Attention for Inhibition

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CHAPTER 8

Summary and general discussion

SUMMARY OF MAIN FINDINGS

The first aim of this thesis was to delineate the contribution of inhibition versus attention problems to the neurobiology of ADHD, and herewith to critically appraise inhibition theories, with a particular focus on Barkley's theory of ADHD (Part I: chapters 2, 3 and 4). The second aim of this thesis was to investigate the behavioural effects of neurofeedback compared to stimulant treatment with methylphenidate (MPH) and physical activity (PA) in children with ADHD, and to identify neural mechanisms of neurofeedback and stimulant treatment that may underlie these behavioural effects, with a specific focus on inhibition (Part II: chapters 5, 6 and 7).

CHAPTER 2: ERP SOURCES OF STOPPING IN ADHD

In Chapter 2, we aimed to assess the influence of early sensory alterations, and subsequent alterations in attentional processes during response inhibition in children with ADHD, as measured with the stop-signal task (SST). Early processing steps as reflected in N1 and P2 amplitude did not differentiate between ADHD (n=46) and TD (n=51) children. However, subsequent N2 and P3 amplitudes were reduced in ADHD. Source localization of N2 differences (240-290ms after stop stimulus) showed evidence for both alterations in inhibition and ventral attention networks, as reflected by reduced activation in right inferior frontal gyrus (rIFG)/supplementary motor area (SMA), and right temporoparietal junction (rTPJ), respectively. Correlations with performance measures were consistent with this distinction, showing evidence for negative relations between rIFG and SSRT (inhibition speed) and rTPJ and omission errors on go trials (attention). Source localization of subsequent P3 differences (320-420ms after stop stimulus) demonstrated evidence of alterations in a monitoring network, as reflected by reduced activation in anterior cingulate cortex (ACC) and SMA. This study shows that impairments in the ventral attention network contribute to ADHD and challenge the dominant view that ADHD is underpinned by impaired inhibitory control.

CHAPTER 3: SPECIFYING INHIBITORY DYSFUNCTION IN ADHD

Chapter 3 elaborated on Chapter 2, by investigating the specificity of the neural network that has been associated with response inhibition while obtaining fMRI data in ADHD (n=21) and TD (n=17) children, using a newly developed SST that controls for the attentional capture effect of stop stimuli. The study described in this chapter aimed to clarify whether previous fMRI findings of the SST in ADHD were confounded with attentional processes. Results of this study showed that children with ADHD activated the rIFG/insula and dmPFC brain areas less than TD

children during successful inhibition. This study confirmed hypoactivation in key inhibition areas in children with ADHD, while controlling for the confounding effects of attentional capture.

CHAPTER 4: NEURAL CORRELATES OF ATTENTION IN ADHD

In Chapter 4, we investigated the underlying neural network that may be related to difficulties with attending to task-relevant events in children with ADHD, as measured with the oddball task. This study complemented Chapter 2 and Chapter 3, by providing a template of typical attentional brain activation that may be associated with confounding attentional processes in inhibition tasks. Results of this study showed reduced P3b amplitudes in the ADHD (*n*=36) group compared to the TD group (*n*=49). Source localization of P3b differences (310-410ms after oddball stimulus) showed reduced activation in frontal polar (Brodmann Area [BA]10) and temporoparietal regions (BA39 and 19) in the left hemisphere in the ADHD group. Reductions in P3b amplitude were related to more inattention and hyperactivity/impulsivity problems in the ADHD group. This study provides evidence for alterations in both top-down (frontal polar cortex) and bottom-up (inferior parietal/superior temporal cortex) attention-related brain areas, which may underlie P3b amplitude reductions in children with ADHD.

CHAPTER 5: BEHAVIOURAL EFFECTS OF NEUROFEEDBACK IN ADHD

In Chapter 5, we explored the effects of theta/beta neurofeedback treatment (NF: *n*=38), stimulant treatment with optimally titrated methylphenidate (MPH: *n*=31), and physical activity (PA: *n*=34) as semi-active control condition, on ADHD symptomology and psychosocial functioning. Primary aims were to compare the effectiveness of NF and MPH, and to compare NF and PA, to assess whether NF can induce specific treatment effects. On the parent reports, results showed comparable improvements in hyperactivity/impulsivity for all treatments (η_p^2= 0.24-0.25, p<0.001), whereas inattention problems improved more in the MPH group than the NF and PA groups (η_p^2= 0.17, p<0.01). Teacher reports showed greater improvements for MPH on all measures compared to NF and PA (range of η_p^2= 0.15-0.32, p<0.001). NF and PA effects were comparable across all outcome measures. Al last, although parent and teacher expectations of treatment effects at baseline were comparable between groups, we only found a relation between higher parent expectancy and greater parent-reported improvements on inattention problems in the NF group, suggesting possible non-specific or bias effects. This study found optimally titrated MPH to have superior effects to NF and PA in decreasing symptoms of ADHD.

