Functional brain laterality in adulthood ADHD
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Chapter 6

General discussion
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Overview of studies

The aim of the thesis was to investigate the relationship between brain laterality, interhemispheric interaction and adult ADHD related problems from the dimensional perspective. To this end, students completed questionnaires designed for detection of ADHD symptoms in adulthood. T-scores were derived to compare the individual’s responses to adult population norms. The scores were transformed from raw scores and have a mean of 50 and standard deviation of 10 (Conners, Erhardt, & Sparrow, 1999). The scores were used to test how ADHD severity is associated with valid behavioral indices of brain laterality, interhemispheric interaction, state regulation, and error-processing. It appeared that all these behavioral indices as well as scores on the self-reported ADHD scales were normally distributed. Consequently, we used dimensional analyses such as regression analysis with ADHD scores as a continuous independent variable and as a covariate in repeated measures analysis of variance.

The main finding of study 1 is that only the combination of ADHD symptoms, especially hyperactivity, and stress is associated with fast interhemispheric interaction. According to Banich and Belger (1990), fast interhemispheric interaction may mirror compromised laterality. This said, the result is not easy to interpret because we do not know the direction of the cause between hyperactivity and stress: is stress causing ADHD symptoms, or is involuntary ADHD-like behavior causing stress? Nevertheless, returning to the subject of the thesis, it must be underlined that self-reported ADHD symptoms were not associated with the interhemispheric interaction index. Therefore, it might be safe to conclude that ADHD does not influence interhemispheric interaction. This conclusion is in accord with the outcome of the few available behavioral studies on clinical cases with ADHD (Amano, 2002; Brown & Vickers, 2004; Hagelthorn, 1998; Rolfe, Kirk, & Waldie, 2007). The conclusion is also in accord with the outcome of so-called structural studies on ADHD. Here, structural abnormalities in the corpus callosum are observed mostly in children (Cao et al., 2010; for meta-analytic reviews, see Chen et al., 2016; Hutchinson, Mathias, & Banich, 2008; Valera, Faraone, Murray, & Seidman, 2007), but not in adults (Dramsdahl, 2011; Dramsdahl Westerhausen, Haavik, Hugdahl, & Plessen, 2012; Onnink et al., 2013). Consequently, in contrast to children, adults with ADHD may have a matured corpus callosum with sufficient intact interhemispheric connections. However, there is little data from adult ADHD and future studies are required to investigate interhemispheric connections in adults (Luders et al., 2009; for review see, Schneider, Retz, Coogan, Thome, & Rösler, 2006).

One might argue that fast interhemispheric interaction could be seen as a physiological stress response. The brain has to cope with stress. Successful coping is promoted by increased interhemispheric interaction (activation/inhibition) between left and right prefrontal cortices (for reviews, see Sullivan, 2004; Cerqueira, Almeida, & Sousa, 2008), which is the main function of the callosal genu (an area located in the anterior part of the corpus callosum). It is worthwhile to mention that in some studies the callosal genu was found to be smaller in subjects with ADHD (Hynd et al., 1995; Luders et al., 2009). In this vein, stress may explain, to some extent, poor high order cognitive functions in ADHD. This statement supports the idea that ADHD is a stress-related disorder (Grosswald, 2013).
Another interpretation of why the combination of ADHD symptoms and stress is associated with fast interhemispheric interaction is that adults with ADHD often complain that their head is full and unquiet. Stress increases this problem by loading the brain with extra stimuli and irrelevant thoughts. Thus, whereas ADHD symptoms on their own may not be related to interhemispheric interaction in normal conditions, in conditions of stress it might.

Study 2 showed no dimensional relation between brain laterality and the severity of self-reported ADHD symptoms. However, the categorical approach contrasting participants with ADHD scores at the low and the high end of the distribution led to a different result. Inattentive symptoms (independent from depression, anxiety, and stress symptoms) showed an association with compromised brain laterality (i.e., poor right hemisphere processing of visuospatial information). This latter outcome is in line with the majority of structural and functional laterality studies in clinical cases with ADHD (Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995; Frodl & Skokauskas, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Poynter, Ingram, & Minor, 2010; Sandson, Bachna, & Morin, 2000; Song & Hakoda, 2012; Valera et al., 2007).

