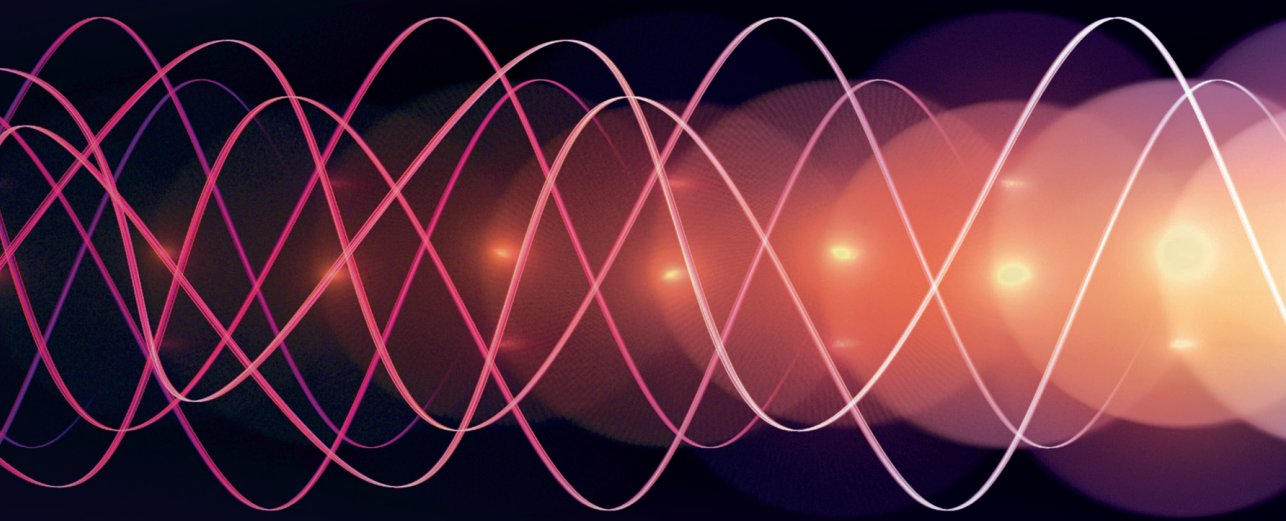
Disentangling Brain Networks in Adult ADHD: Studies with fMRI and TMS

Marc Schneider



Disentangling Brain Networks in Adult ADHD: Studies with fMRI and TMS

Het ontrafelen van neuronale netwerken bij volwassenen met ADHD:
Klinische onderzoeken met fMRI en TMS

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Für meine Familie

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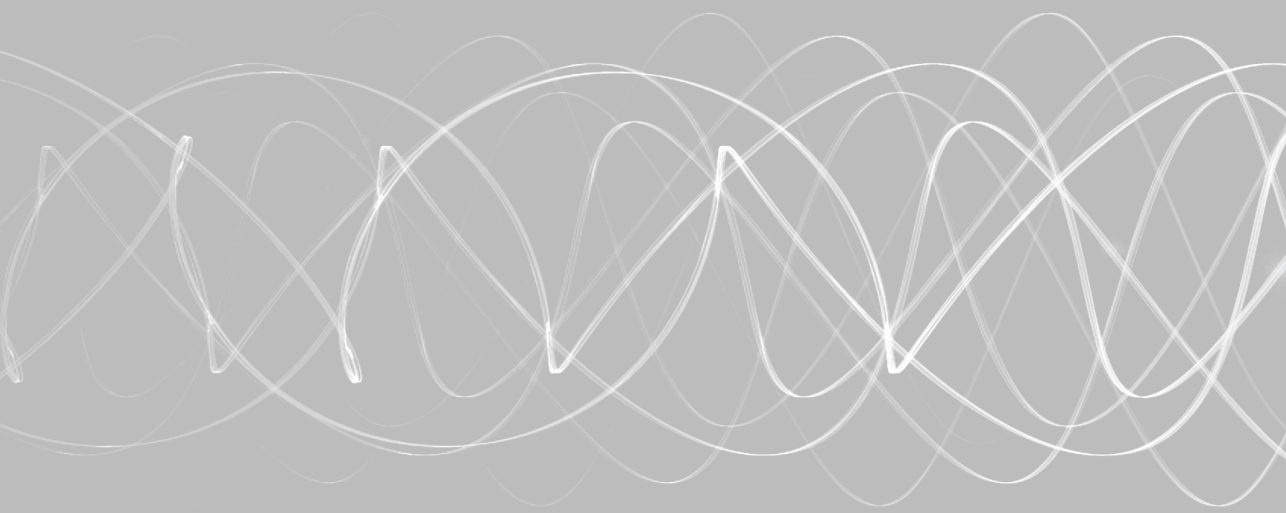
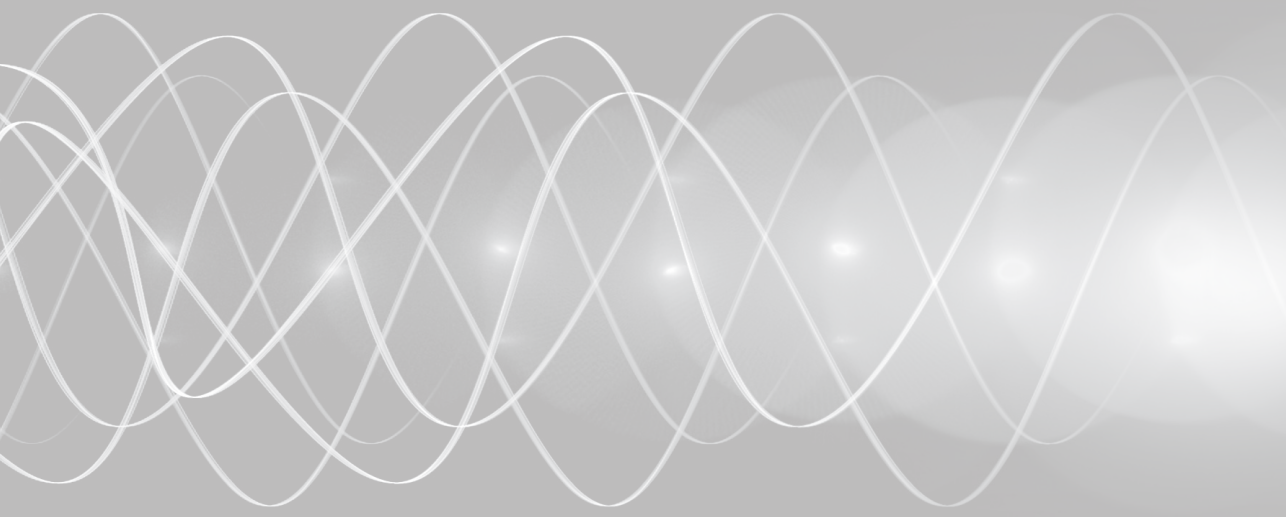


1 General Introduction



1. General Introduction

1.1 ADHD in adults

Attention Deficit/ Hyperactivity Disorder (ADHD) is not only limited to young patients. It is increasingly diagnosed in adults. Although the estimated prevalence in Europe ranges between 2 and 3% (48), the knowledge about adult ADHD pathophysiology and its neurobiological basis developed only in the past two decades, primarily stimulated by the rapid developments in modern genetic and imaging techniques. ADHD in adulthood leads to an array of major psychosocial problems such as social maladaptation, academic underachieving, antisocial and aggressive behaviour, relation problems, high risk sexual behaviour and car accidents (11,12;55;67;66). These factors in total lead to a negative impact on social and economic well-being of the individual.

As can be inferred from Table 1, the key problem in the diagnosis of ADHD in adulthood is that the clinical diagnostic items are still based on childhood criteria. This raises the question whether the diagnostic standards in adults are up to date.

In 1995, Paul Wender and coworkers from the University of Utah stressed that the symptoms in adult ADHD are not just extrapolations from those in childhood and adolescence. This UTAH workgroup developed criteria for adult characteristics that differ significantly from those in childhood (117). The authors pointed out that, apart from the common features such as impulsivity, motor hyperactivity and attention deficit symptoms, affective lability, hot temper/ explosive short-lived outbursts, emotional overreactivity, and disorganization/ inability to complete tasks, are key symptoms of the adult ADHD syndrome. Wender et al. brought these aspects together in a structured interview, the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS,117). The authorized German version is called the Wender Reimherr Interview (WRI,97).

Despite the methodical shortcomings, it was decided to apply the international diagnostic standards and, therefore, the adult ADHD patients participating in the studies of this thesis were recruited fulfilling the combined type DSM IV criteria The WRI was used in the clinical studies to provide additional clinical data of the patients.

ADHD phenotypes in adulthood show a varying psychopathological picture over time. During lifetime, the ADHD core features may change, because impulsivity and hyperactivity become less prominent over time than the attention deficit symptoms (15). Moreover, it has to be stressed that some patients diagnosed with ADHD in childhood don`t display the full clinical symptom scale in adulthood any more, leading to a so-called non-persistent or subclinical form of ADHD. Information about this phenotype is, however, very limited.

Table 1 Diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (DSM IV)

A. Either (1) or (2):

(1) **inattention**: six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
   (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
   (b) often has difficulty sustaining attention in tasks or play activities
   (c) often does not seem to listen when spoken to directly
   (d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
   (e) often has difficulty organizing tasks and activities
   (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
   (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
   (h) is often easily distracted by extraneous stimuli
   (i) is often forgetful in daily activities

(2) **hyperactivity-impulsivity**: six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

   Hyperactivity
   (a) often fidgets with hands or feet or squirms in seat
   (b) often leaves seat in classroom or in other situations in which remaining seated is expected
   (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
   (d) often has difficulty playing or engaging in leisure activities quietly
   (e) is often "on the go" or often acts as if "driven by a motor"
   (f) often talks excessively

   Impulsivity
   (g) often blurts out answers before questions have been completed
   (h) often has difficulty awaiting turn
   (i) often interrupts or intrudes on others (e.g., butts into conversations or games)

Table 1 Continued

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorders, or a Personality Disorder).

Code based on type:
314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months
314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months
314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months
Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.

Finally, with increasing age, adults with ADHD have a serious risk of developing various comorbid psychiatric disorders, in particular affective disorders and substance use disorders (119;60). Personality disorders often coincide with ADHD (69). This severely hampers an adequate description of the core ADHD phenotype or endophenotype in clinical research. It is, therefore, crucial in pathophysiological research to investigate ADHD patients without these kinds of comorbidities. The studies of this thesis aim to contribute to the clarification of the neurobiological basis of impaired attentional and executive networks, as well as of motor disturbances, in adult ADHD patients in whom further comorbidity and history of drug abuse are absent.

1.2 Syndromal views of ADHD in historical perspective

Since decades, ADHD is most frequently diagnosed in child and adolescence psychiatry. Therefore, the history of ADHD primarily means the history of ADHD in childhood. Although the discussion about the diversity of clinical concepts of ADHD is still going on, the historical perspective is important for a good understanding. The earliest mentioning of ADHD-like behaviour in adulthood may be deduced from the description

by Hippocrates more than 2500 years ago. In his "Aphorisms" (2), he depicted a patient who had a "quickened response to sensory experience, but also less tenaciousness because the soul moves on quickly to the next impression". His advice was to treat this "overbalance of fire over water" with changes in nutrition: "barley rather than wheat bread, fish rather than meat, drinking water rather than wine", and he suggested "many natural and diverse physical activities". Such a concept of an association between diet and behaviour was recently "rediscovered" by a Dutch/Belgian research group demonstrating the burden of food substances on the severity of ADHD symptoms in children (87).

In 1789, Sir Alexander Crichton described a "mental restlessness" in children which was associated with incapacity of attending (73). In his historical review, Eduard Seidler (99) described the development over time of the socio-medical interpretation of hyperkinetic behaviours in childhood. Such disinhibited motor signs were observed since the middle of the 19th century and interpreted as "naughtiness" (Hoffmann 1845), followed by "neurasthenia" (Beard 1869), "character weakness" (Strümpell 1890), "neuropathy" (Czerny 1908), "moral defect" (Still 1902), and in the 1950ies was labeled as "minimal brain damage" (see overview 73,99) in the context of ADHD-like clinical syndromatology of children who survived the Encephalitis lethargica and the influenca pandemy.

In 1845, the German general practitioner and later psychiatrist Heinrich Hoffmann described the famous "Zappelphillip" and "Hans Guck in die Luft", presenting the phenotypes of the combined hyperkinetic and the inattentive subtype of childhood ADHD, however, without interpreting those as disorders. He classified this child behaviour as naughtiness only (99). In the same year, Wilhelm Griesinger described children with a "nervous constitution", who "cannot be quiet for a moment … don´t have any attention" and, therefore, suffer from a "disturbed reaction function of the central organ to stimuli that work on it".

Still (105,106) was the first who systematically mentioned the hyperkinetic disorder in the Anglo-saxonian scientific literature. In his opinion, challenging behaviours in children originated from deficits in moral functioning.

The viewpoint that hyperkinetic disorders have to be seen as a syndromal entity started with Bradley in 1937 (18), who discovered that the stimulant drug Benzedrine ameliorated hyperactive behaviour in children and induced relaxation. Subsequently, methylphenidate was synthesized in the 1940ies for the treatment of the hyperkinetic syndrome as a form of "minimal brain damage syndrome". Although in the 1950ies the concept of early birth brain damage was no longer considered to be valid, in the sixties the concept of minimal brain dysfunction in terms of hyperkinetic reaction of childhood was introduced with the DSM II (1968) in order to relativize the hypothesis of brain damage (73).

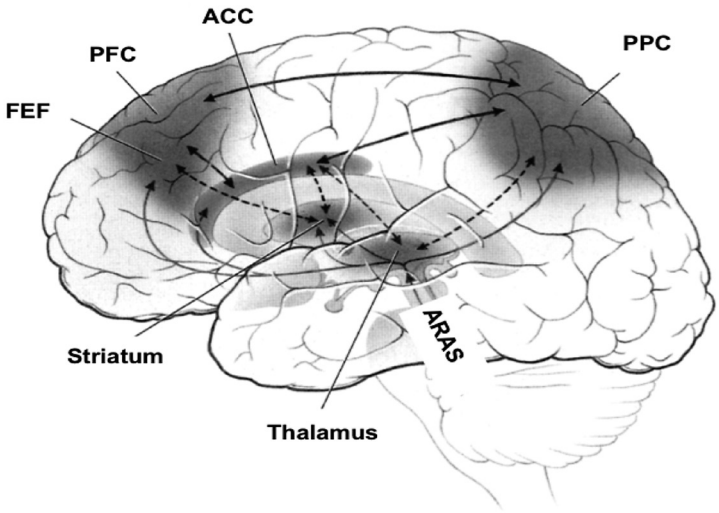
In the 1980 version of the DSM III, the attention deficit component of the hyperkinetic disorder was first introduced and modified during subsequent editions until the present. In the DSM-IIIR (1987), Attention Deficit Hyperactivity Disorder was differentiated from

Attention Deficit Disorder without hyperactivity and termed Undifferentiated Attention Deficit Disorder to accentuate a distinct concept of this entity. At present, hyperkinetic behaviours, attention deficits and their combination are classified apart from each other to underline possible different etiologies of a developmental disorder (DSM-IV-TR, 2000). Further nosological shifts are to be awaited in future classification systems, that may eventually include endophenotypes based on the executive functioning or on attention/motor phenomena in separate genetic subphenotypes.

1.3 Brain mechanisms in ADHD: Attention and executive functions

To understand the differential pathophysiological mechanisms that are implied in adult ADHD syndromatology, it should be emphasized that lack of attention and impulsivity are the most prominent phenotypical features of ADHD in adulthood (100), which points towards the significance of attention deficits and executive dysfunctioning. Symptoms of motor disinhibition from childhood on show a decrease over time or may become more internalized (16). In the studies of this thesis, the first point of interest is the attention deficit syndrome in relation to the brain networks that are involved (see Figure 1).

Figure 1 Different levels of brain attention networks (adapted from (35))



FEF: Frontal Eye Field; PFC: Prefrontal cortex; ACC: Anterior cingulated cortex; PPC: Posterior parietal cortex; ARAS: Ascending reticular activating system.

In the central nervous system, the attention networks comprise three major components (89;30;45). The first constitutes mainly subcortically located arousal and alerting neuronal circuits that comprise the ascending reticular activating system, which projects to brainstem and thalamus and, via the striatum, towards the limbic system with ultimately cortical projections. The main function of this subcortical neuronal network is the activation and synchronization of the cerebral cortex (Behavioural Activating System – BAS) (see for review:35) and is especially active with salient stimuli from external and internal environments.
The second, so-called mixed cortical-subcortical circuits, detect novel stimuli (superior colliculi), filter irrelevant stimuli (pulvinar), or disengage attention focus (posterior parietal cortex).
The third component comprises the selective or directed/cortical attentional network that is of special significance for the pathophysiology of ADHD. This neuronal system is responsible for the generation of volitional saccades (frontal eye fields), inducing motor intention (premotor cortex), is linked to the working memory (dorsolateral prefrontal cortex) and is modulated by the anterior cingulate cortex (ACC; target detection, response selection and inhibition, conflict monitoring, motivation) (23).

This circuit is also named the executive (conflict) system and has been shown to have a strong heritability component (46). Within this network, the dorsal part of ACC (dACC) is strongly connected with serotonergic and dopaminergic neuronal systems.
Regions of the parietal cortex (tertiary visual brain regions) also play an important role in mediating sensory functions. The posterior parietal cortex disengages the attentional focus to a target (91) and the superior parietal lobule has the function of voluntary shifts of attention (29). Dominance of the right hemisphere is considered to be important for orienting as well as for selective attention (84;89).
Executive functions include the targeted control of complex behaviours, where divergent cognitive aspects are coordinated. They converge in a wide spectrum of mental processes that lead to fluent processing of information and coordination of execution via central nervous system processes. The underlying mechanisms of executive functioning include problem solution, planning, action control, and control of motivation and emotions (102,86). Motivation and delay aversion play an intriguing role in executive functioning in ADHD (28,82).
Barkley (1997) postulated a concept of executive control for internally represented information in ADHD via four executive instances: working memory, self regulation of affect/motivation/arousal, internalization of speech, and reconstitution. Motor control is finally modulated via inhibiting task-irrelevant responses, executing goal-directed responses, execution of complex motor sequences associated with goal-directed persistence. This makes a sensitivity to response feedback necessary to control behaviour by internally represented information. Barkley (13) suggested the involvement of several mechanisms

in the behaviour inhibition in ADHD: inhibition of prepotent responses, stopping of ongoing responses, giving feedback on errors, and interference control.
Motor coordination problems are key features of ADHD with an estimated prevalence of about 50 percent (90). Motor difficulties range from sensory-motor dys-coordination to a delay of motor milestones development. Dopaminergic and noradrenergic neuronal structures in fronto-subcortical systems play a crucial role in the pathophysiology of disturbed motor functioning in ADHD (47;88).
Functional imaging techniques can disentangle how brain networks adapt to internal and external influencing factors in adult ADHD. As compared to radionuclid imaging techniques (Positron Emission Tomography (PET) and Single Photon Emission Computer Tomography (SPECT)), the functional Magnetic Resonance Technique (fMRI) is non-invasive and allows registration of attention and executive brain activity with a high spatial resolution. Since its time resolution is relatively low, research on the motor system of adult ADHD patients with its fast dynamic components can be investigated only difficultly by the fMRI technique. To analyze motor functions, the transcranial magnetic stimulation technique (TMS) was therefore chosen because of several advantages. This technique is also non-invasive, usually well tolerated and provides insights into the transmission processes involved in the motor system. Furthermore, specific pulse protocols of TMS can help to visualize pharmacological effects on the human motor system. In the following chapters the used neurophysiological techniques will be delineated in more detail.

1.4 Research techniques

1.4.1 Functional Magnetic Resonance Imaging (fMRI)

The magnetic resonance imaging (MRI) technique was first used in 1977 to visualize human tissues (32). The basic principle of MRI is the changing of the spin of protons which are present in all tissues (see for review:56). In principle, the spin aligns parallels with an extern magnetic field comparable to the way a compass needle is directed by the earth's magnetic field, but it may be also antiparallel to it. A high frequency electro-magnetic coil within the scanner gives impulses with the resonance frequency of a tissue (Larmor frequency) to reach a synchronized spin deviation. This deviation takes place in a gyroscopic movement of the spin axis (precession) and gives a characteristic signal depending on the magnetic field strength and environment of the atomic nuclei, e.g. brain tissue. The time for the spins to reach the original alignment to the magnetic field or transversal to it, is called relaxation time, T_1 and T_2, respectively. Regional differences in susceptibility for magnetization within a tissue lead to imaging contrasts and variations in signal phases, the so-called gradient echo sequences that are depicted by T_2* relaxation. The use of coils that can generate linear changes of magnetic fields for very short moments, and the complex registration of the local frequency changes due to this, forms the basis for functional magnetic resonance imaging (fMRI).

The cerebral perfusion of neuronal or metabolic active brain structures increases much higher than its consumption of oxygen. The paramagnetic desoxygenated hemoglobin has a low signal, whereas the diamagnetic oxyhemoglobine in metabolic active brain regions results in a contrasting strong signal. This blood oxygenation level dependent (BOLD) contrast or the effects from the magnetic characteristics of desoxygenated and oxygenated hemoglobine, are the basic signal principles for fMRI. This non-invasive technique enables to perform repeated measurements of local brain activity. The Echo-Planar-Imaging (EPI) technique generates within a very short time (100ms) a two dimensional picture of brain slices. This is done by means of switching very fast between frequency gradients and different brain slices. As a consequence a whole brain activation picture within a short time frame can be achieved. The fMRI design of this thesis followed an event-related paradigm. This indicates that each event of interest was summarized and averaged in contrast to the block design which measures the same events repeatedly. The event related study design gives better contrasts of salient stimuli, here the NoGo events.

1.4.2 fMRI and ADHD

A large number of neuroimaging studies is available of which the results support the neurobiological basis of ADHD from childhood to adolescence. Imaging data about adult ADHD are still sparse. Chapter 2 reviews the neurobiological aspects of ADHD in adulthood and the different attention networks that are involved in arousal, orienting and sustained focusing on external targets are discussed.

However, only limited information is available about the underlying pathophysiological mechanisms. From imaging studies using stimulants, it has become obvious that dopaminergic dysbalances in forebrain and basal ganglia are involved in attention deficit and hyperactivity/impulsivity symptoms. Ventral and dorsolateral prefrontal cortex, anterior cingulate, insula, amygdala, hippocampus, and ventral striatum are suggested to be involved in ADHD pathology in children and adolescents (44;42,41;96; 70;25;98). Only a few studies are available about the pathophysiology of ADHD in adulthood and its correlation with the clinical phenotype. By means of PET, Volkow et al (111,112) demonstrated depressed dopaminergic activity in caudate and limbic brain regions in adult ADHD patients. The improvement of dopaminergic dysfunctions by application of methylphenidate appeared to be associated with the normalization of the clinical phenotype.

In children with ADHD, Konrad et al. (71) used event related fMRI to investigate brain activations in the neuronal networks involved in attention processes in particular. In contrast to controls, the activation of the attentional networks followed a deviant pattern, in that there was less right-sided activation in the anterior cingulated gyrus during alerting, more fronto-striatal-insular activation during reorienting, and less fron-to-striatal activation for executive control. The BOLD signals appeared to be dysregulated

in the putamen during reorienting and executive control, suggesting altered brain activation strategies in ADHD.
In medication naïve children and adolescents with ADHD, it was demonstrated that functional abnormalities are task-specific and encompass not only fronto-striatal but also parietal and temporal cortices (103). In drug naïve adult patients with ADHD, it appeared that abnormal brain functioning was not limited to complex executive functions, because abnormal processing of numeric stimuli was noticed during both simple and complex cognitive tasks. The data from fMRI measurements during complex tasks performed by the patients showed greater activation of left hemispheric linguistic processing areas and failed to activate the bilateral parietal regions important for complex executive processes (57). There is still a need to understand how the clinical phenotype of adult ADHD correlates with the deviant brain activation patterns and which factors are involved in it. This is the central question of the study in chapter 3, which deals with drug naive adult ADHD patients without axis I comorbidity. In addition, the level of attention networks (ascending reticular activation system/ARAS vs. subcortical vs. cortical – arousal vs. orienting vs. top down system) which are impaired in ADHD, was the focus of interest in this study with adult patients with ADHD. Since patients with subclinical ADHD can also be diagnosed, the question was also whether in these patients pathophysiological parallels may be found or that their compensatory network activations can be differentiated, both qualitatively and quantitatively, from those displaying the full phenotype.