CHAPTER 6: NEURAL MECHANISMS OF TREATMENT IN ADHD: POWER SPECTRA

In Chapter 6, we examined EEG power spectra before and after NF (n=29) compared to MPH (*n*=25) and PA (*n*=27) during resting conditions (eyes open and eyes closed) and an active (effortful) task condition (stop-signal task). This study aimed 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. Both NF and MPH resulted in similar reductions in theta power from pre- to post-intervention during the eyes open resting condition compared to PA (η_p^2=.08 and .12). For NF, greater reductions in theta were related to greater reductions in ADHD symptoms. During the task condition, only MPH showed reductions in theta and alpha power compared to PA (η_p^2=.10 and .12). In this study, we found evidence for specific neurophysiological effects after theta/beta NF and MPH treatments in children with ADHD. However, for NF these effects did not generalize to an active task condition, potentially explaining reduced behavioural effects of NF in the classroom.

CHAPTER 7: NEURAL MECHANISMS OF TREATMENT IN ADHD: ERPs

In Chapter 7, we further explored the effects of NF (*n*=32) compared to MPH (*n*=25), and PA (*n*=24) in children with ADHD on event-related potential (ERP) indices of response inhibition, as assessed with the stop-signal task. The aim of this study was to investigate whether NF and/or MPH affect core neuronal impairments in response inhibition, which are associated with ADHD and play key roles in theoretical models of the disorder. Only the MPH group showed a specific increase in P3 amplitude compared to NF (η_p^2=.12) and PA (η_p^2=.28), which was related to improved response inhibition. Source localization of medication effects on P3 amplitude indicated increased activation primarily in thalamic and striatal nuclei. In conclusion, only stimulant treatment demonstrated improvements in brain function. These results are in line with recent doubts on the efficacy and specificity of neurofeedback as treatment for ADHD.

GENERAL DISCUSSION

Part 1 - Attention for Inhibition

Attention-Deficit/Hyperactivity Disorder is characterized by severe inattention problems in most cases of the disorder (Willcutt, 2012); however, research of the past decades 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). Based on similarities between patients with frontal lobe damage and ADHD in terms of behavioural and cognitive deficits, researchers redirected their efforts to study the higher cognitive functions that were thought to be sub-served by the frontal lobes, such as inhibitory control (Castellanos et al., 2006). Barkley then introduced a comprehensive model of ADHD, stating that inhibition problems lead to secondary impairments in other executive function (EF) domains and inattention problems (Barkley, 1997). The EF deficit model of ADHD has been, and still is, a dominant paradigm in ADHD research and is part of several other contemporary models explaining the disorder, including multiple pathway models (Sonuga-Barke, Bitsakou, & Thompson, 2010; Sonuga-Barke, 2002). However, this paradigm is increasingly challenged

As has been discussed in the general introduction of this dissertation, 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). At the performance level, previous SST findings of slower inhibition speed (increased SSRT) in ADHD have been challenged by recent meta-analyses that cast doubt on the validity of the SSRT metric and instead propose that previous findings actually reflect problems in attention (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). The current thesis extends this discussion to the neurobiological domain of the SST.

The discussion of findings in Part I of the thesis can broadly be separated along the lines of (1) whether inhibitory dysfunction is actually reflected in the neurobiology of ADHD and is not confounded by attentional processes, and (2) whether inhibitory dysfunction underlies secondary impairments in other EF domains, specifically attention problems, as stated in Barkley's theory of ADHD.

The first issue originates from basic research into inhibition mechanisms in healthy participants. Several research groups have identified a major methodological concern in the SST, in that stop stimuli, due to their infrequent appearance, may induce an attentional capture effect in the same way as infrequent oddball stimuli do (Pauls et al., 2012; Sharp et

al., 2010). Conventional contrasts in fMRI studies do not control for this effect (Pauls et al., 2012). Moreover, the rIFG, which has been associated with response inhibition and ADHD, may overlap with the ventral attention system that is important in target detection (Corbetta, Kincade, & Shulman, 2002; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Rubia, Hyde, Halari, Giampietro, & Smith, 2010). The fMRI study that we conducted in Chapter 3 used a stringent design in which we controlled for attentional capture effects. Despite this conservative approach, we found evidence for the specificity of inhibition areas in the brain, including the rIFG, and confirmed that this inhibition network is activated to a lesser extent in children with ADHD than in typically developing children. The ERP source localization results, as discussed in Chapter 2, further validate the specificity of the rIFG in inhibitory dysfunction in children with ADHD. First, the affected areas remarkably resemble those observed in fMRI studies including our fMRI study, with a prominent role for the rIFG. Second, rIFG activation was negatively related to inhibition speed (SSRT), as opposed to the rTPJ, which was related to go omission errors and less activated in ADHD as well. This dissociation is even more important, considering that the rIFG and rTPJ have been proposed to be part of the same ventral attention network (Corbetta, Patel, & Shulman, 2008). Third, although more indirectly, another validation of the specificity of rIFG inhibitory dysfunction, is the fact that the ERP source localization study in Chapter 4, which comprised a classical attention paradigm (oddball task), did not reveal differences in the rIFG. The oddball task can be seen as an instance of the SST, but without strong inhibitory demands only including the attentional capture effect of infrequent oddball stimuli.

