally in both the inattentive and hyperactive-impulsive symptom categories. Common for all the sub-diagnoses is that the symptoms must interfere with social, vocational, or school participation, and must be present in more than one situation (school, work, with family, siblings etc.). In Norway, the DSM diagnostic criteria are mainly used in research, and diagnoses are made according to the International Classification of Diseases (ICD) (NCHS/WHO, 2007). In the ICD, ADHD has the label hyperkinetic disorder. The diagnostic criteria of hyperkinetic disorder are stricter than for ADHD, and requires symptoms to be present prior to age six, but cautions against diagnosis in preschool children (NCHS/WHO, 2007).

The prevalence of ADHD in Norway is, given the strict diagnostic criteria of the ICD, expected to be somewhat lower than that of countries using the DSM criteria (Thapar & Cooper, 2015). Publicly accessible prescription-data from the Norwegian Institute of Public Health indicates some regional, gender, and age-cohort variations in the prescription frequency of common ADHD medications (anatomical therapeutic chemical [ATC] classification N06 BA; centrally acting sympathomimetics like amphetamines and methylphenidate) in Norway (Figure 1). The use of prescription data only provide rough estimates of ADHD prevalence, as some may be prescribed several substances and some choose to manage their symptoms by non-pharmacological means. However, despite stricter diagnostic criteria, prevalence of ADHD medication prescription in the age group 10-19 reaches the estimated worldwide prevalence rates of ADHD (Polanczyk, 2007). Diagnostic prevalence in children also has clear regional differences in Norway (Surén et al., 2013), and prevalence
rates of childhood ADHD also vary between countries, with estimates ranging from 1-19% (Figure 2) (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007).

Accurate ADHD sub-diagnosis is equally challenging, and further highlights certain difficulties regarding ADHD diagnosis. Through development and into adulthood, there is a shift in which ADHD sub-diagnosis is most commonly diagnosed. A meta-analysis of ADHD prevalence across four age cohorts observed how the most common sub-diagnosis shifts from hyperactive presentation in preschoolers to inattentive presentation in pre-teens, and continues to be the most common presentation thereafter (Figure 3) (Willcutt, 2012). The broader discussion on whether ADHD is over-diagnosed in the western world (Polanczyk, 2007), becomes understandable given such apparent geographical and age-related differences. Moreover, several studies have documented what is now called the relative-age effect, where children born right before the cut-off point for school entry in their region are more likely to receive an ADHD diagnosis (Elder, 2010; Evans, Morrill, & Parente, 2010; Morrow et al., 2012). The difficulty in accurate diagnosis in light of such results becomes quite apparent, as relative immaturity and ADHD symptoms are easily confused.

Figure 1 – Norwegian ADHD-medication prescription point prevalence for 2015. Per cent of Norwegian population prescribed ADHD-medications (ATC N06 BA) in Norway (ages 5-59). Data are extracted from the online public prescription repository of the Norwegian Institute of Public Health (accessed August 22nd 2016). Age range was restricted to 59 due to uncertain numbers for the population above this age.
Figure 2 – ADHD prevalence in the world and in Norway. Left: Worldwide prevalence estimates (Polanczyk, 2007). Continents are coloured by their estimated paediatric ADHD prevalence. Error bars in the bottom graph denote the 95% confidence intervals of the estimates. Right: Prevalence of ADHD-medication (ATC: N06 BA) in adults, ages 20-59, in 2015. Data are extracted from the public prescription repository of the Norwegian Institute of Public Health (accessed August 22nd 2016).
The problems with prevalence evaluations and accurate diagnosis are, however, not limited to ADHD. Such difficulties are inherent in any psychiatric diagnosis. They are based on subjective evaluations of behavioural symptom constellations, and are influenced by the clinicians’ and patients’ (and/or parents’ and teachers’) preconceptions of diagnosis. As mentioned, adult ADHD diagnosis requires retrospectively establishing childhood ADHD, commonly assessed by interviews of patients, their parents and/or partner, and through school and medical records (Thapar & Cooper, 2015). Such retrospective evaluation is of course not without difficulties, as memories are reconstructions rather than unbiased recollections (Schacter & Addis, 2007). Indeed, several studies have highlighted the difficulties in objectively evaluating both diagnosis and treatment of ADHD. Privitera et al. (2015), for instance, found that by suggesting having a previous positive score for ADHD diagnosis on the commonly used adult ADHD self-rating scale (ASRS), healthy participants shifted their answers from an initial negative to a positive score, when retested. Interestingly, other studies have indicated that adolescents with ADHD tend to under-report

Figure 3 – ADHD prevalence by age and sub-diagnosis. Diagnosis of ADHD presenting with primarily hyperactive symptoms is highest in pre-school children, and inattentive presentation becomes and remains the most common ADHD presentation after age six. Estimates are from Polanczyk et al. (2014), error bars denote the 95% confidence intervals.
symptoms (Sibley et al., 2012), while young adults without ADHD tend to over-report symptoms (Barkley, Fischer, Smallish, & Fletcher, 2002). The possibility that such tools inflate ADHD symptoms in healthy adults, while at the same time deflating symptoms in patients with ADHD, renders their diagnostic utility uncertain. Additionally, agreement across diagnostic instruments is low to moderate (Posserud et al., 2013). However, despite the fundamental difficulties in diagnosing purely based on subjective evaluations, there is little evidence for the increase of ADHD prevalence over the last three decades when basing prevalence estimates on random population samples (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014).

While prevalence rates might not be increasing, there are still very large regional differences in ADHD diagnosis, and the diagnostic tools allow too much subjective influence. There is thus still a need for better diagnostic tools, and aids for more tailored treatment. Researchers and clinicians have long searched for biological and neuropsychiatric markers that can be used to objectively aid diagnostic accuracy. Genetic and pharmacological studies searching for biomarkers of ADHD have largely targeted genes and substances that affect the release and reuptake of dopamine (Faraone & Khan, 2006), as this neurotransmitter has been implicated as important to the pathophysiology of ADHD. Dopamine’s assumed role in the pathophysiology of ADHD is implied by the improvement of symptoms through medication with certain dopamine agonists (such as methylphenidate and amphetamines), and abnormalities in neural circuits heavily innervated by dopamine in the brain (Minzenberg, 2012; Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016; Thapar & Cooper, 2015). While less research has focused on noradrenaline’s involvement in the pathophysiology of ADHD than that of dopamine, it is likely that noradrenaline also plays an important role in – at least a subset of – ADHD patients (Del Campo, Chamberlain, Sahakian, & Robbins, 2011). This is, among other, suggested by stimulant medications also modulating noradrenalin availability in addition to dopamine (Del Campo et al., 2011), and that the second-line pharmacological treatment to stimulants is a noradrenaline reuptake inhibitor (Thapar & Cooper, 2015).

Unfortunately, while advances have been made towards identifying biological and behavioural markers of ADHD (Eloyan et al., 2012; Karalunas, Geurts, Konrad, Bender, & Nigg, 2014), these have yet to provide the sensitivity required in order to
gain practical assistance in diagnostic accuracy (Thome et al., 2012). Therefore, despite increasing research efforts to uncovering the neurobiology of ADHD, the pathophysiology of ADHD remains elusive.

The dopamine system

Several years of research have indicated that there are irregularities in dopamine availability in ADHD (Sagvolden et al., 1992; Solanto, 2002; Volkow et al., 1998; Williams & Dayan, 2005). Neurobiological accounts of ADHD have thus primarily focused on the presumed deficiency in synaptic availability of dopamine in the brain (Volkow et al., 1998; Volkow, Wang, Fowler, & Ding, 2005), or implicate corticostriatal brain circuits that are known to be innervated with dopamine terminals (Killeen, Russell, & Sergeant, 2013; Sonuga-Barke & Fairchild, 2012; Sonuga-Barke, 2003). The efficiency of central stimulants in reducing ADHD symptoms may be explained by the medication blocking dopamine reuptake and thus increasing synaptic dopamine availability (Buitelaar et al., 2012; Coghill et al., 2014; Fredriksen & Peleikis, 2015).

The neuromodulator dopamine acts both through inhibitory D2-like receptors (D2, D3, and D4-receptors) and excitatory D1-like receptors (D1 and D5-receptors), and is primarily released in the striatum and prefrontal cortex (Meyer & Quenzer, 2005; Schultz, 2007). The inhibitory D2-like receptors have high affinity (i.e., easily bind with dopamine) and have rapid effect onsets (Dreyer, Herrik, Berg, & Hounsgaard, 2010). D1-like receptors, on the other hand, show slower effect onsets, and are generally in a low affinity state (Durstewitz & Seamans, 2006). It has been suggested that D1-like and D2-like dopamine receptors play an important role in balancing the trade-off between goal-directed behaviour and being able to flexibly respond to novel environmental demands (Durstewitz & Seamans, 2002). This is supported by seminal research showing that D1-like and D2-like receptors have antagonistic effects in certain situations (Seamans, Gorelova, Durstewitz, & Yang, 2001).
Dopamine is produced in cells within the midbrain substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). From there, three main dopaminergic pathways that project (Meyer & Quenzer, 2005) (Figure 4):

- A *nigrostriatal* pathway projects from SNc to the caudate nucleus and putamen (dorsal striatum).

- A *mesolimbic* pathway projects from the VTA to limbic system structures (like nucleus accumbens [ventral striatum], hippocampus and amygdala).

- A *mesocortical* pathway projects from the VTA to the cerebral cortex, especially medial prefrontal areas.