1.4.3 Paired pulse Transcranial magnetic stimulation (ppTMS)

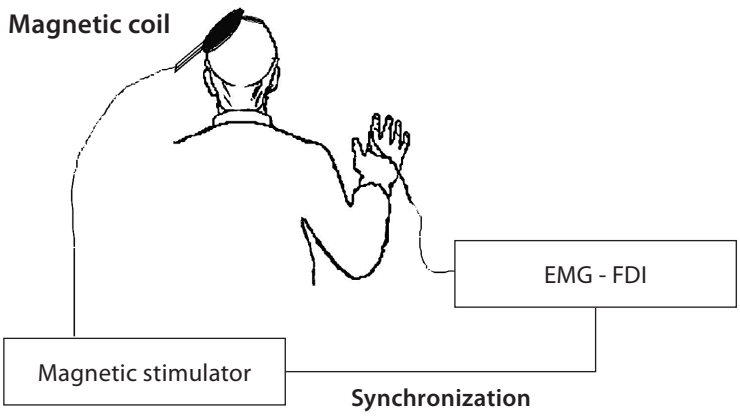
The transcranial magnetic stimulation technique has been shown to be useful for studying the complex central neuronal systems that are implicated in motor brain networks (123,72,85). Barker and colleagues were the first to use transcranial magnetic stimulation (TMS) techniques in men in 1985 (10). In contrast to the transcranial electric stimulation of the human cortex, the magnetic stimulation is non-invasive and painless. A further advantage of TMS is that the magnetic impulses penetrate skin, skull and brain tissues without Ohmic resistance or relevant energy loss. TMS results in an indirect transsynaptic activation of, in general, tangentially oriented interneurons, in contrast to the direct electrical stimulation of pyramid cell axons or the Ranvier nodes (92).
A magnetic stimulator consists of two main components, the generator which is a large capacitor and the coil with a certain inductance and resistance that transfers the energy to the tissue. The capacitor is charged to about 2 kV and, after discharge, a strong biphasic peak current of 5-8 kA is generated for 300 µsec. The current pulse induces a magnetic field which again results in an electric field perpendicular to it. Typically, the figure of eight coil used in these experiments generates a maximum magnetic field strength of about 2,5 Tesla. The use of a figure of eight coils has, as compared to with the standard round coils, the advantage of generating very focused electric fields

perpendicular to the coil currents. The strength of the magnetic field declines with the inverse third power of the distance (43) and, consequently, the electric field intrudes the brain to about 2 cm. When the magnetically induced current sufficiently flows parallel to the brain surface, depolarization of neuronal membranes occurs, and hence an action potential is generated. Interneuronal structures that are oriented horizontally to the surface of the brain (34) are activated.

TMS is thought to activate predominantly the pyramidal cells transsynaptically through excitatory interneuronal elements (3;34;36;81). Thus, cortical and some subcortical white matter brain structures can easily be stimulated with this technique.

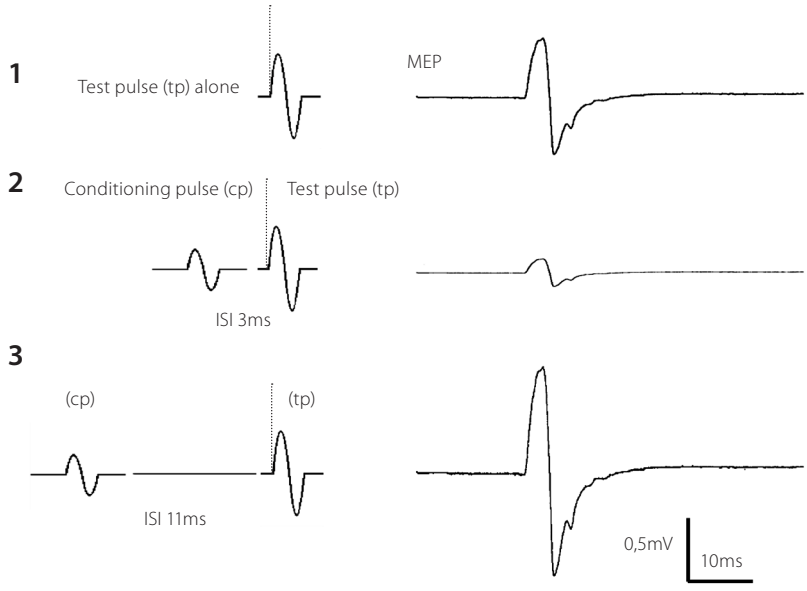
As first step, the resting motor threshold (RMT) and the active motor threshold (AMT) have to be defined via electrodes placed on the target muscle (in our studies: the first dorsal interosseus [FDI] muscle). RMT and AMT are supposed to be markers of membrane stability of cortical neurons (123). In our studies, RMT and AMT were determined according to the protocol of Kujirai et al. (72). Briefly, RMT was the minimal stimulus intensity that was required to produce motor potentials of more than 50 μV peak to peak amplitude in 50% of the test pulses. AMT was determined in analogy to RMT, while the subject tonically distended a dynamometer with the FDI at 10–20% of the maximum power.

Figure 2 TMS setup with magnetic coil in a typical position at the primary motor cortex and EMG recording of the first dorsal interosseal muscle (FDI); adapted from (74)



While the magnetic coil is at the same place, the paired pulse TMS (ppTMS) technique induces two magnetic pulses: a conditioning pulse which is subthreshold in relation to the RMT and a test pulse which is suprathreshold in relation to the RMT. This technique was introduced by Kujirai et al. (1993) and enables to investigate primarily intracortical excitability (85). Between the subthreshold conditioning pulse (CP) and the suprathreshold test pulse (TP) there is a variable interstimulus interval (ISI) which modulates the magnetically evoked potential (MEP) amplitude of the target muscle. Inhibition is a cortical phenomenon which is considered to reflect the inhibitory activity of interneurons or connections between cortical output cells (115). Facilitation occurs at the level of the corticospinal neurons and upstream (123,125). ISI, and CP and TP amplitudes determine the brain circuits that are involved in the generation of the magnetically evoked motor potential (MEP). At an ISI of 1-5 msec, short intracortical motor inhibition (SICI) can be investigated, whereas at an ISI of 5-20 msec intracortical motor facilitation (ICF) can be studied.

Figure 3 A typical set of MEPs elicited by the ppTMS technique. **1**: MEP with a suprathreshold test pulse alone. **2**: a paired pulse stimulus with a subthreshold conditioning pulse and a suprathreshold test pulse. The short interstimulus interval (ISI) leads to a amplitude reduction of the originally MEP elicited by the test pulse alone: short intracortical inhibition (SICI). **3**: with a longer ISI the MEP size gets higher than with the test pulse alone. This leads to intracortical facilitation (ICF).



The cortical excitability as reflected by SICI and ICF is supposed to be modulated through complex neuronal transsynaptic systems (mainly GABA, dopamine, glutamate, serotonine). Several drugs influence the ppTMS motor inhibition as well as the facilitation (121). Dopaminergic and noradrenergic agonists have been shown to increase SICI, while dopamine antagonists have an inverse effect (121). The degree of SICI is also assumed to be increased by GABAergic action via cortical GABAergic interneurons, while ICF is decreased (65;118;122,74). Pharmacologic interactions with SICI and ICF may also vary dependently from e.g. health state, as it is known that paroxetine enhances ICF in healthy probands, but decreases ICF in schizophrenic patients (50). On the other hand, serotonine reuptake inhibitors can have opposite effects on SICI, dependent on the 5-HT transporter phenotype (40). In patients with Parkinson's disease, it has been shown that dopamine deficiency is associated with reduced SICI (95;124). In addition, a shortening of silent period and reduction in SICI was observed in patients with Tourette disorder as compared to healthy controls. Cortical excitability was found to be asymmetric in treatment-refractory major depressive disorder compared to healthy controls (75). With the ppTMS technique, these investigators found that the left primary motor cortex showed significantly higher intracortical inhibition and facilitation whereas there was no significant hemispherical asymmetry in healthy controls.
Thus, both the endophenotype of an individual and the clinical diagnosis influence the response of SICI and ICF to pharmacological agents.

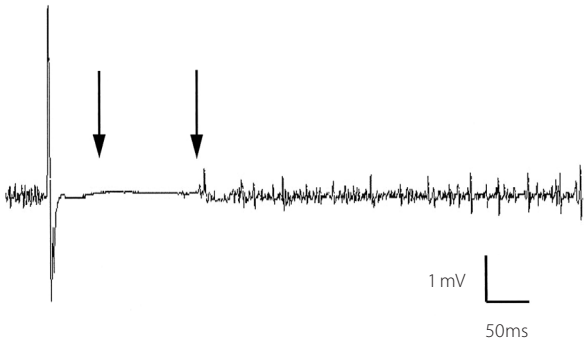
1.4.4 Principles of the Cortical Silent Period (CSP)

The TMS impulse at the motor cortex during maintained voluntary muscle contraction results in the so-called cortical silent period (CSP), which reflects multifactor inhibitory mechanisms (ref). Dependent upon the strength of the TMS impulse, the ongoing electromyographic activity is discontinued for a moment of several milliseconds. The CSP is defined by the time of salience until reappearance of the ongoing electromyographic activity. Although the neuronal mechanisms underlying the CSP are not fully understood as yet, GABAergic neurotransmission has been suggested to be involved (77). Lesion studies have led to the hypothesis that the CSP is generated in the primary motor cortex (114). Finally, it was shown that CSP and SICI have an inverse relationship and that SICI is suppressed while ICF is facilitated during CSP. The CSP can be considered as a measure of motor cortex excitability via influences from basal ganglia, ventrolateral thalamus and inhibitory interneurons (1)

1.4.5 ppTMS and ADHD

The ppTMS technique has been shown to provide a reliable test-retest stability of SICI and ICF in adults (93,74). Compared to the data from children with ADHD (78,79,19,20,21), the number of studies with ppTMS in adult patients is rather limited (61,62,94) and their results are equivocal.

Figure 4 A typical recording of electrical myographic activity during ongoing muscle contraction and after a suprathreshold magnetic test pulse. Note that after an initial magnetically evoked muscle potential the ongoing electromyographic activity shows a silent phase (csp) until the baseline EMG activity reappears. Adapted from (1)



Both reduced and enhanced as well as not significantly changed SICI amplitudes have been reported dependent on the use of psychostimulant agents in adult ADHD (51,52,62,68). A further methodical issue has to be considered in the studies that investigate SICI and ICF as well as the effects of Methylphenidate (Mph) in adults with Tourette disorder with comorbid ADHD symptomatology (51,52). This underlines the need to perform studies with ADHD patients without axis I comorbid disorder, when the primary target is to elucidate the neurobiological mechanisms underlying ADHD symptomatology. It has to be underlined that the interpretation of the effect of Mph on neurotransmitter functionality is complicated since the compound affects not only dopaminergic and noradrenergic transmission, but also a variety of other neurotransmission systems related to serotonine and muscarinic acetylcholine transmission systems (113,76).

Conflicting results about the ppTMS effect of Mph on SICI and ICF can partly be explained by the limited number of studies that use TMS techniques in adult ADHD with Tourette syndrome as comorbid disorder (51,52). Moreover, pharmacokinetic and pharmacodynamic variations in the Mph preparations may be implicated (125,51,64). As presented in chapter 4, a study of this thesis comprising a group of appropriately diagnosed drug naive adult ADHD patients of both sexes without any comorbid axis I disorder and a sex and age matched group of healthy controls. This investigation also included the analysis of potential hemispherical effects on cortical motor excitability

and the correlation of the neurophysiological parameters with the clinical ADHD phenotype. In the long acting Methylphenidate (LA-Mph) study with ppTMS, the main focus of interest is the investigation of the impact of the chronically applied stimulant drug methylphenidate on motor overexcitability in adult ADHD and its correlation with the objective clinical phenotype.

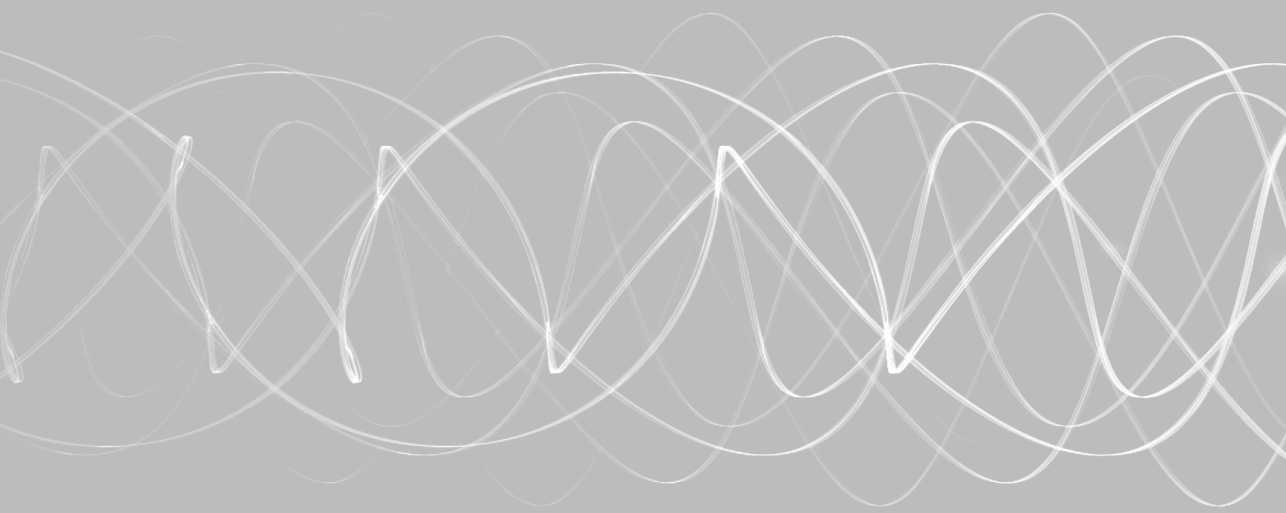
2. Aims of this study

Since little is known about the general pathophysiological mechanisms underlying the phenotypical presentation of ADHD in adults, the aim of this thesis is to elucidate impairments in brain networks involved in attention processing and executive functioning by means of functional imaging techniques. Secondly, motor system functionality in adult ADHD is studied using ppTMS, a non-invasive technique that is considered to be the most appropriate for depicting the intracortical excitability and its modulation by compounds such as LA-Mph. As the psychopathology of ADHD is supposed to originate from a dysequilibrium of dopaminergic transmission, it is of special interest to investigate psychiatric symptoms which are assumed to be related to dopaminergic dysfunctionality, e.g. attention deficits, executive dysfunctioning and psychomotor disturbances. The results from the studies that include patients with (first episode) schizophrenia, may provide a better understanding of the specific psychopathology of adult ADHD. More specifically, the aims of these studies were

1. To analyse central nervous systems involved in attention and execution by means of functional magnetic resonance imaging, following a continuous performance test paradigm (Go/NoGo), in order to identify correlations between dysfunctions in these networks and the adult ADHD symptom profile.
2. To study cortical motor inhibition and facilitation with the paired pulse transcranial magnetic stimulation (ppTMS) technique in order to delineate relationships between overexcitability of the motor cortex and phenotypical presentation of adult ADHD.
3. To explore the effects of LA-Mph on cortical overexcitability in adults with ADHD by means of ppTMS.
4. To investigate the excitability of the motor neuronal system with ppTMS in another psychiatric disorder which is associated with dopamine driven cognitive and executive functioning deficits and disturbances of motor excitability, namely first-episode schizophrenia, and to compare the motor cortex excitability with ADHD patients in order to delineate putative overlapping pathophysiological mechanisms.

3. Outline of the thesis

Chapter 2 provides an overview of imaging data in adult ADHD.
Chapter 3 deals with a controlled fMRI study focused on attention networks and executive functions in adults with ADHD.
Chapter 4 comprises a study with ppTMS in which this technique was used to investigate motor cortex excitability and executive functioning in adults with ADHD. In addition, the ppTMS parameters that reflect motor disinhibition were correlated with the symptom profile of adult patients with ADHD.
Chapter 5 constitutes a clinical study in which the ppTMS technique is used to correlate motor overexcitability with the symptom profile of adult ADHD patients before and during treatment with LA-Mph.
Chapter 6 describes a ppTMS study on abnormalities in motoneural systems of adult patients with first-episode schizophrenia and chapter 7 describes a study with adult patients with ADHD or first episode schizophrenia, diseases that are both supposed to have a dopaminergic brain transmission dysbalance. The motor excitability networks and hemispheric balance is evaluated in both patient categories.
Chapter 8 concerns a general review of the fMRI and ppTMS data obtained from the above listed studies, and discusses the clinical relevance of the findings as well as the limitations and strengths of the subsequent clinical investigations. Some outlines for future investigations and the conclusions are also presented.



2 Brain imaging in adult Attention deficit hyperactivity disorder (ADHD)

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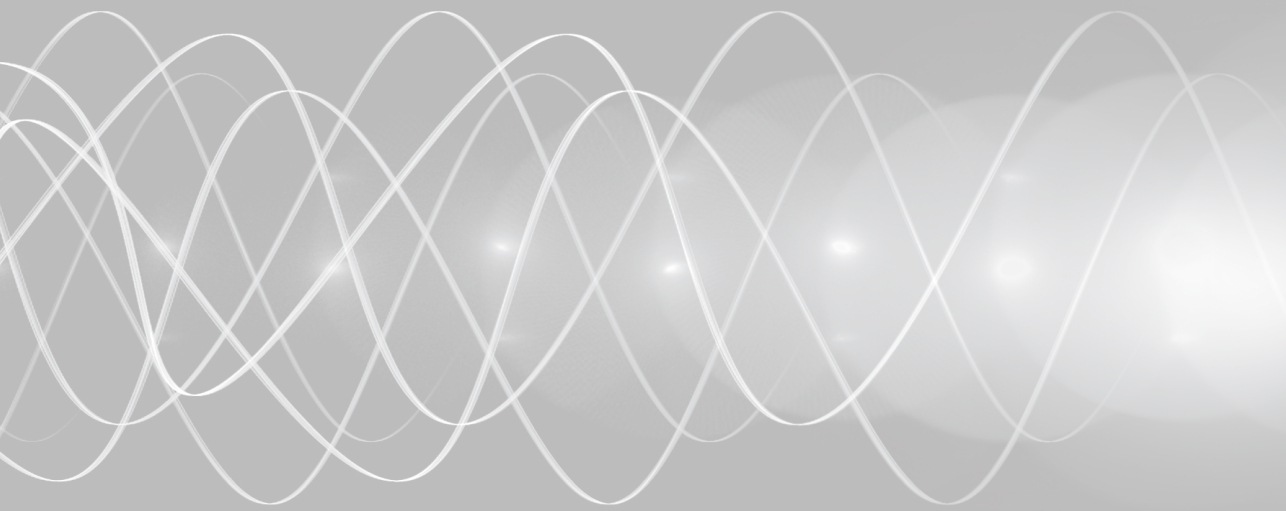

Abstract

This review provides an overview about recent findings in attention-deficit hyperactivity disorder (ADHD) brain imaging. ADHD is understood as a developmental disorder and several studies have addressed brain development in children and adolescents. The hallmarks of impairment of cerebral processing in ADHD are executive dysfunctions (motor execution, inhibitory control, working memory), as well as deficient attention processing. In adulthood, imaging studies have revealed disturbances in the prefrontal cortex, and anterior cingulated cortex (dACC) which are involved in the regulation of selective attention, executive control and decision-making. Dysfunction of basal ganglia is also a consistent finding in ADHD from childhood to adulthood. These findings suggest a persistent dysregulation of frontostriatal circuitries. The cerebellum, and its role in affect and cognition, is also persistently implicated in the pathology of ADHD. The cerebello-(thalamo-)striato-cortical network includes different attention networks and executive control instances. It appears from brain-imaging data in adults that the pathophysiological principles of ADHD do not profoundly change from childhood and adolescence to adulthood, regardless of some changes in psychopathology. The hypothesis of a neurodevelopmental disorder seems to be reinforced on the basis of imaging data of the adults.

Introduction

Attention-deficit hyperactivity disorder (ADHD) affects adults with a prevalence of about 3–4% [1]. Whereas key symptoms of the psychopathological core symptoms in childhood are inattention, hyperactivity and impulsivity, adults with ADHD tend to be predominantly impaired by attention deficits and disorganization, whereas hyperactivity and impulsivity tend to ameliorate [2, 3]. Emotional dysregulation, mood and anxiety disorders as well as substance abuse are commonly described features and comorbidities in adult patients [4]. As clinical patterns differ between ADHD children and adults, and given that more than half of the children with ADHD do not continue being clinically affected in adulthood, one could hypothesize that adult patients with ADHD represent a distinct subpopulation with distinct neurobiological or environmental background. Therefore, there is a substantial need for neuroanatomical and functional neuroimaging investigations in adults suffering from ADHD. Indeed, like in many areas in neuropsychiatry, neuroimaging techniques have been intensively used also in ADHD research in the past few years.

It is a principle question whether impairment of brain networks compares to those that have been extensively described in ADHD children. Thus, a key question in adult ADHD research is whether there is also impairment of frontostriatal/frontosubcortical networks. These pathways are involved in executive and motor control, as well as in inhibition of behavior and voluntary decision-making. Frontosubcortical networks contain a large amount of noradrenergic, dopaminergic as well as serotonergic projections. Striatal structures, such as putamen, globus pallidum and caudate nucleus, form a frontostriatal network and are typically impaired in ADHD [5]. Areas of particular interest are also the prefrontal and dorsolateral prefrontal cortex (PFC). The anterior cingulated cortex (ACC) seems to play a pivotal role in ADHD psychopathology. This region has widespread connections to forebrain and limbic structures. Besides its function as a conflict monitoring center, the ACC has the role of integrating polymodal inputs from different brain regions in the control of executive and inhibitory functions [6]. Finally, increasing attention is being paid to the cerebellum, which exerts strong influences on affective and cognitive function via thalamic connections [7, 8].

Brain Structure in ADHD

Global Neuroanatomical Findings

Total cerebral volume reduction is well described in children and adolescents with ADHD [9–16], which is most prominent in the right hemisphere. The right hemisphere is hypothesized to play a dominate role in decision-making, inhibitory control and selective attention [17, 18]. It has been shown that damage of the right hemisphere can

lead to desynchronization of brain activity and neglect of sensory stimuli [19, 20]. Sowell et al. [21] showed that brain alterations in children with ADHD are focused on those brain regions which are relevance for attention, executive control and linguistic performance. More specifically, they could demonstrate that cortical abnormalities are mainly localized in inferior portions of dorsal PFC and bilateral anterior temporal cortex. Increased gray matter was seen in large portions of the posterior temporal and inferior parietal cortex bilaterally.

Recently, Seidman et al. [22] investigated 24 adults with DSM-IV ADHD and 18 healthy controls comparable on age, socioeconomic status, sex, handedness, education, IQ, and achievement test performance. Compared to controls, adults with ADHD had significantly diminished overall cortical gray matter, and smaller prefrontal and ACC volumes in particular. The authors concluded that adults with ADHD have volume differences in brain regions associated with attention and executive control. These data are largely consistent with studies of children with ADHD, supporting the hypothesis that ADHD is a valid disorder with persistent biological features through all stages of life.

