CHAPTER 1
General introduction
**INTRODUCTION**

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common childhood neuropsychiatric diagnosis, and is characterized by persistent and developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity, occurring in various situations, to such a degree that these symptoms severely interfere with daily functioning (American Psychiatric Association, 2000, 2013). Prevalence rates of ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) have been estimated to be between 6-7% of the population (Willcutt, 2012). ADHD broadly impacts academic and social functioning in children (Biederman, 2005; Coghill et al., 2008) and persists into adolescence in 70% of cases (Langley et al., 2010). ADHD-related impairments may underlie subsequent difficulties in adulthood, such as associated psychopathology, school and occupational failure, family and peer difficulties, emotional problems and low self-esteem (Biederman et al., 1998; Biederman, Faraone, Monuteaux, Bober, & Cadogen, 2004; Wilens, Biederman, & Spencer, 2002).

The scientific community has been searching for an explanatory model of ADHD for many decades. Despite the fact that most cases of ADHD are characterized by inattention problems, research into the aetiology of ADHD failed to identify specific attentional dysfunctions (i.e. divided, selective or sustained) (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Huang-Pollock, Nigg, & Carr, 2005). Influential theoretical models of ADHD have considered inattention problems secondary to more fundamental problems in behavioural inhibition (Russell A Barkley, 1997), motivation (Luman, Oosterlaan, & Sergeant, 2005) or arousal (Sergeant, 2000; Zentall & Zentall, 1983).

More recently, in contrast to these unidimensional models, ADHD is thought to be a heterogeneous disorder, with multiple aetiologies (Sonuga-Barke, Bitsakou, & Thompson, 2010; Sonuga-Barke, 2002). Deficits in behavioural inhibition still figure prominently in these new attempts to understand ADHD, at least in a subgroup of the population (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). However, parallel to these endeavours, some researchers have started to doubt the interpretation of well-known tasks that provided essential evidence in support of theories that emphasize inhibitory dysfunction in ADHD, and argue that previous results with these tasks actually reflect fundamental problems in attention (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). Ironically, this would put attention problems centre stage, again, in ADHD.
This thesis aims to further unravel the contribution of inhibition versus attention problems to the neurobiology of ADHD using complementary techniques and methods of Event-Related Potentials (ERP), ERP source imaging, functional Magnetic Resonance Imaging (fMRI) and neuropsychology.

The second aim of this thesis is to explore the behavioural effects of neurofeedback, stimulant medication and physical activity treatment for children with ADHD, and to explore the neurophysiological effects of these interventions, which may provide new insights into the neural mechanisms that govern behavioural changes. Specific questions are tailored to intervention effects on inhibitory, attentional and arousal mechanisms that have been associated with the psychopathology of ADHD. A better understanding of these mechanisms may stimulate research into new or more effective treatment options for ADHD.

INHIBITION THEORY OF ADHD

In a triad of lectures, Sir George Frederick Still (1868-1941) explicated a psychological disorder, which he described as “an abnormal defect of moral control in children” (Still, 1902) that can now be considered prophetic for many developments that have taken place in the field of ADHD and child psychopathology. He described moral control as “the control of action in conformity with the idea of the good of all”. Moral control was thought to arise out of a cognitive comparison of the individual’s volitional activity with that of the good of all, a comparison he termed “moral consciousness” (Barkley, 2006). To make such a comparison involves functions that, in contemporary accounts, correspond to executive functions (EF), or cognitive capacities that permit self-regulation. Still believed that the primary impairment in what we currently call ADHD, was in “volitional inhibition”, or as he described: “a stimulus to act must be overpowered by the stimulus of the greater good of all and the likely future outcomes of one’s behaviour”. Based on clinical observations, he thought that impairments in these children were of an organic nature (instead of nurture) and even speculated a perversion or physical abnormality in higher nervous centres that were probably hereditary.