The second issue can be regarded as a more formal test of Barkley's inhibition theory of ADHD, which states that inhibitory dysfunction actually precedes other EF and attentional impairments. In other words, how fundamental are the inhibition problems that we specified in the fMRI study? In Chapter 2, we addressed this question by localizing altered ERP components during the SST. Our approach enabled us to gain both high temporal and spatial resolution of processes involved in stopping a prepotent motor response. In line with the literature we found reduced N2 amplitudes (approximately 265ms after the stop stimulus) and reduced P3 amplitudes (approximately 370ms after the stop stimulus) in children with ADHD, but no differences in earlier sensory processing. Interestingly, source localization of N2 revealed not only a typical inhibition network (rIFG and SMA) that was affected, but also a major hub of the ventral attention system, the right temporoparietal junction (rTPJ). The ventral attention system supports attentional reorienting to salient and behaviourally relevant external stimuli (Corbetta et al., 2008). The fact that this ventral attention network is implicated in the same 50ms

time window (240-290ms after stop stimulus) as the inhibition network creates a challenge to Barkley's theory of ADHD. At the very least, these results may bring attention problems from being secondary in a chain of impairments to being concurrent with inhibition problems. We used a 50ms time window to arrive at a more favourable signal-to-noise ratio. Therefore, it remains unknown whether or how deficits in these networks succeeded each other in this short time period.

It may not be surprising that attentional reorienting and response inhibition are intimately related in inhibition tasks such as the SST. This is exemplified by a study that employed a modified go/no-go task in which evidence was found for a functional segregation within the rIFG, with the posterior part (pIFG) specifically involved in response inhibition and the more dorsally located inferior frontal junction (IFJ) involved in reorienting attention (Chikazoe et al., 2009). Closer examination of N2 source imaging findings in Chapter 2 may point to such segregation within the rIFG in our data as well. The 3-dimensional rendering of group differences shows, within the larger rIFG cluster, two separate loci that correspond to a more dorsally located IFJ and a more inferiorly located IFG area. Possibly, both the rTPJ and the rIFJ loci are part of an impaired ventral attention system in children with ADHD.

The potential dysfunction of the ventral attention system has been infrequently considered in ADHD. However, a recent meta-analysis of 55 fMRI studies across various cognitive tasks demonstrated that impairment in this network is actually the most dominant among different networks in children with ADHD (Cortese et al., 2012). It should be noted, however, that besides reduced activation in het ventral attention network (44% of total), the canonical frontoparietal network (39% of total), which has been more conventionally associated with ADHD, contributed significantly to the pathophysiology of ADHD. This network supports goal-directed executive processes and guides decision making according to the integration of information from the external world and internal representations (Corbetta et al., 2008). In the meta-analysis of Cortese et al. (2012), other networks, such as the default mode, somatomotor, dorsal attention and visual networks were affected as well, although to a lesser extent. It seems that ADHD is underpinned by dysfunction in multiple large-scale brain networks. How fundamental the role of the ventral attention system is, remains an open question. The current thesis and similar studies into this subject as reviewed in this thesis, however, do indicate that specific attentional dysfunctions in the brain of children with ADHD need more consideration than they have previously received.

Chapter 4 emphasizes the complex brain alterations that are present in children with

ADHD, even during a relatively simple oddball task. This task requires the detection of infrequent, salient target stimuli or 'oddballs'. Around 300ms post-stimulus, electrical brain recordings of the oddball condition show a posterior distributed positive wave, the P3b, which has been associated with contextual-updating of working memory (Donchin & Coles, 1988). To effectively perform this task, both bottom-up (attentional capture and reorienting) and top-down brain processes (maintaining task rule representations) have to work together. Our results suggest that both processes are afflicted in children with ADHD. First, we found bottom-up attentional disruptions, as reflected in reduced activation in the left angular gyrus (AG), at the boundary of superior temporal, inferior parietal and occipital cortices. Although it is generally thought that the ventral attention network is strongly lateralized to the right (Corbetta et al., 2008), this view has been challenged in a review of fMRI studies in which it was found that the left inferior parietal lobe (IPL) mediates attentional capture by memory content (Ciaramelli, Grady, & Moscovitch, 2008), and a recent review on the ventral attention system indicated evidence for the involvement of this area in attentional reorienting and processing of rare deviant stimuli (Vossel, Geng, & Fink, 2014). It has been suggested that the AG is an important interface between bottom-up and top-down predictions (Seghier, 2013). Second, we found evidence for top-down disruptions, as reflected in reduced activation in a ventral region of the left frontal pole, including middle and superior frontal gyri, mainly located in Brodmann area (BA)10. The frontal-polar cortex has been suggested to be a hub region in a cinguloopercular network that is associated with the ability to maintain the representation of task rules (Dosenbach et al., 2007). It could be speculated that children with ADHD have difficulty in maintaining task rule representations (reduced activation in left frontal polar region) and therefore introduce less consistent top-down control (predictions), thereby affecting the AG. Conversely, these systems may influence each other in reversed order, reciprocally, or may be affected independently

In conclusion, the various results of Part I of this thesis suggest that inhibition problems are present in the neurobiology of ADHD; however, inhibition problems may not be as fundamental in ADHD as proposed by Barkley and others that emphasize inhibitory dysfunction in ADHD. Problems in the ventral attention system seem to play a more important role in the neurobiology of ADHD than previously considered. This thesis lends further support to recent concerns about the effects of dysfunctional attentional processes during the SST in children with ADHD, and may have implications for theories that emphasize inhibitory dysfunction in ADHD.