Region-Specific Neuroanatomical Findings

Frontal Lobe

Several studies have confirmed volume reductions of PFC in ADHD children, namely of the dorsolateral part (DLPFC) [9, 10, 13–16, 23]. The DLPFC plays an important role in attention, working memory, planning and organization of a task [18], whereas the ventrolateral prefrontal cortex (VLPFC) is involved in the regulation inhibitory control [24, 25]. The orbitofrontal cortex regulates social behavior and balance of inhibition and desinhibition as well as emotional attribution to decisions.

Hesslinger et al. [26] found diminished left orbitofrontal brain volumes in adult ADHD patients. These regions are associated with social behavior and impulse control. Also in adults with ADHD, selective thinning of cerebral cortex in the networks that subserve attention and executive function was found by Makris et al. [27]. Significant cortical thinning in ADHD was seen especially in the right hemisphere involving the inferior parietal lobule, the dorsolateral prefrontal, and the anterior cingulated cortices. These neuroanatomical data give evidence to the frontal brain abnormalities also in ADHD adults, but the findings need further replication.

Anterior Cingulated Cortex

The dorsal part of the anterior cingulated cortex (dACC) is crucial for executive functioning, inhibitory control monitoring, target detection, error processing as well as reward-based learning. Volume reductions in the right posterior cingulated gyrus in ADHD children have been reported [28]. In adults, lower volumes of the ACC could be shown by in the anatomical study of Makris et al. [27].

Temporal Lobe

Temporal lobes have polymodal sensory integration functions in language comprehension as well as object identification ('what system'), emotional regulation and memory function. The right temporal convexity plays an important role for visuospatial functions, whereas the left temporal convexity contains a large auditory association area which contributes to language comprehension [29]. Sowell et al. [21] demonstrated by anatomical brain surface analysis that children with ADHD had reduced anterior temporal lobe volumes bilaterally. Temporal lobe volume reduction as part of a general brain volume reduction in children and adolescents with ADHD was described by Castellanos et al. [12]. However, there is no substantial information about the interplay between cognition and affect in sensory processing, and its modulation by temporal lobes in ADHD.

Basal Ganglia

The basal ganglia comprise of five nuclei: the caudate nucleus ('cognitive associative' striatum), putamen (sensorimotor striatum), nucleus accumbens (limbic striatum), globus pallidus and subthalamic nucleus. They are closely related to brainstem structures such as substantia nigra and the pedunculopontine nucleus. The striatum comprises the putamen and the pallidum, and displays a high density of dopaminergic neurons. Its main function is procedural learning and automatization of motor programs and behaviors and it serves to assemble complex response habits to strategically adapted environmental needs [30, 31]. ADHD-associated symptoms are associated with striatal damage [32].

Basal ganglia volume reductions have been shown in several studies with ADHD children and adolescents. In most of them uni- or bilateral reduction of caudate volumes were found [9–12, 29, 33–36]. Schrimsher et al. [37] could predict the cumulative severity ratings of inattentive behaviors by measuring caudate volume asymmetry from serial sagittal magnetic resonance images from childhood to adolescence. Also unilateral volume reduction of the pallidum has been shown in several studies in children with ADHD [10–12, 28, 38].

Until now, no evidence for basal ganglia volume reduction in adult ADHD has been reported. A possible explanation is that differences between controls and ADHD almost disappear with increasing age before adulthood [12].

Corpus Callosum

The corpus callosum connects homonymous regions of the cerebral hemispheres. Injury of callosal structures can lead to problems in holding sustained attention [39], with associated deficits in learning and memory [40]. The neuropsychological deficits after injury of corpus callosum are often subtle or lacking.

Volume reduction of the corpus callosum is a common finding in studies with ADHD children and adolescents. Posterior regions of the corpus callosum are mostly affected [15, 41–45]. Data from adult ADHD are lacking so far.

Parietal Lobe

Posner and Petersen [18] have described a posterior attention system located in the parietal lobe, which seems to be mainly modulated by noradrenergic transmission in contrast to the predominantly dopaminergic modulation of the frontal attention system. The posterior part of the parietal cortex is involved in orienting and selective attention networks [46]. It disengages the attentional focus from the contralateral target [47], and lesions of this region can lead to impaired attention [48, 49].

Only few studies have addressed to parietal lobe structure and function in ADHD. Castellanos et al. [12] have shown that posterior parietal volume is reduced, whereas conversely Sowell et al. [21] have demonstrated an increase in cortical volume in children with ADHD. Given its importance in visuospatial orienting and as a region for polymodal sensory integration, it was Makris et al. [27] who pointed out volume reductions in the right inferior parietal lobule in adults with ADHD.

Occipital Lobe

In line with the general findings of Castellanos' work [12], pronounced reduction of left occipital brain volume in children with ADHD was also found by another study group [16]. No data are presently available regarding occipital lobe anatomy in adults with ADHD.

Cerebellum

The role of the cerebellum in cognitive and affective function has been described in 20 patients with cerebellar lesions [50]. Aside from the well-known motor coordination problems, patients with cerebellar lesion display impairment of executive functions, visuospatial cognition deficits as well as blunting of affect and disinhibition of behavior. Cognitive cerebellar functions are located mainly in the posterior lobe (neocerebellum), whereas executive, visuospatial, and memory functions of neocerebellum are impaired when the lesions are located in the hemispheres and dentate nucleus [50, 51]. The vermis has been shown involved with affective disturbances [51]. The cerebellum projects via thalamus to areas in the PFC [52] and there are reciprocal projections from the PFC to cerebellum, thus forming a functional network that influences rather than generates motor control, inhibitory and executive functions. Moreover, several studies have shown that the cerebellum has modulatory effects on forebrain dopamine outflow [53–56].

Several studies in ADHD in childhood and adolescence have shown structural cerebellar impairment [10–12, 15, 16, 57–59]. Indeed, the most marked neuroanatomical anomaly in ADHD has been described in the cerebellum, with volume changes more marked than in the PFC [12]. In children, reductions in right cerebellar hemisphere and vermis volume have been reported [11, 15, 16, 57–59]. These volume reductions correlated with attentional problems and global clinician ADHD ratings [12]. At present there are no data on cerebellar volume in adult ADHD.

Other Brain Regions

In children and adolescents with ADHD an increased volume of the hippocampus bilaterally, which is involved in attentional processes such as visuospatial working memory and executive functions, has been reported [60]. Moreover, some evidence for a reduced size of the basolateral amygdala was found in this study. Since affective symptoms and emotional instability are typical features of and affective disorders are highly prevalent in adult ADHD, altered amygdala and hippocampus volumes are of particular interest also for adults with ADHD. However, in a recent study with adults suffering from ADHD, no differences regarding hippocampus and amygdale volumes were found [61].

Brain Function in ADHD

Functional MRI (fMRI), MRI relaxometry and ligand-bound imaging techniques like SPECT or positron emission tomography (PET) have been used to study functional abnormalities of brain networks in ADHD. From a neurological viewpoint, attention networks can be basically distinguished into three components [18, 46, 62]:

- The arousal and alerting networks are mainly subcortically located and constitute of the ascending reticular activating system. They project to the whole brainstem and thalamus and, through the striatum, up to the limbic system to form cortical projections. The main function of this component is the activation and synchronization of the cerebral cortex during behavior and motivation, and has affinity to salient stimuli and memorization.
- The mixed cortical-subcortical orienting networks are involved in detection of novel stimuli (superior colliculi), filtration of relevant stimuli (pulvinar) and disengagement of attention focus (posterior parietal cortex).
- The selective (or directed/cortical) attentional network is of particular interest for ADHD pathophysiology. It involves frontal brain structures for generation of volitional saccades (frontal eye fields), induces motor intention (premotor cortex), is linked to the working memory (DLPFC) and is modulated by the ACC (target detection, response selection and inhibition, conflict monitoring, motivation) [63]. This network is also called executive (conflict) network and has been shown highly heritable [64]. Within this network, the dACC has strong connectivity to frontal brain structures with dense serotonergic and dopaminergic components. Regions of the parietal cortex also play an important role in mediating sensory functions. Th e posterior parietal cortex disengages the attentional focus to a target [47] and the superior parietal lobule has the function of voluntary shift s of attention [29]. Right hemisphere dominance could be found for the orienting as well as selective attention [17, 18].

Konrad et al. [65] have used event-related fMRI to investigate brain activations related to these three particular aspects of attention. It could be shown that children with ADHD recruited deviant brain regions for all three above-mentioned attentional networks. ADHD children had less right-sided activation in the anterior cingulated gyrus during alerting, more frontostriatal-insular activation during reorienting, and less frontostriatal activation for executive control. Dysregulation of blood oxygenation level-dependent signals was described in the putamen during reorienting and executive control, suggesting altered strategies in children with ADHD. In medication-naïve children and adolescents with ADHD, task-specific functional abnormalities in frontostriatal but also to parietal and temporal areas were found [66]. Hale et al. [67] concluded from their data that abnormal brain function among adult ADHD participants was not limited to complex executive functions. Abnormal processing of numeric stimuli was indicated during both simple and complex cognitive operations. For example, during the difficult tasks, they exhibited greater activation of left hemispheric linguistic-processing areas and failed to activate bilateral parietal regions important for the complex executive operations.

Anterior Cingulated Cortex

Hypoactivation of the dACC has been consistently described in children and adolescents with ADHD using continuous performance paradigms, with results being similar using fMRI of PET-imaging techniques [25, 68–71]. These findings have led to the hypothesis that dACC plays a significant role in ADHD pathophysiology.

Zametkin et al. [71] were the first to describe hypoactivity of dACC with PET in adult ADHD patients. According to the hypothesis of impairment of selective attention, several studies in adult ADHD have also shown hypofunctionality of the ACC [68, 70]. Following the executive attention hypothesis, the earliest fMRI study in adult ADHD was performed by Bush et al. [70], using a specially designed counting Stroop paradigm. This study demonstrated that the 'cognitive division' of the dACC was not activated in adult ADHD patients during interference conditions. As a compensatory mechanism, ADHD patients activated an alternative frontostriatal network by using different regions of lateral PFC, insular cortex, as well as unilateral activation of caudate, putamen, thalamus and pulvinar. These results may be interpreted as impairment of dACC function in ADHD subjects under conditions where interferences occur, while under conditions where subjects could focus on salient stimuli, there was no difference in dACC activation. This 'normal attention but abnormal stimulus alerting and conflict effect' has also been reported from a neuropsychological point by Oberlin et al. [72]. Only ADHD subjects with the combined type were impaired in their reactions to abrupt visual cues or those that contain conflicting spatial cues. These features were not found in adults with the ADHD-inattentive type.

Besides the role of dACC in selective attentional processing, response selection and inhibition and performance monitoring [73], dACC is also thought to influence reward-based decision-making [74]. The larger the gain, the higher the activity in the pregenual ACC during the decision phase [75]. Ernst et al. [73] found differences in motivational behaviors in ADHD, especially when the patients had to weigh long-term versus short-term rewards. The patients used more parts of the right ACC than healthy controls.

Memory performance was associated with activation of the ACC in healthy adolescents but with activation of the superior parietal lobe (SPL) and precuneus in adolescent ADHD patients [76]. The authors suggested that increased SPL activation in ADHD reflected attentional compensation for low ACC activation during the encoding and that the higher salience of emotional stimuli, in contrast, regulated the interplay between ACC and SPL in conjunction with improving memory to the level of healthy adolescents.

Using a working memory paradigm, Wolf et al. [77] could recently demonstrate lower connectivity in ACC and higher connectivity in dorsal cingulate cortex in adults with ADHD and healthy controls. Another fMRI study found evidence for decreased functional connectivity between ACC and posterior cingulated regions including the precuneus [78].

Motor System

The execution of simple motor tasks reveals distinct cerebral activation pathways. Using a simple finger-tapping task, Mostofsky et al. [79] reported that children with ADHD had decreased contralateral motor cortex and right parietal cortex activation during right- and left-handed finger sequencing. These findings could be interpreted as anomalous development of cortical systems necessary for execution of patterned movements.

In a study with PET, a correlation between motor hyperactivity with lower binding potential values for dopamine transporter (DAT) in the midbrain was shown in adolescents with ADHD [80]. Thus, altered dopamine signaling might have a causal relationship to hyperactivity. Studies with adult ADHD patients are not available so far.

Frontal Cortex

The most consistent findings in the neuroimaging literature of ADHD are deficits in neural activity within frontostriatal and frontoparietal circuits. However, the results vary across subregions of the frontal cortex, suggesting that ADHD is not associated with dysfunction of any particular part of frontal cortex.

The PFC is critical for the regulation of behavior, attention, and affect by use of representational knowledge. The PFC is important for sustaining attention over a delay, inhibiting distraction, and dividing attention, while more posterior cortical areas are essential for perception and the allocation of attentional resources. The PFC in the right hemisphere

is particularly important for behavioral inhibition. Lesions to the PFC produce a profile of distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity. Variable findings have been described for VLPFC and DLPFC. These brain regions also monitor attention, planning, working memory and executive control, especially with regard to inhibitory control [18, 81]. Rubia et al. [25] found hypoactivation in the right VLPFC and left caudatus of adolescents with ADHD, whilst Durston et al. [82] reported different activation of frontostriatal regions. Children with ADHD displayed more diffuse network activations including more posterior and dorsolateral prefrontal regions. Rubia et al. [83] reported that medication-naïve adolescent patients with ADHD showed significantly reduced brain activation in the right inferior PFC during successful motor response inhibition and in the precuneus and posterior cingulate gyrus during inhibition failure. These deficits correlated with behavioral scores of ADHD and persisted when corrected for medication history and performance discrepancies. Conversely, Ernst et al. [73] showed using PET that adult ADHD patients, as well as healthy controls, activated VLPFC and DLPFC including insula during a decision-making task. However, the activation of the dACC and hippocampus, subserving emotional and memory processes, was less extended in the ADHD group, who instead recruited the caudal part of the right ACC. These results were interpreted as a basis for problems of motivated behavior in ADHD.

Evidence for significant frontal hypoactivity, including anterior cingulate, dorsolateral prefrontal and inferior prefrontal cortices comes from a meta-analysis of studies with fMRI in children and adolescents with ADHD [84]. Analyses of studies which used other than response inhibition paradigms revealed a more extensive pattern of hypofunction in patients with ADHD than those of response inhibition (thalamus, basal ganglia and parietal cortex). Studies of response inhibition displayed more limited group differences regarding activation of inferior PFC, medial wall regions, and the precentral gyrus.

In adult ADHD patients, less activation and lower functional connectivity was observed during a working memory task in the left VLPC, while connectivity of the right PFC was increased when compared to control subjects together with functional changes in other brain regions [77]. Moreover, a correlation between activation of frontal cortical areas of adult ADHD subjects and inattention scores has been reported, suggesting a functional deficit within this network that depends on the degree of attention deficits [85]. On the other hand, increased activation of orbitofrontal cortex was found in response to gain outcomes during a monetary incentive delay task, suggesting that this part of frontal cortex is involved in abnormal reward processing in adult ADHD [86].

Cerebellum

Due to its involvement in cognitive, emotional processing and behavioral control, the cerebellum seems to be an important region of interest in ADHD research [50]. Anderson et al. [7] reported abnormalities of the vermis in children and adolescents in a MRI

relaxometry study that could be influenced by methylphenidate, suggesting an influence of cerebellar function in ADHD. The effects of methylphenidate on cerebellum depended on pretreatment activity level. With fMRI, Schulz et al. [87] described a higher activity of the cerebellum in adolescents with ADHD. In contrast, Valera et al. [88] found significantly decreased activity in cerebellum and also occipital lobe of adult patient with ADHD, even though working memory performance did not differ significantly between ADHD and controls. Kim et al. [89] examined ADHD children with PET and found decreased bilateral cerebellar blood flow in ADHD compared to controls. Volkow et al. [90, 91] reported that methylphenidate could increase metabolic activity of the cerebellum in normal adults, dependent of dopamine receptor activity.

Preliminary results from a study with ADHD children [92] hinted to a relation between cerebellum and forebrain dysfunction and ADHD symptomatology. The authors found with an ADHD diffusion tensor-imaging technique (DTI) prominent white matter abnormalities in the right premotor, right striatal, right cerebral peduncule, left cerebellar peduncule, left cerebellum and left parieto-occipital areas. In adults with ADHD, less activation during a working memory task and changes of functional connectivity of the cerebellum and cortical brain regions was described [77]. These results give additional evidence for corticopontocerebellar circuit deficits in ADHD.

Parietal Cortex

The parietal cortex belongs to an attentional system that includes frontoparietal network structures [18, 93]. For example, orienting networks include the SPL, as well as the temporal parietal junction and frontal eye field [94]. Krauel et al. [76] suggested increased activation in some parietal regions as an attentional compensation for low ACC activation in healthy adolescents. Together with frontal brain areas, the alerting attentional network activates parietal and thalamic areas that are potentially susceptible to the actions of norepinephrine [95–97].

Superior parietal and middle frontal areas are involved in visuospatial processing [98]. Silk et al. [99] have shown in an fMRI study with a mental rotational task, that ADHD children with combined subtype have lower activation of the action attentional system including superior parietal cortex as well as middle frontal areas. Patients had also increased activation of the posterior midline attentional system. This indicates that ADHD patients might also have parietal dysfunction as well as dysfunctions of the widespread frontal and striatal systems. As is the case with many of the networks discussed so far, these findings in children have yet to be extended to adults with ADHD. A first step towards this direction has been performed by Tamm et al. [100], who showed that adolescents with ADHD had significant impairments in their ability to direct and allocate attentional resources. This was associated with bilateral aberrations in the parietal attentional system.

Basal Ganglia

In line with PET findings showing reduced basal ganglia perfusion in patients with ADHD [101], subsequent fMRI studies have reported abnormal activation of the striatum [25, 102–104].

Although the main focus of the study of Bush et al. [70] was not the basal ganglia, they observed increased activation of the right putamen in adults with ADHD while performing a Stroop task. Recently, Plichta et al. [105] could show hyporesponsiveness of the ventral-striatal reward system in adults with ADHD, who were examined during a series of choices between two monetary reward options. In addition, they reported increased activation of the dorsal caudate nucleus and amygdala associated with delayed reward. Similarly, decreased activation in the ventral striatum during the anticipation of gain in a monetary incentive delay task was described in another recent study [86]. Moreover, the authors described in this study a negative correlation of ventral striatal activation with self-reported impulsivity and hyperactivity. Similar findings have been reported in a previous fMRI study of brain activation during a reward-anticipation task in adolescents with ADHD [104]. The negative correlation between impulsivity and striatal activation, which was found in both studies, has also been shown by Schneider et al. [85], who used an impulse-control paradigm. Taken together, these results suggest that striatal activation is involved in the processing of reward and the regulation of impulsive-hyperactive traits in adults with ADHD.

ADHD and Comorbid Disorders

Studies with patients who have comorbid disorders or brain lesions are of interest because they may help to validate the specificity of the hypothesized frontostriatal(-cerebellar) dysfunctions and compensatory mechanisms in ADHD.

Bussing et al. [58] have suggested that no differences in cerebellar morphology could be found between ADHD children with and without comorbid conduct disorder. Also, in this study no differences were reported in volume measurements of frontostriatal structures. On the other hand, electrophysiological studies with event related potentials showed abnormalities in prefrontal lobe activation in teenagers with conduct disorder [106].

Tourette's syndrome (TS) is frequently comorbid with ADHD [107, 108]. In TS, basal ganglia volume reduction and loss of left > right side asymmetry of the globus pallidus is described in some but not all studies [108–110]. Some studies could not differentiate between TS and comorbid ADHD in terms of brain structure alterations, whereas some could find that patients with comorbid ADHD tended to have larger volumes across all cortical portions of those circuits to dorsal prefrontal and parietooccipital regions and smaller caudate nucleus volumes [111].

Adler et al. [112] have used a simple attention task in adolescents with bipolar disorder and showed that comorbidity with ADHD was associated with less activation of the VLPFC, ACC and higher activation in posterior parietal cortex as well as middle temporal gyrus. Thus, comorbidity with ADHD might result in less activation of prefrontal regions while posterior parietal and temporal cortical areas are used as alternative pathways. Facial recognition is also impaired in ADHD in a similar way when compared with patients with schizophrenia [113]. Both groups display reduced activity in the medial prefrontal and amygdala brain regions required to process emotional faces.

Autism may occur with ADHD and impairment of attention has been consistently reported in autism [114]. In anatomical studies, patients with autism displayed larger total brain and white matter volumes in caudate, globus pallidum, most cortical brain regions and in the cerebellum as compared to ADHD subjects [115]. Reduced fMRI activation was found primarily in amygdala of autistic patients during social tasks [116], but autistic spectrum disorders also display dysfunctional cerebellofrontal spatial attention system [117, 118] similar to ADHD.

Conclusions

In contrast to neuroimaging investigations in children and adolescents with ADHD, the number of studies in adult patients is still limited. Imaging data in general are often confounded by small sample sizes, non-replicated and sometimes even contradictory results. However, recent findings have shown similarities between abnormalities in adult ADHD patients and children with ADHD suggesting impairment of frontostriatal(-cerebellar) networks. Consistent findings have been reported regarding dysfunction of the striatum and the ACC. Prefrontal cortical structures also seem to play a pivotal role in ADHD psychopathology, although these findings are not specific to ADHD. As in children, the cerebellum is also dysfunctional in adults with ADHD. Moreover, there is increasing evidence that also parts of the posterior attention networks are less active in both childhood and adult ADHD. Functional abnormalities comprise frontostriatal, parietal and also temporal cortical areas in a task-specific manner. Attention orienting is less affected than salient stimulus or conflict alerting. Also, several 'vertical' levels of attention networks – beginning from the arousal to the orienting up to the selective attention network – are affected in ADHD.

Data on ADHD patients with comorbid psychiatric disorders are not consistent so far and their contribution to our understanding of ADHD pathophysiology is limited. However, it seems that ADHD symptoms combined with other disorders are associated with frontostriatal dysfunction.

Structural and functional brain-imaging investigations are an important source for our growing knowledge of ADHD pathophysiology. However, due to the lack of sensitivity

and specificity of the findings, neuroimaging techniques are not ready to be used as a diagnostic tool. It seems possible that with the progress in understanding the pathogenesis of ADHD together with the technical progress in brain-imaging techniques, we might overcome this shortcoming in future.