Dopamine signalling is commonly divided into tonic and phasic. Phasic dopamine is characterized by brisk, event-related neural firing, and may either spike at high concentrations by release of dopamine (Dreyer et al., 2010), or dip by the shut-down of dopamine release and rapid reuptake of synaptic dopamine by dopamine transporters (Schultz, 2007). Tonic dopamine signalling, on the other hand, is the slowly varying levels of dopamine in the extracellular fluid surrounding dopaminergic

![Figure 4 - Dopamine pathways.](image-url) The nigrostriatal pathway (green) projects from SNc to the caudate nucleus and putamen. The mesolimbic pathway (pink) projects from the VTA to limbic system structures (like nucleus accumbens, hippocampus and amygdala). The mesocortical pathway (yellow) projects from the VTA to the cerebral cortex. Own illustration adapted from Meyer & Quenzer (2005).
terminals. These levels are varied through, for instance, increase as a result of long-term dopamine availability or decrease through enzymatic breakdown of extracellular dopamine (Grace, Floresco, Goto, & Lodge, 2007). Tonic and phasic signalling are furthermore associated with different behavioural functions (Goto, Otani, & Grace, 2007; Schultz, 2007; Tsai et al., 2009). In the striatum, phasic dopamine release is important for evaluation and reinforcement learning, and has been particularly implicated as the possible carrier of the brain’s prediction error signal (Doya, 2008; Levy & Glimcher, 2012; Niv, 2009; Schultz, 2007, 2010). Tonic dopamine is likely to have a modulatory role on phasic dopamine (among others), and can be changed by e.g. uncertainty, novelty, and movement (Schultz, 2007).

There are several reasons to assume genetic and neurobiological components to the pathophysiology of ADHD, mainly suggested through animal models and pharmacological interventions. The most commonly used animal model of ADHD, the spontaneously hypertensive rat (SHR), displays behaviours similar to ADHD, such as increased hyperactivity and inattention, as well as deficient reward processing (Meneses et al., 2011; Sagvolden, 2000; Sagvolden et al., 1992). While some have questioned the validity of the SHR as an animal model of ADHD (Alsop, 2007; van den Bergh et al., 2006), the SHR mimics multiple important behavioural characteristics of ADHD and is likely to provide valuable information about the underlying neurobiological mechanisms of these features (Meneses et al., 2011). Most animal models of ADHD point towards deficits in dopamine, noradrenaline and, to some extent, serotonin functioning, with particularly strong evidence towards decreased activity of dopamine neurons (Russell, 2007).

Genetic studies of single nucleotide polymorphisms (SNPs) have consequently focused on primarily testing associations to genes whose effects are related to dopamine function. Particularly, catecholaminergic genes DRD2, DRD3, DRD4, DRD5 (D2, D3, D4, and D5 dopamine receptor genes, respectively), and SLC6A3 (dopamine transporter gene, DAT1) have been studied (Johansson et al., 2008), among other dopaminergic, serotonergic and noradrenergic candidate genes (Faraone & Khan, 2006). Results from SNP studies, however, show small and inconsistent results (Gallo & Posner, 2016), and broad-searching genome wide association studies (GWAS) implicate several small genetic contributions to ADHD (Akutagava-Martins, Rohde, & Hutz, 2016). This has led to the assumption that genetic influences to
ADHD are compound effects of multiple genes with small individual contributions. However, while researchers continue to investigate the genetic contributions to ADHD, there is still a large gap between the estimated heritability of ADHD from twin-studies and the genetic effects derived from GWAS. Results are diverging and our understanding of genetic influence on ADHD is still limited (Gallo & Posner, 2016).

The Dynamic Developmental Theory (DDT) of ADHD by Sagvolden et al. (2005) was based on work with the SHR, and has received further support through the group’s extended studies on children with ADHD (Johansen et al., 2009; Sagvolden, Aase, Zeiner, & Berger, 1998). This neurobiological account of ADHD posits that impaired reinforcement learning is the underlying impairment in ADHD, which arises as a result of reduced tonic dopamine in the brain, that in turn hampers reward-related phasic dopamine firing in corticostriatal brain circuits (Goto et al., 2007; Solanto et al., 2001). Behaviourally, reduction of phasic dopamine signalling during reinforcement learning is thought to underlie several cognitive impairments (Sagvolden et al., 2005). For instance, the DDT proposes that deficits in sustained attention arise from lack of stimulus control over time. Rewards temporally distant to desired behaviour would furthermore be inefficiently reinforced and could lead to reinforcement of inappropriate behaviour. Moreover, hyperactivity is thought arise from reduced reward extinction (Sagvolden et al., 2005; Sagvolden & Aase, 1998). Similar theories focusing on deficits in reward processing as a result of aberrant dopamine (and noradrenalin) functioning have been proposed (Frank, Santamaria, O’Reilly, & Willcutt, 2006; Killeen et al., 2013; Sonuga-Barke, 2003; Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016; Tripp & Wickens, 2008). These theories mainly differ in the underlying neurobiological assumptions of behavioural deficits in ADHD, such deficits in tonic and phasic signalling, or dysfunctions in dopamine dense brain circuits (Ziegler, Pedersen, Mowinckel, & Biele, under revision). However, they largely agree that deficits in catecholamine signalling in the brain lead to deficits in reward processing.

In humans, adults with ADHD have increased dopamine transporter binding in the striatum compared to healthy controls (Spencer et al., 2007; Spencer, Fischman, Krause, & Madras, 2012), indicating that dopamine is more easily removed from the extracellular space. Oral methylphenidate blocks dopamine transporter binding and
thus increases the synaptic availability of dopamine (Volkow et al., 1998, 2005). However, a meta-analysis by Fusar-Poli et al. (2012) indicates that higher dopamine transporter density in adults with ADHD might be a result of an adaptation to long-term blockade of dopamine transporters due to previous medication with psychostimulants. Indeed, the highest weighted study in their meta-analysis is from a positron emission tomography (PET) study including a large non-comorbid, medication-naïve sample, where patients had lower levels of dopamine transporters than healthy controls (Volkow et al., 2009). This same study also found lower levels of dopamine receptor binding in the midbrain of the ADHD sample. While the cause is different, reduced dopamine binding would nevertheless entail diminished activity of dopamine neurons in ADHD. Empirical evidence thus suggests that there is a dysfunction in midbrain dopamine signalling in ADHD, but the cause of this deficiency remains uncertain.

Imaging studies of higher-order cognitive processes in children with ADHD commonly find hypoactivations in the fronto-striatal brain networks (Paloyelis, Mehta, Kuntsi, & Asherson, 2007), which is consistent with theories positing reduced dopamine availability in ADHD. However, such processes are less studied in ADHD adults. Adult and paediatric fMRI show striking similarities (Cubillo, Halari, Smith, Taylor, & Rubia, 2012), but studies that results from adult ADHD are less consistent than that of children, showing both hypo and hyperactivations in the same brain regions (Cubillo & Rubia, 2010). One pioneering imaging study of adult ADHD provided evidence for hypoactivation in the fronto-striatal network, which was normalized with long-term methylphenidate treatment (Bush et al., 2008). This is consistent with the increase in dopamine availability through methylphenidate medication (Volkow et al., 1998) considering the projections of dopamine from the striatum to the frontal cortex (Figure 4). Researchers have furthermore postulated that dopaminergic dysregulation in a fronto-striato-amygdalar functional network in ADHD causes deficits in processing and evaluating outcome cues, leading to suboptimal decision-making (Sonuga-Barke et al., 2016; Sonuga-Barke & Fairchild, 2012).
**Reward based decision-making**

The crucial role of the dopamine system for reward processing and decision-making has been documented in an extensive amount of research literature (Schultz, Dayan, & Montague, 1997; Schultz, 2010). Dopamine deficiency has, for instance, been associated with disruptions in decision-making processes (Clark, Manes, Antoun, Sahakian, & Robbins, 2003; Shiner et al., 2012). The involvement of dopamine in reward processing in particular is evidenced by the firing rate of midbrain dopamine neurons that correlate with the amount of reward (Tobler, 2005), and by observing dopamine neuron activity proportional to the probability of receiving reward (Fiorillo, Tobler, & Schultz, 2003). Following animal experiments, fMRI studies also document the role of striatal dopaminergic activity for reward processing in humans (e.g. Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006).

In a broad sense, decision-making can be operationalized as any action process where one of several choice alternatives is selected. Decision-making can thus include cognitive processes like perceptual learning, reinforcement learning and multi-attribute choice, among others. Successful reinforcement learning is, for instance, thought to depend on the ability to learn reward associations by updating expectations of future rewards when unexpected rewards occur (Miller, Barnet, & Grahame, 1995; Rescorla & Wagner, 1972). Empirical evidence from animal models and human neuroimaging suggests that this *reward prediction error* is coded by midbrain dopamine neurons, which then guide learning by passing information to the basal ganglia and frontal cortex (Glimcher, Fehr, Daw, & Tobler, 2014). This is supported by single-cell recordings from dopamine neurons in monkeys (Schultz, 2007), and fMRI studies in humans (Krugel, Biele, Mohr, Li, & Heekeren, 2009; Schönberg, Daw, Joel, & O’Doherty, 2007). Pharmacological interventions in humans have, moreover, shown how dopamine agonists and antagonists can lead to improved and reduced learning, respectively (Pessiglione et al., 2006), and that learning is improved in dopamine deprived Parkinson’s patients treated with dopamine medication (Frank, 2004; Graef et al., 2010).

The signalling of reward information in midbrain neurons is not limited to unexpected rewards, and there is an increasing number of studies indicating both the striatum and amygdala as important structures for the representation of reward-
related information (Basten, Biele, Heekeren, & Fiebach, 2010; Beck et al., 2009; FitzGerald, Friston, & Dolan, 2012; Peters & Büchel, 2010). Decisions that depend on such value coding will hence also rely on the correct representation and proper evaluation of reward values (Basten et al., 2010). For instance, both Basten et al. (2010) and Metereau & Dreher (2015) found that activation in the medial prefrontal cortex was associated with the expected values of reward. The medial prefrontal cortex has even been found to express top-down control in suppressing striatal dopamine response to rewards, thus disturbing normal reward behaviour (Ferenczi et al., 2016). The medial prefrontal cortex thus plays a pivotal role in successful decision-making, not only by evaluating reward information from subcortical regions, but also by regulating reward processing in the striatum.