The outcome of study 2 suggests that the right hemisphere dysfunction theory may hold only for clinical cases with ADHD. Note: a proportion of participants with high scores on ADHD scales may suffer from clinical ADHD or other mental problems. As the right hemisphere dysfunction seems to be an inherent feature of many psychiatric syndromes such as Schizophrenia, Bipolar Disorder, Depression, Asperger syndrome, and Nonverbal Learning Disabilities (Chakrabarty, Sarkar, Chatterjee, Ghosal, Guha, & Deogaonkar, 2014; Gold, & Faust, 2010; Spreen, 2011; Rocca, Heuvel, Caetano, & Lafer, 2009), one might argue that right hemisphere dysfunction is not specific to ADHD. Future research might sort out in what kind of task-specific areas of the right hemisphere show deviant functioning in ADHD, using advanced techniques such as fMRI.

Study 3 underscored the role of deficient left hemisphere-functioning in ADHD, the decreased left hemisphere processing appeared to be associated with state regulation difficulty and the severity of ADHD symptoms. This implies that the state regulation deficit might be seen as a core deficit in ADHD because it is related to the continuous dimension of ADHD symptoms. Moreover, previous clinical studies have shown that poor task performance of children with ADHD is related to poor effortful/energetic state control and such a deficit persists in adult ADHD (Wiersema, van der Meere, Antrop, & Roeyers, 2006).

Study 4 compared error processing in participants with higher and lower ADHD scores on a self-report scale. Geburek, Rist, Gediga, Stroux, and Pedersen (2013) argued that “error monitoring can be viewed as part of the self-monitoring of one’s own behavior, enabling an individual to evaluate his own response regarding an actual demand, recognize a potential error and adjust his response to prevent further errors. As making careless mistakes is at the heart of the ADHD syndrome, we may expect dysfunctions in the neurocognitive processes underlying error monitoring in many situations”. Results of study 4 indicated that adults with more severe ADHD symptoms have impaired error monitoring. The results of post-error response latency and accuracy are partly consistent with the outcome of a meta-
analytic review by Geburek et al. (2013), showing a deficit in the conscious recognition of an erroneous response in ADHD. In the meta-analysis, electrophysiological and behavioral indices of error monitoring were compared in adolescent and adult samples with ADHD and healthy controls. The electrophysiological indices were error negativity (Ne) and error positivity (Pe). The behavioral indices were reaction time measures of correct responses and errors and error rates on Go/No-go and flanker tasks. Although the meta-analysis was done on heterogeneous data, it was concluded that a deficit in error monitoring and response inhibition control is a central feature of ADHD because results of their behavioral measures of inhibition correspond with the model of Barkley (1997). However, evidence in contrast to this conclusion comes from our results showing that impaired error monitoring was confined to the task condition that requires extra effort allocation and left hemisphere processing only. In addition, the impairment was expressed in a different behavioral measure (choice reaction time task), which does not tap response inhibition in a strict sense.

In contrast to adults who have more severe ADHD symptoms, healthy adults with low ADHD symptoms increased their ability to monitor errors and showed a dominant role of the left hemisphere when extra effort allocation is needed to complete lexical decision performance. This finding is indirectly supported by meta-analyses of Metin et al. (2012) and Balogh and Czobor (2014), implying that error processing increases as a function of increased effort allocation. The finding is also consistent with the evidence, proposed by Hochman, Eviatar, Barnea, Zaaroor, and Zaidel (2011), showing that the left hemisphere is sub-serving error monitoring; however, the authors discussed a possibility that error processing is complex routine, which may involve several mechanisms, each controlled by a different hemisphere. All in all, results of study 4 emphasized the involvement of the left hemisphere functioning and state regulation in error monitoring deficit in adult who have more severe ADHD symptoms measured by a self-report questionnaire.