Strengths and Limitations

Some limitations to the various studies in this dissertation should be noted. One of the most important limitations of Part I of this thesis is that we do not take the heterogeneity within ADHD into account. Studies have only found moderate associations between different neuropsychological deficits and ADHD (Coghill, Seth, & Matthews, 2013; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), suggesting substantial distributional overlap between ADHD and TD children. Moreover, neuropsychological deficits are by no means descriptive of the total group of children with ADHD, with relatively small subgroups that actually show clinical levels of neuropsychological deficits, such as in working memory (30%), inhibition (23%), or delay aversion (36%) (Nigg et al., 2005). Nigg et al. (2005) found only 30% of patients with deficits in at least 3 cognitive tasks. Although inhibition problems can not be considered necessary in all cases of ADHD, multiple-pathway models of ADHD still consider poor inhibitory control a separate aetiological pathway in ADHD, besides delay-related pathways (Sonuga-Barke, 2002) and timing-related pathways (Sonuga-Barke et al., 2010). Our results are relevant for the inhibitory dysfunction pathway and may contribute to a better understanding of underlying neurobiological mechanisms in this ADHD subgroup.

Regarding the ADHD group composition, we did not explore the impact of comorbid psychiatric disorders on the results. Although in clinically referred samples the majority of children with ADHD show a wide variety of comorbid disorders (Gillberg et al., 2004), such as oppositional defiant disorder (ODD) and conduct disorder (CD), with prevalence estimates of 60% for ODD and 40% for CD (Connor, Steeber, & McBurnett, 2010), our sample received relatively few comorbid diagnoses (20%). Subgroups were therefore too small for statistical comparisons, with only six children with comorbid ODD, five children with learning disorder, or even smaller numbers for other diagnoses. Comorbid problems, instead of formal diagnoses of comorbid disorders, may have been considerably more common. However, children in our sample received their ADHD diagnosis close to study entry. Comorbid diagnoses may be established later in the clinical process. A second, methodological limitation is the fact that source imaging is an estimation of brain activity instead of an indirect measurement like fMRI, with less spatial resolution, and should therefore be interpreted with more caution. Furthermore, distributed source imaging can produce spurious activations, or 'ghost' sources (Fuchs, Wagner, Kohler, & Wischmann, 1999). However, both problems were reduced in the current study by calculating individual source estimations, which make it unlikely that spurious activations will be consistently observed across individuals, and the stringent statistical group comparisons

applied here, give more confidence than source localization of grand averages.

Another limitation is that the control conditions in the fMRI study may have induced inhibition-related activation that in turn would have diminished differences obtained in our successful and failed inhibition contrasts. Although task instructions clearly stated that control trials did not require a response, their infrequency compared to go trials could have triggered partial inhibition, comparable to a no-go trial in a go/no-go task. The successful inhibition contrast showed activation in key motor inhibition areas, but effects in other brain areas, especially basal ganglia nuclei such as the striatum, could have been diminished; although this could also be the result of the cluster-size thresholding method, which may be less likely to show smaller activation areas. Future study designs of the stop task could use a neutral stimulus in the control condition to reduce the go/no-go inhibition effect.

Strengths of the studies in Part I of this thesis are the well-defined ADHD samples, with stringent inclusion criteria of a clinical diagnosis of ADHD according to the DSM-IV (American Psychiatric Association 1994) as established by a child psychiatrist, and confirmed by the parent version of the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer et al., 2000), and by parent and teacher ratings on the Disruptive Behaviour Disorders Rating Scale (DBDRS; Pelham et al., 1992), which required scores above the 90th percentile for parents and teachers. Furthermore, previous ERP studies with the SST did not correct for or only reduced overlap of ERPs elicited by preceding go stimuli that distort stop ERPs, especially early components such as N1 and P2. We employed the 'adjacent response filter method (ADJAR)' (Woldorff, 1993), which is effective in removing the overlap of preceding go ERPs (see Bekker et al. (2005) for a discussion and demonstration of ADJAR for the SST). At last, individual distributed source localization of differentiating components was implemented for both ERP studies. One of the main advantages over equivalent current dipole methods is that it is less prone to operator bias, and that is can handle multiple spatially extended sources (Pizagalli, 2007).

Part II - Brain Gym?