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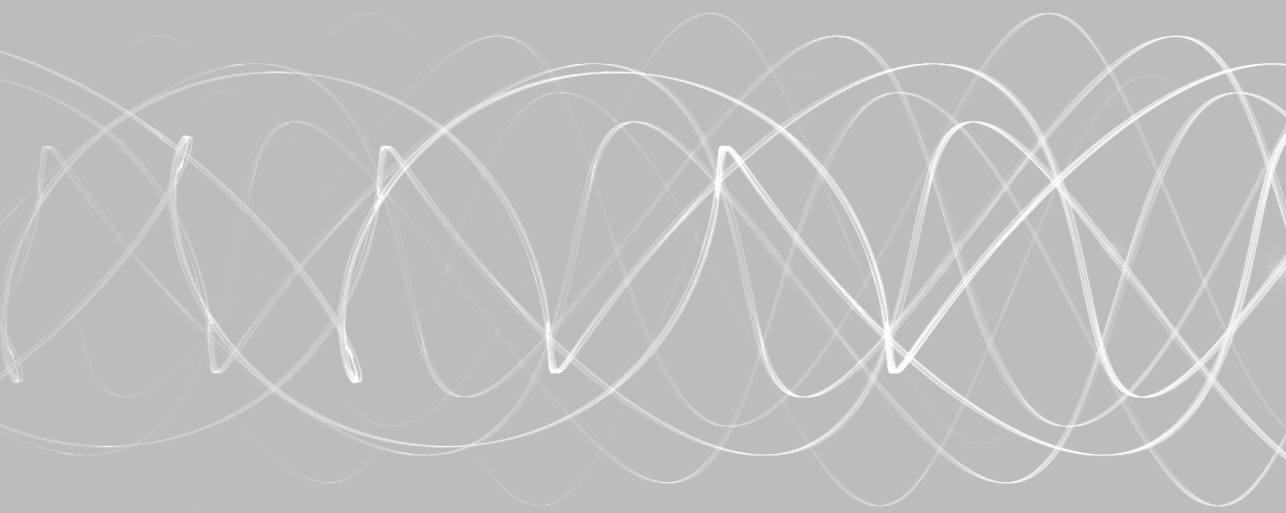

3 Impairment of fronto-striatal and parietal cerebral networks correlates with Attention Deficit Hyperactivity Disorder (ADHD) psychopathology in adults – a functional magnetic resonance imaging (fMRI) study

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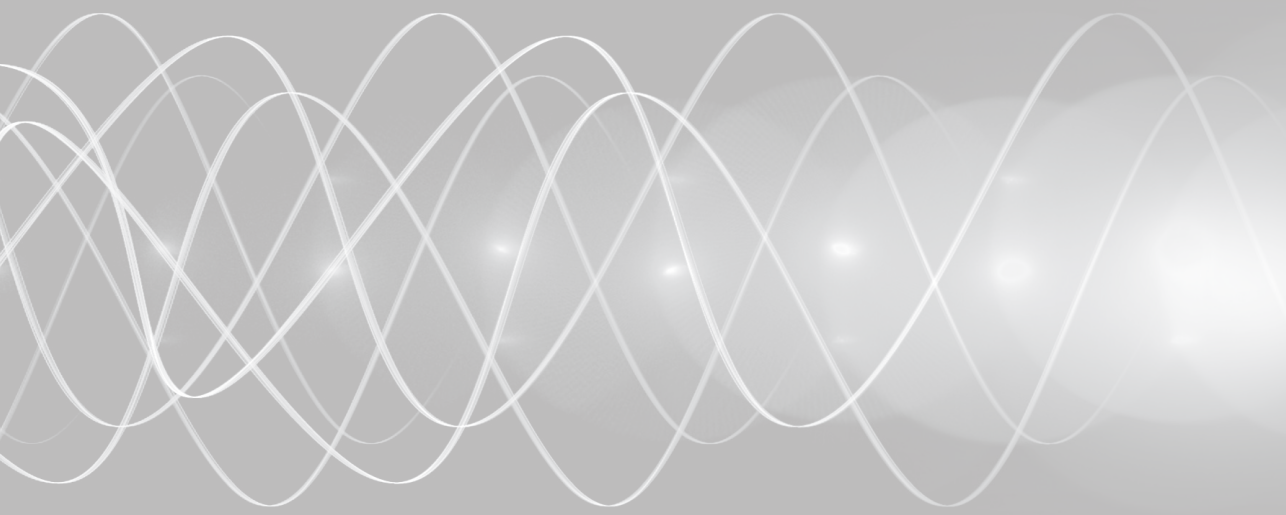


Abstract

Attention deficit hyperactivity disorder (ADHD) is a common, genetically transmitted childhood onset disorder with a high rate of persistence in adulthood. Although many studies have shown anatomical and functional abnormalities in children and adolescents, studies with adult patients are rare. 19 adults with ADHD (11 ADHD, combined type; 8 ADHD, partially remitted) and 17 controls were included in this functional magnetic imaging (fMRI) study. Brain activation was investigated with a continuous performance test (CPT). Impaired activation of a fronto-striatal and a parietal attentional network was observed during the NoGo condition in ADHD subjects. Correlations of reduced activity of caudate nuclei, anterior cingulate cortex as well as parietal cortical structures and increased activity of insular cortex with inattention and impulsivity symptom scores were found. The activation patterns were similar to those known from children and adolescents with ADHD. In conclusion we found not only a widespread dysfunction of brain regions that are involved in cognitive processing in adults with ADHD compared to controls, but also correlations between symptom severity and dysfunction of neuronal systems across adult subjects without ADHD, childhood but not persistent and persistent ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common, genetically transmitted childhood onset disorder characterized by inattention, hyperactivity and impulsivity (Wender, 1995). According to the dimensional character of ADHD psychopathology, this condition has been suggested rather the extreme variant of a psychopathological continuum than a distinct disorder. Follow-up studies show that up to 60% of patients suffering from this disorder still show some or all of the ADHD characteristics as adults (Barkley, 2002). A cross-national prevalence of 3.4% for adult ADHD has been reported (Fayyad et al., 2007). Regarding the negative impact of ADHD concerning functional impairment and social outcome, and the need for optimizing diagnosis and treatment in adulthood, there is high interest in understanding the pathophysiological mechanisms in ADHD across the lifespan.

Structural and functional imaging data are mainly based on studies with ADHD children (Sowell et al., 2003; Pliszka et al., 2006). Studies with functional neuroimaging techniques performed with ADHD children suggest dysfunction of the ventral and dorsolateral prefrontal cortex, the anterior cingulate, insula, amygdala, hippocampus, and ventral striatum (Ernst et al., 2002; Elliot et al., 1999; Rogers et al., 1999; Elliot et al., 2000; Knutson et al., 2001; Bussey et al., 1997; Schultz, 1999). In addition, it has been reported that methylphenidate, which is highly effective in the treatment of ADHD and which exerts its effects via dopaminergic pathways, was able to normalize striatal circuitry function and could improve frontal activation in children and adolescents with ADHD (Vaidya et al., 1998; Shafritz et al., 2004).

In detail, imaging data seem to be somewhat divergent and suggest that many brain regions are involved in the pathophysiology of ADHD, which might be at least partially due to small samples investigated and different neuropsychological paradigms applicated. However, there is converging evidence from these studies that behavioural and cognitive problems associated with ADHD are mainly associated with dysfunction of fronto-striatal regions or mainly in the forebrain located regions that influence inhibitory control mechanisms (Durston et al., 2002).

In adults with ADHD marked reduction of global metabolism in both hemispheres (Zametkin et al., 1990) and also diminished dopaminergic uptake in the left and medial prefrontal cortex have been reported (Ernst et al., 1998). Similarly to childhood ADHD it has been shown that prefrontal cortex, anterior cingulate cortex and basal ganglia are also involved in adult ADHD (Bush et al., 1999; Ernst et al., 2003; Zametkin et al., 1990). In a functional magnetic resonance imaging (fMRI) study Bush and colleagues (1999) showed that specific regions of Anterior Cingulate Cortex (ACC), which have been shown to be involved in attention focusing and mediation of response selection, were disturbed in patients with ADHD, but a frontostriatal-insular network was activated instead.

Literature gives evidence for negative correlation of ventro-striatal activity with impulsivity and hyperactivity in adolescents and adults with ADHD (Scheres et al., 2007, Ströhle et al., 2008). ADHD patients can also overreact with defined cerebral regions in response to reward outcomes (Ströhle et al., 2008). Thus, recent imaging data underline the central role of fronto-striatal circuits in ADHD including the orbitofrontal, mesial and lateral prefrontal brain regions (Ernst et al., 2003; Durston et al., 2003; Rubia et al., 1999). Bush et al. (2008) pointed out the importance of the dorsal anterior midcingulate cortex that plays a key role in cognition, attention, target detection, motor control, error detection and feedback-based decision making and could show with fMRI technique in adult ADHD that methylphenidate could normalize hypofunction in this area.

Due to the still limited number of studies with adults with ADHD and the lack of follow-up investigations of ADHD children, it remains unclear whether disturbed network activation differs between ADHD children and adults and whether clinical remission of ADHD psychopathology runs parallel to normalization of brain function. It should be considered that adults with ADHD might use at least partially compensatory mechanisms which are not yet present in ADHD children.

In this study we aimed to investigate activation patterns of attentional networks in adults with ADHD. Due to the dimensional character of the disorder and the decline of symptoms in a considerable proportion of patients with age, we hypothesized that compared to controls there might be not only different activation patterns in ventro-striatal and parietal cortex, but also correlations between symptom severity and brain dysfunction across adult subjects without ADHD, childhood but not persistent and persistent ADHD.

2. Methods

2.1. Subjects

Adult patients were recruited from a specialized ADHD outpatient unit of the Neuro-center located at the Saarland University Hospital. ADHD was diagnosed according to DSM-IV criteria after careful clinical investigation. None of the participants of the study had received any kind of stimulant medication before. They were diagnosed for the first time with ADHD. All participants of the study were right handed and without any medication. Subjects had no other psychiatric axis I disorder beside ADHD and no history of any CNS-affection in the 6 months before entering the study. SKID I interviews (Wittchen et al., 1997) were used to exclude relevant actual psychiatric and neurological disorders. IQ was assessed by use of the multiple-choice vocabulary test (MWT-B), which is a verbal test with German norms (Lehrl, 1995).

Only ADHD patients with a total score of 30 or more on the German validated form of the Wender-Utah-Rating-Scale (WURS-k; Retz-Junginger et al., 2003) participated in this

study, in order to ensure for childhood onset of ADHD symptoms. According to former validation studies, scores above this cut-off are highly indicative for childhood ADHD. Quantification of current ADHD symptoms according to DSM-IV was performed using a standardized and validated self-rating scale for adults (ADHD-SR; Rösler et al., 2004, 2008). The ADHD-SR consists of 18 items according to DSM-IV ADHD symptoms, which are rated on a 0 – 3 Likert scale. The maximum total score is 54 points, those of the inattention subscale 27 (9 items), of the impulsivity subscale 12 (4 items) and for the hyperactivity subscale 15 (5 items), respectively. ADHD-SR total and subscores were used for further correlation analyses of brain activations in the functional magnetic resonance imaging procedures.

The term "not persistent ADHD" was used for patients with childhood ADHD who were partially remitted on the syndromatical level as discussed by Biederman and colleagues (2000). These patients have lost the full diagnostic status according to DSM-IV but still showed symptoms of ADHD and functional functional impairment.

2.2. Continuous Performance Test (CPT)

According to Barkley (1997) the fundamental deficit in individuals with ADHD is one of self-regulation and the control over behavioral inhibition. It has been argued that this results primarily from frontal lobe dysfunction and not because of adverse environmental conditions. According to this concept, executive dysfunction including working memory, internalization of speech, sense of time and goal directed behavior are secondary psychological and functional problems of impulse control deficit and frontal brain plays a crucial role in its regulation. Therefore, the CPT NoGo condition was chosen as the primary target stimulus in statistical analyses.

We used the continuous performance test (CPT), which is conceptualized for investigating sustained attention, vigilance and inhibitory control (Rosvold et al., 1956; Fallgatter and Strik, 1997). Briefly, a pseudorandom sequence of letters was presented 420ms each. Subjects were instructed to push a button of a MRI compatible optical fiber pad, if the letter 'O' (predatory condition) was immediately followed by the letter 'X' (Go condition), but not when another letter than 'X' followed the 'O' (NoGo condition). In neurophysiological studies a robust physiological frontalization of the brain electrical field during the NoGo condition and reduced frontal brain activity in ADHD children and adults has been shown (Fallgatter et al., 1997, 2004, 2005). CPTs with low rates of signal probability would likely demonstrate different relationships with ADHD symptoms and symptom domains (Conners 1994). But there is a controversial discussion over which CPT gives the best correlates with the ADHD symptoms (Corkum et al., 1993, 1995; Koelega, 1995). In a study examining performance on measures over time, increased mean hit reaction time and standard errors over time was highly associated with most ADHD symptoms (Epstein et al., 2003). In summary there is no "goldstandard" which CPT best fits with ADHD symptoms or subtypes.

The projection of the letters was performed by a computer-guided beamer on a screen while participants watched the screen through a mirror on the head coil positioned above their eyes. The speed of presentation for each letter in the CPT was set near the limit of overall cognitive attention and reaction time capacity. Thus, drifting away of the attention from the task presentation was minimized.
Given the fact that eye fields were limited through a mirror system and the narrowed projection into a relative dark environment there were few possibilities to lose the optical focus. An automatic eye tracking system was not used.
During fMRI recordings 30 Go events and 30 NoGo events were presented in a pseudorandomized manner. A total of 285 sequences were recorded.

2.3. Magnetic Resonance Imaging

2.3.1. Anatomical sequences

Imaging was performed with a 1.5T Siemens Magnetom Vision whole body scanner system. A standard head coil was used. Head position was stabilized with vacuum cushion and fixed with adhesion bands to minimize head movements.
For each subject T2-weighted anatomic sequences (data matrix 256 x 256 voxel, 0.9375^2 mm^2 pixel size, 5 mm slice thickness, TR 4.6s, TE 99ms) in plane with the echo planar images were performed. Thus, functional images could be aligned with the three dimensional images. Anatomical abnormalities or symptomatic causes for attention deficit syndromes like liquor circulation disturbances, inflammatory syndromes or stroke could be excluded from the study.

2.3.2. Event related functional MRI

Gradient-echo EPI sequences with a TE of 60ms, flip angle of 90° and TR of 2.69 sec were recorded. The matrix of 64 x 64 had a field of view of 240mm, resulting in a planar resolution of 3.75 x 3.75 mm. The total number of slices was 24, the slice thickness was 5mm, the interslice gap was 0.5mm.
Four volumes were discarded to allow stabilization of magnetization before starting of recording. A total of 285 volumes were recorded, containing 30 Go and 30 NoGo events, each. The runs were completed after 12 minutes.

2.4. Data Processing and Analysis

Offline reconstruction and realignment of functional images were performed using the procedure of Friston et al. (1995) using Statistical Parametric Mapping (SPM 99, The Wellcome Department of Cognitive Neurology, University College London, UK). Prior to data analysis motion artifacts were screened. All subjects with a translational artifact of more than 2.5mm and rotational head movement of more than 2.5° were excluded. In a second step, recordings were corrected for these movement artifacts and then filtered for low frequency signal fluctuations (high pass cut off frequency: $1/123\ s^{-1}$; low pass cut

off period: HRF waveform). Each mean image volume was then spatially normalized into the modified Talairach space employed in SPM 99 to a resulting resolution of 2x2x2mm using both affine and non-linear components. Finally, with a Gaussian kernel of two voxels/ 8x8x8mm spatial smoothing was performed in respect to the Gaussian random field theory.

Group comparisons of mean functional images were done by independent two samples t-test for the conditions Go and NoGo, respectively. Correlation analysis of mean functional images with ADHD-self rating scores was done with linear regression analysis (SPM99). If not otherwise mentioned standard p threshold was set at 0.001 (uncorrected). Voxel extension was set at k=5.

Correlation analyses were calculated by linear regression implemented in SPM with the activation - t values as the dependent and the explanatory variable of interest as the independent variable. In addition, t values at the respective correlated region of interest (ROI; see below) were extracted from SPM and Spearman correlations with the respective variable of interest were calculated.

3. Results

3.1. Patients characteristics

19 subjects with lifetime ADHD (ADHD - 6 male/ 5 female; age 32.6 ± 9.4 years (mean ± SD), range 19-48 years; ADHD partially remitted - 7 male/ 1 female; age 32.4 ± 8.3 years (mean ± SD), range 18 – 45 years) and 17 controls (10 male/ 7 female; age 29.4 ± 8.6 years; range 18-45 years) entered the study. 11 subjects of the ADHD group fulfilled the diagnostic criteria for ADHD, combined type, 8 patients were diagnosed with ADHD, partially remitted according to DSM-IV. Mean IQ of ADHD subjects (106 ± 13 (mean ± SD), range 88-124; ADHD partially remitted 115 ± 18 (mean ± SD), range 95-145) was somewhat lower than mean IQ of the control group (126 ± 12 (mean ± SD), range 100-143), t-test, T=3.3, df(27) p=.003), but all IQs were within normal range. Ratings on the WURS-k and ADHD-SR of ADHD subjects and controls are given in table 1. There was no significant difference of the WURS-k scores between subjects with persisting ADHD and those with ADHD, partially remitted (Mann-Whitney test, Z=-.58, p=.60) whereas the current ADHD symptom scores (ADHD-SR) were significantly higher in the persistent ADHD group compared to subjects with ADHD, partially remitted and controls (Mann Whitney test, Z=-3.4 and -4.4, respectively, p=.000).

3.2. Continuous performance test

Concerning results of the CPT, patients with ADHD, combined type made significantly more omission errors and had longer reaction times at the Go condition than controls. There was a non significant trend that patients with persisting ADHD made more

Table 1 Clinical ratings and neurophysiological data from Continuous Performance Test (CPT) of adults with ADHD and controls

	ADHD Group (N=19)		Controls (N=17)	Statistic Kruskal-Wallis-Test * ANOVA**
	ADHD, combined type (N=11)	ADHD, partially remitted (N=8)		
WURS-k Score	43.0 ± 11.6	38.4 ± 7.0	6.6 ± 4.5	*χ^2=25.5 p=.000
ADHD-SR Total Score	40.6 ± 4.8	26.8 ± 7.9	6.1± 6.0	*χ^2=28.8 p=.000
ADHD-SR Inattention Subscore	20.6 ± 2.9	15.3 ± 6.0	2.4 ± 3.3	*χ^2=26.7 p=.000
ADHD-SR Hyperactivity Subscore	11.4 ± 2.3	6.6 ± 4.1	1.1 ± 1.5	*χ^2=26.0 p=.000
ADHD-SR Impulsivity Subscore	8.6 ± 2.3	4.9 ± 2.4	1.4 ± 1.6	*χ^2=25.3 p=.000
Omission errors (CPT Go condition)	3.91 ± 1.70	4.75 ± 2.55	1.24 ± 1.44	**F=13.1 p=.000
Reaction time (ms) (CPT Go condition)	478 ± 78	459 ± 43	414 ± 48	**F=4.42 p=.020
Comission errors (CPT NoGo condition)	0.64 ± 0.81	1.13 ± 1.46	0.24 ± 0.44	**F=2.97 p=.065
Reaction time (ms) (CPT NoGo condition)	330 ± 259	185 ± 93	202 ± 122	**F=0.86 p=.454

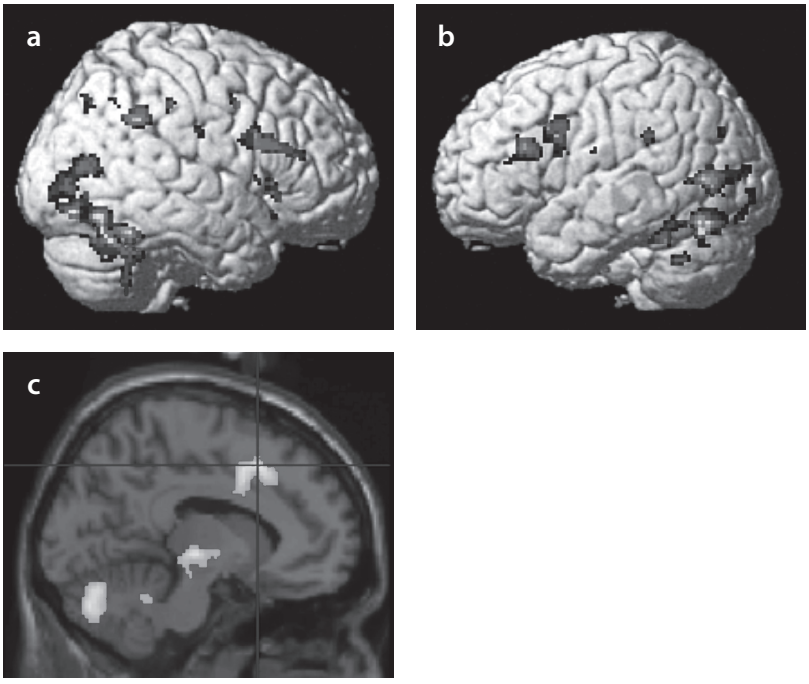
commission errors than controls. No significant difference between the ADHD, combined type group and controls could be seen regarding the reaction time during the NoGo condition (table 1).

There was a significant correlation between accuracy of CPT Go-responses and reaction time within the entire study population (r=.489, p=.002) but not regarding NoGo-responses (r=.026, n.s.). Within the study subgroups, no correlations between CPT responses and reaction time were found (ADHD probands:r= .289, n.s.(Go), r=.716, n.s. (NoGo); ADHD partially remitted: r=.31, n.s. (Go), r=-.622, n.s. (NoGo); controls: r=.424; n.s. (p=.09) (Go), for NoGo-response not calculated due to lack of variance).

3.3. fMRI activation patterns of CPT paradigm

Figure 1 shows general activation patterns of healthy participants of the CPT in the NoGo condition. Besides the involvement of brainstem and thalamic regions, CPT performance lead to bilateral activation of parts of forebrain, namely the prefrontal cortex as well as parietal and occipital brain regions. These regions have been shown to be part of an orienting and selective activation network (Fan et al., 2002). The activation pattern also comprises the essential elements of a cerebello-thalamico-subcortico-cortical attention network seen in tasks that modulate different levels of attention. Important brain structures activated here were the bilateral cerebellum, thalamus, nucleus ruber, putamen, insula, inferior, middle and superior frontal gyri, cingulate gyri,

Figure 1 Brain activation patterns of CPT paradigm in healthy controls (Significance level set at p<.001; voxel extension k=5);
a) BOLD signals in the NoGo condition; aspects from the right hemisphere.
b) BOLD signals in the NoGo condition; aspects from the left hemisphere.
c) BOLD signals in the NoGo condition; aspects from the midsagittal view.



middle temporal gyri, respectively. In the parieto-occipital cortex, a posterior attention network activation was seen in the bilateral postcentral gyri, fusiform gyri, middle occipital gyri, and inferior parietal lobules, respectively.

3.4. Group comparison analysis

Analysis of group differences revealed lower NoGo activation in several brain regions of ADHD subjects (figure 2). While the right frontal and parietal lobes were generally less activated in ADHD patients compared to the healthy controls, bilateral parts of the occipital cortex displayed higher activation during CPT paradigm. In group comparison with healthy controls, ADHD patients revealed less activation also in parts of the right fronto-striatal network (Brodman area [BA] 8) and right caudate nucleus as well as right temporal lobe. In the parietal cortex there was less activation in left and right polymodal sensory integration areas (left parietal lobule and right supramarginal gyrus). Detailed information about significant results ($p<.001$) are given in table 2 a) and b). These activation differences were also evident but less significant with statistical correction with IQ. Lowered temporal brain activity from ADHD patients was then not any more significant.

Group comparison between patients with ADHD combined type and ADHD partially remitted revealed significantly higher activities in the ADHD pr group in the left premotor and prefrontal cortex but no differences in the striatal or parietal cortex activation. Patients with ADHD combined type tended to show higher activation of the right temporal lobe (middle and inferior temporal Gyrus), bilateral cerebellar hemispheres and bilateral paramedial thalamus and finally dorsal pontine brainstem (data not shown). Facing the small number and clinical/ symptomatical similarity from subjects of these groups one can mainly argue from these data that with regard to fronto-striatal and parietal activation patterns there are only few significant differences between the ADHD combined type and the ADHD partially remitted group. Further studies with bigger test populations are needed to analysis these aspects more in detail.

3.5. Correlations of activation patterns with ADHD-SR scores

Cerebral activation provoked by the CPT NoGo condition was correlated and anticorrelated with ADHD-SR subscores in several brain regions. The data analysis was focused on neural regions that are involved in attention processes and inhibitory control, i.e. fronto-striatal as well as parietal brain. Brain regions with a significant increase or decrease of activation are listed in tables 3a) to f) in detail. The level of significance was set at $p<.001$, no correction for multiple tests was performed.