More than 80 years later, several early neuropsychological theories of ADHD emphasized inhibitory dysfunction in children with ADHD (Nigg, 2001). Barkley (1997) extended and further specified a model that applied work by Bronowski (1967), which was aimed at creating a more unifying account of various cognitive deficits found in ADHD. He suggested that the central impairment in ADHD involves a deficit in behavioural inhibition, which subsequently leads to
secondary impairments in executive functions (EF) that are partially dependent on inhibition for their effective execution. Behavioural inhibition was defined as a combination of three interrelated processes, including (1) inhibition of an initial pre-potent response to an event, (2) stopping of an on-going response, which thereby permits a delay in the decision to respond and (3) protection of this period of delay from disruption by competing events and responses (interference control). Crucial in the theory of Barkley was the notion that inhibitory dysfunction in ADHD results in reduced delay in decision, and therefore disrupts functions that operate during, or are dependent on this delay to occur effectively. Finally, these secondary impairments would lead to decreased control of motor behaviour by internally represented information and self-directed action. Especially important in this thesis is his suggestion that inattention problems are secondary to this chain of executive dysfunctions.

Empirical support for Barkley's theory of ADHD originates for an important part from the stop-signal task (SST) (Logan, Cowan, & Davis, 1984; Logan & Cowan, 1984). The SST requires participants to withhold a pre-potent motor response to a frequently presented go signal when prompted by an infrequent and unpredictable stop signal, corresponding with the first two inhibition processes as proposed by Barkley. The horse-race model of this task suggests that stopping processes race against processes underlying on-going thought and action (Logan et al., 1984). If the stop processes win, thought and action are inhibited; but when the on-going processes win, thought and action run to completion (Logan et al., 1984). Unique to this task is that both overt mean reaction time (MRT) to go stimuli, and covert stop-signal reaction time (SSRT) to stop stimuli, can be measured. SSRT is an indirect estimation of the speed of the covert ('hidden') inhibition process. The speed of this inhibition process appears to be slower in children with ADHD, as reflected in slower SSRTs (Oosterlaan, Logan, & Sergeant, 1998). Although this finding has been considered as relatively robust evidence for inhibition theories, other researchers identified confounding factors in more ‘primitive’ cognitive functions such as processing speed (MRT) that, when accounted for with an appropriate control task, rendered most inhibitory dysfunction findings in ADHD insignificant (Marks et al., 2005; Rhodes, Coghil, & Matthews, 2005).

In line with these concerns, more recent meta-analyses of the SST in ADHD further investigated this important topic with serious implications for inhibition theories of ADHD. The first meta-analysis tested for possible attentional confounds by statistically comparing the effect sizes (ES) of MRT and SSRT differences in children with ADHD compared to typically developing (TD) children (Lijffijt et al., 2005). Although children with ADHD showed both increased
MRT and SSRT (ES 0.52 and 0.58), the ES of SSRT was not significantly greater than the ES of MRT. Furthermore, the largest ES was found for reaction time variability (RTV), which has been associated with lapses of attention (Tamm et al., 2012). The authors interpreted these findings as indicative of inattention problems (increased MRT and RTV), rather than deficient inhibitory control. A subsequent meta-analysis (Alderson et al., 2007) used a different methodology to assess the influence of attention processes, by comparing groups not only on MRT and SSRT, but also on stop-signal delay (SSD). Following the horse-race model, SSRT is calculated by subtracting the average delay between the go and stop stimuli (SSD) from MRT (Logan et al., 1984). Accordingly, Alderson et al. (2007) reasoned that SSRT differences could only be interpreted as a reflection of inhibitory problems in ADHD when SSD also differs between children with ADHD and healthy controls. Elsewhere, SSRT differences merely reflect MRT differences. As it turned out, SSDs were equal between groups, suggesting that SSRT differences reflect a more generalized deficit in attention rather than behavioural inhibition. In conclusion, although the inhibition process seems to be less efficient in ADHD, as reflected by robust findings of increased SSRT, more stringent research casts doubt on the validity of the SSRT metric and instead proposes that previous findings actually reflect problems in attention.