At the time of conceptualisation of the current intervention study, Brain Gym, the efficacy of neurofeedback as treatment for ADHD was described as “efficacious and specific” by Arns et al. (2009) in a meta-analyses covering both controlled and uncontrolled studies, or more cautiously described as “a promising alternative” in most other reviews (Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; Moriyama et al., 2012), although few were more sceptical concerning the efficacy of theta/beta neurofeedback for ADHD (Loo & Makeig, 2012). In 2013, an impactful meta-study conducted by the European ADHD guidelines group (EAGG) looked into the efficacy of nonpharmacological interventions for ADHD, including neurofeedback (Sonuga-Barke et al., 2013). Compared to other reviews on this topic, stringent selection criteria were used to ensure that only studies employing a rigorous methodological approach were examined. Importantly, the meta-study distinguished between most proximal assessments (often unblinded and closest to the therapeutic setting, mostly parents) and probably blinded assessments (either blinded or further away from the therapeutic setting, mostly teachers). Results showed that the medium sized effects of neurofeedback reported by most proximal assessments decreased to non-significant levels when only probably blinded assessments were considered. Although the authors favoured the interpretation that these contrasting findings reflected a bias of the most proximal informants, who are probably more inclined to evaluate effects positively due to their investment in the treatment, an alternative explanation may be that effects did not generalize to the classroom (probably blinded informants were mostly teachers ratings). Currently, the efficacy of neurofeedback for ADHD is still an intensively debated subject. The findings of Part II of this thesis will be discussed along the distinction of most proximal (parents) and probably blinded assessments (teachers), as we think this is a useful distinction when considering possible bias effects, but also generalization effects.

The first aim of our study was the comparison of neurofeedback with stimulant medication (methylphenidate; MPH) on behavioural outcome measures of ADHD symptoms to explore whether theta/beta neurofeedback is a viable alternative to pharmacological intervention. The second aim was to compare neurofeedback with physical activity (PA) as semi-active control group, to control for non-specific treatment effects such as parental engagement and personal attention (Chapter 5). This comparison allows studying specific effects, or treatment effects that are specifically related to altering brain activity, which is the intended effect of neurofeedback.

According to most parent and teacher outcome measures, methylphenidate was more effective than neurofeedback and physical activity (with large effect sizes) in ameliorating symptoms of ADHD. It is worth noting that the study of Ogrim and colleagues (2013) is the only other study that found superior behavioural effects for medication treatment compared to neurofeedback, with other studies showing comparable efficacy for neurofeedback and medication treatment (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). Possibly, the double-blind medication management procedure that was used in one-third of the participants in the study of Ogrim and colleagues, similarly to the current study, resulted in more optimal doses, and hence, greater clinical effects. Although neurofeedback could be less effective in ameliorating ADHD symptoms than optimally titrated methylphenidate, smaller-sized specific effects could potentially exist. However, direct comparisons between neurofeedback and physical activity, which was designed to control for non-specific effects, could not establish evidence for this proposition.

Although exploratory and beyond the primary aims of the study, parents reported small improvements in inattention symptoms over time as opposed to teachers in the neurofeedback group (note that these analyses were not corrected for non-specific effects). The discrepancy between parent and teacher reports is in line with the meta-study by Sonuga-Barke et al. (2013), which found effects only for the most proximal assessments (mostly parents), but not for the probably blinded assessments (mostly teachers). The authors suggested, as described previously, that the former assessment may have been biased. We were able to actually estimate one possible bias, pre-intervention expectation of treatment success, which may have influenced parent and teacher evaluation at post-treatment. Interestingly, only for the neurofeedback group, greater parent expectation predicted greater parent-reported improvements in inattention symptoms. Moreover, although not reported in Chapter 5, time effects on parent-reported inattention symptoms were reduced to non-significant when corrected for pre-treatment expectation. It should be noted that a more complex explanation, such as that greater expectation could lead to a more effective treatment implementation and therefore greater specific effects of neurofeedback, may alternately explain this pattern of results. However, non-specific effects were controlled by comparing neurofeedback with the physical activity semi-active control group, which yielded negative results.

In Chapter 6 and Chapter 7 we had the opportunity to explore neural mechanisms that may underlie the behavioural findings in our study. Surprisingly, even though we failed to find evidence for specific behavioural effects of neurofeedback, we did demonstrate reductions in

theta power in the neurofeedback and methylphenidate groups compared to the control group during the eyes open resting condition. This theta reduction in the neurofeedback group was further signified by the behavioural correlates that we found, as higher baseline theta was predictive of greater parent-reported ADHD symptom reduction, and greater changes in theta power were related to greater parent-reported symptom reductions as well. These findings are similar to Gevensleben et al. (2009). Our findings extended those by Gevensleben et al. (2009), by including an effortful task condition (stop-signal task) to explore whether electrophysiological effects generalize to a context more similar to the classroom. In contrast to the methylphenidate group, children that received neurofeedback did not demonstrate reduced theta power during the task condition. It seems therefore that the effects of neurofeedback did not generalize to an active task condition. These results are in line with the behavioural effects of our study, and the meta-study by Sonuga-Barke et al. (2013). An interesting contrast with Chapter 5, however, is the fact that parent-reported symptom reductions were (partly) explained by treatment expectations, which probably reflect a non-specific effect or bias, while Chapter 6 showed that parent-reported symptom reductions were related to specific theta power reductions. Although these findings seem contradictory, neurofeedback may induce both strong non-specific effects and smaller specific effects that do not generalize.

The ERP findings of the stop-signal task in Chapter 7 further specify the differential effects that we found in power spectra changes between neurofeedback and methylphenidate. The principal finding of the study in Chapter 7 was a specific increase in P3 amplitude with stimulant treatment that reflected improved response inhibition. However, no specific effects were found in the neurofeedback group. This result is in line with Ogrim et al. (2013) who showed superior P3 increases in medication responders compared to non-responders and neurofeedback.