Figure 2 Group contrast of fMRI activation (NoGo condition);
a) Grey dots indicate brain regions where controls activate more than ADHD patients. Activity is reported for clusters with a contiguity threshold of k=5 voxels. Brightest gray reflects the threshold of p=.001, whereas black reflects the maximum p level that was found in the whole brain analysis (p=.00001). **b**) anatomical sections from this group contrast showing left superior parietal lobule and right caudate nucleus: regions were controls activate more than ADHD patients (Significance level set at p<.001; voxel extension k=5)

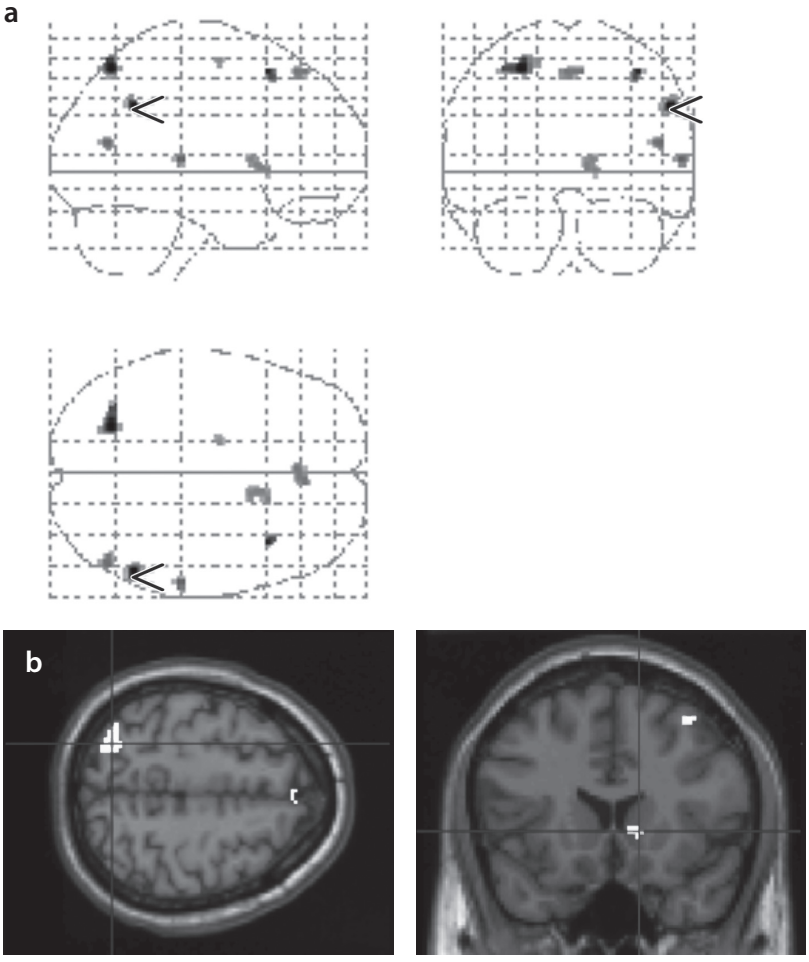


Table 2 **a**) Group comparison showing brain regions where ADHD patients revealed lower activation compared to healthy controls (NoGo condition; p<0.001 (uncorrected)

Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Right superior frontal gyrus	38,21,50 4,40,48	8 8	17 29	3.61 3.76	n.s. 3.39
Left superior frontal gyrus	-16,-4,54	6	9	3.20	n.s.
Right caudate nucleus (head)	13,15,2		35	3.81	3.22
Right superior temporal gyrus	57,-30,9	42	17	3.49	n.s.
Right middle temporal gyrus	51,-66,18	39	23	3.34	n.s.
Right supramarginal gyrus	54,-51,35	40	38	3.60	3.51
Left superior parietal lobule	-26,-62,51	7	87	3.61	3.25

b) Group comparison showing brain regions where ADHD patients revealed higher activation compared to healthy controls (NoGo condition; p<0.001 (uncorrected)

Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Left fusiform gyrus	-20,-82,-9	19	42	4.65	3.56
Right lingual gyrus	2,-87,0 12,-90,-2 20,-92,-2	17,18	42	3.67	n.s.
Left lingual gyrus	-24,-93,1	18	16	3.59	n.s.
Fusiform gyrus	-48,-59,-9	37	5	3.27	n.s.

Table 3 **a**) Brain regions with decreasing activation correlating with higher scores in inattention; NoGo condition; p<0.001(uncorrected)

Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Right and left superior frontal gyrus	16,27,53 5,42,47 -3,36,48	6 8 8	33 163	3.42 3.91 3.94	3.97 4.21 4.51
Right middle frontal gyrus	41,32,42	8	12	3.44	n.s.
Left middle frontal gyrus	-28,15,56	6	6	3.33	3.65
Right caudate nucleus	11,13,4 15,5,10		159	3.86 3.77	3.72 4.01
Left caudate nucleus	-9,6,11		16	3.47	3.56
Left praecentral gyrus	-28,-14,59	6	5	3.32	n.s.
Right inferior parietal lobule	56,-51,36	40	27	3.74	3.55
Left superior parietal lobule	-26,-62, 51 -38,-60,49	7	86	3.75 3.38	n.s. 3.73
Left supramarginal gyrus	-55,-48,33	40	10	3.25	n.s.

b) Brain regions with increasing activation correlating with higher scores in inattention; NoGo condition; p<0.001(uncorrected)

Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Right lingual gyrus	12,-89,1	17	6	3.46	n.s.
Left middle occipital gyrus	-22,-84,9	18	5	3.44	3.58

Table 3 **c**) Brain regions with hypoactivation correlating with higher scores in impulsivity; NoGo condition; p<0.001(uncorrected)

Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Right superior frontal gyrus	18,24,53 6,38,47	8 8	57 9	4.13 3.24	4.42 3.3
Right middle frontal gyrus	34,24,40 42,28,44	8 8	6 6	3.23 3.15	3.57 n.s.
Left middle frontal gyrus	-37,36,35 -32,3,56	9 6	16 8	3.31 3.24	n.s. n.s.
Right gyrus cinguli	2,19,38	32	37	3.66	4.13
Left precentral gyrus	-28,-14,58	6	43	3.42	3.34
Right inferior parietal lobule	60,-47,40 62,-25,26 52,-44,30	40 40 40	56 14 27	4.15 3.37 3.80	4.11 n.s. 3.54
Left superior parietal lobule	-30,-62,51	7	69	3.95	3.49

d) Brain regions with increasing activation correlating with higher scores in impulsivity; NoGo condition; p<0.001(uncorrected)

Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Left anterior Insula	-37,12,1	13	188	3.81	3.72
Left lingual gyrus	-1,-89,0	18	6	3.49	n.s.

3.5.1. Correlation with Inattentiveness

Lower activation associated with higher inattention scores were mainly found in brain areas that belong to a fronto-striatal network, suggesting a functional deficit within this network that depends on the degree of attention deficits according to ADHD DSM-IV (table 3a, figure 3a). Also activation of brain regions which belong to the parietal network was weaker when attention deficit scores increased. When we controlled data analysis for IQ, the same activation patterns were seen, even on a higher level of statistical significance (see table 3b).

Table 3 **e**) Brain regions with decreasing activation correlating with higher scores in hyperactivity; NoGo condition; p<0.001(uncorrected)

Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Right superior frontal gyrus	25,50,3	10	13	3.42	3.98
Left middle frontal gyrus -20,-6,58 -28,0,59 Left precentral gyrus -28,-14,59	-12,1,58	6 6	6 58	3.16 3.18 3.21 3.67	n.s. 3.31 3.45 3.23
Left superior parietal lobule	-34,-60,51	7	41	3.76	3.27

f) Brain regions with increasing activation correlating with higher scores in hyperactivity; NoGo condition; p<0.001(uncorrected)

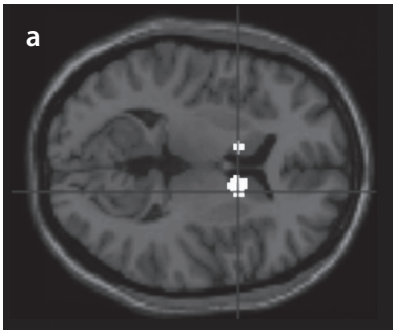
Region	Talairach coordinates x,y,z (mm)	Brodman area	Number of voxels	z-score	z-score corrected for IQ
Left anterior Insula	-42,-8,5	13	73	3.75	n.s.
Right inferior temporal gyrus	45,-9,-20	20	8	3.30	3.70
Left lingual gyrus	-1,-87,0	18	6	3.45	n.s.

Increased brain activation was seen in secondary visual areas in lingual gyri (BA 18), arising the hypothesis that with increasing lack of attention there might be more effort in visual polymodal brain areas to try to compensate this lack of attention (table 3b).
Non-parametric statistic revealed a significant negative correlation with medium correlation coefficient between left and right caudate nuclei activation and ADHD-SR inattention score (r_{left}=-.51, p=.002; r_{right}=-.60, p=.0001; figure). This result is shown in figure 3b.

3.5.2. Correlation with Impulsivity

When brain activity was correlated with ADHD-SR impulsivity subscores, also a fronto-parietal network appeared to be impaired with increasing psychopathology (table 3c). Frontal hypofunction comprised parts of the cingular cortex (BA 32) as an important region for integrating decisions and controlling motor execution (figure 4a). In this region

Figure 3 **a)** Caudate Nuclei. Picture displays anticorrelation of brain activation with increasing ADHD-SR inattention subscore Significance level set at p<.001; voxel extension k=5. **b)** Scatter plot depicting the anticorrelation between activation in the right caudate and ADHD-SR inattention subscore in adults with ADHD combined type (black triangles), ADHD, partially remitted (open triangles) and normal controls (circles);r=-.60; p=.000.



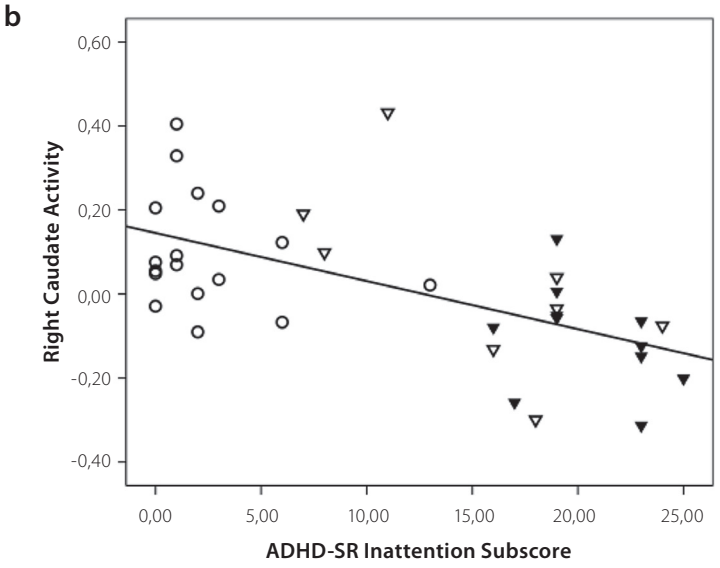
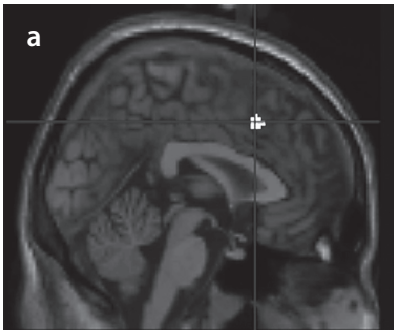


Figure 4 **a)** Anterior Cingulate Cortex (ACC/BA 32). Picture displays anticorrelation of brain activity with increasing ADHD-SR impulsivity subscore.
b) Scatter plot depicting the anticorrelation between activation in the anterior cingulate cortex (BA 32) and ADHD-SR impulsivity subscore in adults with ADHD combined type (black triangles), ADHD, partially remitted (open triangles) and normal controls (circles); r=-.41; p=.014.



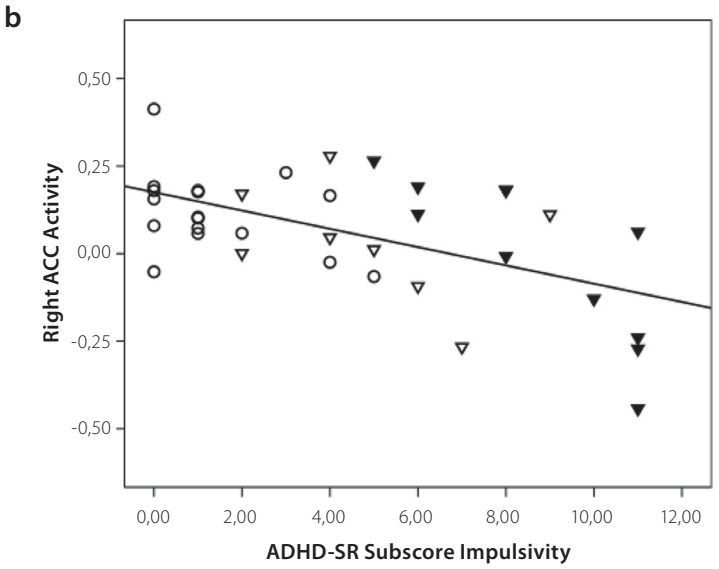
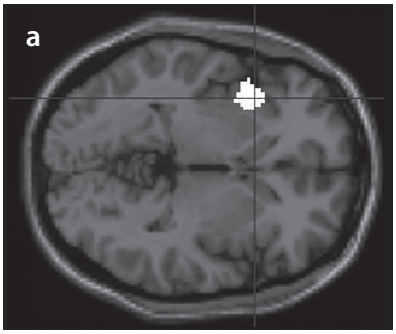
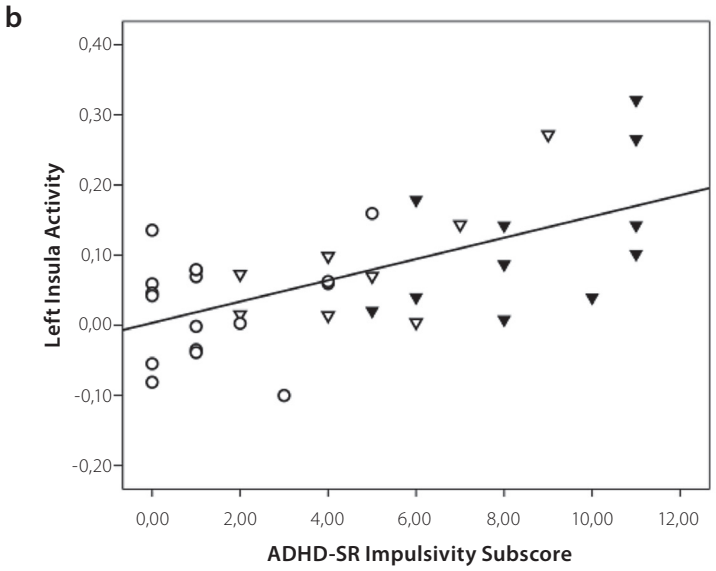


Figure 5 **a)** Left Insular Cortex. Picture displays correlation of brain activity with increasing ADHD-SR impulsivity subscore;. **b)** Scatter plot depicting the correlation between activation in the left insula and ADHD-SR impulsivity subscore in adults with ADHD combined type (black triangles), ADHD, partially remitted (open triangles) and normal controls (circles);r=.52; p=.001.





of interest, non-parametric analysis revealed a medium correlation coefficient and a significant negative correlation between ADHD-SR impulsivity subscore and impaired activation (r=-.41, p=0.014), which is shown in figure 4b. Statistical control for IQ resulted in higher significance concerning the lowered activity from the right cingulated gyrus, but the lowered activity in the left middle frontal gyrus with increasing impulsivity was not any longer statistically significant.
Increasing activation of left insula and secondary visual fields was detected with increasing impulsivity (figure 5a) also when corrected for IQ. For this region a medium correlation coefficient was found (r=.52, p=.001) (figure 5b).

3.5.3. Correlation with Hyperactivity

Concerning correlation of ADHD-SR hyperactivity subscore with activation of brain regions displayed a pattern similar to that found for inattention measures (tables 3e and 3f). Decreased activation of predominantly left frontal and parietal brain areas and an increased activation of insular cortex and gyrus lingualis were correlated with hyperactivity scores. When controlled for IQ, no correlation with left anterior insula and left lingual gyrus activation was found.

4. Discussion

According to our hypothesis of altered activation patterns in adults with ADHD, we found in this fMRI study correlates of decreased function within fronto-striatal and parietal brain networks associated with ADHD psychopathology. These findings corroborate functional imaging evidence of disturbed fronto-parietal networks, which has been described in adolescents with ADHD (Silk et al., 2005). In agreement with the literature concerning anatomical and functional changes within the brain of children, adolescents and adults with ADHD, the brain regions suggested to be involved in ADHD pathophysiology were found to be affected also in our study. These regions of interest are the anterior cingulate cortex (ACC), the prefrontal cortex, striatum, insula, the parietal cortex and cerebellum (Makris et al., 2007; Schneider et al., 2006).
Makris et al. (2007) reported thinning of prefrontal and parietal cortical regions belonging to attention and executive networks in adult ADHD and of the ACC in particular. Also Seidman and colleagues (2006) could show in adult ADHD patients morphological alterations of the ACC and prefrontal cortex. The ACC is the largest component of the limbic system. It plays a crucial role in the coordination of complex cognitive functions and in motor control. Two functional subdivisions of the ACC are specialized in "cognitive/attentional" and "affective emotional" information processing (Bush et al., 1998, 1999). Bush et al. (1999) found that ACC activation in adult ADHD patients was specifically impaired during the interference condition of a counting stroop task. They

could also show improvement of ACC activity after 6 weeks of methylphenidate therapy (Bush et al., 2008). ACC dysfunction has been reported also in ADHD children (Rubia et al., 1999; Durston et al., 2003). In adult patients with ADHD dysfunction of ACC has been demonstrated also with positron emission tomography (Ernst et al., 2003) and neurophysiological techniques (Fallgatter et al., 2005).

Alike, also striatal structures have been suggested to play a crucial role in ADHD pathophysiology. An elevated dopamine transporter density in the basal ganglia compared to healthy controls has been reported in ADHD adults (Krause et al., 2000, 2005; Dougherty et al., 1999). Using positron emission tomography (PET) Zametkin and colleagues (1990) demonstrated decreased metabolism of caudate nuclei during cognitive tasks in adults with ADHD. In functional imaging studies decreased activation of the striatum in ADHD has been described (Lou et al., 1984, 1989; Vaidya et al., 1998; Durston et al., 2003). Ströhle and colleagues (2008) described decreased ventral striatal activation during a reward task in ADHD, underlining the pathophysiological importance of fronto-striatal structures in ADHD also in the frame of reward paradigms. The diminished bilateral activation of caudate nuclei found in this study is in line with these findings and support the notion of disturbed dopaminergic transmission in adult ADHD patients.

A robust finding in our study was a dysfunction of the parietal cortex in adults with ADHD compared to controls. Diminished activation of the parietal lobule with increasing psychopathology was found throughout all ADHD-SR subscores. Only a handful of studies have addressed to parietal lobe structure and function in ADHD so far (Tamm et al., 2006; Smith et al., 2006), although this brain area plays an important role in orienting and selective attention networks (Fan et al., 2005). Posner et al. (1990) have described a posterior attention system located in the parietal lobe, which seems to be mainly modulated by noradrenergic transmission in contrast to the predominantly dopaminergic modulation of the frontal attention system. The posterior parietal cortex disengages the attentional focus from the contralateral target (Rafal et al., 1995), and lesions at this region can lead to impaired attention (Posner et al., 1995; Ro et al., 2001). Given its importance in visuo-spatial orienting and as a region for polymodal sensory integration, the parietal brain seems to be generally underestimated in context with attention deficits in ADHD.

A lower metabolism and smaller volume in parietal regions has been shown in ADHD children (Castellanos et al., 2002, Filipek et al., 1997, Ernst et al., 1997). Konrad et al. (2006) have used fMRI to investigate brain activations related to these particular aspects of attention. In that study parietal brain regions were less recruited by ADHD compared to control children. Task-specific abnormalities of parietal and temporal cortices in children and adolescents with ADHD were also demonstrated by Smith and colleagues (2006). Booth and coworkers (2005) could show in children with ADHD that a small region of the superior parietal lobule displayed a weaker activation during a selective attentional task. The findings of our study compare to these reports and underline the role of

parietal cortical dysfunction even in adult ADHD. Moreover, these findings lead to the hypothesis that in addition to the well described frontal brain regions also polymodal integrative cortical functions of the parietal cortex are impaired in ADHD pathology. The dysfunction in this brain area might lead to difficulties in integrating different inputs to an executive program and its inhibition.

Interestingly, we did not only find decreased activation of fronto-striatal and parietal attention systems in ADHD subjects, but also an increase of activation of some brain regions. Activation of the insular cortex in adult ADHD has been found in a prior fMRI study in which a counting Stroop paradigma was used (Bush et al., 1999). It has been speculated that the "insular pathway" might present an alternative to the activation of ACC and the prefrontal network during attention tasks (Bush et al., 1999). Thus, adults with ADHD might rather activate a different neuronal network than just use a given brain network that works insufficiently. Another hypothesis might be the higher anticipatory fear during task performance because of cognitive and inhibitory impairments (Chua et al., 1999). Wager and Barrett (2008) could demonstrate that shifting attention and executive working memory activate anterior insulae. This could be enhanced with emotional tasks. The authors found that recall generated emotion activated especially the left insula. Thus, it should be also considered that ADHD patients might tend to subvocalize during their task, which might be an attempt to compensate inhibitory dyscontrol resulting from hyperactivity and impulsivity (Morris et al., 1999). Fear and subvocalization have been post-hoc reported from some individuals in our study, but this was not systematically documented.

The results of this study indicate that ADHD associated dysfunction of attention networks might persist across the lifespan. Even in those individuals with a history of childhood but partially remitted ADHD in adulthood displayed abnormalities similar to those of subjects with persisting ADHD, combined type. Assuming that remission of ADHD psychopathology in these subjects is not a diagnostic artefact due to inappropriate diagnostic criteria for adult ADHD, it might be concluded that clinical remission depends on the individual's capability to compensate persisting dysfunction of attentional networks via activation of alternative pathways.

In this study we did not only compare brain activation patterns of adults suffering from ADHD with healthy controls during a cognitive task, but also looked for correlations between regional brain dysfunction and the degree of psychopathological abnormalities across the ADHD symptom domains. By doing this, we found that decrease of activation of frontal and parietal cortical areas was associated with an increase throughout the psychopathological domains of ADHD, inattention, hyperactivity and impulsivity. However, also differential effects were observed regarding the correlations between ACC dysfunction and impulsivity and between basal ganglia activation and inattention, supporting the concept of syndromatical ADHD subtypes (Biederman et al., 2000) and the hypothesis of independent changes of inattention and

hyperactivity-impulsivity symptom domains with age on a neuronal basis. However, it appears to be important to note that the correlations found in this study reflect a direct association between the severity of the clinical syndrome and the neuronal substrate of ADHD and underline the dimensional character of this disorder also in terms of their neuronal pathology. Several lines of evidence support the concept of ADHD as a dimensional disorder. For example, subthreshold ADHD cases showed fewer deviations regarding personality traits compared to full ADHD subjects, suggesting to present a milder form of ADHD that is consistent with dimensional views of this disorder (Faraone et al., 2009). Likewise, latent class analyses show that ADHD is best modeled as a continuum that is not caused by discrete dysfunction (Haslam et al., 2006). Further support comes from genetic studies, which have demonstrated the appropriateness of quantitative loci approaches in ADHD research, indicating no threshold effects on the risk for ADHD (Chen et al., 2008).

DSM-IV refers to the dimensional character of the disorder by requiring at least 6 of 9 typical criteria of inattention and/or 6 of 9 of hyperactive-impulsive features. If less than at least 6 criteria of either inattention or hyperactive-impulsive behavior are observed, no diagnosis of ADHD can be made, even if some characteristics of the disorder are present. According to DSM-IV, adults who suffered from ADHD in childhood but do not longer fulfill at least 6 items of either syndrome domain are diagnosed with ADHD, partially remitted. Thus, the diagnoses of ADHD, partially remitted directly refers to the dimensional character of this disorder and reflects the well known decline of the disorder with age, at least on a diagnostic and to lesser extend to a syndromatic level (Biederman et al., 2000). Concerning the dimensional character of attention, motor activity and impulsive behavior in general, and the lack of specific psychopathological ADHD features, a syndromatic continuum from healthy persons to those with sub-syndromatic and full ADHD can be assumed.