NEUROBIOLOGY OF INHIBITION IN ADHD

Neuroimaging studies in healthy participants have shown that successful stopping activates a brain network comprising the inferior frontal gyrus (IFG)/anterior insula, dorsal medial prefrontal cortex (dmPFC) including the pre-supplementary motor area (pre-SMA)/SMA and dorsal anterior cingulate cortex (ACC), and striatal and subthalamic nuclei (Swick, Ashley, & Turken, 2011). The rIFG is part of a putative inhibition network, connected via a direct pathway with the subthalamic nucleus (STN), both of which are connected with the pre-SMA (Aron, 2007). Aron et al. (2007) propose that the rIFG implements inhibition at a neural level by activating the STN, which activates the globus pallidus, resulting in thalamo-motorcortical inhibition.

Children with ADHD seem to activate this inhibition network to a lesser extent than TD children. A recent meta-analysis (McCarthy, Skokauskas, & Frodl, 2014) of five SST studies in children with ADHD showed reduced activation in bilateral IFG/insula, right medial frontal gyrus, and right superior and middle frontal gyri. Partially overlapping results were found in another meta-analysis (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013) of 15 studies using the SST or go-nogo (GNG) tasks, with reduced activation for ADHD in the right IFG/insula, right SMA and
ACC, right thalamus, left caudate and right occipital cortex.

Although the validity of the SST in ADHD research has been questioned in the performance domain – with implications for the inhibition theory of ADHD, this is less true for imaging findings that have been obtained with this task. As will be argued, however, similar concerns can be identified for the brain-imaging domain. One major methodological concern is the attentional capture effect of infrequent stop stimuli in the SST (Pauls et al., 2012; Sharp et al., 2010), which in the same way as oddball stimuli, may induce activation in a ventral attention network important for target detection/saliency that partly overlaps with inhibition-related areas such as the right inferior frontal gyrus (rIFG) (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). Conventional contrasts that are used in fMRI studies to locate inhibitory activity subtract the go condition from the stop condition. This approach clearly fails to account for the attentional capture effect of stop stimuli, given the fact that go stimuli occur very frequently (75%) in contrast to stop stimuli (25%), and therefore are not equally potent in inducing oddball effects. Attentional confounds in SST imaging studies are particularly relevant for ADHD research, considering similar concerns about the validity of the main inhibition metric, SSRT, as has been discussed.

FMRI is limited in temporal resolution and is therefore not suitable to clarify whether inhibition deficits actually precede other EF dysfunctions and more relevant in this thesis, attentional dysfunction, as hypothesized in Barkley’s inhibition theory of ADHD. Electroencephalography (EEG) studies that use the Event-Related Potential (ERP) method can complement fMRI studies to learn more about the temporal dimension of dysfunctions in children with ADHD; however, the EEG technique is inherently limited in spatial resolution (Luck, 2014).

The main focus of ERP studies that use the SST are mostly late endogenous components, such as N2 and P3, which have been related to response inhibition (Ramautar, Kok, & Ridderinkhof, 2004; van Boxtel, van der Molen, Jennings, & Brunia, 2001). The N2 component peaks around 200-250ms after the stop stimulus, and has been more specifically associated with an early mechanism of inhibitory control, reflecting a “red flag” signal generated in the prefrontal cortex to trigger the inhibitory process (Kok, 1986). However, according to alternative accounts, the N2 may signal conflict (Enriquez-Geppert, Konrad, Pantev, & Huster, 2010; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003), or signal both a top-down inhibition process and an attentional “mismatch” process that is sensitive to infrequent deviations from the prevailing context (Eimer, 1993; Nieuwenhuis et al., 2003). The N2 is followed by the P3, peaking around 300-350 ms after the stop stimulus, which may reflect inhibition or a late stage of monitoring
of the outcome of the inhibitory process (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005). The amplitude of these N2 and P3 components are reduced in children with ADHD according to most studies (Johnstone, Barry, & Clarke, 2007; Liotti et al., 2007; Liotti, Pliszka, Higgins, Perez, & Semrud-Clikeman, 2010; Pliszka et al., 2007a). The exploration of preceding early exogenous ERP components has been relatively neglected, although some studies suggest early processing alterations (Shen, Tsai, & Duann, 2011; Dimoska, Johnstone, Barry, & Clarke, 2003; Johnstone, Barry, & Clarke, 2007), which may prove relevant for the concerns that have been raised in this thesis.