Correlational analyses and source localization of P3 effects provided further insights into the neuropharmacological mechanisms of methylphenidate in children with ADHD. First, our results suggest that P3 is strongly related to SSRT at baseline, and therefore offers a physiological index of response inhibition. Furthermore, the strong relation between larger increases in P3 amplitude and improved response inhibition (shorter SSRT) in the medication group shows that the effect of methylphenidate is closely related to this inhibition mechanism. Source localization of P3 changes from pre- to post-intervention indicated increased activation primarily in thalamic and striatal (caudate and lentiform) nuclei during successful and failed inhibition. FMRI studies show that these areas are under activated in children with ADHD during

inhibition tasks (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013) and PET studies in adults with ADHD indicate lower D2/D3 dopamine receptor availability in the caudate (Volkow et al., 2009). The therapeutic action of methylphenidate seems to concentrate on the striatum by inhibiting the reuptake of dopamine and thereby increasing extracellular concentrations of dopamine (Rosa-Neto et al., 2005). In line with this putative mechanism, a meta-study by Hart et al. (2013) showed that long-term medication users showed increased activation in the right caudate

Although the thalamic and striatal effects of methylphenidate can be quite readily explained, the lack of cortical changes may be considered unexpected. Chapter 2 and Chapter 3 provided evidence for deficient inhibition and attention-related brain activity (during the N2, approximately 265ms after the stop stimulus), and deficient monitoring brain activity (during P3, approximately 370ms after the stop stimulus) in the same children with ADHD. Possibly, methylphenidate primarily acts on arousal mechanisms that are subserved by deep nuclei with more variable downstream cortical effects. Therefore, no consistent pattern of cortical changes may be found in the group analyses. The reduction of alpha and theta power during the stop-signal task in Chapter 6 further support the notion that methylphenidate acts on more general arousal mechanisms (Barry, Rushby, et al., 2005; Barry, Clarke, Johnstone, Brown, et al., 2009).

In conclusion, results of Part II of this thesis could not confirm the clinical effectiveness of theta/beta neurofeedback as intervention for children with ADHD. Although children that received neurofeedback demonstrated some specific effects at the electrophysiological level, these effects did not generalize to an effortful task-related context, possibly explaining the lack of clinical effectiveness. Stimulant treatment with methylphenidate, however, showed superior behavioural and electrophysiological effects compared to the neurofeedback treatment and the control condition, physical activity.

Strengths and Limitations

Although the theta/beta neurofeedback protocol is used in the majority of studies (Loo & Makeig, 2012), the actual implementation of the training differs widely among studies. Protocols differ in total number of sessions, number of sessions per week, automatic or manual thresholding of difficultly level, kind of feedback and rewarding, frequency bandwidth, whether or not using transfer trials, etcetera. Furthermore, besides theta/beta neurofeedback, other studies train slow cortical potentials (SCP) or implement more extensive protocols, such as the Lubar (Lubar, 2003) protocol (increase SMR and beta activity, decrease theta activity and gamma activity) or

even use individualised protocols. No consensus exists on the optimal neurofeedback protocol, although theta/beta and SCP protocols appear to have comparable effects (Gevensleben, Holl, Albrecht, Vogel, et al., 2009). However, our findings can not be generalized beyond the theta/beta neurofeedback literature.

Theta/beta has originally been interpreted as a marker for central nervous system (CNS) arousal; however, this proposition is increasingly challenged. Studies have failed to find a relation between theta/beta and skin conductance level (SCL), with the latter being considered the gold-standard index of CNS arousal. In contrast, alpha power shows a negative relation with SCL (Barry, Clarke, McCarthy, Selikowitz, & Rushby, 2005; Barry, Clarke, Johnstone, Brown, et al., 2009). Another complicating issue, is the inconsistency in the literature in using the terms arousal and activation (Barry, Clarke, et al., 2005). Barry et al. (2005) define arousal at a particular time to be the energetic state at that time, reflected in electrodermal activity (SCL), which is an amplifying factor in response evocation, serving to modulate the stimulus-response reflex. Activation is defined as the change in arousal from a resting baseline to a task situation, or as task-related mobilization of arousal, and seems to be a better predictor of task performance. Barry et al. (2009) suggest that elevated theta/beta in ADHD may not reflect an arousal deficit, but rather an activation deficit or poor processing, as theta/beta is related to task performance. The conceptual shift away from arousal to activation challenges the rationale for theta/beta neurofeedback – increasing arousal in under aroused children with ADHD. Slow cortical potential (SCP) neurofeedback training may better correspond to the increasing emphasis on activation, as SCP training addresses the regulation of phasic cortical activity to optimize allocation of cortical resources (Holtmann, Sonuga-Barke, Cortese, & Brandeis, 2014), although it should be noted that theta/beta and SCP neurofeedback show comparable treatment effects (Arns et al., 2009). Another challenge for the foundation of theta/beta neurofeedback, is recent evidence that questions the association between theta/beta ratio as clinical biomarker and ADHD (Arns, Conners, & Kraemer, 2013; Loo et al., 2013; Snyder, Rugino, Hornig, & Stein, 2015), and several research groups increasingly embrace the possibility that neurofeedback does not address a neural dysfunction, but rather learns compensatory mechanisms (Arns, Heinrich, & Strehl, 2014; Gevensleben, Rothenberger, Moll, & Heinrich, 2012).