A limitation of this study is the recruitment of the patients from a specialized ambulance for ADHD and the high degree of preselection regarding psychiatric comorbidity and premedication. Therefore, the ADHD patients in this study might be not representative for typical adults with ADHD. However, the relatively low treatment prevalence of ADHD children in the past and the still lacking licence for any ADHD medication for ADHD adults in Germany allowed to include a quite homogeneous group of never medicated, but even moderately to severely affected ADHD patients in this study.

Moreover, the limited number of ADHD patients in this study did not allow differentiating gender effects on ADHD neurophysiology. Also, no individuals with ADHD, inattentive or hyperactive-impulsive type underwent imaging procedures. The effects of these ADHD subtypes on attention network activation could thus not be worked out. Further studies with specific design will be necessary to investigate these aspects.

Hyperactivity of some ADHD patients led to the problem that movement artefacts prohibited from fMRI data analyzing procedures. Especially the severely hypermotoric

ADHD patients had to be excluded from the study which could lead to a systematic bias. Finally, lacking structural data in this population, functional impairments might be confounded with structural differences between ADHD patients and controls, as they also concern the typical neural networks affected in attention processing (Makris et al., 2007).

In conclusion the results of this study give evidence to the hypothesis of dysfunction of fronto-striatal as well as parietal attention networks in adult ADHD. Moreover, the results underline the notion that ADHD is a dimensional disorder and that the severity of symptoms correlates with the degree of dysfunction of these networks. The mechanisms underlying ADHD in adulthood seem to be very similar to those in childhood and adolescence, suggesting that there might not be a qualitative difference between childhood and adulthood regarding ADHD pathophysiology. In addition, adults diagnosed with ADHD, partially remitted according to DSM-IV displayed activation patterns that resembled those of the persistent ADHD subjects and therefore seem to close the pathophysiological gap between healthy adults and adults with persisting ADHD, combined type.

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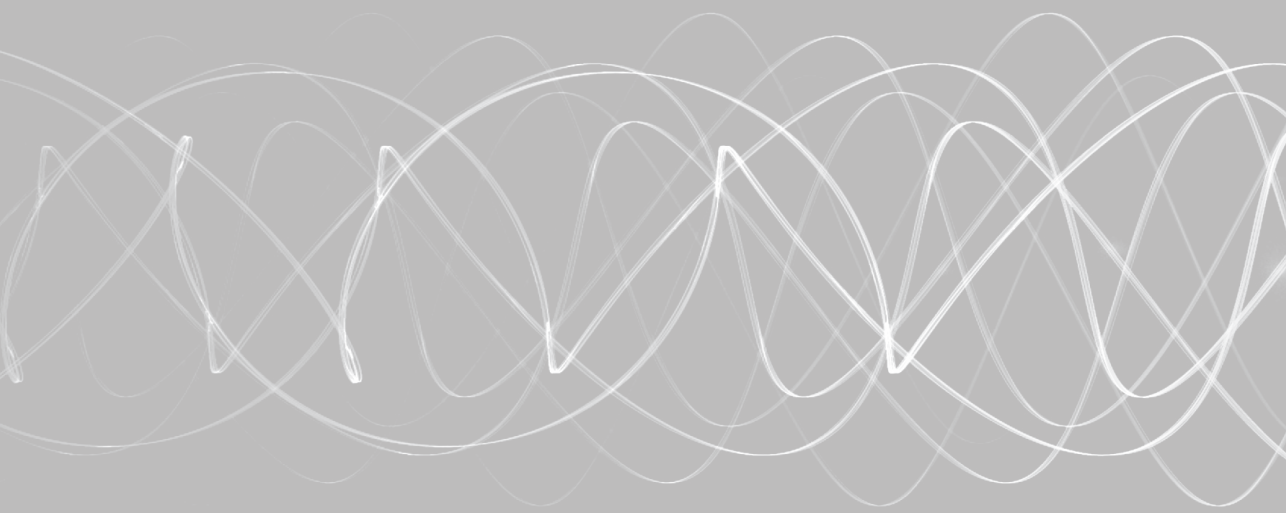

4 Impaired cortical inhibition in adult ADHD patients: a study with transcranial magnetic stimulation

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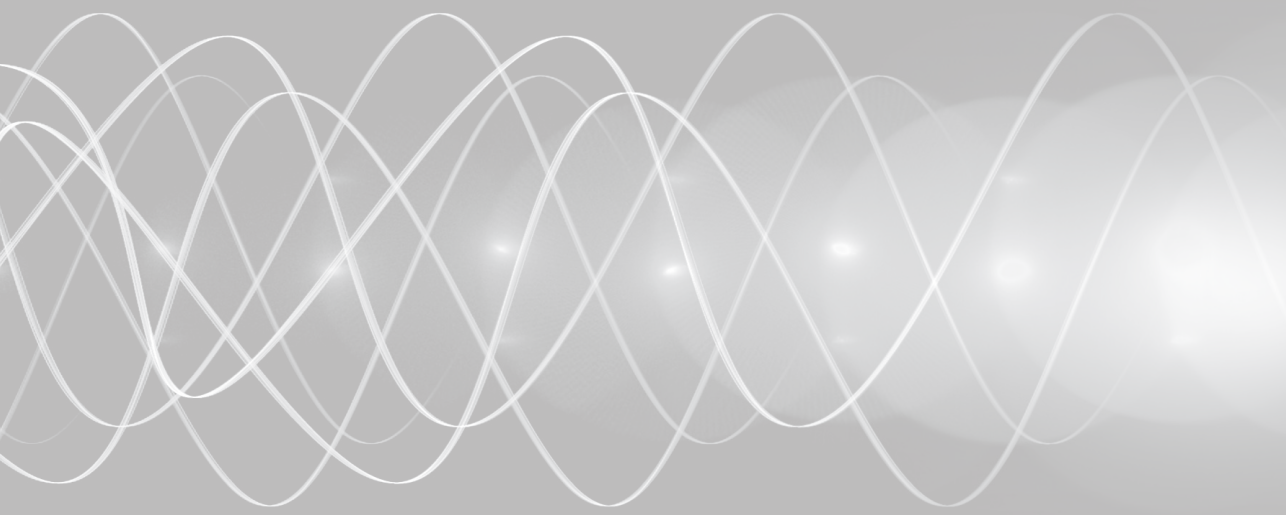


Abstract

The aim of this study was to analyze motor inhibition and facilitation of adult ADHD patients using double pulse transcranial magnetic stimulation (TMS). Twenty-six right handed adult ADHD patients according to DSM-IV were investigated and compared to 26 age and sex-matched controls. In the left hemisphere, mean motor inhibition was 0.53 ± 0.33 (mean ± SD) in ADHD patients and 0.34 ± 0.16 (mean ± SD) in controls (p=0.012). There were no significant differences in motor excitability concerning facilitation or in the right hemisphere. Decreased motor inhibition correlated with a higher symptom score derived from the Wender Reimherr Interview (WRI) (rho=0.28; p=0.04) and also with self rated hyperactivity/impulsivity symptoms (rho=0.30; p = 0.03).

In conclusion, decreased motor inhibition in adult ADHD corroborate similar findings in children with ADHD (Moll et al. 2000) and reflect disturbed impulsivity and hyperactivity on a neurophysiological level.

Introduction

The Attention Deficit-/ Hyperactivity Disorder (ADHD) is one of the most frequent disorders not only in child and adolescent psychiatry but also in general psychiatry. The prevalence in adulthood has been determined as 4% (Kessler et al. 2006). According to DSM-IV the core psychopathology in all ages comprises hyperactivity, impulsivity and attention deficits. These symptoms are significantly correlated with deficits in social functioning (Barkley et al. 2006). In comparison with healthy controls individuals with ADHD have lower levels of school and vocational education, more job changes, higher rates of divorces (Biederman et al. 2006) and are at increased risk of severe accidental injuries (Grützmacher 2001). Persons with ADHD commit significantly more traffic violations compared with controls (Jerome et al. 2006). The prevalence of ADHD in forensic populations is remarkably high (Vermeiren 2003), particularly in young male offender populations (Rösler et al. 2004a).

In this respect it is useful to question which abnormalities of the cerebral structures and functions may contribute to the emergence of psychopathology and social dysfunction. There is an overwhelming amount of evidence that ADHD is a disease with a profound genetic component (Faraone 2004). From twin studies, heritability estimates of 0.7 and higher were derived. These are among the highest heritability estimates in psychiatric disorders besides autism spectrum disorders. In molecular genetic studies associations were found predominately with genes controlling for the dopaminergic and serotonergic transmitter system (Heiser et al. 2004). Both transmitter systems are involved in the function of the prefrontal cortex. Dopamine plays a significant role in the anterior attention system (Pliszka 2005) and serotonin is a major component of the anterior cingulate cortex (Mantere et al. 2002), which seems to be affected in ADHD (Fallgatter et al. 2004, Seidman et al. 2006). In structural and functional imaging studies abnormalities of the prefrontal cortex are widely accepted findings, in addition to changes in the striatum and the cerebellum (Schneider et al. 2006).

Transcranial magnetic stimulation (TMS) is a non-invasive method to examine cortical function and to study the activation of brain regions based on the ability of a magnetic field to penetrate skull and brain meninges, subsequently inducing neuronal depolarization and the generation of action potentials (Bailey et al. 2001). Single or paired pulse TMS and repetitive TMS (rTMS) is differentiated on the basis of stimulation type. The effects of single or paired pulse TMS do not outlast the period of stimulation, whereas rTMS can produce effects which outlast the stimulation period depending on the stimulation parameters (Ziemann 2004). TMS is presently under investigation as a treatment for different psychiatric disorders, mainly affective disorders (Simons and Dierick, 2005). In addition to therapeutic approaches, TMS can also be used to examine cortical function in different brain areas. One of the main areas of TMS application is the investigation of cortical excitability, which is mediated by neurochemical and synaptic processes in

neurons, which are affected by TMS. Strafella et al. (2003) demonstrated that rTMS of the prefrontal cortex induced focal dopamine release in the ipsilateral caudate nucleus and increased extracellular dopamine concentrations. TMS studies subsequently reported that excitability of the motor cortex was changed by stimulation of contralateral cortical areas (Baumer et al. 2006; Porro et al. 2007).
Only a limited number of TMS investigations have been performed in individuals with ADHD. In ADHD children, Moll et al. (2000) reported reduced intracortical inhibition (ICI) associated with normal intracortical facilitation (ICF). After application of 10mg methylphenidate (MPH) ICI was enhanced in these children. Gilbert et al (2005) reported that ADHD scores in a sample of children and adults with Tourette syndrome were inversely correlated with ICI measured with TMS. In their study, hyperactivity scores, but not inattention, accounted for this finding. Moreover, disturbed transcallosally mediated contralateral motor inhibition in children with ADHD (Buchmann et al. 2003, Garvey et al. 2005) and modulation of cortical excitability by MPH and atomoxetine have been described (Buchmann et al. 2006, Gilbert et al. 2006) in TMS studies .
In this study we hypothesized that impaired cortical inhibition found in children (Moll et al. 2000) is also present in adults with ADHD. We also hypothesized that reduced motor inhibition or increased facilitation is correlated with the severity of ADHD.

Methods

Subjects and Instruments

The study was performed on 26 right-handed subjects with ADHD recruited from a specialized ambulance for ADHD-associated disorders. Each group consisted of 13 female and male subjects, respectively. All patients were without any DSM-IV axis 1 diagnosis, and were completely drug naïve. Further exclusion criteria were any history of neurological events, such as brain injury or any kind of vascular, inflammatory or degenerative brain disturbance (e.g. meningitis, encephalitis in childhood, developmental or degenerative disorder). Patients with low intelligence (IQ<85) were not included in the study.
The patients of the ADHD study group were initially diagnosed by experienced psychiatrists and fulfilled the diagnostic criteria of DSM-IV according to the ADHD-DC (ADHD Diagnostic Checklist, Rösler et al. 2004b). Twenty-four patients were classified as ADHD combined type and 2 as ADHD hyperactive/impulsive subtype. Control subjects were recruited from the staff of different university departments. They were matched with ADHD patients according to their sex and age.
Table 1 gives descriptive statistics for ADHD cases and controls with regard to age, sex distribution and ADHD symptoms.

Table 1 Descriptive statistics for cases and controls

	ADHD (N=26) Mean (Std)	Controls (N=26) Mean (Std)	Z-value p-value
Age (SD)	32.4 (9.1)	32.2 (7.9)	Z= -0.2 0.857
Gender	13 male 13 female	13 male 13 female	
WURS-k*	47.3 (13.6)	7.0 (9.2)	Z=6.1 < 0.0001
ADHD-SR* total score	36.8 (6.3)	6.0 (5.17)	Z=6.4 < 0.0001
ADHD-SR attention deficit subscore*	18.2 (4.6)	3.0 (2.5)	Z=6.3 < 0.0001
ADHD-SR hyperactivity/ impulsivity subscore*	18.6 (4.1)	3.0 (3.3)	Z=6.4 < 0.0001
WRI score*	43.3 (5.4)	9.3 (8.2)	Z=6.4 < 0.0001

* information missing on one individual with ADHD.
WURS-k: Wender-Utah-Rating Scale, German short version (Retz-Junginger et al. 2002, 2003)
ADHD-SR: ADHD self-rating (Rösler et al. 2004b)
WRI: Wender-Reimherr Interview (Rösler et al., 2008)

All patients displayed a sum score of at least 30 points in the Wender-Utah Rating Scale (WURS-k, Retz-Junginger et al. 2002, 2003), which is highly indicative for childhood ADHD symptoms, obtained by self assessment. Diagnostic criteria of ADHD were first obtained from the ADHD self rating scale (ADHD-SR) for adults according to DSM IV (Rösler et al. 2004b). Total scores ranged from 0 to 54 points. Maximum score for the attention deficit subscale is 27 and 27 for the hyperactivity/impulsivity subscale.
Second, individuals were interviewed by expert clinicians with the authorized German version of the Wender Reimherr Interview (WRI, Rösler et al., submitted) to obtain Utah criteria for adult ADHD. The WRI is also known as TAADDS (Wender 1995). The WRI is a semi-standardized diagnostic interview for the assessment of adult ADHD. It comprises 28 psychopathological items on 7 subscales which are inattention, hyperactivity, temper, affective lability, emotional hyperreagibility, disorganisation and impulsivity. Each item is quantified on a Lickert Scale ranging from 0 to 2 resulting in a maximum total WRI score of 56.

Patients with the clinical diagnosis of ADHD were included in the study only if (1) the WURS-k score was at least 30 points, (2) at least 6 of 9 items of inattention and/or hyperactivity/impulsivity were rated as present (score ≥ 1) on the ADHD-SR and (3) ADHD-SR attention deficit and/or hyperactivity/impulsivity subscores were at least 12 points.

Transcranial magnetic stimulation technique (TMS)

TMS utilizes the principle of electromagnetic induction by the discharge of very large currents over a short period which flow through a copper-wire coil. A rapid time-varying magnetic field is induced by an impulse of approximately 270μsec. When the coil is held to the head of a subject, the magnetic field pulse induces a small current parallel to the plane of the coil in the adjacent second conductor, the brain. When the induced current flowing parallel to the brain surface is sufficient, depolarization of neuronal membranes occurs, and hence an action potential is generated. Thereby preferentially interneuronal elements are activated, which are oriented horizontally to the surface of the brain (Day et al. 1989). TMS is thought to predominantly activate the pyramidal cells transsynaptically through excitatory interneuronal elements (Amassian et al. 1990; Day et al. 1989; Di Lazzaro et al. 1998; Nakamura et al. 1996).

With this technique, two magnetic stimuli are delivered in close sequence to the same cortical spot through a single stimulation coil (Kujirai et al. 1993). The first, conditioning, pulse (CP) is a subthreshold pulse and is considered to condition the response for the second, the test stimulus (TS) which is a suprathreshold stimulus and follows within a time period of several milliseconds. The magnetically evoked potential (MEP) obtained depends on the intensity of the CP, the interval between the stimuli (interstimulus interval, ISI), and the intensity of the TS (Pascual-Leone et al. 1998). Different circuits are recruited by varying intensities of CP and TS. At a ISI of 1 to 20 ms ICI and ICF may be studied. In our study, MEP's after an ISI of 1, 3, and 5 ms were accepted to indicate inhibition, and MEP's after an ISI of 7, 9, 11, 13, and 15 ms to indicate facilitation.

TMS was applied with a Medtronic MagPro X 100 Stimulator with MagOption (Medtronic, Denmark). A figure of eight coil with a diameter of 65mm was placed at the skull above the supposed hand area of the motor cortex. Surface electromyography was recorded from the contralateral first dorsal interosseus muscle (FDI) with a standard electromyographic amplifier (Medtronic Keypoint 4; recording software Medtronic Keypoint V 5.01). The bandwidth of the filters was set to 1 Hz and 10 kHz, respectively. The optimal position of the coil was determined by moving the coil by 0.5 cm steps until an optimal MEP could be registered. Resting (RMT) and active motor thresholds (AMT) were determined according to the protocol of Kujirai et al. (1993). Briefly, RMT was the minimal stimulus intensity which was required to produce motor potentials of more than 50μV peak to peak amplitude in 50% of the testpulses. AMT was determined in analogy to RMT, while the subject tonically distended a dynamometer with 10-20% of maximum power.

"In-Out"-curves were determined by increasing stimulus intensity in steps of 10% beginning from subthreshold intensities up to maximum stimulus output at 100%. Eight MEP´s were averaged at each stimulus level.

Double-pulse stimulation was performed according to the technique of Kujirai et al. (1993). The subthreshold conditioning pulse (CP) was set at 80% of RMT and was followed by a suprathreshold test stimulus (TS). The TS was adjusted to produce a mean MEP of 0.5 to 1.2 mV peak to peak amplitude, when unconditioned (uMEP). The interstimulus intervals were set between 1 and 15 ms at distances of 2 ms. At each interstimulus interval 8 trials were averaged. The time between two measurements was at least 5 seconds to avoid secondary effects, such as potentiation. Peak-to-peak amplitudes of these conditioned MEP´s (cMEP) were set into relation to a MEP elicited by the mean of 8 testpulses without any conditioning prepulse (unconditioned MEP, uMEP). Data are presented as relative amplitudes of the uMEP (relative amplitude = cMEP/uMEP). Care was taken to relax the subjects and to avoid any movements of the extremities during recordings. Each MEP was checked optically to ensure that first dorsal interosseus muscle (FDI) was completely relaxed. Recordings were discarded if any evidence of electromyographic activity was detected and repeated.

Statistical analysis

Descriptive statistics to compare ADHD scores and mean MEP after different ISI in cases and controls were performed by the non-parametric Wilcoxon rank sum test. Spearman correlations were calculated to assess correlation of ADHD scores with mean inhibitory MEP, i.e. the averaged response after an ISI of 1, 3, and 5ms.

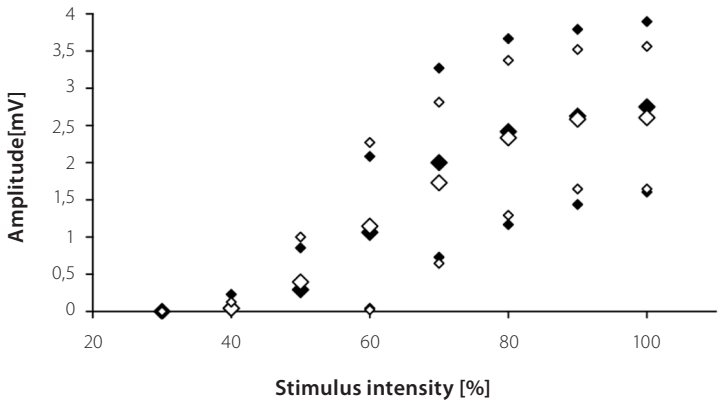
To compare inhibition and facilitation between groups, multivariate statistical analysis of co-variance (MANCOVA) adjusted for age, was performed on four blocks of variables: log transformed MEP after the ISI 1ms, 3ms, and 5ms on the (1) right and (2) left (inhibition) and log transformed MEP after the ISI 7ms, 9ms, 11ms, 13ms, and 15ms on the (3) right and (4) left (facilitation). Due to this multivariate analysis, no further adjustment for multiple testing was made. To assess the influence of attention and hyperactivity/impulsivity on inhibition, exploratory linear regression analyses were performed with the log transformed mean MEP after ISI 1ms, 3ms and 5ms (inhibition) of the left hemisphere as the dependent, and the ADHD self assessment scores or the Wender-Reimherr-Interview score as the independent variables, adjusted for age. Residuals were normally distributed.

Statistical analyses were performed using SAS 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

In table 1, descriptive data for ADHD patients and healthy controls are shown. There was no age difference in ADHD patients and controls. Groups were matched for sex. ADHD scores of the patients were significantly elevated compared to controls.
Mean relative amplitude of resting motor threshold (RMT) was 50.0 (SD 6.5) (left hemisphere - LH) and 51.9 (SD 8.9) (right hemisphere - RH) in the ADHD group and 47.7 (SD 5.8) (LH) and 49.6 (SD 9.96) (RH) in the control group. For active motor threshold the mean relative amplitude was 43.6 (SD 6.2) (LH) and 42.9 (SD 7.5) (RH) in the ADHD group and 39.8 (SD 5.6) (LH) and 41.7 (SD 9.7) (RH) in the control group. Neither AMT nor RMT differed significantly between the groups on either hemisphere. There was also no correlation of thresholds with ADHD symptom rating scores. Means and standard deviations of input-output curves did not differ between patients and controls, indicating that excitatory mechanisms of motor systems did not differ between groups (figure 1).

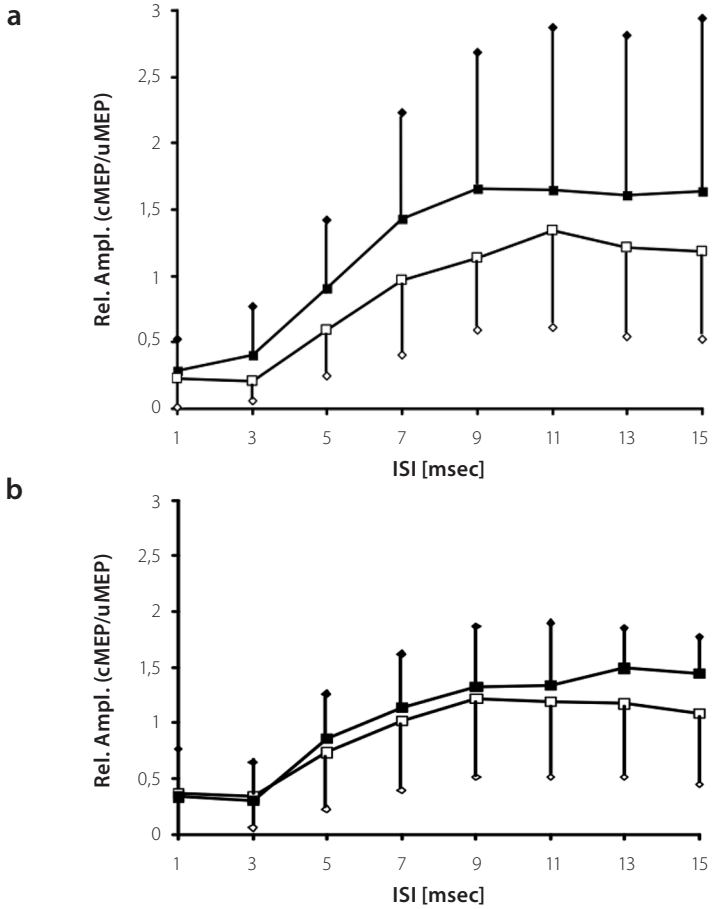
Figure 1 Input-output eyefit curve (stimulation left hemisphere); stimulus intensity [%] of maximum stimulator output; mean absolute amplitudes of the MEP [mV]; filled diamonds represent mean (SD) MEP in ADHD; open diamonds represent mean (SD) MEP in controls



Significant differences in motor excitability between ADHD patients and controls were found with the double pulse protocol. As shown in figure 2, the relative MEPs (cMEP/uMEP) increased with longer ISIs and displayed a sigmoidal curve in both groups. Lowest relative amplitudes (<1) were found in short ISI (1–5ms) of paired-pulse curves, reflecting intracortical inhibition (ICI). Intracortical facilitation (ICF), corresponding to

relative amplitudes >1 occurred at ISI of above 5ms and reached maximum values at 15ms ISI. ADHD patients showed generally higher mean relative amplitudes at each ISI compared to controls. There was also an increasing variability of the MEPs with increasing ISI in ADHD patients.