Although studies utilizing different techniques and methods suggest attentional confounds in the SST that can have important implications for inhibition theories of ADHD, limitations in temporal or spatial resolution impede further progress to more specifically pinpoint the neurobiological mechanisms in ADHD. Unfortunately, no single technique combines the advantages of fMRI and EEG. However, considerable progress has been made lately in statistically localizing ERPs in the brain (Pizagalli, 2007), thereby providing both high temporal and spatial resolution. These methods promise some interesting new avenues in research, and may contribute to further delineate various neurocognitive dysfunctions in children with ADHD. Part I of this thesis will take advantage of the latest developments in ERP source imaging to address these outstanding issues.

TREATMENT OF ADHD

Stimulant medication is the first-choice treatment for ADHD and is effective in short-term symptom reduction (Faraone & Buitelaar, 2010). However, stimulant medication use has several limitations, including a considerable group of 30-44% non-responders (Spencer et al., 1996; Swanson et al., 2001) and adverse effects (Graham & Coghill, 2008), such as sleep problems, reduced appetite and headaches and dizziness. These disadvantages have spurred the development of non-pharmacological treatments for ADHD, such as neurofeedback.

Neurofeedback is a behavioural therapy that is based on operant conditioning of specific brain states by providing real-time feedback of EEG signals. The feedback signal of interest in ADHD has been theoretically derived (Lubar, 1991) from studies that show increased slow wave activity (theta: 4-8Hz) and decreased fast wave activity (beta: 13-21Hz) in the spontaneous EEG of children with ADHD (Snyder & Hall, 2006). Theta and beta activity have been related to vigilance and attention respectively (Banaschewski & Brandeis, 2007). These findings have
been originally interpreted as indices of hypo-arousal that may play a causative role in ADHD symptomatology, in line with the cognitive-energetic model of ADHD (Sergeant, 2000; Zentall & Zentall, 1983). Accordingly, decreasing the ratio of theta/beta and/or increasing sensorimotor rhythm (SMR: 13-15Hz) with neurofeedback is hypothesized to ameliorate symptoms of ADHD. The efficacy of neurofeedback as treatment for ADHD is, however, heavily debated. Although most researchers agree that treatment studies should be randomized and controlled, most of the discussion revolves around which kind of control group is appropriate to control for non-specific treatment effects (Loo & Makeig, 2012). Not surprisingly, systematic reviews differ in conclusions from “no evidence for effectiveness using blinded assessments” (Sonuga-Barke et al., 2013) to “neurofeedback is effective and specific” (Arns, Ridder, & Strehl, 2009), with “specific” defined as effective compared to a credible sham control group.

Neural mechanisms that underlie behavioural effects of theta/beta neurofeedback are yet unknown. Pre- and post-treatment recording of EEG provides a means to study the effects of neurofeedback on brain functioning. Although neurofeedback aims to target brain function directly, EEG treatment effects have received little consideration. One of the primary questions is whether neurofeedback can induce sustained alterations in theta and/or beta power. Gevensleben et al. (2009) is the only randomized controlled trial (RCT) that found a reduction in theta activity at midline scalp sites for children that received neurofeedback compared to a control group. No changes were demonstrated for beta activity or theta/beta ratio. Two other studies failed to show any changes in power spectra (Kropotov et al., 2007; Ogrim & Hestad, 2013).