**Integrating the results and conclusion**

To what extent do lateral brain functions (left and right hemisphere-functioning) and interhemispheric interaction contribute to the severity of ADHD symptoms and related problems? Studies presented in the thesis are conducted to address this question. In the following paragraph, we compare results of the studies and characterize the impact of each.

Results from study 1 suggest that there is no contribution of interhemispheric interaction to the severity of ADHD symptoms. A weak relation with a small effect size ($R^2 = .10$) only appears after considering comorbid stress factor. Results from study 2 suggest that also the left and right hemisphere-functioning do not contribute to the severity of ADHD symptoms as far as ADHD index, inattention, hyperactivity and impulsivity measures are only of concern. This was statistically confirmed by negligible effect size of the relationship between severity of ADHD symptoms and laterality indices ($R^2 = .06$). So, the concept of brain laterality as such seems not to be related with self-reported ADHD symptoms. The picture becomes different when brain laterality is combined with state regulation. As shown in study 3, when effort allocation was manipulated the left hemisphere processing of words becomes compromised with a medium negative effect on the severity of ADHD symptoms ($\eta^2 = .13$). Evidence in favor of this suggestion comes from study 4, which showed problems to adjust responses
after errors, i.e., slowing down with more accurate responses, \( \eta^2 = .07 \) when combining effort allocation with ADHD symptoms. This was interpreted as a medium effect of the left hemisphere dysfunction. Please note. For interpreting the magnitude of effect sizes, we used the guidelines of Cohen (1988).

All in all, with a medium effect, the state regulation hypothesis in ADHD seems to be a more promising candidate to explain ADHD symptomatology compared to the laterality hypothesis. That is to say, the traditional indices of ADHD, namely, inattention, impulsivity and hyperactivity are dimensionally linked with poor task performance and abnormal laterality when effort allocation is needed. Therefore, the traditional indices could be seen as an epiphenomenon of the state regulation dysfunction.

Arrived at this point, several important questions emerging with respect to state regulation.

**Question 1. What is the contribution of the thesis to the model?**

To answer this question, the model is shortly explained first. For extensive reviews the reader is referred to van der Meere (2005) and Sergeant (2005). According to the state regulation model, originally developed by Sanders model (1983; 1998), the efficiency of information processing is based on three levels. Using a metaphor, the first level could be seen as the engine of cognition consisting out of a sequence of processing steps starting from stimulus input to giving a motor response: level 1. The engine needs fuel. Sanders formulated two fuel resources (arousal linked with input processes and activation linked with output processes) that are under command of the effort mechanism. The three energetic pools together form the so-called energetic mechanism: level 2. The third level is a management or evaluation mechanism associated with planning, self-monitoring, error-detection, and error-correction.

Armed with the Sanders model, previous research focused on clinical samples (children and adults) indicated that especially the activation/effort level is compromised in ADHD: subjects fail to compensate for their sub-optimal low activation state due to insufficient effort allocation (see reviews, see van der Meere, 2005; van der Meere, Börger, & Wiersema, 2010). The first contribution of the thesis to the compromised state regulation theory in ADHD is that the state regulation deficit is also found in a non-clinical sample with ADHD symptomatology (study 3 and study 4). The second contribution of the thesis is as follows. As discussed by van der Meere, Börger and Wiersema (2010) it remained unclear whether the state regulation deficit is located at the motor activation/effort level (level 2), or located at the management/evaluation level (level 3). The results of study 4 indicate that the deficit is located at the activation/effort level because the ability of error monitoring decreases only when subjects with ADHD symptomatology become under-activated. The conclusion of the thesis that ADHD symptomatology is more linked with compromised motor activation/effort is supported by an EEG evidence showing a decreased Contingent Negative Variation (CNV) amplitude in ADHD, reflecting motor readiness (Banaschewski et al., 2003; Mayer, Wyckoff, & Strehl, 2015; Valko et al., 2009; Van Leeuwen et al., 1998).