While higher-order cognitive dysfunctions are pivotal in the current understanding of the manifested behavioural symptoms arising in ADHD (Barkley, Murphy, & Kwasnik, 1996; Noreika, Falter, & Rubia, 2013), deficient reward processing has been gaining attention as a core problem in ADHD (Sagvolden et al., 2005; Sonuga-Barke & Fairchild, 2012; Sonuga-Barke, 2011; Wilbertz et al., 2012). Patients with ADHD have been observed to have similar responses as their peers in seeking actions leading towards rewards in reinforcement learning paradigms (Johansen et al., 2009), but they also struggle in learning punishment avoidance (Luman, Tripp, & Scheres, 2010). Increased propensity towards risky decisions in ADHD is suggested by the higher prevalence of unprotected sex (Flory, Molina, Pelham, Gnagy, & Smith, 2006), comorbid gambling addictions (Grall-Bronnec et al., 2011), and increased use of narcotic substances in this patient group (Charach, Yeung, Climans, & Lillie, 2011). Research on children with ADHD clearly indicates higher tendency towards riskier decisions compared to typically developing controls in experimental settings, but the evidence for the same in adults is less certain (Groen, Gaastra, Lewis-Evans, & Tucha, 2013).

A recurring finding in the paediatric ADHD literature is the abnormal preference for small and immediate rewards to larger more distant rewards in comparison to healthy peers. This phenomenon, called temporal discounting, is possibly the most studied decision-making processes in paediatric ADHD (Scheres, Tontsch, et al., 2010). Studies have suggested that temporal discounting also occurs for penalties (punishment), where the effect of penalties decays faster in children and
adolescent with ADHD than typically developing controls (Luman, Oosterlaan, Knol, & Sergeant, 2008; Toplak, Jain, & Tannock, 2005). Temporal discounting is related to reinforcement learning, as reinforcers that decay too rapidly lead to reduced reinforcement learning if reward-behaviour intervals are too large. Several theories of ADHD are specifically centred on abnormal temporal discounting and reinforcement learning (Sagvolden et al., 2005; Sonuga-Barke, 2003), where reinforcement learning is increasingly impaired in ADHD, the more distant a reinforcer is to the reinforced behaviour, or may lead to unintended reinforcement of incorrect behaviour.

The dynamic development theory (DDT), for instance, suggests that a delay-of-reinforcement gradient leads to inappropriate behaviours becoming reinforced rather than the intended behaviour, if the time interval between correct behaviour and reward is too large (Sagvolden et al., 2005). Similarly, the dopamine transfer theory (DTD) by Tripp and Wickens (2008) suggests that propagation of dopamine signalling from reward receipt to reward cue is reduced in ADHD, leading to a dysfunction in the ability to predict future rewards. A more recent neuroeconomic theory of ADHD attempts to integrate empirical evidence and theoretical assumptions from multiple disciplines in order to provide a broader account of deficits in decision-making in ADHD and other developmental disorders (Sonuga-Barke et al., 2016). While less detailed in specific neuromodulatory actions, this theory posits that patients with ADHD have disturbed prospection of future events, inabilities in generating and implementing plans consistently, and difficulties in learning from experience due to a disrupted prediction error signal. These dysfunctions are explained by disturbances in frontostriatal and intrinsic default mode (network of midline, temporal and parietal structures that is associated with self-referential thoughts) networks (Sonuga-Barke et al., 2016).

The importance of decision-making deficits to our current understanding of ADHD is becoming increasingly established, and it has even been suggested to be a reinforcement learning disorder (Sonuga-Barke, 2011). The number of prominent ADHD theories focusing on reward-based decision-making as important to the pathophysiology of ADHD further highlights the continued significance of studying how decision-making is deficient, where these deficits arise, and how we can remediate these deficits. The importance of dopamine for successful decision-making,
and the theoretical and empirical suggestions of dopamine’s involvement in the pathophysiology of ADHD, further illuminate the significance of studying how dopamine availability alters decision-making in ADHD.
MAIN RESEARCH OBJECTIVES

There are thus strong indications of decision-making deficits in adult ADHD, given the importance of dopamine (and noradrenaline) for decision-making and the observed deficiencies in ADHD patients dopaminergic system. If decision-making is aberrant in ADHD, it might aid the development of targeted treatments and diagnostic accuracy if elucidated properly. The overarching goal of these collected works is thus to better understand the extent of decision-making deficits in young adults with ADHD, and to study both cognitive and brain mechanisms underlying decision-making in this group.

A complete understanding of decision-making in ADHD involves research from fields including pharmacology, neurobiology, psychiatry, psychology, and computer science, which is more than can be covered in a single thesis. Rather, the intent here is to narrow the focus of the research so that specific questions may be answered. In this way, we may slowly piece together an increased understanding of decision-making and brain functioning in adult ADHD, and hopefully contribute to improved diagnostic awareness of decision-making deficits in this group.

Does the current literature support that there are decision-making deficits in adults with ADHD?

Deficits in decision-making are quite established in paediatric ADHD (Ernst & Paulus, 2005; Sonuga-Barke et al., 2016), which is why most central neurobiological theories about the pathophysiology of ADHD include attempts in explaining the origins of these deficits (Frank et al., 2006; Killeen et al., 2013; Sagvolden et al., 2005; Tripp & Wickens, 2009). In order to assess the current understanding of decision-making in adult ADHD, we aimed to produce a quantitative summary of the current research results. Individual research projects only provide suggestions to what the true nature of a phenomenon is. Alone, they are merely small pieces to a larger puzzle. Meta-analyses are important contributions to scientific research, as they consolidate numerous studies to provide a clearer representation of study effects. Not only do meta-analyses provide the opportunity to assess whether theoretical constructs are supported by evidence across several studies, but also inquire about the likelihood of different studies mapping the same phenomenon and whether there are indications of publication bias (Duval & Tweedie,
2000; Viechtbauer, 2010). By comparing the effect sizes from studies of decision-making in adults with ADHD, we map which sub-domain(s) of decision-making that research implies to be most affected. Adding the comparison to the widely accepted difficulties in attention, as measured by the continuous performance task (CPT), provides a benchmark in evaluating the extent of decision-making deficits. Such a review could contribute to the delineation of functional deficits in adult ADHD, and improve the understanding of ADHD in adults.

**At which stage of the decision-making process do deficits occur in adults with ADHD, and does methylphenidate remediate this deficit?**

Reduced reinforcement learning and aberrant reward processing has been studied quite extensively in children with ADHD, while there are still only a few studies on adults. Research on reward processes in ADHD has moreover been highly focused on reinforcement learning and reward anticipation and receipt, whereas basic representations and integration of reward values in the brain during decision-making remain less examined. By adopting a previously used neurocognitive model of reward-based decision-making (Figure 5)(Basten et al., 2010), we could distinguish

![Figure 5 - Neurocognitive model of reward-based decision-making by Basten et al. (2010).](image)

Associated gain and loss values are represented in the striatum (top left) and amygdala (bottom left), respectively. This information is sent to the ventromedial prefrontal cortex, which evaluates the magnitude of the gain-loss difference (centre). The evaluation of the difference signal is influenced by neural noise, and the difference signal is accumulated in the intraparietal sulcus until sufficient evidence for a decision is acquired (right). The accumulation of decision evidence is estimated by a computational model of two-alternative forced-choice decisions (for further information see Ratcliff & McKoon, 2008). Image adapted from Basten et al. (2010), with permission.
between three stages of decision-making: value representations in the striatum and amygdala, value computation in the medial prefrontal cortex, and evidence accumulation in the intraparietal junction. A more mechanistic approach to decision-making could contribute to increased understanding of the origins of value-based decision-making deficits in this patient group. Moreover, it could potentially disentangle at what stage in the decision-making process deficits occur in ADHD. Deficits in different stages may require targeted interventions. Furthermore, by specifically studying the effects of dopamine agonists on behavioural and brain processes of decision-making, we could increase our understanding of the underlying dopaminergic processes in both ADHD and decision-making.

*Can decision-making deficits in ADHD be captured by disturbances in large-scale functional brain networks, and to what extent does methylphenidate alter the dynamics of these networks?*

A second approach to understanding brain processes underlying cognition is by studying the brain’s intrinsic functional networks. The interplay between networks with spatially distant but temporally correlated activity has been increasingly implicated as important for normal functioning (Haatveit et al., 2016; Johnston et al., 2008; Kaufmann et al., 2016), and has been shown to be dynamically changed by task engagement (Alnæs et al., 2015; Calhoun, Kiehl, & Pearlson, 2008). One particular network, the *default mode network* (DMN), has been described to be dysfunctional in several psychiatric disorders, including ADHD (Haatveit et al., 2016; Mohan et al., 2016; Zhou et al., 2015). This has led to suggestions of dysfunctions in this network underlying common symptoms of ADHD, such as inattention and hyperactivity (Sonuga-Barke & Castellanos, 2007; Sonuga-Barke et al., 2016). By employing multiple approaches to studying functional network dynamics, we sought to capture different aspects of these networks during decision-making. The (hopeful) convergence of results from these methods could help us to elucidate the extent of intrinsic network dysfunction in ADHD, and its possible remediation through methylphenidate.
METHODOLOGICAL CONSIDERATIONS

The main descriptions of the study design and sample can be found in the three articles at the end of this thesis, which also include short discussions of the limitations of the sample and design. In this section I will discuss broader aspects of the study that have not been covered by the papers, such as more in-depth accounts of the current patient sample, choice of experimental design, issues with interpretation of fMRI data, and limitations of the pharmacological intervention.