Another notable observation is that beta power did not change between pre-and post-intervention for the neurofeedback group, as opposed to theta power. Other studies also failed to demonstrate treatment effects in the beta power band (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Kropotov et al., 2007; Ogrim & Hestad, 2013). This may be explained by

several factors. First, increased theta power seems to be a more robust marker of ADHD than decreased beta power (Loo & Barkley, 2005). This seems to be true for the current study as well, as we found highly significant correlations between teacher reported ADHD symptoms and theta power, but not for beta power. The theta band, therefore, may be more strongly related to ADHD symptoms than beta activity. Second, theta power may be more reliably measured with EEG than beta power. Conventional EEG frequency bands overlap with the frequency spectrum of electromyographic (EMG) activity produced by skeletal muscles (Goncharova, McFarland, Vaughan, & Wolpaw, 2003; McMenamin, Shackman, Greischar, & Davidson, 2011). Although the peak frequency of EMG is at relatively high frequencies, the spectrum of EMG is very broad and may influence adjacent beta frequencies more than lower frequency bands such as theta. Despite specific instructions during neurofeedback training to prevent excessive muscular tension, it can not be ruled out that some children used more subtle covert muscular tension to influence the theta/beta ratio. Third, in this study we used a theta/beta index as feedback signal that was biased to represent theta more than beta. This bias was implemented to weigh theta and beta bands for their bandwidth. An advantage of this index calculation is that extreme theta/beta values, which may result from muscular artefacts, have less disruptive effects on the training. However, our method of index calculation may have reduced training effects in the beta band.

The absence of specific ERP effects of theta/beta neurofeedback in this study should be considered in the context of possible limitations. First, although the neural mechanisms behind neurofeedback are yet unknown, physiological effects may be observed in other neurocognitive domains than response inhibition. One other study looked at ERP effects on an attention task, and found decreased P3 at post-intervention for the children receiving neurofeedback as well as the control group (Wangler et al., 2011). However, the authors suggested that this effect might indicate task adaptation, as more intelligent children showed larger P3 decreases. Second, the effects of neurofeedback may be of a transitory nature and therefore not observable in a laboratory setting. Third, although theta/beta ratio may be increased in ADHD at the group level (Snyder & Hall, 2006), several studies found considerable heterogeneity in power spectra measures within ADHD (Loo & Makeig, 2012). The effects of neurofeedback may therefore be dependent upon etiological subtypes.

Implications and Future Directions

The various results of Part I of this thesis suggest that inhibition problems are present in the neurobiology of ADHD; however, inhibition problems may not be as fundamental in ADHD as proposed by Barkley. Problems in the ventral attention system seem to play a more important role in the neurobiology of ADHD than previously considered. This thesis lends further support to recent concerns about the effects of dysfunctional attentional processes during the SST in children with ADHD, and may have implications for Barkley's inhibition theory of ADHD and more recent multi-pathway models of ADHD. Indeed, the renewed interest in attention problems in ADHD gives an ironic twist to our quest for understanding the disorder.

The distributed source localization method, which we used in Chapters 2, 4 and 6, provides valuable information on both temporal and spatial aspects of information processing in ADHD, and potential treatment mechanisms. These results can lead to novel and testable hypotheses on the causal cascade of processing deficits that underlie ADHD. Future studies could extend on the current findings, by using connectivity analyses (such as functional and effective connectivity) to explore directional effects within and between ventral attention and inhibition networks. Another useful approach to ERP analysis, which better fits the concept behind distributed source imaging, is microstate analysis. Conventional ERP analysis is hampered by the inherent fact that no point records zero potential over time, meaning that any statistical comparison of amplitudes at a given electrode between groups will change when the reference is changed, making results ambiguous (Brunet, Murray, & Michel, 2011). In contrast, microstate analysis is based on topographic measures, which are reference-independent. Furthermore, differences in topography directly indicate changes in the configuration of neural generators, thereby providing useful markers for source localization.

Another interesting topic worth investigating is the relation between the ventral attention network and the dorsal attention network, as described in Corbetta et al. (2008), in children with ADHD. These networks seem to depend on each other for effective attentional functioning. The dorsal system is goal-driven and specifically active during focused attention, while the ventral attention system is deactivated. When an unexpected but important event evokes reorienting of attention, both dorsal and ventral attention networks are (transiently) activated. Dorsal network regions may send top-down biases to the ventral attention network to restrict ventral activation to behaviourally important stimuli. Our data show evidence for impaired recruitment of the ventral attention system in children with ADHD when confronted with infrequent and unexpected stop signals, probably affecting inhibitory requirements that

come with the stop-signal. When considering the interplay between dorsal and ventral attention systems, an alternative explanation of our findings may be that the dorsal system does not produce consistent top-down signals to bias the ventral attention network to effectively reorient attention to behaviourally important stop-signals. Dysfunctional dorsal attention areas may be present in ADHD during frequent go signals in the stop-signal task, which require sustained focused attention. Future studies could further probe these distinct but interrelated attentional systems to substantiate this hypothesis.