Neurofeedback may exert effects on other brain mechanisms that play important roles in the neurobiology of ADHD, such as response inhibition. Effects of neurofeedback on ERPs obtained during inhibition tasks are mixed, with evidence for increased P3 for children that were able to increase relative beta activity (Kropotov et al., 2007) or no P3 increase (Ogrim & Hestad, 2013). Although ERP studies are scarce and inconsistent, some evidence indicates that neurofeedback may affect response inhibition in children with ADHD.

Methylphenidate (MPH) is the most widely prescribed medication for ADHD and has been shown not only to ameliorate ADHD symptomatology, but also neurocognitive deficits (Coghill et al., 2013), including deficits in inhibitory control. Surprisingly, most studies on the effects of MPH on EEG power spectra are uncontrolled, with EEG recorded off and on medication. These studies mostly show decreases in theta activity (Clarke et al., 2003; Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Song, Shin, Jon, & Ha, 2005; Swartwood et al., 1998), and/or
increases in beta activity with MPH (Clarke et al., 2003, 2002; Song et al., 2005). ERP studies show evidence for acute enhancing effects of MPH on N2 and/or P3 amplitudes during inhibition tasks (Groom et al., 2010; Paul-Jordanov, Bechtold, & Gawrilow, 2010; Pliszka et al., 2007b; Seifert, Scheuerpflug, Zillessen, Fallgatter, & Warnke, 2003). Possibly, MPH acts on dopamine transmission in striatal nuclei and associated cortical structures (Rosa-Neto et al., 2005), which are involved in response inhibition deficits in ADHD (Hart et al., 2013), resulting in enhanced N2/P3 signals.

Direct comparisons of neurofeedback and stimulant medication have produced inconsistent results, with studies showing comparable clinical effects (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013) or superior effects for medication (Ogrim & Hestad, 2013). Only the study of Ogrim et al. (2013) examined EEG power spectra and ERPs as well, and found no changes in theta and beta for both groups, but did find increased P3 amplitudes in medication responders as opposed to medication non-responders and participants treated with neurofeedback.

In conclusion, the clinical effectiveness of theta/beta neurofeedback as treatment for children with ADHD and the effectiveness of neurofeedback compared to stimulant treatment, remain controversial. Furthermore, neural mechanisms that underlie behavioural effects of neurofeedback are largely unknown, although improvements in neural circuitry related to inhibition may be an important element. Randomized controlled trials (RCT) are required to further elucidate the clinical and neurophysiological effects of neurofeedback. Part II of this thesis will address the behavioural and neurophysiological effects of an RCT with neurofeedback and stimulant treatment in children with ADHD.

**STUDY DESIGN**

All EEG/ERP and treatment studies included in this thesis were based on data from the Brain Gym study, conducted between September 2010 and January 2015. This randomized controlled multicentre three-way parallel group study was designed to compare treatment effects of theta/beta neurofeedback (NF), stimulant treatment with methylphenidate (MPH) and physical activity (PA) on a broad range of outcomes, including behavioural, cognitive and electrophysiological measures. Eligible participants were Dutch-speaking children, aged between 7-13 years, with a primary clinical DSM-IV-TR diagnosis of ADHD, an estimated IQ>80, and no primary diagnosis of autism spectrum disorder or neurological disorders. The ADHD group was tested before
treatment commenced (T0), directly after treatment (T1) and at six months follow-up (T2). Parallel to this treatment study, typically developing (TD) children, in the same age range, participated during a single measurement that was identical to the pre-treatment (T0) test day of the ADHD group. FMRI data were collected in a separate study with comparable ADHD and TD groups as described.