Experimental design and hierarchical models

Randomized clinical trials (RCT) are the gold standard of treatment research, and are important when testing the effects of pharmacological substances on behaviour. The effects of mock treatment, or placebo, are well established, and in order to delineate the effects of the pharmacological intervention from expectancy effects it is necessary to test both conditions and compare their effects. There are several ways to set up RCTs, depending on what the main purpose of the trial is. In some instances, it might be fruitful to divide the pharmacological intervention and placebo in two separate groups, while in other instances it might be better to administer both conditions to all participants at different time points (cross-over). There are advantages and disadvantages to both approaches. The advantage of crossover designs is that each participant is compared to themselves in both conditions, which increases the likelihood of estimating the effect of the intervention rather than arbitrary differences between persons (Yuan & Zhou, 2005). On the other hand, crossover designs also entail repeated testing, which leads to possible carryover effects between the testing time points (Millar, 1983). For instance, it is possible that the order of intervention administration affects one administration sequence but not the other, or that participants improve performance at the second testing due to learning or habituation. Concerns regarding crossover designs have been voiced regarding the validity of estimating pharmacological effects in such designs, but these are mainly based on the use of statistical tests whose assumptions are violated by the design (such as non-independence of observations) (Brown, 1980; Mills et al., 2009; Wellek & Blettner, 2012).
However, by applying appropriate statistical methods, the repeated measures acquired through crossover designs may provide robust estimations of the studied intervention and the influence of possible carryover effects (Hedeker & Gibbons, 1994; Lee & Nelder, 2006). Extensions of the classical general linear model called linear mixed models (sometimes also referred to as hierarchical or multilevel linear models), allow for the estimation of both fixed and random predictors (Lee & Nelder, 1996). Such models do not rely on group homoscedasticity, can easily handle missing data, and groups of unequal sizes, due to their use of likelihood functions rather than sums squared (Magezi, 2015). The hierarchical, or multilevel nature of data from repeated measures can be modelled through random linear predictors, where, for instance, the fully or partially crossed nature of the groups may be specified (Magezi, 2015). By specifying the hierarchical structure of the data, such models can handle both the non-independence of observations and heteroscedasticity (unequal variances) between groups (Tuerlinckx, Rijmen, Verbeke, & De Boeck, 2006). The partial pooling that the parameters undergo in such models provides an added benefit of shrinking estimates towards the mean, and thus outliers have diminished influence on the effect estimates (Bafumi & Gelman, 2006). Lastly, through the use of likelihood functions, assessment of model-fit to the data may be compared between models, and one may identify and base interpretations on the model that best explains the data (Vehtari, Gelman, & Gabry, 2016).

Still, while linear mixed models have properties that make them more applicable to the hierarchical data often collected in experimental psychology and crossover clinical trials, if there are too few observations for high-dimensional models, there is not enough data to provide estimates for all specified effects. These problems restrict our possibilities in discovering the best fitting model, as we are unable to test models with high complexity (i.e. estimating many effects). In a Bayesian framework, we iteratively sample large quantities of model parameters, providing posterior distributions of the model parameters, which thus accommodate high-dimensional models (Gelman et al., 2013; Kruschke, 2010). Furthermore, Bayesian sampling shrinks estimates not only towards the means, as likelihood functions, but also towards prior information provided to the model. The posterior densities thus become conservative without sacrificing power and do not require corrections for multiple comparisons, which would normally be a problem when
testing high-dimensional models (Gelman, Hill, & Yajima, 2012; Gelman & Tuerlinckx, 2000).

Where possible, we used Bayesian hierarchical models with weakly informative priors, which not only allow us to utilize the increased statistical power of within-subjects comparisons and all individual observations, but also to compare different hypotheses given the collected data. Do the data better fit a model only distinguishing between controls and patients, rather than a model that includes the pharmacological within-subjects manipulation in the patient sample? Perhaps models with information limited to just the two time points, disregarding the data coming from different groups, is better? We may increase the model complexity in a step-wise manner and evaluate which of all the tested models are best accounted for by the data. Of course, none of the models may be the “correct” one, this discussion is of a different nature.

**Event-related functional MRI**

Neuroimaging data require a lot of processing before any results may be derived from them. The processing of functional MRI data is constantly being evaluated and developed to (hopefully) create more reliable results (Winkler et al., 2016). Such data processing has in the last year been under special scrutiny after a software bug in the fMRI analysis software AFNI was detected, and inflated Type-I error rates were detected across different parametric analysis approaches to fMRI (Eklund, Nichols, & Knutsson, 2016). FSL’s FLAME was the only parametric tool for fMRI that did not inflate this type of error. Furthermore, high flexibility in acceptable analysis approaches could potentially lead to different results from the exact same dataset (Carp, 2012). The larger concern of the reproducibility and validity of fMRI results have thus become increasingly voiced in the fMRI field.

There are also difficulties in the interpretation of fMRI results. Functional MRI measures the change in blood oxygen level dependency signal in the brain (BOLD), which is the change from oxygenated haemoglobin to deoxygenated haemoglobin as a result of underlying neural activity. Simply put, the magnetic field around haemoglobin is weaker when deoxygenated than when oxygenated, and the strong electromagnetic pulses of the MRI-scanner record these different magnetic
fields. The measurements from fMRI have low temporal resolution compared to the underlying neural activity because they depend on the BOLD signal, which is more sluggish. The BOLD signal relies on the *hemodynamic response function* (HRF), which is a combination of the curve of increase and decrease of both deoxygenated and oxygenated haemoglobin relative to baseline as a result of neural stimulation (Huettel, Song, & McCarthy, 2014). It increases at stimulus onset, peaks around 6 seconds, declines to below baseline values at around 12 seconds and returns to baseline at 22 seconds. Event-related fMRI seeks to understand the functions of the brain by measuring BOLD while participants perform certain tasks. By convolving general linear models (GLM) of task event information with the *haemodynamic response function* (HRF), we derive which areas of the brain have BOLD signals that correlate with the convolved GLM.

These BOLD signals in response to task events are usually only 1% of the total variance of BOLD activity of the brain (Raichle, 2006), which means there is little signal, and much noise. Some of this noise stems from artefacts known to influence the BOLD signal, like head movement, pulse and respiration. A lot of progress in the development of fMRI analysis procedures is indeed made in the identification and filtering of such artefacts with increasing precision. For instance, while standard motion corrections are applied in all fMRI software, studies have suggested that residual head motion may still influence the end result, creating particular difficulties when studying samples prone to increased movement (Couvy-Duchesne et al., 2016; Mowinckel, Espeseth, & Westlye, 2012). Tools have thus been developed in order to minimize this influence, such as the combination of independent component analysis with hierarchical fusion classifiers (Salimi-Khorshidi et al., 2014). Moreover, by recording pulse with an oximeter and respiration with a chest band, the registered waves from these can be used to further filter the fMRI data by modelling known physiological noise in the first-level analyses (Brooks et al., 2008). While all these extra steps and procedures are developed and used in order to increase the reliability of the results, the increased number of possible analysis choices also makes it difficult to compare results across studies. Good analysis pipelines are thus important to the end result of fMRI analyses. The processing steps required to derive information from the data are many, and mistakes are easily made. However, through increased transparency and sharing of analysis scripts, it is slowly becoming easier to
Functional MRI is thus a powerful, non-invasive tool for understanding human brain functioning. Brain function may be viewed in two ways: one where the brain is reflexive and reacts to the momentary demands of the environment, and another where the brain’s activity is mainly intrinsic and maintenance based (Raichle, 2009). The juxtaposition of these two views portray the brain as a collection of dynamic, fundamental networks in continuous operation that also react to environmental demands (Raichle, 2006). In this sense, the 99% of unaccounted for BOLD signal from task GLMs is not all noise (such as pulse, respiration, or head movement), but reflects continuous and necessary operations for normal functioning. While most fMRI studies to date have focused on task-evoked signal change, recent technological and statistical advances have created the opportunity to also study the intrinsic properties of the BOLD signal (Snyder & Raichle, 2012). At its inception, the study of intrinsic brain functions was limited to studying the “resting” brain, i.e. the brain’s activation without stimulus events. This led to the establishment of several functional networks that showed temporal correlation while being spatially distributed (Calhoun et al., 2008; Damoiseaux et al., 2006; Filippini et al., 2009). The integration of these two views has seen an enormous increase of interest as new technological and statistical advances have become available. By combining and extending methods, researchers are starting to explore the changes in functional intrinsic networks in relation to task events (Smith et al., 2009), and provide richer accounts of the interdependence of brain regions for functioning. The identification of brain functions can thus be both reliant on the identification of focal processing regions for cognitive functions, and also on seeking how the brain connects, distributes resources, and relays information between such regions.

In article II, we intended to identify different stages of decision-making in adults with ADHD and how methylphenidate might alter these stages. It was thus a study of identifying regions of basic processing required for decision-making, as established by a previous study on healthy adults (Basten et al., 2010). The analysis-strategy was already set, as an important part was the attempt to replicate the results of the original study before continuing to identify differences between patients and controls, and of the intervention. While the original study used the Matlab toolbox...
SPM, we used FMRIB’s FSL, which has slightly different approaches to fMRI analysis. However, a recent paper has shown that the two analysis packages produce similar results despite some differences in approach (Pauli et al., 2016). Moreover, the results from our study were largely in line with the results from the original study, which in turn strengthens the validity of both.

In the third article, a more data-driven approach was adopted, where we combined approaches to event-related data (task GLMs) with methods more common to the analysis of model-free (resting-state) data. We intended to test how intrinsic functional networks, identified through a type of principal component analysis (independent component analysis; ICA) and dual-regression (Filippini et al., 2009), responded to task events, how they were connected and if the temporal signal variation of the components could provide further information about the components’ functions. In particular, we wished to investigate a functional network called the default mode network that has been repeatedly implicated as dysfunctional in ADHD and has been suggested to cause common symptoms of ADHD (Sonuga-Barke & Castellanos, 2007). By applying several analysis methods including and all identified intrinsic networks, the potential convergence or conflict in results could provide valuable information about the response of fundamental brain networks to external events.

**Participants**

The exclusion criteria applied in this project will arguably have produced an adult ADHD sample that is not representative of the general adult ADHD population. In every experiment a number of decisions must be made in order to properly answer the research questions. Many of these choices entail some sacrifice in order to obtain a benefit. The balance between internal and external validity merits careful deliberation. The choice of how particular the sample of participants is inevitably affects how broadly the results can be applied. The participant criteria were all carefully selected with the specific purpose of better understanding the underlying processes that were studied, without the uncertainty introduced by a more heterogeneous sample. In other words, we chose to emphasize the internal validity of the study.
**Drug and treatment status.** In an attempt to specifically study ADHD without possible contamination of results by participants with previous drug problems, no participants with a history of drug abuse were allowed to enter the study. The clinic that the participants were recruited from has published an in-depth description of over 250 adults with ADHD indicating a substantial proportion of patients with comorbid drug abuse problems (Fredriksen, Dahl, & Martinsen, 2014). Moreover, several international studies have found an increased tendency towards drug abuse in this patient group (Dekkers, Popma, van Rentergem, Bexkens, & Huizenga, 2016; McCabe, Dickinson, West, & Wilens, 2016; Ottosen, Petersen, Larsen, & Dalsgaard, 2015). The clear advantage of excluding based on previous drug problems is the increased certainty that the study effects are not due to previous substance abuse problems. This is particularly important given the pharmacological intervention of the study.