The locus coeruleus norepinephrine (LC-NE) system may be important in connecting our findings of alterations in the ventral attention network and cognitive-energetic models of ADHD (Sergeant, 2000; Zentall & Zentall, 1983). The LC is the sole source of norepinephrine in the brain, with diffuse projections to the brainstem, cerebellum, diencephalon and neocortex (Aston-Jones et al., 1991). LC-NE neurons can discharge in tonic and phasic modes, with no tonic state during deep sleep (low arousal) and tonic firing (1-3Hz) during alert wakefulness (increased arousal) (Aston-Jones & Bloom, 1981a, 1981b). Phasic discharge of LC-NE neurons is related to alerting and orienting attention (target detection), and is reflected in the production of P300 in attention tasks (Howells, Stein, & Russell, 2012). The P300 is also influenced by tonic discharge of LC-NE neurons (Polich & Kok, 1995). Phasic discharge appears to be partly dependent on tonic activity levels, where the association follows Yerkes-Dodson inverted u-shape (Winton, 1987), with less robust phasic responses under conditions of lower tonic discharge levels (lower arousal), optimal phasic responses with moderate tonic discharge levels, and again less robust phasic responses during high tonic discharge levels (high arousal) (Berridge & Waterhouse, 2003). The combined action of tonic and phasic activity in LC-NE affect thalamic and cortical neuronal activity (Berridge & Waterhouse, 2003). Interestingly, manipulations of noradrenergic neurotransmission in humans affect attentional and memory processes, especially functions that are dependent on fronto-striatal circuits, such as planning, working memory, and sustained attention (Mehta, Sahakian, & Robbins, 2001), which are impaired in ADHD (Coghill et al., 2013). Furthermore, the LC-NE system may be functionally connected to the ventral attention network in relation to behavioural state transitions (e.g. from low to high arousal tonic signals) and target detection (phasic response) (Berridge & Waterhouse, 2003). Our findings of reduced activity in the ventral attention system, particularly in the rTPJ, may therefore be a consequence of suboptimal arousal states associated with the LC-NE.

Most evidence for dysregulation of the noradrenergic system in ADHD comes from pharmacological studies (Hohmann et al., 2014), although several genetic studies further support

the role of norepinephrine in ADHD. A genetic study into associations between specific genetic variations in children with ADHD and performance on a continuous performance task (CPT), showed an association between a single nucleotide polymorphism (SNP) in the norepinephrine transporter (NET) gene (rs3785155) and reaction time variability (RTV). RTV is thought to index attention and attentional lapses, which are largely mediated though noradrenergic pathways (Biederman & Spencer, 1999). Another, more recent genetic study, found that homozygous carriers of the NET variant (rs28386840) displayed a higher rate of lifetime ADHD diagnosis, while individuals heterozygous for the NET (rs3785157) variant made fewer omission errors on the CPT than homozygotes. These studies further support the association between dysregulation of the noradrenergic system, arousal and attention in ADHD. Future studies that explore associations between attention and arousal, and LC-NE and ventral attention networks in children with ADHD, would be useful extensions to the current thesis. Furthermore, imaging genetic studies could reveal more about the underlying aetiology of altered attention networks in children with ADHD.

Results in Part II of this thesis could not confirm the clinical effectiveness of theta/beta neurofeedback as intervention for children with ADHD. Although children that received neurofeedback demonstrated some specific effects at the electrophysiological level, these effects did not generalize to an effortful task-related context, possibly explaining the lack of clinical effectiveness. Stimulant treatment with methylphenidate, however, showed superior behavioural and electrophysiological effects compared to the neurofeedback treatment and the control condition, physical activity.

There may be a noteworthy association between the potential influence of arousal-related effects of the noradrenergic system on attentional and inhibitory functioning, as described previously, and the neural mechanisms of methylphenidate in children with ADHD. Although the effects of methylphenidate are predominantly ascribed to the dopaminergic neurotransmitter system (Rosa-Neto et al., 2005), another important catecholamine, norepinephrine, is involved as well (Berridge et al., 2012). The blockage of norepinephrine transporter (NET) in the LC-NE may increase tonic firing to afferent thalamus and cerebral brain areas (Berridge & Waterhouse, 2003), resulting in higher arousal levels and improved cognitive performance. This mechanism may explain our findings of the prominent activation increases of bilateral thalamus with methylphenidate, besides effects in the striatum that are likely dopaminergic.

Considering the fact that effects of neurofeedback were confined to the theta band during rest, and that children with increased theta showed larger improvements, neurofeedback

protocols may benefit from training solely theta activity during both task and non-task conditions in children with elevated theta. Despite evidence for some specific electrophysiological effects of neurofeedback, with possible clinical implications as mentioned, we found evidence for non-specific effects as well, which may represent reporter bias. Both non-specific and specific treatment effects should therefore be more frequently and systematically evaluated to delineate the effective components of interventions such as neurofeedback. However, given the lack of behavioural effectiveness of neurofeedback, the current thesis adds to a growing literature that casts doubt on the efficacy of neurofeedback as treatment for children with ADHD.

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