THE AIMS AND OUTLINE OF THE CURRENT THESIS

The overall aim of this thesis is to further unravel the contribution of inhibition versus attention problems to the neurobiology of ADHD, and to investigate the behavioural and neurophysiological effects of neurofeedback and stimulant treatment on inhibitory control, attention and arousal mechanisms in children with ADHD.

Part I of this thesis will be a critical in-depth analysis of inhibition problems in ADHD and how these are influenced or explained by other cognitive processes, particularly attention processes. In Chapter 2, the influence of early processing deficits during response inhibition will be explored, and altered exogenous (early processes) or endogenous (late processes) ERP components will be anatomically localized with distributed source localization to gain both temporal and spatial insights in the involved neural networks. The aim of the study presented in this chapter is to clarify whether inhibition deficits are preceded or accompanied by more fundamental processing deficits, such as attentional deficits, which may challenge Barkley's inhibition theory of ADHD. Chapter 3 will elaborate on chapter 2, by investigating the specificity of the neural network that has been associated with response inhibition, using a stringent controlled version of the SST while obtaining fMRI data in ADHD and TD children. This modified SST controls for the attentional capture effect of stop stimuli, whereby inhibition-related brain activity can be delineated from attention-related activity. The study described in this chapter aims to clarify whether previous fMRI findings of the SST in ADHD were confounded with attentional processes, possibly challenging inhibition theories of ADHD. At last, Chapter 4 will focus on a classical attention paradigm, the oddball task, to localize ERP alterations that are associated with attentional dysfunction in ADHD. In this study we aim to determine whether the same network may be (partly) involved in ADHD during an attention task (oddball task), as during an inhibition task (stop-signal task). The aim of the study in this chapter is to clarify the extent to which inhibition task findings in ADHD reflect oddball-related activity, which may accompany infrequently presented stop stimuli, thereby complementing chapter 2 and chapter 3.
Part II of this thesis will focus on the behavioural and electrophysiological effects of neurofeedback (NF), stimulant treatment with methylphenidate (MPH) and physical activity (PA) in children with ADHD, with a specific focus on response inhibition. The first question of interest is how NF and MPH compare in relation to behavioural and electrophysiological outcome measures. The second question is whether neurofeedback results in specific treatment effects compared to the semi-active control group, PA, which is matched in duration and intensity to account for non-specific treatment effects, such as parental engagement and personal attention. This comparison allows studying specific effects, or treatment effects that are specifically related to altering brain activity, which is the intended effect of neurofeedback. Untangling specific from non-specific effects is important for understanding which factors contribute to the behavioural effects of neurofeedback, thereby providing clues to increase the efficacy of neurofeedback. Furthermore, psychophysiological effects of stimulant treatment will be further explored. Chapter 5 will focus on behavioural treatment effects on core ADHD symptoms. Chapter 6 will explore EEG treatment effects in the theta, alpha and beta frequency bands during resting eyes open (EO), eyes closed (EC) and task conditions (using the SST). This study aims to investigate whether NF and/or MPH can induce sustained alterations in brain function that are related to arousal/attention mechanisms, and if these changes generalize to an active task situation. The latter might be especially important, given concern about the generalisation of NF effects to classroom behaviour and performance. Chapter 7 will more specifically explore treatment effects during the SST by investigating ERP components that are related to response inhibition. Furthermore, treatment effects will be anatomically localized with distributed source localization to gain further insight into neural network alterations, which may elucidate the treatment mechanisms behind behavioural changes. Finally, Chapter 8 will provide the general summary and discussion of the findings. In this chapter, results will be reviewed, strengths and limitations of the thesis will be discussed, clinical implications will be explored, and future research avenues will be proposed. Findings of the various chapters will be discussed according to Barkley's inhibition theory and contemporary models of ADHD.
REFERENCES


Clarke, A. R., Barry, R. J., Bond, D., McCarthy, R., & Selikowitz, M. (2002). Effects of stimulant medications on