Furthermore, as a main objective of the study was to investigate the influence of methylphenidate on decision processes in ADHD, a decision to exclude participants receiving treatment with other psychopharmacological substances (also indicating strong current comorbidity) was reached to minimize the influence of other medications on the study results. While possible cessation of any medication prior to study participation might have sufficed, the speed of breakdown in the body differs between medications, and the possible adverse effects of withdrawing multiple treatments simultaneously would arguably also bias the results of the study.

Patient recruitment was also restricted to only those who were already receiving methylphenidate treatment. Treatment with methylphenidate usually stabilizes only after 3-6 months medication, with the patients steadily up-regulating the medication until the desired effect has stabilized (Thapar & Cooper, 2015). Restricting recruitment to participants who were already on a stable regiment of methylphenidate medication increased the number of prospecting participants we could contact, and the decision was largely pragmatic. While we also recruited participants who were medication naïve to the study, these were only tested in naïve state with perfusion MRI, as an attempt to elucidate the blood-flow change from stimulant-naïve to stimulant-exposed. However, given other strict exclusion criteria, these were few and far in-between, and we were only able to obtain a sample of 10 medication-naïve participants. Clinical and treatment variables are summarized in
Table 1. Most participants had been prescribed methylphenidate over 60 days prior to testing, with the exception of the medication-naïve participants.

Restricting the patient group to those only using methylphenidate also produces a sample skewed from the complete distribution of patients. While the majority of patients are methylphenidate users, there are several other medications on the market for those who do not respond well to methylphenidate. Wanting a sample that had a positive response to the medication enabled us to explore whether we could document this subjective positive response in an objective way. Lastly, testing participants already using methylphenidate also creates uncertainty to whether the effects observed during the placebo condition indeed were the effect of having ADHD and being unmedicated, or if the effects were merely caused by methylphenidate withdrawal. While cessation of minimum 20 hours before testing should be sufficient to remove clinical effectiveness of methylphenidate, we cannot be certain to which extent the results from the placebo condition were influenced by withdrawal effects (Table 1). However if the results fall in line with previous studies and theories of ADHD, we can be more certain of the reliability of our results.

Clinical assessment of ADHD. Two board-certified psychiatrists conducted assessments of the patients’ mental health problems, and the assessments were completed independently from the project. The patients were receiving care at a specialized adult ADHD outpatient clinic in Tønsberg, Norway, and fulfilled ICD criteria for Hyperkinetic disorder. The ADHD diagnosis was ascertained by a multistage and multisource procedure (American Psychiatric Association, 1994) with The structured Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0; Kooij & Francken, 2010), The MINI International Neuropsychiatric Interview Plus (M.I.N.I.-Plus; Sheehan et al., 1997), The investigator rated Iowa Personality Disorder Screen (IPDS; Langbehn, Pföhl, Reynolds, & Clark, 1999), and other informant sources (i.e. parents, siblings, significant-others etc.).
<table>
<thead>
<tr>
<th>Health and intervention information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental records</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>ADHD</strong></td>
</tr>
<tr>
<td>(n=20)</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
</tr>
<tr>
<td>(n=27)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Mean  SD  Range</td>
</tr>
<tr>
<td>Mean  SD  Range</td>
</tr>
<tr>
<td>Mean  SD  Range</td>
</tr>
<tr>
<td>fMRI Pulse</td>
</tr>
<tr>
<td>69.7  10.5  48 - 92</td>
</tr>
<tr>
<td>75.8  12.0  60 - 104</td>
</tr>
<tr>
<td>66.0  9.9  48 - 84</td>
</tr>
<tr>
<td>Sleep Quality</td>
</tr>
<tr>
<td>4.1  1.5  2 - 7</td>
</tr>
<tr>
<td>4.2  1.7  2 - 7</td>
</tr>
<tr>
<td>4.3  1.0  3 - 7</td>
</tr>
<tr>
<td>Medication delay (hours)</td>
</tr>
<tr>
<td>1.2  0.2  1 - 2</td>
</tr>
<tr>
<td>1.3  0.3  1 - 2</td>
</tr>
<tr>
<td>Medication cessation (hours)</td>
</tr>
<tr>
<td>31.2  15.3  20 - 72</td>
</tr>
<tr>
<td>34.6  16.7  20 - 72</td>
</tr>
<tr>
<td><strong>Methylphenidate</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>(n=13)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>(n=7)</td>
</tr>
<tr>
<td><strong>Tiredness</strong></td>
</tr>
<tr>
<td>Number  Percent</td>
</tr>
<tr>
<td>Number  Percent</td>
</tr>
<tr>
<td>7       27%</td>
</tr>
<tr>
<td>2       14%</td>
</tr>
<tr>
<td>3       12%</td>
</tr>
<tr>
<td>0       0%</td>
</tr>
<tr>
<td>4       15%</td>
</tr>
<tr>
<td>0       0%</td>
</tr>
<tr>
<td>9       35%</td>
</tr>
<tr>
<td>1       7%</td>
</tr>
<tr>
<td>6       23%</td>
</tr>
<tr>
<td>2       14%</td>
</tr>
<tr>
<td>2       14%</td>
</tr>
<tr>
<td>0       0%</td>
</tr>
<tr>
<td>9       35%</td>
</tr>
<tr>
<td>2       14%</td>
</tr>
<tr>
<td>0       0%</td>
</tr>
<tr>
<td>0       0%</td>
</tr>
<tr>
<td><strong>Treatment and diagnosis</strong></td>
</tr>
<tr>
<td>(n=13)</td>
</tr>
<tr>
<td>(n=7)</td>
</tr>
<tr>
<td><strong>Treatment duration (days)</strong></td>
</tr>
<tr>
<td>Mean  SD  Range</td>
</tr>
<tr>
<td>Mean  SD  Range</td>
</tr>
<tr>
<td>124  114  22 - 348</td>
</tr>
<tr>
<td>153  110  21 - 295</td>
</tr>
<tr>
<td><strong>WURS main</strong></td>
</tr>
<tr>
<td>52   18  16 - 80</td>
</tr>
<tr>
<td>36   13  17 - 60</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
</tr>
<tr>
<td>Number  Percent</td>
</tr>
<tr>
<td>Number  Percent</td>
</tr>
<tr>
<td>8       62%</td>
</tr>
<tr>
<td>7       100%</td>
</tr>
<tr>
<td>5       38%</td>
</tr>
<tr>
<td>0       0%</td>
</tr>
</tbody>
</table>

Table 1 – Health and intervention information. **Experimental records**: Data catalogued during the clinical trial assessment. Pulse is heartbeats per minute during fMRI scan acquisition. A 7-item scale assessed sleep quality where 1 was bad, 7 was excellent. Medication delay is the hours (in decimals) between administration of trial drug and first fMRI scan. Cessation was total hours of drug cessation from the last time the subjects reported taking medication to administration of trial drug. **Methylphenidate withdrawal**: Participants answered yes or no on each withdrawal item after 20 hours of cessation. Summary of data acquired from medical registry regarding treatment duration with methylphenidate (days from first received prescription to first test date), score on the main part from the Wender-Utah Rating Scale (WURS), and number of participants within the different ADHD presentations. **Treatment and diagnosis**: Summary of data acquired from medical registry regarding treatment duration with methylphenidate (days from first received prescription to first test date), score on the main part from the Wender-Utah Rating Scale (WURS), and number of participants within the different ADHD presentations.
After completion of the DIVA 2.0, participants needed to have: 1) at least six out of nine DSM-IV symptoms of inattention and/or hyperactivity/impulsivity in childhood; 2) at least six out of the same nine DSM-IV symptoms for the last six months prior to examination currently as adults; 3) describe a chronic course from childhood to adulthood without any indication of ADHD-free periods; 4) five out of nine symptom criteria for each symptom domain in adulthood given they had met full symptom criteria in childhood (DSM-IV: ADHD Not Otherwise Specified); 5) the current ADHD symptoms should cause clinically significant impairment in social, educational, or occupational functioning.

Assessments with the DIVA 2.0 allow clinical evaluation of symptom criteria of childhood and adulthood ADHD symptoms separately. Collateral information about current symptoms and impairment were also obtained from a close relative invited to participate during the DIVA interview with the patient. Historical data about pedagogical assistance in primary school, reading or arithmetic problems, grades from school reports, relevant information from other sources on childhood symptoms, such as school records and psychological-pedagogic service records, were also collected systematically.

To examine whether ADHD symptoms might be better explained by another mental disorder and to check for comorbid mental disorders, the M.I.N.I.-Plus was used. The M.I.N.I.-Plus is a fully structured diagnostic interview for DSM-IV anxiety disorders, mood disorders, somatoform disorders, substance use disorders, psychotic disorders, eating disorders, antisocial personality disorder (ASPD), and adjustment disorder (Sheehan et al., 1997). Screening for personality disorders was done with the IPDS (Langbehn et al., 1999). Those meeting criteria were still included in the study if the ADHD symptoms were not considered better accounted for by a personality disorder.

**Particular sample characteristics.** The ADHD sample obtained for this study bears some particular characteristics that deserve attention. Perhaps one of the most striking discrepancies of our sample from the general ADHD population is the proportion of women (65 %). The gender differences in paediatric ADHD diagnosis are quite clear, with a clear majority of diagnosed children with ADHD being boys (Polanczyk, 2007). In Norway, the ratio between women and men that are prescribed ADHD medication in the age group between 20 and 39 is less than 2:3 (Figure 1),
meaning the gender imbalance seen in school-age children is clearly reduced. Women furthermore have a higher tendency to volunteer for research, and together increase the likelihood of our sample having more women.