**Question 2. Does the state regulation model explain all of ADHD symptoms?** Again, as stated earlier, the state regulation indices associated with the ADHD symptoms. But, the issue has
been thoughtfully addressed by Johnson, Wiersema, and Kuntsi (2009). The authors consider the severity of ADHD symptoms to be dependent on energetic resources and task demands. Inattention symptoms may arise from boring and slow tasks, and the impulsive or hyperactive symptoms may result from a compensation mechanism to increase self-stimulation (see also Börger & van der Meere, 2000).

**Question 3. What is the relation between the state regulation model and the most popular models in ADHD?** The most popular model in the field is the response inhibition model (Barkley, 1997). Admittedly, many studies have shown that subjects with ADHD are poor response inhibitors. However, as reviewed by Willcutt et al., (2005) effect sizes are small and findings are not specific to ADHD. Moreover, the response inhibition hypothesis of Barkley is challenged because of the repeated finding showing that the quality of response inhibition in ADHD is dependent on the motor activation state (see for instance the meta-analysis of Metin et al., 2012).

Another model, delay aversion model (Sonuga-Barke, 2002), proposes that subjects with ADHD have greater sensitivity to delay compared to typical subjects. That is to say, ADHD subjects focus their attention on environmental elements that enable them to avoid their subjective experience of delay. For example, subjects with ADHD tend to choose smaller sooner reward over larger delayed reward. Symptoms of inattention and hyperactivity reflect an attempt to create stimulation in a way to alter their subjective experience of delay. With respect to the issue of how state regulation is related to delay aversion, it is important to remark that one of the core findings of the state regulation model, namely poor task performance during a slow event rate could be explained otherwise by the delay aversion theory. The delay aversion model predicts that the slower the stimulus presentation rate is, the more delay is experienced, and the greater tendency to shorten their waiting for the next stimulus by giving a late response. This, in turn, leads to a linear performance decline as a function of the length of the experienced delay (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010).

The discrepancy in interpretation between the state regulation and the delay aversion model resulted in a set of head to head studies between the two models. Some results were in favor of the delay aversion model, but far the majority of findings were in favor of the state regulation hypothesis (Buyck & Wiersema, 2014; Metin et al., 2013; Metin et al., 2015; Metin et al., 2016).

**Question 4. What are the weak points of the state regulation model?**

Recent reviews have formulated a few challenges with respect to the state regulation model (Johnson, Wiersema, & Kuntsi, 2009; Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010). One of the most important issues is to find evidence for a structural or physiological basis for activation and arousal concepts as used by Sanders (1998) and originally defined by Pribram and McGuinness in 1975. According to Tucker and Williamson (1984) the motor activation state involves the dopaminergic regulation, sub-served by the left hemisphere, which evokes a tonic level of brain activity to support motor readiness (required for executing actions) and internally-directed attention in vigilance. In contrast, the arousal state sub-served by the right hemisphere involves noradrenergic pathways, which mediates a phasic brain
response to perceptual input and externally-directed attention (i.e., perception of reward, novel and repetitive stimuli). Since then, the two states have been used to explain lateral asymmetries in attentional (first level), motivational (second level), and cognitive control (the third level) in psychopathology (see, Nigg, Hinshaw, & Huang-Pollock, 2006). However, research on distinct anatomical bases for arousal and activation states is still ongoing and no clear conclusion can be drawn (Barry et al., 2015; Damanpak, Mokhtari, & Mousavi, 2014). In fact, the lateralization of motor activation and arousal state has been questioned with the argument that each hemisphere mediates both energetic states (see, Tucker, 2011; Tucker, 2008). According to this recent view, it is not simply left-activation and right arousal, but also anterior and posterior systems are involved: the anterior cortical system facilitates the motor activation, while the posterior cortical system modulates arousal (see, Duff, 2014; Tucker, 2011).