Figure 2 Relative amplitudes (conditioned MEP (cMEP)/unconditioned MEP (uMEP)) after double pulse stimulation in ADHD patients and controls: **a**) left hemisphere; **b**) right hemisphere.



Filled squares represent mean relative amplitudes in ADHD, filled diamonds represent standard deviation in ADHD; open squares represent mean relative amplitude in controls, open diamonds represent standard deviation in controls. ISI: interstimulus interval

Table 2 TMS paired pulse stimulation. The table shows mean relative amplitudes (cMEP (conditioned magnetically evoked potential) / uMEP (unconditioned magnetically evoked potential))

Inter-stimulus interval		Left hemisphere Mean (SD)		Statistic*	Right hemisphere** Mean (SD)		Statistic*
		ADHD	Controls		ADHD	Controls	
Intracortical Inhibition (ICI)	1 ms	0.29 (0.23)	0.23 (0.22)	Wilk's Lambda=0.84; F=3.23 (3, 51) P=0.030	0.37 (0.40)	0.34 (0.44)	Wilk's Lambda=0.95; F=0.72 (3, 46) P=0.543
	3 ms	0.40 (0.37)	0.21 (0.15)		0.34 (0.31)	0.31 (0.25)	
	5 ms	0.91 (0.51)	0.59 (0.34)		0.74 (0.52)	0.86 (0.63)	
Intracortical Facilitation (ICF)	7 ms	1.44 (0.79)	0.97 (0.54)	Wilk's Lambda=0.84; F=1.92 (5, 49) P=0.108	1.02 (0.60)	1.14 (0.74)	Wilk's Lambda=0.90; F=1.01 (5, 45) P=0.425
	9 ms	1.66 (1.02)	1.13 (0.54)		1.22 (0.65)	1.32 (0.80)	
	11 ms	1.65 (1.22)	1.30 (0.79)		1.19 (0.71)	1.34 (0.82)	
	13 ms	1.61 (1.20)	1.21 (0.67)		1.17 (0.68)	1.49 (0.97)	
	15 ms	1.64 (1.30)	1.18 (0.66)		1.08 (0.69)	1.44 (0.99)	

* MANCOVA on log-transformed values

** Measures missing on 3 ADHD and 2 control individuals

Multivariate analysis of co-variance (MANCOVA) performed on the four ISI blocks (ICI and ICF, left and right hemispheres) revealed significantly impaired inhibition of the left hemisphere in ADHD patients compared to controls (Wilk´s Lambda = 0.84; F=3.23; 3, 51 DF; p=0.030; see table 2). A similar change was found, when the mean of the MEP after an ICI of 1, 3, and 5 ms was compared between groups (mean motor inhibition in ADHD 0.53 ± 0.33 (mean ± SD); in controls 0.34 ± 0.16 (mean ± SD; F=6.85; 1 DF, p=0.012). There was no further statistically relevant difference concerning facilitation of the left hemisphere and in the inhibition or facilitation of the right hemisphere (table 2).

Mean relative MEP significantly correlated with the WRI total score (β-estimate = 0.009; p=0.029; ρ = 0.30) and the impulsivity/hyperactivity score of the ADHD-SR subscale (β-estimate = 0.019; p=0.037; ρ = 0.30), but not with the attention deficit subscore or the ADHD-SR total score respectively (table 3).

Table 3 Correlation of ADHD-scores with left hemisphere inhibition in the combined ADHD and control sample. Results of the linear regression analyses on the log-transformed mean of relative MEP after ISI 1ms, 3ms, and 5ms as dependent variable

Independent variable	β-estimate	Standard Error	t-value	P
ADHD-SR total score	0.008	0.004	1.71	0.092
ADHD-SR attention deficit subscore	0.010	0.009	1.17	0.248
ADHD-SR hyperactivity/impulsivity subscore	0.019	0.009	2.14	0.037
WRI total score	0.009	0.004	2.23	0.029

ADHD-SR:ADHD self-rating (Rösler et al. 2004b)
WRI: Wender Reimherr Interview (Rösler et al. submitted)

Discussion

In this study, we found reduced intracortical inhibition in a sample of adult ADHD patients compared to controls, using transcranial magnetic double pulse stimulation. The findings are in line with a previous study in ADHD children (Moll et al. 2000) and a preliminary report in adults with ADHD (Richter et al. 2006). In our adult ADHD sample we found no significant increase of cortical facilitation, in agreement with previously

reported findings in ADHD children (Moll et al. 2000). Our findings therefore suggest that changes of motor excitability in adults with ADHD are similar to those in children with ADHD.

When the dimensional characteristics of ADHD were assessed, inhibitory deficits in our ADHD subjects were positively correlated with two different symptom scores, i.e. the less inhibition the more symptoms. Interestingly, we found a significant correlation with hyperactivity and impulsivity, but not with inattention scores. Similarly, Gilbert et al. (2005) reported an inverse correlation (r=0.53) of ICI with ADHD symptom scores in Tourette patients. The strength of the association in the latter study was also greater with the hyperactivity/impulsivity subscore than with the inattention subscore, suggesting that hyperactive/impulsive behaviours are linked with cortical inhibitory dysfunction in Tourette patients. Compared to the study of Gilbert et al. (2005) however, the correlation between ICI and hyperactivity/impulsivity in our study was less pronounced**.** This difference could be due to a lack of motor tics or spontaneous motor activity in our study population without Tourette disorder or might be based on different pathophysiological mechanisms underlying these disorders.

Moreover, the WRI score that comprises not only ADHD core symptoms but also additional emotional components of adult ADHD according to the Utah criteria (Wender 2005) was significantly related to inhibitory deficits. This finding suggest, that emotional problems in ADHD like affective lability, emotional overreagibility and hot temper might be related to the same neuropathological processes as impulsivity and hyperactivity, i.e. deficits of cortical inhibition.

Another result of our study was the identification of inter-hemispheric asymmetry of ICI deficits in ADHD patients, which was not present in healthy controls. In adults with ADHD, ICI deficits occurred only in the left hemisphere. Brain asymmetry in ADHD has been reported several times in the literature. Schrimsher et al. (2002) could predict the cumulative severity ratings of inattentive behaviours by measuring caudate volume asymmetry from serial sagittal magnetic resonance images from childhood to adolescence. Unilateral volume reductions of the pallidum have also been shown in several studies in children with ADHD (Aylward et al. 1996, Castellanos et al. 1996, 2002, Overmeyer et al. 2001). Most studies however, describe volume reductions within the right hemisphere. Therefore, the hypothetic mechanisms leading to reduced inhibition of the left side can only be deduced from unknown and complex mechanisms leading to contralateral effects.

In our study we did not find differences between ADHD subjects and healthy controls regarding resting motor (RMT) and active motor thresholds (AMT). Also simple stimulus response curves did not differ between ADHD patients and controls. This agrees with previously reported observations in children with ADHD (Moll et al. 2000). Thus, there is no evidence for motor hyperexcitability within the motor system in ADHD at the membrane level of cortical neurons (Ziemann et al. 1996d).

In general, our results suggest that TMS, and the paired-pulse technique in particular, is a useful tool for motor excitability research in ADHD. It allows the study of intracortical circuits (Ziemann 1999; Kujirai et al. 1993; Valls-Sol et al. 1992; Ziemann et al. 1996d) and displays little inter- and intraindividual variability (Maeda et al. 2002). ICI deficits have been shown to have reliable test-retest stability in adults with ADHD (Richter et al. 2006). ICI and ICF appear to be due to activation of separate circuits (Ziemann et al. 1996d), represented by inhibitory interneurons or inhibitory connections between cortical output cells (Wassermann et al. 1996) and facilitatory interactions partially in the motor cortex, at or upstream from corticospinal neurons (Ziemann et al. 1996d). Conditioning pulses in the double-pulse stimulation technique are thought to activate inhibitory interneurons within the motor system including projections onto corticospinal neurons (Kujirai 1993). Several neural transmission systems like GABAergic, dopaminergic and glutamatergic systems appear to play an important role in these mechanisms. Medications that enhance GABAergic activity have been shown to increase the degree of ICI and decrease ICF evoked by paired TMS stimuli (Inghilleri et al. 1996, Werhahn et al. 1998, Ziemann et al. 1996b, 1996c). Dopaminergic drugs have been shown to enhance ICI in normal subjects (Berardelli et al. 1996, Priori et al. 1994, Ridding et al. 1995, Ziemann et al. 1996a). Glutamatergic drugs have been shown to increase intracortical inhibition and decrease facilitation (Schwenkreis et al. 1999, Ziemann et al. 1998).

In conclusion, this paired-pulse magnetic stimulation study is the first to demonstrate that intracortical inhibition in adult ADHD is reduced compared to matched controls and occurs only in the left hemisphere. These deficits correlate with ADHD symptomatology, especially with hyperactivity and impulsivity behaviour. The findings therefore corroborate the hypothesis of inhibition deficits on a neuronal level. Compared to previous findings of double pulse TMS in ADHD children our results suggest that there is no fundamental difference between affected children and adults with respect to excitability of the frontal motor cortex. Further studies are needed to confirm and to further define these excitatory phenomena in ADHD to gain a greater insight into the etiology of ADHD and to generate useful endophenotypes of this disorder.

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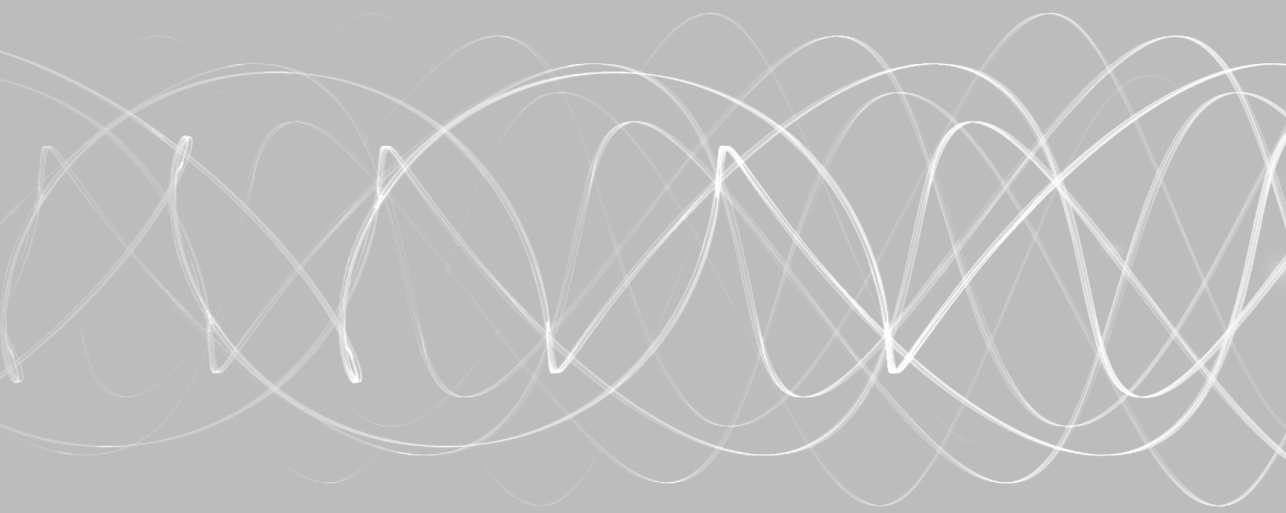

5 The effects of long acting Methylphenidate in adults with Attention Deficit Hyperactivity Disorder: A study with paired pulse Transcranial Magnetic Stimulation

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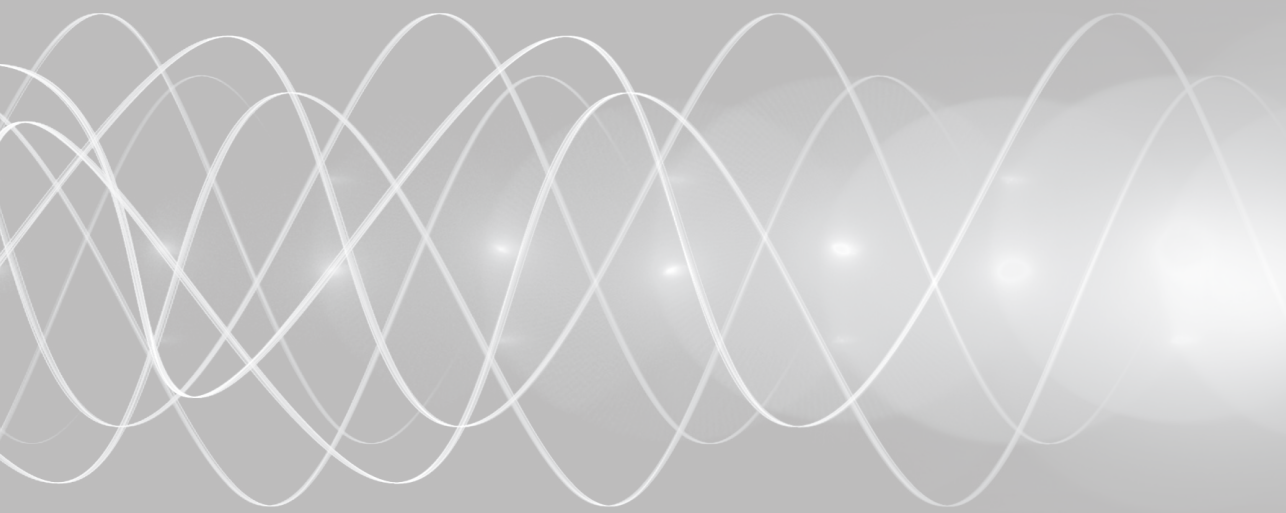


Abstract

Background: Methylphenidate improves attention deficits, hyperactivity and impulsivity in ADHD. Recent investigations into motor cortex excitability with paired pulse transcranial magnetic stimulation technique (ppTMS), have shown inhibition deficits in ADHD which correlate with the clinical symptomatology. Therefore, we investigated the neurophysiological effects of long acting methylphenidate (LA-Mph) with the ppTMS technique in adult patients with ADHD.

Methods: Thirteen right handed adult ADHD patients who were first diagnosed with ADHD were included in this ppTMS study. Measurements took place before and under treatment with LA-Mph (30-54mg daily dose). Statistical analyses were performed to investigate treatment effects and correlations with clinical symptomatology.

Results: LA-Mph significantly decreased the relative short intracortical motor inhibition (SICI) magnetically evoked potential (MEP) amplitude at 3ms interstimulus interval (conditioned/ unconditioned MEP amplitude: 0.84±0.76 drug-free vs. 0.29±0.19 with Long acting-methylphenidate (LA-Mph); p=0.020). The relative intracortical facilitation (ICF) MEP amplitude at 11ms interstimulus interval (conditioned/ unconditioned MEP amplitude: 1.51±0.92 drug-free vs. 1.79±0.95 with LA-Mph) was not significantly increased. The reduced relative SICI MEP amplitude with LA-Mph correlated significantly with the improvement of the psychopathological ADHD self-rating total scores (p=0.046).

Conclusion: These results show that in adult patients with ADHD, LA-Mph significantly improves motor disinhibition and might have differential stabilizing effects on motor hyperexcitability.

Introduction

Methylphenidate (Mph) is a psychostimulant and is used for more than 50 years in the treatment of attention deficit, hyperactivity and impulsivity symptoms in ADHD. It increases dopaminergic and noradrenergic synaptic efflux throughout the brain and has a rapid onset of action without attenuation of drug effects [1]. Low doses of Mph have limited influences on dopamine (DA) and norepinephrine (NE) in the prefrontal cortex only, without inducing effects on other areas of the brain at higher dosages [2]. The behavioural and cognitive effects of this stimulant drug are not specific and occur in ADHD as well as in normal subjects. The well known clinical experiences with Mph contrast with the lack of detailed knowledge about the neurobiological mechanisms of stimulant action on motor cortex in human ADHD. Recent imaging studies converge mainly towards improvement of disturbed fronto-striatal activity [3,4].

With the paired pulse transcranial magnetic stimulation (ppTMS) technique, the short intracortical inhibition (SICI) and intracortical facilitation (ICF) can be analyzed [5]. The ppTMS technique is also an useful and non-invasive tool to investigate the influence of pharmacological modulation on intracortical motor excitability [6]. The recent literature is inconsistent regarding the effects of immediate release Mph on SICI and ICF in ADHD and their underlying mechanisms [7-12]. Indeed, immediate release Mph has disadvantages, in that it has to be given several times per day, whereas long acting Mph (LA-Mph) can be administered once or twice a day and induces less fluctuations in plasma concentration. Therefore, LA-Mph given once or twice per day has pharmacokinetic advantages for the treatment of adults with ADHD [13], although the plasma concentration may show interindividual variations [14]. Over the past years, a limited number of studies with TMS in ADHD patients has been published in which immediate release Mph was used with, however, unequivocal results [7-12]. Until now, no study has been performed with the ppTMS technique that investigated the effects of LA-Mph. With LA-Mph, the clinical state of the ADHD patient is more stable and allows, therefore, for better clinical state correlations.

In this study, it is hypothesized that LA-Mph improves disturbed ppTMS intracortical excitability in adult patients with ADHD and that these effects are positively correlated with clinical improvement of the ADHD symptoms.

Methods

Patient characteristics and medication procedures

Thirteen right handed patients were recruited by experienced board certificated psychiatrists (MS, GG, WR) from specialized outpatient centres for ADHD-associated disorders (SHG Klinik für Psychiatrie und Psychotherapie, ADHS Ambulanz, Saarbrücken;

Neurozentrum der Universität des Saarlandes, ADHS Ambulanz, Homburg) . They were diagnosed with ADHD combined type for the first time according to the diagnostic criteria of DSM IV (ADHD-DC: ADHD Diagnostic checklist [15]), and had used no stimulant medication before. The Wender Utah Self Rating Scale (WURS-k) [16,17]) was used to indicate childhood ADHD symptoms. Statistical test analysis indicated a sensitivity of 85% and specificity of 76% at a cutoff of 30 points. Its inner consistency is high (Cronbach α= 0.91) [17]. Patients with the clinical diagnosis of ADHD were included in the study if the WURS-k score was at least 30, and when at least 6 of 9 items of inattention and/or hyperactivity/impulsivity were present. As indicator of severity of symptoms, the ADHD self-rating scale for adults (ADHD-SR) according to DSM IV [15] was used (total score: 0 to 54; attention deficit and hyperactivity/impulsivity subscores: each maximal 27; test-retest reliability 0.80, inner consistency Cronbach α=0.90). A semistandardized expert clinical assessment for adult ADHD, the German validated version of the Wender Reimherr Interview (WRI) [18,19], was applied to quantify the Utah criteria for adult ADHD. The WRI is also known as WRAADDS [19] and comprises the subscales inattention, hyperactivity, temper, affective lability, emotional hyperreagibility, disorganization and impulsivity, yielding 28 psychopathological items, each being quantified on a Lickert Scale ranging from 0 to 2. This results in a maximum total WRI score of 56. The internal consistency of this interview is also high (Cronbach α=0.82) [18]. SCID-1 and 2 interviews were used to exclude further axis I and II DSM categorical diagnoses.

The recruited patients had no psychoactive medication prior to the diagnosis of ADHD. None of them had additional DSM IV axis I or II diagnoses. As additional exclusion criteria served: drug abuse, relevant somatic problems, as well as any known conditions with metabolic or immunologic pathology. Other exclusion criteria were any kind of degenerative, traumatic, inflammatory or vascular brain disturbance (e.g. developmental disorder, meningitis, encephalitis in the anamneses, neurodegenerative brain disease), and low intelligence (IQ<85). Estimation of intelligence was done by the "Mehrfachwahl Wortschatztest (MWT-B)", a verbal IQ test [20] .

The patients gave written informed consent to participate in the study. The TMS study was approved by the local ethical committee.

In this clinical study, oral dose of LA-Mph was increased gradually to obtain both an optimal individual dosage and to avoid side effects. Patients were examined by a board certified and experienced academic psychiatrist with intervals of two weeks. The first clinical and electrophysiological measurement took place just before the start of the medication. After the patients had reached the optimal individual dose of LA-Mph (Medikinet ret®, Concerta®) for at least two weeks, they were re-assessed with the above mentioned ADHD instruments. The second electrophysiological measurement was performed two weeks after the ADHD scores were decreased by at least 50% (ADHD-SR) according to the clinical interviews (WRI, ADHD-DC). The patients had to take the medication at an exactly defined time point (8.00h). The medication dosage should be

in the range of 0,3 to 1,0 mg/kg bodyweight. An optimal dosage was defined as the dosage that reached optimal subjective profit for the patients in daily living without or with a minimum of tolerable side effects. The LA-Mph medication had to be stable for at least two weeks before TMS tests. A follow up TMS test was performed 4 to 6 hours after the last medication intake. Eleven patients were treated with Medikinet ret® (range of daily dosage 30-40mg), and 2 patients with Concerta® (daily dosage 36/54mg).
Thirteen adult ADHD patients (11 male, 2 female), aged 34.3±11.8 years (mean±SD, range 18-49 years) participated in the study. All patients fulfilled DSM IV criteria for adult ADHD combined type (for ADHD scores, see Table 1). The ADHD patients displayed a total score of more than 30 in the self-assessment WURS-k [15], which is strongly indicative for childhood ADHD symptoms (49.23±12.05). There was a highly significant reduction of ADHD clinical symptoms (see Table 1) under medication of 30-54mg LA-Mph (34.62±7.28). The average therapeutic daily dose of LA-Mph was 0.50±0.1 mg/kg bodyweight (range 0.41-0.78 mg/kg).

Table 1 Basic ADHD scores and neurophysiological data (mean ± STD) in drug naïve and after two weeks of stable treatment with LA-Mph (30-54mg)

	drug-free	with LA-Mph	Paired t-test statistic
ADHD-SR total score	38.15 ± 7.00	16.54 ± 4.37	**t=16.645; p<.000**
ADHD-SR subscore attention deficit	19.85 ± 4.1	9.08 ± 3.59	**t=18.252; p<.000**
ADHD-SR subscore hyperactivity/ impulsivity	18.31 ± 5.07	7.46 ± 2.73	**t=11.223; p<.000**
WRI- score	42.23 ± 6.11	19.92 ± 6.28	**t=13.883; p<.000**
RMT	54.00 ± 7.20	56.00 ± 6.84	n.s.
AMT	44.46 ± 6.75	45.69 ± 6.87	n.s.
SICI 3ms	0.83 ± 0.76	0.29 ± 0.19	t= 2.679; **p=0.020**
ICF 11 ms	1.51 ± 0.92	1.79 ± 0.95	n.s.

TMS protocol

Patients were lying comfortably in a supine position with elevated stand of the upper body and head. TMS was applied with a Medtronic MagPro x100 Stimulator with MagOption (Medtronic, Denmark). A figure of eight coil with a diameter of 65 mm was placed at the left motor cortex area where the hand motor region was subjected. The rapid time-varying magnetic field induced an impulse of approximately 270 µsec. Surface electromyography was recorded from the contralateral first dorsal interosseus

muscle (FDI) with a standard electromyographic amplifier (Medtronic Keypoint 4; recording software Medtronic Keypoint V 5.01). The bandwidth of the filters was set to 1 Hz and 10 kHz, respectively. The optimal position of the coil was determined by moving the coil by 0.5 cm steps until an optimal magnetically evoked potential (MEP) could be registered. When the induced current flowing parallel to the brain surface was sufficient, depolarization of neuronal membranes occurred, and hence an action potential was generated and recorded at the FDI muscle of the right hand. Care was taken to relax the subjects and to avoid any movements of the extremities during recordings. Each MEP was checked optically to ensure that the FDI was completely relaxed. Recordings were discarded if any evidence of electromyographic background activity was detected and repeated.