The amount of neurocognitive research attempting to delineate brain dysfunction in the three presentations of ADHD is sparse, mostly because the samples do not contain enough participants to produce reliable sub-diagnosis results (Cortese et al., 2012). One of the project’s aims was to further investigate differences between the presentations in regards to dysfunctions of decision-making, as most fMRI research on ADHD have had samples with all, or majority of, combined type ADHD (Cortese et al., 2012). There is, for instance, evidence suggesting distinct differences between the presentations of ADHD in reward processing (Edel et al., 2013). If further studies could validate and elucidate the distinct differences in reward processing between ADHD sub-types, such differences could increase diagnostic specificity. We were, unfortunately, unable to expand on this, as only 5 of our 20 patients had combined-type ADHD, and the rest were of inattentive presentation.

The increased number of patients with inattentive presentation in our sample is not particularly surprising. Hyperactive-impulsive symptoms are less common in adults (Sobanski et al., 2008), while inattentive symptoms are particularly disabling (Fredriksen, Dahl, Martinsen, et al., 2014; Stavro, Ettenhofer, & Nigg, 2007). Moreover, a recent longitudinal study from New Zealand found evidence for the existence of adult onset ADHD, and their adult ADHD sample showed higher instances of inattentive symptoms than hyperactive-impulsive (Moffitt et al., 2015). Thus, while it is unfortunate that we were unable to obtain enough participants with other presentations than inattentive, the scare number of neurocognitive research on inattentive adults with ADHD makes this study an important contribution to understanding the functioning of this group.

To assess general cognitive functioning, two subtests of Wechsler Adult Intelligence Scale (WAIS) version IV were administered on the first day of testing. For an estimate of verbal comprehension, the subtest Similarities was used. The Similarity subtest has 18 word-pair items, where the participant must name the similarity between the two words of the pair. It is designed to measure verbal concept formation and reasoning. For assessing perceptual reasoning, the subtest Matrix Reasoning was used. The participant is shown an incomplete matrix or series, and
selects the presented option that completes the image. These two subtests cannot yield a proper composite full-scale intelligence quotient, but provide an indication of general cognitive functioning. Participants scoring less than a mean scaled score of four were excluded, as this would be below average intelligence. Healthy controls and patients had similar matrix reasoning scores, while patients scored less on similarities. Such discrepancy is of course difficult to predict and account for. Patients generally also had lower educational attainment than controls, and Similarities, which to a certain extent tests both vocabulary and abstract thinking, is known to correlate with educational attainment (Crawford & Allan, 1997; Shuttleworth-Edwards et al., 2004). All participants scored well within the normal range for their age group on both subtests, and had normal to above normal educational attainment for Norway (i.e. high-school/upper secondary equivalent) (Holøien, Zachrisen, & Holseter, 2016). Patients with ADHD, who have known difficulties with attention and hyperactivity, will as a consequence of these core symptoms have behavioural mannerisms that decrease probability of pursuing higher educational degrees (Fredriksen, Dahl, Martinsen, et al., 2014). While having patient and control samples that match on key characteristics is important, over-matching on educational attainment might in some instances lead to underestimation of disorder abnormalities (Seidman, Biederman, Faraone, Weber, & Ouellette, 1997).
SUMMARY OF ARTICLES

Article I

A Meta-Analysis of Decision-Making and Attention in Adults With ADHD

Objectives: Attention-deficit hyperactivity disorder has been thoroughly studied in children. This research has traditionally focused abnormalities in attention-related processes, such as vigilance and motivation. At the neurobiological level, the pathophysiology of ADHD has been linked to the cortical availability of dopamine, a neurotransmitter purportedly involved in decision-making processes. Studying this common neurobiological factor can provide valuable insight into decision-making processes in general, the scope of ADHD symptoms, and the alteration of these by elevating dopamine availability. It is therefore prudent to assess the current data on adult ADHD and decision-making, and contextualize them by comparison to attention deficits, in order to identify knowledge gaps and guide future research.

Methods: This meta-analysis searched the current literature comparing adults with and without ADHD using either a CPT or a decision-making paradigm. From the initial 14,000 published articles fulfilling the search queries, a total of 47 and 16 studies using the CPT and decision-making tasks, respectively, met our criteria. Meta-regression analyses were conducted on data from all studies, providing information on possible publication bias, study heterogeneity, and effect of ADHD on measures. An additional analysis with the EZ drift diffusion model was done on 9 studies providing the required information for such an analysis.

Results: The results suggest that deficit magnitudes of attention and decision-making in adults with ADHD are comparable; they struggle equally with attention and decision-making.

Conclusion: Decision-making deficits are an important, but little investigated, problem for adults with ADHD. Future research should further explore the extent of decision-making deficits in adults with ADHD, and how pharmacotherapy affects such deficits.
Article II

Aberrant reward processing is alleviated by methylphenidate in adults with ADHD: A randomized, placebo-controlled trial

Objectives: ADHD is commonly treated with methylphenidate, which increases dopamine availability in the brain. Moreover, ADHD is associated with deficits in decision-making, which is known to be dependent on dopamine. The specific effects of methylphenidate on neurocognitive mechanisms of decision-making in adults with ADHD, however, remain unclear. Research elucidating the effect of methylphenidate medication on brain processing during decision-making could increase our understanding of the mechanisms underlying decision-making deficits in ADHD, and provide valuable insight as to how methylphenidate improves decision-making.

Methods: Methylphenidate was administered in a randomized double-blinded, placebo-controlled, crossover clinical trial to 20 adults with ADHD. We tested 27 healthy controls twice for comparison. The participants performed a value-based decision-making task during functional magnetic resonance imaging, in order to study brain processing during decision-making, and the effects of methylphenidate on such processes.

Results: Patients on placebo showed reduced representation of stimulus gain information in the striatum, which was alleviated by methylphenidate medication. While methylphenidate increased patients’ decision accuracy, patients were still less accurate than the healthy controls. Exploratory analyses revealed that connectivity between subcortical areas processing value representations and the dorsomedial prefrontal cortex was increased by methylphenidate as a function of symptom severity.

Conclusion: Patients with ADHD have weakened representation of subcortical reward information and methylphenidate alleviates this dysfunction. It is likely that decision-making deficits in adults with ADHD arise already in the basic coding of reward information in the brain. This study also implicates the DMPFC as a possible support structure for decision-making in ADHD, which is increasingly recruited when under the influence of methylphenidate for severely affected patients.
Article III

Diminished default-mode suppression during decision-making in ADHD: remediation by methylphenidate?

Objectives: A potential mediator for cognitive dysfunction in ADHD is insufficient suppression and aberrant connectivity of the default mode network (DMN). It is still, however, unclear whether alterations in sustained DMN suppression, variability, and connectivity during prolonged cognitive engagement are involved in the pathophysiology of adult ADHD, and whether methylphenidate remediates any possible dysfunctions in network dynamics.

Methods: We explored the dynamics of large-scale brain networks in 20 patients with ADHD in a randomized, double-blinded, clinical trial of methylphenidate, and 20 control subjects without pharmacological intervention. Functional MRI was acquired while participants performed a value-based decision-making task. Task-related activation, temporal variability, and connectivity of functional networks were estimated and compared between groups and conditions using independent component analysis, dual regression, and Bayesian linear mixed models.

Results: More variable activation patterns were observed in the DMN in unmedicated patients compared to healthy controls. There were group differences in functional connectivity both between and within functional networks. Moreover, functional connectivity between and within attention and DMN networks was sensitive both to task performance and case-control status. Within-network connectivity was altered by methylphenidate, but no reliable effects of methylphenidate on between-network connectivity were found.

Conclusion: This study provides novel evidence of reduced sustained DMN suppression being associated to poor decision-making, and that ADHD adults struggle with sustaining DMN suppression. Converging evidence from multiple analysis approaches support the default-mode interference hypothesis, namely that excessive DMN activity during cognitive engagement is negatively associated with externally oriented cognition and is evident in ADHD.
GENERAL DISCUSSION

The three articles presented investigate the possibility of decision-making deficits in adults with ADHD from different angles. In the meta-analysis, we evaluated the magnitude of decision-making deficits juxtaposed to attention deficits in adults with ADHD by quantitatively summarizing the results from previous studies. From this, we could establish that decision-making and attention deficits in adult ADHD are of equal size. Decision-making deficits are therefore important aspects of ADHD that warrant clinical awareness and further research. The model-based fMRI analysis in the second article allowed us to identify impaired reward representations in the striatum of patients in the placebo condition compared to controls, which was improved by methylphenidate. We hence continued to implicate striatal dysfunction in ADHD. Moreover, the mechanistic approach providing evidence of reduced reward coding clearly implicates dysfunctions in lower-level cognitive functions in ADHD, not just higher-order functions like attention and executive functions. The final, data-driven fMRI article provided novel evidence of reduced sustained suppression of a closed-task-negative functional network (DMN) in adults with ADHD. Importantly, decrease in sustained DMN suppression was associated with reduced task performance, clearly implicating the importance of successful sustained DMN suppression in making good choices. Lastly, we found that methylphenidate improved decision-making and remediated dysfunctions in striatal reward response in adults with ADHD. While we observed already established increase of DMN precuneus connectivity by methylphenidate medication, the pharmacological intervention had little effect on intrinsic network activity during decision-making. Our studies thus suggest that methylphenidate has specific, rather than global, effects on brain processes underlying decision-making.

In what follows, results from the three studies will be briefly compared as an attempt to consolidate the contribution of the current work to the general understanding of reward processing in adults with ADHD. In order to do this, I will endeavour to comparatively discuss their main findings and evaluate how the results converge or conflict without extensive reiteration from the articles attached. This discussion will furthermore consider the recent literature related to the subject, and in this way piece together a temporary account of the neurocognitive processes of decision-making in adults with ADHD.
Behavioural deficits in decision-making

The study of decision-making in adults with ADHD is still an emerging field, as indicated by the small number of studies included in our meta-analysis (16 studies). The large number of studies using variants of the continuous performance task (CPT) confirms how vital attention deficits are to our current understanding of ADHD. Finding reinforcement learning deficits to be of equal magnitude as attention deficits in adult ADHD, however, highlights the crucial – often ignored – role of decision-making deficits in ADHD. While we expected to observe decision-making deficits in adults with ADHD, given the strong indications in children, the magnitude of this dysfunction when compared to attention deficits was unexpected. As implied by the disorder’s name, attention deficits are core in our current understanding of ADHD. The evidence towards equally deficient decision-making implies a much stronger influence of decision-making deficits on behavioural problems in ADHD than previously thought.