The present studies of the thesis did not investigate the contribution of anterior and posterior cortical brain systems; hence, the contribution of these systems cannot be ruled out. Nevertheless, the outcome appears overall to be in favor of less efficient left-lateralized motor activation with increasing ADHD symptomatology. Having said that, it remains difficult to provide a definite answer to the question whether poor performance in ADHD is exclusively caused by the activation or arousal state at the moment. From this perspective, a recent study by Metin et al. (2016) is of importance. They showed that a deficiency in arousal regulation (by means of environmental stimulation, i.e., pink noise) may contribute to ADHD pathogenesis. Combining the Metin study (2016) and the results of our studies 3 and 4 it might be suggested that both impairments in arousal and activation regulation are involved in the ADHD psychopathology. All in all, experimental designs have so far been exclusively focused on either arousal or activation. The time is ripe to set up experimental designs tapping arousal and activation to explore the independent roles of the two energetic pools in ADHD symptomatology.

Another challenge is that the exact operational definition of effort is not clear. Notwithstanding the fact that research is devoted to this subject. For instance, recently, the effort concept as originally used by Sanders has been linked with lactate supply (see, Killeen, 2013; Killeen, Russell, &Sergeant, 2013). Another promising evolution of the model is the link between effort allocation and its counterforce the Default Mode Network (Metin et al., 2015). Time will tell to what extent the effort concept could be indexed by neural parameters.

The Sanders model has also been linked to the concepts of top-down and bottom-up information processes in ADHD. The first refers to higher-order cognitive operations needed to select, execute and maintain optimal response strategies and progress toward a goal. The second is considered to be state related (Krawczyk, 2002; for reviews, see Nigg & Barkley, 2014; Sergeant, Geurt, Huijbregts, Scheres, & Oosterlaan, 2003). According to Nigg (2009) and Martel, von Eye, and Nigg (2010) bottom-up processes reflect behaviors that do not demand conscious mental resources and are heavily influenced by immediate incentive or affective response. These processes might be influenced by the presence of stressors (e.g., reward versus punishment, stimulus presentation rate, and the presence versus absence of the experimenter).
There is evidence that ADHD is related to poor top-down processing (Dramsdahl, 2011; Friedman-Hill, Wagman, Gex, Leibenluft, & Ungerleider, 2010; Robert, Milich, & Barkley, 2015). Also, the outcome of the present thesis might support impaired top-down processing, because complex tasks require higher order control, and indeed we found a relationship between ADHD symptoms and cognitive performance during complex tasks (verbal tasks in study 3 and 4), but not during simple tasks (verbal tasks in study 1 and 2). However, the relationship was found only during the condition with a slow presentation rate underlining the bottom up factor. Future research is needed to pinpoint more precisely the interplay between bottom-up and top-down processes in ADHD.

**Methodological considerations**

It is well-recognized that the relationships between structural and functional measures of the human brain is largely unknown (Fears et al., 2015, Yang, Qiu, Wang, Liu, & Zuo, 2016). In ADHD research, many studies reported neuroanatomical alterations without having a direct link with the behavioral consequences. Thus, identifying brain–behavior associations are very welcome in our field. The thesis outcome confined itself to behavioral measures. It is obvious that future research on laterality and state regulation should incorporate behavioral, psychophysiological, and neuroimaging methodologies to extend our understanding of brain–behavior associations in ADHD (Anderson, Northam, Jacobs, & Mikiewicz, 2002; Semrud-Clikeman et al., 2000). However, using neuroimaging and physiological measures may influence real natural performance, eliciting questions about its ecological validity. Furthermore, practically speaking combining behavioral and neuroimaging methodology involves costly equipment and is more time consuming in terms of experimental preparation and testing participants.

Another methodological issue concerns the question what is a fast, medium and slow event rate? As has been discussed earlier (Kuntsi, Wood, van der Meere, & Asherson, 2009; Laurie-Rose, Bennett-Murphy, Curtindale, Granger, & Walker, 2005), this depends on factors such as age and type of task. In our study 3 and 4, no effect on task performance was found for the fast event rate. It can be argued that the fast event rate was not fast enough to induce over-activation in the students or that all students, including those with high degree of self-reported ADHD symptoms are easily able to decrease their motor activation to the optimal level required for efficient task performance. Consequently, studies using even faster event rates are needed to obtain a straightforward conclusion.