The meta-analysis indicated that deficits in reinforcement learning showed the greatest effect of the three decision-making categories included, making aberrant reinforcement learning a possible candidate for a behavioural marker of ADHD. Indeed, this result is quite similar to that of reinforcement learning deficits in children (Luman, Tripp, & Scheres, 2010; Luman, Van Meel, Oosterlaan, Sergeant, & Geurts, 2009; Sagvolden et al., 2005), which implies that these deficits persists with age in ADHD. Decreased reinforcement learning in ADHD fits well with the established importance of the dopamine system for successful reinforcement learning (Maia & Behav, 2010; Schultz, 1998) and the reported reduced availability of dopamine in ADHD (Krause, Dresel, Krause, Kung, & Tatsch, 2000; Volkow et al., 2009). As mentioned in the introduction, aberrant reinforcement learning has been suggested to be the core deficit leading to ADHD symptoms (Sagvolden et al., 2005). These impairments are so established in paediatric samples that some have even suggested that ADHD may be viewed as a reinforcement learning disorder (Sonuga-Barke, 2011). Deficits in, or deviations from, normal reinforcement learning may be – at least partly – remediated through targeted pharmacological and non-pharmacological interventions. Increased knowledge about reinforcement learning mechanisms in ADHD may thus influence the way we think about and treat ADHD, and should therefore be targeted by future translational research.
The behavioural results from the value-based decision-making task further support decision-making as dysfunctional in adults with ADHD, and thus fall in line with expected effects based on the meta-analysis. The strong result of patients’ poor performance when unmedicated compared to controls provide clear evidence of poor value-based decision-making in adults with ADHD. The weaker, but still probable, improvement in choice accuracy as an effect of methylphenidate further implies that common ADHD medications at least partly are able to improve decision-making in adults with ADHD. We furthermore expected differences between the groups in reaction time variability, as increased reaction time variability showed strong effects in our meta-analysis and has been suggested as a behavioural marker of ADHD (Kofler et al., 2013; Tamm et al., 2012). However, as this was an event-related fMRI task, inter-stimulus intervals were jittered (varied) to capture the hemodynamic response to events in different brain regions (Friston et al., 1998). Such jittering has been shown to reduce reaction time variability in ADHD to normal levels (Lee et al., 2015; Ryan, Martin, Denckla, Mostofsky, & Mahone, 2010). Thus, the lack of effect in this study should not be seen as evidence against increased reaction time variability in ADHD.

Based on both the meta-analysis and the behavioural results from our value-based decision-making task, deficits in decision-making are increasingly obvious in adults with ADHD. This being said, still few studies have studied decision-making in adults with ADHD, and even fewer have investigated the brain functions underlying these deficits in adult ADHD.

**Irregular brain functioning**

The diverging evidence on brain activation patterns in adults with ADHD have been a source of confusion, as they show remarkable resemblance to observations in children but at the same time show large inconsistency across studies (Cubillo & Rubia, 2010). While there are increasing numbers of fMRI studies of adults with ADHD, the literature is still sparse, especially when it comes to decision-making. The hypotheses for this study were thus mainly based on paediatric, behavioural literature and theories of ADHD and decision-making, and the few studies available at the time.
Using the neurocognitive model of Basten et al. (2010), we made clear predictions of the expected outcomes of the study. Children with ADHD are less influenced by losses in the Iowa gambling task (IGT) than controls (Dekkers et al., 2016; Scheres, Sumiya, & Allison Thoeny, 2010), and we hence expected decreased association between loss values and amygdala activations in the unmedicated patients. Additionally, as ADHD is associated with a hypodopaminergic state, reduced association between gain value and striatal activation could also be expected according to certain theories (Frank, Scheres, & Sherman, 2007). In our study, unmedicated ADHD adults showed reduced striatal response to reward gains compared to controls, but we could not document reduced amygdaloid activation to reward losses. Our observation of reduced reward response in the striatum of adults with ADHD fall in line with several studies over the last 8 years (Bush et al., 2008; Plichta & Scheres, 2014).

These observations fit well with theories proposing that reduced dopamine availability may restrict phasic dopamine firing in response to rewards in ADHD, and thus lead to weak reward processing (Frank et al., 2006; Sagvolden et al., 2005). Aarts et al. (2015), however, found increased striatal reward response in ADHD participants, but only in carriers of a specific dopamine transporter gene allele. Striatal response to rewards have furthermore been observed both as hyper and hypoactive in adolescents with ADHD (Plichta & Scheres, 2014; Von Rhein et al., 2015). However, another recent study found hyporesponsive striatal reward activations in adults with ADHD and not children (Kappel et al., 2015). Our observations are thus in line with the majority of studies, as we find hypoactive striatal reward response in adults with ADHD. Importantly, through the use of a mechanistic decision-making model, novel evidence towards abnormal coding of actual gain values in ADHD is provided, which is somewhat different from other studies finding dysfunction in reward anticipation or receipt (Bush et al., 2008; Kappel et al., 2015).

The second stage of the neurocognitive model by Basten et al. (2010) proposes that value information from the striatum and amygdala is conveyed to the ventromedial prefrontal cortex (VMPFC), which in turn compares these values. We hypothesized that here too the patients would have decreased activation in association with the gain-loss difference signal. Our data did not, however, provide evidence for
the gain-loss difference calculation to be aberrant in ADHD. This does not mean there is no deficit in this value comparison process in ADHD, but that our study was unable to uncover any such deficit. However, given the weaker coding of gain values in the striatum in ADHD, the VMPFC is fed insufficient information to obtain informed decisions. Even if the remaining decision-making process after value coding might function normally, misrepresentations of basic values required for a decision will result in ill-informed choices.

As article II established the representation of gains and losses in the striatum and amygdala respectively, and the evaluation of these in the ventromedial prefrontal cortex across all subjects – as originally found in Basten et al. (2010) – we expected functional networks covering these areas to display similar associations in article III. No networks were, however, associated to the gain or loss values of the stimuli. An association between task difficulty (the absolute difference between gain and loss values) and the executive network was observed, which makes sense as the comparison of gain and loss values is a higher-order cognitive function and the executive network also includes part of the medial prefrontal cortex (Hugdahl, Raichle, Mitra, & Specht, 2015). Of course, analyses of dual-regression time series are quite different from the conventional fMRI approach, and thus discrepancies of results must be expected. Dual-regression time series are results of principal component analyses, and are thus fairly different than time series of regions corresponding to (HRF convolved) task GLMs. The activations from the model-based analysis were found in small voxel clusters that would only account for very little of the total variance in the large network structures that are observed with dual-regression.

Nevertheless, we found dysfunctions in the brain’s intrinsic functional networks, particularly in the default mode network (DMN), in the patient sample. Reduced DMN suppression in ADHD during task execution has been previously reported (Liddle et al., 2011; Van Rooij et al., 2015), but has been difficult to replicate in adults with ADHD (Mostert et al., 2016; Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2016). Our data suggests sustained DMN suppression is aberrant in adult ADHD, something we corroborate with multiple approaches. Adults with ADHD showed increased trial-triggered DMN suppression, increased DMN temporal variance, and increased coupling between the DMN and an attention
network. Moreover, the two latter effects were additionally associated with reduced performance on the decision-making task, clearly implying that the pattern of dysfunctional DMN activity and connectivity seen in the ADHD sample is also related to poor decision-making.

By itself, the observation that adults with ADHD demonstrate greater stimulus-evoked DMN suppression is contrary to expectation. According to the default mode interference hypothesis, DMN suppression during externally oriented cognition is attenuated in ADHD (Sonuga-Barke, 2005). While this assumption has some support (Castellanos et al., 2008), a recent study found that cued DMN suppression was intact in adults with ADHD (Sidlauskaite et al., 2016). If the initiation of DMN suppression is not attenuated, this could explain why stimulus-evoked DMN suppression in our experiment was strong in the ADHD patients, but it could not explain why it would be greater than the controls’. The increased DMN temporal variance in the ADHD group provided the next clue. For the temporal variance of the DMN to be increased, time courses must fluctuate more between high and low activation. As the DMN is suppressed during cognitive engagement (Fox, Zhang, Snyder, & Raichle, 2013), and decreases of DMN suppression precedes attentional lapses (Weissman, Roberts, Visscher, & Woldorff, 2006), increased temporal variance of the DMN indicates that DMN suppression is not sustained for longer periods. The results from the task GLMs on the networks indicate the same: all subjects needed to suppress the DMN at each trial. Thus all participants to some extent struggled with keeping the DMN suppressed over longer periods. However, as the patients had stronger stimulus-evoked suppression and increased variance, this indicates that they had greater difficulties in sustaining the DMN suppression, allowing it to engage more in-between task events. While increased DMN suppression has been associated with increased task performance in other studies (Guitart-Masip et al., 2015), this is not the observation in our data. Increased temporal variance was, in our study, negatively associated with overall task accuracy, clearly implying that increased DMN variance is also related to decreased task performance.

Increased functional and structural connectivity between attention networks and the DMN in ADHD have been reported before (Kessler, Angstadt, Welsh, Sripada, & Kessler, 2014; Sripada, Kessler, & Angstadt, 2014), and it has been suggested that DMN activation disrupts attention processes (Fassbender et al., 2009;
Weissman et al., 2006). The increased DMN variance and increased coupling between the DMN and attention networks in our sample might reflect the increased interruption of attention processes by the DMN, but this would only be speculation. Collectively, these results provide support both for the hypothesis that DMN activity during cognitive engagement is negatively associated with performance, and that sustained DMN suppression is dysfunctional in adult ADHD.

The group comparisons between unmedicated patients and healthy adults in relation to brain functions underlying decision-making deficits in ADHD provide two interesting insights. Firstly, decision-making deficits in ADHD already emerge in lower-level cognition, not just higher-level cognitive processes. Secondly, the ability to sustain DMN suppression over longer periods is reduced in ADHD, a reduction that is also related to reduced performance. Together these illuminate two ways of how decision-making may be altered in ADHD: one by deficits in regional, process specific dysfunctions (such as striatal reward dysfunction), and the other by the insufficient sustained down-regulation of a task-independent network (DMN). The former is specific to reward processing, and thus provides valuable information about particular disturbances in the decision-making process. The latter is likely not specific to decision-making, but is rather a broader phenomenon that might be the cause of internal interruptions to externally oriented cognition.

The effects of methylphenidate

Low baseline levels of dopamine has been suggested as central to the pathophysiology of ADHD (Sikström & Söderlund, 2007; Thapar & Cooper, 2015; Volkow et al., 2007), and as a dopamine agonist, methylphenidate increases synaptic availability of dopamine (Volkow et al., 2012, 2005). Furthermore, several studies have found methylphenidate to normalize reward processing in adults with ADHD (Aarts et al., 2015; Bush et al., 2008). Based on the current understanding of dopamine’s importance for decision-making and the hypodopaminergic state in ADHD, we had clear expectations of methylphenidate improving decision-making and reward processing. The reduced striatal reward response in the unmedicated patients was alleviated through methylphenidate, thus confirming our hypothesis.
There are several suggestions to how increased dopamine might improve reward processing. As mentioned in the introduction, rewards are signalled by dopamine neurons through phasic signal peaks, i.e. the sudden increase of synaptic dopamine (Schultz et al., 1997). In the current context, it is possible that reduced extracellular availability of dopamine in the striatum restricts phasic dopamine signalling of rewards in the unmedicated patients (Sagvolden et al., 2005). This limitation on the phasic dopamine signal would lead to weaker coding of reward values. By increasing synaptic dopamine, the phasic signal might have more flexibility to produce higher peaks, and thus provide stronger associations between reward stimuli and neural firing in the striatum (Frank et al., 2006; Johansen et al., 2009).

Another possible explanation proposes that the signalling of rewards is dependent on the phasic dopamine signal relative to the tonic. The moderate brain arousal theory by Sikström and Söderlund (2007) proposes that when tonic dopamine levels are low, normal noisy dopamine firing will produce sufficiently high peaks relative to baseline to be coded as signal. Neural over-activity thus reduce the ability to distinguish signal from noise (Sikström & Söderlund, 2007), as noise will more frequently reach signal thresholds. This possibility is supported by a recent PET study observing reduced tonic and enhanced phasic dopamine release in the right caudate of adults with ADHD (Badgaiyan, Sinha, Sajjad, & Wack, 2015). By increasing tonic dopamine in ADHD, the relative increase of phasic signalling of rewards in the striatum may be more clearly distinguishable from basic neural noise.

While not strong enough to survive corrections for multiple comparisons, there was also an increase in the correlation between amygdalar activation and loss values, suggesting that methylphenidate improves representation of both punishment and reward. While we were unable to detect aberrant amygdalar activation when patients were on placebo compared to the controls, deficits in both reward and punishment sensitivity have been documented in children and adolescents with ADHD (Humphreys & Lee, 2011; Masunami, Okazaki, & Maekawa, 2009). Given a larger sample, we might have been more able to detect increased amygdala activations related to loss values. Alternatively, some research has suggested that learning from worse-than-expected outcomes is more dependent on noradrenaline availability than dopamine (Frank, Samantha, Moustafa, Sherman, & Frank, 2007). While
methylphenidate also produces some increase in noradrenaline availability, it is possible that a more specific noradrenergic agonist, like atomoxetine, would provide stronger improvement of loss representation in the amygdala than methylphenidate.

Methylphenidate furthermore reduced temporal signal variability in the sensorimotor network, cerebellum, and orbitofrontal cortex in the network analysis, which was an unexpected result. Dopamine has been suggested to increase signal integrity and flexibility such that increased signal variance implies increased functional range (Garrett et al., 2015). Thus, the assumption was that increasing dopamine availability through methylphenidate medication would lead to increased temporal variability in networks important for task execution. The reduction of variance in several networks was thus unexpected. While it is possible that methylphenidate restricted known heightened motor activity in ADHD (Mostofsky et al., 2006), this seems unlikely as our analyses did not indicate abnormal activations in these networks.

In line with previous research, we also found reduced functional connectivity of the precuneus in the default mode network when comparing placebo and methylphenidate conditions. Methylphenidate has previously been shown to increase precuneus deactivation in adolescents with ADHD during a Stroop task (Peterson et al., 2009), and to facilitate precuneus deactivation through decrease of dopamine transporter binding in the striatum (Tomasi et al., 2009). Moreover, recent studies implicate task-related DMN suppression as reduced in both elderly individuals (Garrett et al., 2015) and schizophrenic patients (Haatveit et al., 2016), which are both groups associated with dopamine depression (Bäckman, Lindenberger, Li, & Nyberg, 2010; Dørum et al., 2016). Together, these suggest that down-regulation of the precuneus during cognitive engagement facilitates attention through dopamine signalling, and the increased availability of dopamine by methylphenidate increases the ability to deactivate the precuneus.

In order to explore the effect of symptom severity on the effect of methylphenidate, we additionally performed analyses within the ADHD group using the three-stage neurocognitive model by Basten et al. (2010). We tested whether the effect of methylphenidate was dependent on symptom severity at any stage of the decision-making process. The results revealed that the increased connectivity between the subcortical value regions and the dorsomedial prefrontal cortex (DMPFC) as a
result of methylphenidate intake was dependent on symptom severity (as measured by the Wender-Utah rating scale). This might indicate that for severely affected adults with ADHD the evaluation of value-evidence in decision-making is improved with methylphenidate by recruiting supporting cortical structures in addition to the VMPFC. Several studies have implicated the DMPFC as important to decision-making in several capacities, such as strategy and decision control (Venkatraman, Rosati, Taren, & Huettel, 2009), and as an accumulator of decision-evidence (Hare, Schultz, Camerer, O’Doherty, & Rangel, 2011). Furthermore, the DMPFC has been implicated as important to gain and loss anticipation in pathological gamblers (Balodis et al., 2012), and similar fronto-striatal network disruptions have moreover been established in both pathological gambling and ADHD (Cubillo & Rubia, 2010; van Holst, van den Brink, Veltman, & Goudriaan, 2010). Some common neural disruptions can be expected between ADHD and pathological gambling, given the association between gambling problems and ADHD persistence (Breyer et al., 2009). Together this might suggest that these two groups use the DMPFC as a support structure for value comparisons. While the role of the DMPFC for decision-making is still debated, it is clearly implicated in the later stages of decision-making.

The results from our studies thus suggest that methylphenidate improves lower-level reward processing in ADHD, and improves DMN suppression in the precuneus. While the drug effects from the model-based analyses were closer to our expectations, the effects of methylphenidate on network dynamics were weak. Methylphenidate thus likely does not globally improve brain function, but rather has high regional specificity in dopamine dense fronto-striatal circuits that improve particular behavioural deficits.
CONCLUDING REMARKS

The work presented herein contributes to the further understanding and establishment of decision-making deficits in adults with ADHD. The meta-analysis in article I clearly identifies deficits in decision-making as an important factor in ADHD. The mechanistic, model-based fMRI analysis in article II provides strong evidence for reduced striatal reward coding in ADHD, and that treatment with methylphenidate at least partly remediates this abnormality. Lower-level cognitive functions are thus disrupted in ADHD, not only higher-order cognitive processes such as attention or executive functions. The data-driven network analysis in article III provided novel evidence for the importance of sustained default mode suppression for successful decision-making, and that adults with ADHD had difficulties in sustaining such suppression.

The novelty of this work lies in the multiple approaches employed to elucidate abnormal decision-making in ADHD. By adopting a mechanistic approach to decision-making, we could divide the decision-making process into several stages and test where the dysfunction occurs. Employing a data-driven approach with multiple measures of interest, allowed us to – through the convergence of evidence – piece together the importance of sustained default mode suppression for normal decision-making. Together these results clearly implicate insufficient reward coding and inability to successfully maintain default mode suppression to poor decision-making in adults with attention-deficit hyperactivity disorder.

There are still many questions regarding value-based decision-making in adults with ADHD that remain unanswered. While the work presented herein contributes towards greater understanding of reward processing in adult ADHD, it is a small piece in a larger enterprise. The continued implication of brain dysfunctions related to reward processing in adult ADHD warrants further study. For instance, while we could not establish that amygdala activations in response to losses were different between controls and patients, methylphenidate did show a tendency to increase amygdala response to losses. A study with a larger sample, and perhaps stimuli with stronger associative values, could provide clearer evidence of this association to loss in the amygdala. Moreover, using several pharmacological interventions combined with fMRI, one might delineate the different roles of
dopamine and noradrenaline to decision-making, and in ADHD. As previously mentioned, methylphenidate to some extent also blocks noradrenaline reuptake, but in comparison to a stronger noradrenergic agonist – like atomoxetine – one might delineate the effect of these two substances on decision-making in adults with ADHD more clearly. This would be particularly informative, as methylphenidate and atomoxetine are the first and second-line pharmacological treatments for ADHD, respectively.

Moreover, while the neurocognitive model used here provides an excellent method for testing value-based decision-making, I also believe the study of the striatal reward prediction error during reinforcement learning in adults with ADHD warrants further study. In particular, elucidating reinforcement learning with computational models that estimate underlying cognitive variables (Miller et al., 1995; Rescorla & Wagner, 1972) in combination with functional MRI, may increase our understanding of the origins of dysfunctional reinforcement learning in adult ADHD. Furthermore, dopamine and noradrenaline have been suggested to differentially affect learning from better-than-expected and worse-than-expected outcomes, respectively (Frank et al., 2006). Studying the associated brain functions of these reward processes as influenced by dopamine and noradrenaline agonists in ADHD could further inform us on the origins of reinforcement learning deficits in ADHD, and the possible selective effects of these catecholamines on reinforcement learning.

It is, in my opinion, crucial to increase knowledge and clinical awareness about decision-making deficits in ADHD. Such impairments are not completely remediated by pharmacological treatments, but may be further improved by other non-pharmacological therapies. Enhancements in decision-making may decrease some of the negative life-outcomes associated with ADHD, and thus improve quality-of-life in this patient group.
REFERENCES


American Psychiatric Association, [APA]. (1994). Diagnostic and Statistical Manual of Mental Disorders DSM-IV.