A final issue concerns the ecological validity of the medium effects of state regulation on reaction time performance. To address this issue correlations were calculated between the reaction time data and data obtained from ecological valid tests: 1) academic achievement (Grade Point Average; GPA scores), 2) functional impairments in major life domains of family, work, learning and school/college, life skills, self-concept, social functioning, and risk taking (scores on the Weiss Functional Impairment Rating Scale; NACE, 2014; Weiss, 2010), and 3) executive functions in daily life contexts (scores on the Executive Function Index Scale; Spinella, 2005). Results, not presented in the four studies, are summarized as follows:

The sample of study 3 showed a moderate correlation between executive functioning and the
left hemisphere processing of words at a slow stimulus presentation rate \((n = 77, r = .249, p = .029)\): subjects with more severe ADHD symptoms and decreased left hemisphere processing manifested decreased executive functioning in daily life contexts. The sample of study 4 showed a moderate correlation between functional impairments in daily life and post-error slowing for RVF stimuli presented at slower rate \((n = 56, r = -.272, p = .043)\): subjects with more severe ADHD symptoms and decreased post-error slowing demonstrate more daily life functional impairments. Correlation tests also showed significant relations between scores the ADHD index scale and both scores on the WFIRS \((n = 84, r = .71, p \leq .005)\) and scores on the EFI scales \((n = 84, r = .60, p \leq .005)\): higher ADHD scores were associated with more functional impairments and reduced executive functions in daily life context.

All in all, the moderate relations between experimental performance and self-reported daily life problems indicated that our laboratory outcome has ecological relevance.

**Limitations**

Studying university students has disadvantages and advantages at the same time. On one hand, adults with high levels of ADHD symptoms who attend college display higher ability levels and greater academic success and more sophisticated compensatory skills relative to the typical adult ADHD population (Chang, Davies, & Gavin, 2009). Put in other words, on the one hand our sample may represent a subgroup in the overall adult ADHD population, and consequently the outcome of studying such a sample may not be generalized. On the other hand, studying such a sample may be advantageous, because it reduces the inter-subject variability in many factors such as IQ and co-existing disorders such as conduct disorder. Thus, a purer impact of ADHD can be observed. However, college life is known to be stressful and students may experience mood disturbances (i.e., anxiety and depression) caused by a challenging academic environment. This may trigger ADHD symptoms in individuals who are vulnerable to develop certain mental disorders (Eberhart, Auerbach, Bigda, Peyton, & Abela, 2011; Ingram & Luxton, 2005).

In the present thesis, we studied right handers only. It is well-known that the pattern of lateralization is affected by handedness, for example non-right-handers tend to have less lateralized brain functions (Beaumont, 2008; Lust et al., 2011; Willems & Francks, 2014). In this way, limiting our data to right handers may help to minimize variation in laterality caused by handedness factor. However, Rodriguez et al. (2010) found that mixed-handedness was associated with greater severity of ADHD symptoms and greater likelihood of having language, scholastic, and mental health problems. This calls for future research to estimate the effect of handedness on the relationship between ADHD severity and lateral dysfunctions.

Samples of study 1 and study 2 include more females than males. In study 3 and 4, we controlled for gender factor. As mentioned earlier, meta-analytic reviews indicated that the prevalence rate of ADHD is higher in males than in females, and that there are gender differences in cognitive impairments (Gershon & Gershon, 2002; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009), and lateralized brain functions (Kret & De Gelder, 2012; Tomasi & Volkow, 2012; Herlitz & Lovén, 2013). The outcomes of study 1 and study 2 need a replication examining effects of gender in a sample with equal gender distribution. Nevertheless, the CAARS scores
are corrected for gender and the performance data showed no significant differences between males and females.