Resting (RMT) and active motor thresholds (AMT) were determined according to the protocol of Kujirai et al. [5]. Briefly, RMT was the minimal stimulus intensity which was required to produce motor potentials of more than 50 μV peak to peak amplitude in 50% of the test pulses. AMT was determined in analogy to RMT, while the subject tonically distended a dynamometer with 20% of maximum power.

Two magnetic stimuli were delivered in close time sequence to the same cortical spot through a single stimulation coil [5] to perform the paired pulse protocols. The first, conditioning pulse (CP), was a subthreshold pulse that was considered to condition the response for the second, the test stimulus (TS), which was a suprathreshold stimulus. The TS followed within a time period of milliseconds. Different brain circuits are recruited by varying intensities of CP and TS.

Eight MEP's were averaged at each stimulus level. Paired pulse stimulation was performed according to the technique of Kujirai et al. [5]. The subthreshold conditioning pulse (CP) was set at 80% of RMT. The TS was adjusted to produce a mean MEP of 0.5–1.2mV peak to peak amplitude, when unconditioned (uMEP). The interstimulus intervals were set at 3ms and later at 11ms. At each interstimulus interval 8 trials were averaged. The time between two trial pulses was at least 5 sec to avoid secondary effects, such as potentiation. Peak-to-peak amplitudes of these conditioned MEP's (cMEP) were set into relation to the uMEP. TMS data are presented as relative amplitudes (=cMEP/uMEP). At ISI 3ms, arelative MEP ratio of smaller than 1 is to be considered as short intracortical inhibition (SICI). At ISI 11ms, a ratio of more than 1 is to be considered as intracortical facilitation (ICF). In our study, relative MEP's at an ISI of 3ms were accepted to indicate inhibition, and relative MEP's at an ISI of 11ms to indicate facilitation [5,36].

Statistical analysis

To compare the differences of the dependent neurophysiological variables between the pre- and under medication with LA-Mph measurements, the Student's t-test was performed. For the correlations between neurophysiological and clinical parameters, the Pearsons PM correlation coefficient (r) is used. An analysis of covariance (ANCOVA)

was applied to study the influence of the covariates ADHD-SR total and subscores (attention deficit, hyperactivity/ impulsivity), WRI total and subscores (inattention, hyperactivity, temper, affective lability, emotional hyperreagibility, disorganization and impulsivity), intelligence, age, medication doses as well as body weight adapted medication doses, on the relative MEP amplitudes before and after treatment. The level of significance was set at p = .05. All analyses were performed witch SPSS 15.0

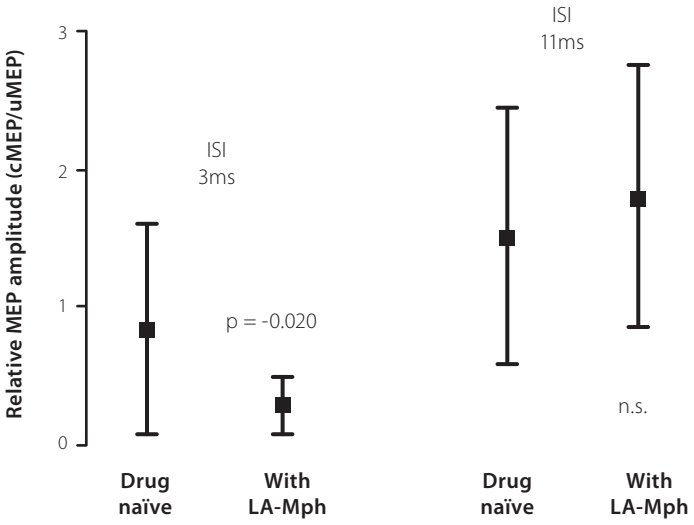
Results

In this study, thirteen adult ADHD patients with an age range of 18-49 years who met DSM IV criteria for adult ADHD combined type were treated with LA-Mph. Paired pulse transcranial magnetic stimulation was performed before and after 2 weeks of stable individualized oral dose.
In the drug naïve condition, the left hemisphere resting motor threshold (RMT) in ADHD patients was 54.0±7.2% and 56.0±6.8% during treatment with LA-Mph. There was no significant difference between the RMT with or without LA-Mph, or between the AMT with or without LA-Mph (44.5±6.7% vs. 45.7±6.9% with MPH). There was also no significant correlation with motor thresholds and ADHD symptom rating scores.
There was a significant difference in relative MEP amplitudes (cMEP/uMEP) between drug naïve conditions and medication with LA-Mph (Table 1 and Figure 1). The relative MEP amplitude at ISI of 3ms corresponds to SICI, whereas the ISI of 11ms corresponds to ICF (see also [21]). At ISI 3ms, the mean relative MEP was 0.83±0.76, and with LA-Mph it was lowered to 0.29±0.19. This relative amplitude reduction was significant (t=2.679; p=0.02). At ISI 11ms, drug naïve mean relative MEP amplitude was 1.51±0.92. With LA-Mph, it was 1.79±0.95. This increase in relative amplitude was not significant. The SICI and ICF amplitudes did not correlate with LA-MPH dosage.

The drug naïve relative MEP amplitudes at ISI 3ms correlated significantly with the ADHD-SR total score (r=0.590; p=0.034/ see Figure 2) and the ADHD-SR hyperactivity/ impulsivity subscore (r=0.604; p=0.029). The relative MEP amplitude at ISI 3ms under LA-Mph medication, correlated only weakly with the difference on the ADHD-SR score between drug naïve and medication condition (r=0.56; p=0.046). Correlations with ADHD-SR inattention subscores or WRI scores with relative MEP amplitudes at ISI 3 or 11 ms, as well as with the amplitude differences with and without LA-Mph, revealed no statistical significance.

Further analysis of covariance revealed that the neurophysiological data were not significantly influenced by medication doses, ADHD-SR and WRI subscores, age, and intelligence.

Figure 1 Effects of long acting methylphenidate (LA-Mph) on relative short intracortical inhibition (ISI 3ms) and intracortical facilitation amplitude (ISI 11ms) in a paired pulse TMS protocol (N= 13, MPH: 30–54mg).



Ordinate: relative MEP amplitude (cMEP/uMEP). Squares represent mean values, bars representing SD

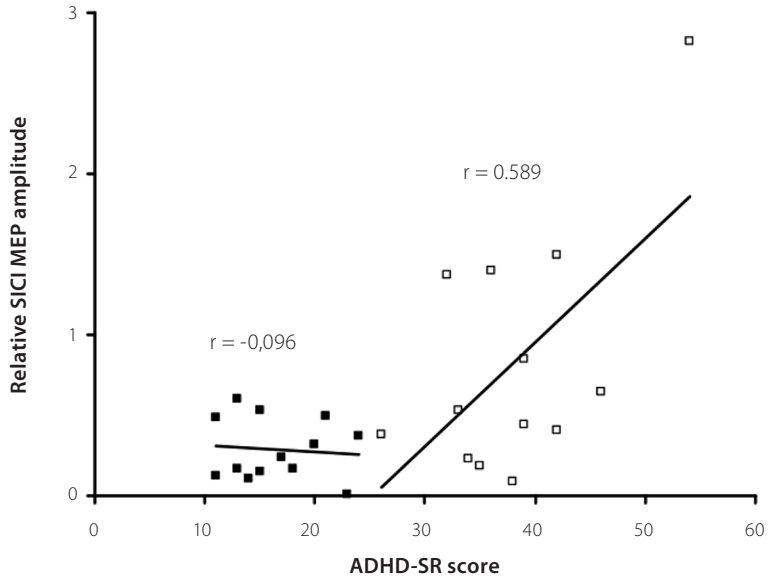
Discussion

In this study, it was assessed whether LA-Mph has an influence on motor excitability in adult patients with ADHD. For that purpose, the ppTMS technique was used, which previously had already revealed a lowered SICI in adults with ADHD [21,22]. The ppTMS technique has been shown to provide a reliable test-retest stability of SICI and ICF in adults with ADHD [5,23].

RMT and AMT are supposed to be markers of membrane stability of cortical neurons [24]. In the present study, LA-Mph had no influence on RMT and AMT. These results are in line with those from other recent studies [7,9,10,11,25] and support the hypothesis that Mph does not affect membrane characteristics.

Inhibition is a cortical phenomenon which is considered to reflect the inhibitory activity of interneurons in the motor cortex or of connections between cortical output cells [26]. In contrast, facilitation occurs at the level of the corticospinal neurons, and upstream [27,

Figure 2 Scatterplot of relative SICI MEP amplitudes (ISI 3ms) in drug naïve condition (open squares) and under medication with LA-Mph (black squares).



Abscissa: ADHD-SR scores. Linear regression fits are displayed: r= 0.589, p= 0.034 (drug naïve condition) and r= -0.096, n.s. (under medication with LA-Mph)

24]. SICI and ICF are supposed to reflect cortical excitability independently and to be modulated through complex neural transsynaptic systems (mainly GABA, dopamine, glutamate, serotonine). Several drugs influence the ppTMS motor inhibition as well as the facilitation [6]. Pharmacologic interactions with SICI and ICF are suggested to depend from the clinical state, since it is known that paroxetine may enhance ICF in healthy probands, but decreases this parameter in patients with schizophrenia [28]. In healthy volunteers, it has been shown that, dependent on the 5-HT transporter genotype, serotonergic reuptake inhibitors may, however, have differential effects on SICI [29]. Thus, drug effects of Mph on motor excitability may vary dependent on the genetic phenotype.

Mph increases the synaptic levels of dopamine via blockade of the dopamine transporter (DAT). In addition, Mph binds to and inhibits the neuronal norepinephrine transporter (NET) [30]. More neuronal transporters and receptors are affected, since Mph binds also

to muscarinic and serotonergic receptors and to serotonin transporters in the brain [31]. Dopaminergic and noradrenergic agonists have been shown to increase SICI, while dopamine antagonists have a decreasing effect [6]. It is also suggested that the degree of SICI is increased by GABAergic action via cortical GABAergic interneurons, whereas ICF is decreased [32-35], [6],[36].

Whilst the clinical and pharmacological treatment effects of Mph are well described, the underlying basic pharmacological mechanisms in the motor cortex remain unclear as yet [37,38]. It is actually hypothesized that in ADHD a general deficit in the behavioural inhibition is present [39] and also in the inhibition of motor systems [40]. No direct evidence, however, is available which motor inhibition deficit is specifically involved in ADHD. This may be explained by the complex interactions between the motor cortex and the frontocortical regulatory systems (prefrontal cortex, caudate nucleus, and globus pallidus) and the parietal cortex which are all disturbed in ADHD [3,41]. Since Mph exerts effects on the total spectrum of ADHD symptoms, studying the effects of Mph in ADHD cannot be interpreted as an influence on motor systems only [38]. Although the data that support direct interactions of Mph on motor cortex are scarce, Lou and colleagues [42] demonstrated with PET-scan technique that Mph administration reduces blood flow in the primary motor and sensory cortex. These findings were interpreted as improvement of inhibition and consequently of motor overactivity also.

Previous studies have shown higher basic SICI MEP amplitudes in ADHD patients, not only in childhood [11], but also in adults [8, 21]. The latter phenomenon appeared to correlate also with the clinical ADHD scores and ADHD hyperactivity/impulsivity subscores [8,21]. The here presented results show that LA-Mph in daily dosages between 30 and 54mg significantly reduces elevated SICI MEP amplitudes, but do not influence ICF MEP amplitudes. A significant correlation was found only between the difference in the two scores on the ADHD self rating instruments (baseline and 8 weeks treatment with Mph) and the second measurement of SICI MEP amplitude. This might be attributed to other factors than the ADHD phenotype influencing motor cortex exitability. Significant lowering of elevated SICI MEP amplitudes under Mph medication was reported by Moll and coworkers [11], as well as by Buchmann and coworkers in children with ADHD [7]. The latter also reported a correlation of reduced SICI MEP amplitudes with clinical ADHD symptomatology under treatment with Mph which is comparable to the here described results in adults with ADHD. The decline of hyperactivity/impulsivity symptoms in ADHD during lifetime [9,43] may explain why the power of the associations of the neurophysiological data with hyperactivity/impulsivity scores becomes less pronounced as observed in the present study.

Our findings that SICI MEP amplitudes decrease during treatment with LA-Mph are partially in line with the observations in healthy adults by Ilic [10] and coworkers and also by Kirschner and coworkers [25] The latter investigators described, in addition to a lowering of SICI MEP amplitudes with Mph, an increase in ICF MEP amplitudes. This

could lead to the hypothesis that Mph exerts effects on the cortical motor system but not specifically in ADHD.

It is questionable whether short time treatment with 30mg Mph is sufficient to investigate putative effects of Mph on ADHD neurophysiology [8]. Therefore, the recruited patients were kept in a stable clinical condition for at least 2 weeks prior to the experimental phase. Furthermore, LA-Mph was used in order to achieve the most consistent biological availability and TMS was performed after the most optimal clinical response was achieved.

The lack of correlation effects of LA-Mph and SICI with the inattention scale of ADHD-SR underlines our previously formulated hypothesis that the ppTMS technique reflects motor cortex excitability (hyperactivity/impulsivity) and not the attention dysfunction [21]. Furthermore, it should be mentioned that the WRI measures primarily disorganization, attention deficit and temper regulation problems, as well as affective aspects of impulsivity, but not motor phenomena. Therefore, effects on motor symptoms cannot be evaluated with this instrument.

A limitation of this study is the open label design without including relevant control groups (healthy subjects treated with immediate release and/or long acting Mph, unmedicated ADHD patients). Moreover, the statistical power of the data with this small group of ADHD patients is low. Furthermore, plasma concentrations of LA-Mph, that could have elucidated abnormal metabolism of the compound, were not measured [14]. The latter might explain why clinical symptoms as assessed with the ADHD scoring instruments, had no significant influence on the variability of the neurophysiological data. Finally, genetic factors like subtypes of DAT or noradrenaline transporter may also account for different motor behaviours elicitated by Mph [29] cited in the literature.

In conclusion, the results from this study demonstrate that LA-Mph decreases SICI MEP amplitudes in adults with ADHD, which correlated with the clinical improvement of ADHD symptoms. These results are in line with those from treatment studies with Mph in ADHD children. It can therefore be hypothesized that the pathophysiological mechanism, as reflected by paired pulse TMS in children with ADHD, is also present in adulthood. This may explain the identical response to pharmacological treatment in adults. Since the reports on treatment effects of Mph in adults with ADHD are so far equivocal, further studies are warranted especially with respect to pharmacokinetics and release of Mph.

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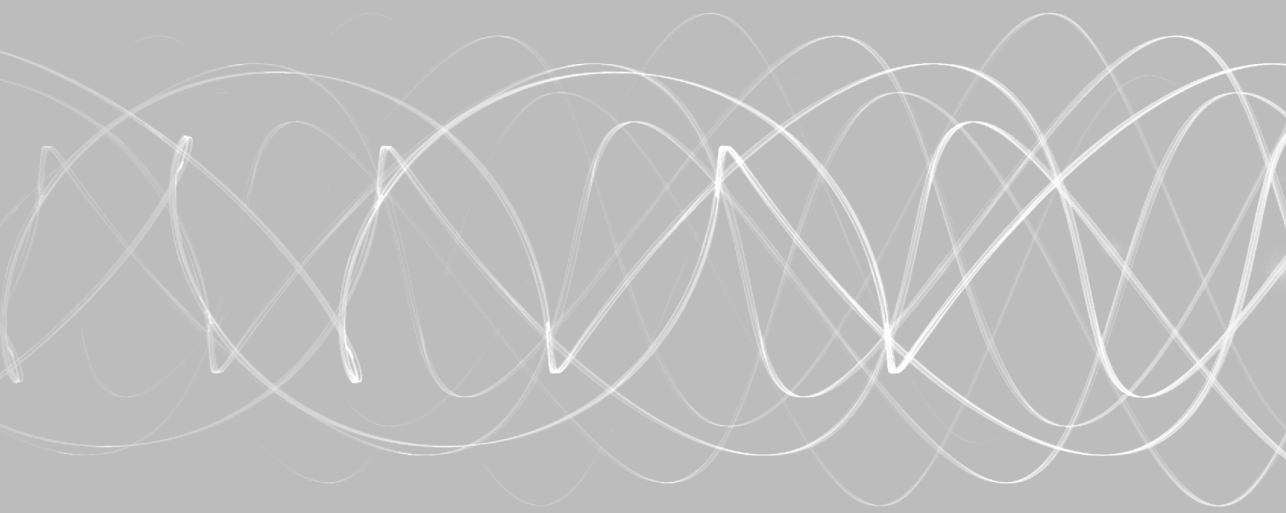

6 Reduced cortical inhibition in first-episode schizophrenia

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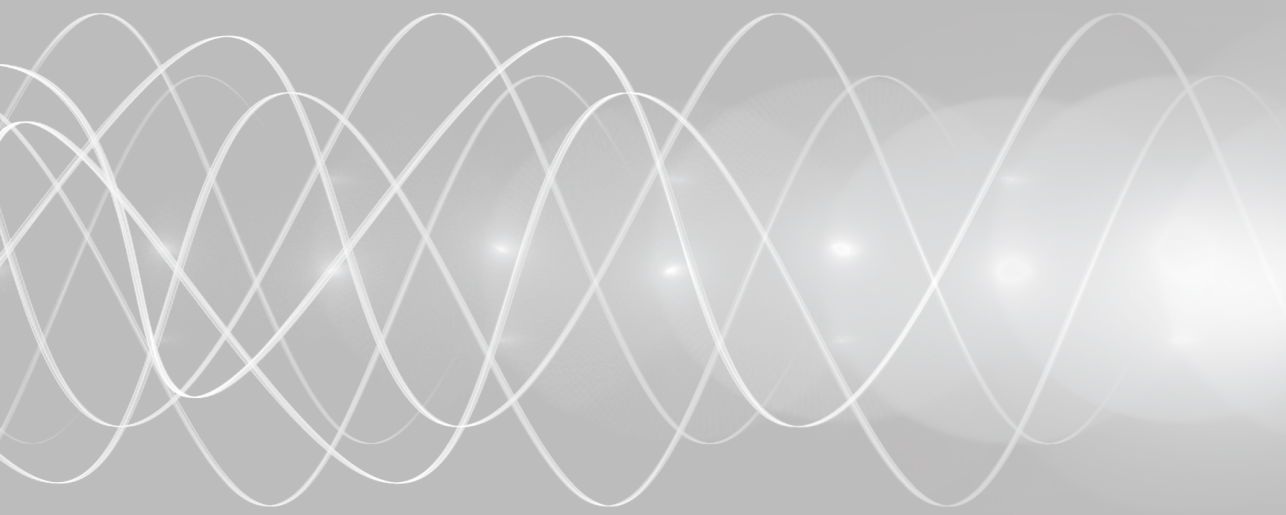


Abstract

Disturbances in corticocortical and corticosubcortical circuits in schizophrenia have been described by previous neuroimaging and electrophysiological studies. Transcranial magnetic stimulation (TMS) provides a neurophysiological technique for the measurement of cortical excitability, especially of the motoneural system. Previous studies using paired-pulse TMS to investigate short-interval cortical inhibition (SICI) and intracortical facilitation (ICF), mainly involving chronic patients, have been inconsistent and only one study in first-episode patients has been conducted so far.

We assessed SICI (interstimulus interval, ISI, 3 milliseconds, ms) and ICF (ISI 7 ms) in 29 first-episode schizophrenia patients (FE-SZ) with limited exposure to antipsychotic treatment compared to 28 healthy controls (HC). The amplitudes of the motor evoked potentials (MEPs) were measured in the left and right first dorsal interosseus muscle (FDI). The conditioning stimulus was set at 80 % intensity of resting motor threshold (RMT) and test stimulus (TS) was set at an intensity that produced a MEP amplitude of about 1 millivolt.

Patients with first-episode schizophrenia demonstrated significant higher MEP amplitudes on left motor cortex (right FDI) and higher amplitudes at a trend level on right motor cortex (left FDI) for SICI compared to healthy control subjects (FE-SZ 41 % vs. HC 21 % of TS, $p = 0.017$ for left motor cortex, and FE-SZ 59 % vs. HC 31 % of TS, $p = 0.059$ for right motor cortex; Mann-Whitney-U-Test). No significant difference in MEPs could be detected for ICF on both hemispheres. In addition no difference was seen in left and right RMT comparing patients and control subjects.

Our result of a reduced SICI in a large sample of well characterized first-episode schizophrenia patients suggests that a GABAergic deficit may be involved in schizophrenic pathophysiology, already early in the disease course, supporting the intracortical dysconnectivity hypothesis.

1. Introduction

Transcranial magnetic stimulation (TMS) of the motor cortex has been investigated as a noninvasive approach for in vivo evaluation of inhibitory and excitatory cortical circuits (Maeda and Pascual-Leone 2003). In the primary motor cortex, TMS is thought to predominantly activate the pyramidal cells transsynaptically through excitatory interneuronal elements (Day et al. 1989).

With paired-pulse techniques, interactions between the first and the second pulse occur. Typically, a subthreshold first (conditioning) stimulus induces a shortterm modulation of the motor evoked potential (MEP) from a suprathreshold second (test) stimulus (Kujirai et al. 1993). Short interstimulus intervals (ISIs) of 2–5 ms inhibit, and longer ISIs of 7–20 ms facilitate the MEP amplitude. This TMS-induced modulation must at least in part be generated cortically, presumably by intracortical interneurons modulating the activity of corticospinal neurons (Kujirai et al. 1993; Ziemann et al. 2000). It is believed that in short-interval intracortical inhibition (SICI), using ISIs of 2-5 ms, the sub-threshold first pulse produces an inhibitory post-synaptic potential (IPSP) at the corticospinal neurones through activation of a low-threshold cortical inhibitory circuit, which inhibits action potential generation by excitatory post-synaptic potentials (EPSPs) elicited by the supra-threshold second pulse (Kujirai et al. 1993, Ziemann 2004). The SICI is discussed to be mediated through GABAergic interneurons via $GABA_A$-receptors, which modulate ligand-gated ion channels causing most of the fast synaptic inhibition in the mammalian brain (Nakamura et al. 1997). Consistent with this hypothesis $GABA_A$ agonists enhance SICI (Ziemann 2004). Intracortical facilitation (ICF), using ISIs longer than 7 ms, seems to be influenced by excitatory neuronal circuits in motor cortex, which are at least in part dissociable from the SICI network (Ziemann 2004). ICF may represent a net facilitation consisting of prevailing facilitation and weaker inhibition. The latency to onset of EPSP mediated by NMDA receptors is in the order of 10 ms, which would be consistent with the time course of ICF, and points towards the importance of glutamatergic transmission for ICF. According to this assumption, NMDA receptor antagonists, and in addition $GABA_A$ agonists, mostly decrease ICF (Ziemann 2004).

Post-mortem investigation demonstrated reduced numbers of cortical gabaergic interneurons in the brain of patients who suffered from schizophrenia (Benes 1998), suggesting abnormalities in interneuro-pyramidal modulation. Reduced glutamic acid decarboxylase (GAD67) mRNA expression in the dorsolateral prefrontal cortex, an enzyme that synthesizes GABA, is one of the most consistent findings in schizophrenia in post mortem studies (Knable et al. 2002). Furthermore, a dysfunction of subpopulations of gabaergic interneurons in dorsolateral prefrontal cortex with the consequence of alteration in perisomatic inhibition of pyramidal neurons is made responsible for deficits in working memory, a core syndrome in schizophrenia (Lewis et al. 2005).

Motor deficit is a known feature in patients with schizophrenia with or without medication (Chen et al. 2000, Smith et al. 1999), and cortical inhibition deficit has been suggested as one component of the possible pathophysiological mechanisms in schizophrenia (Freedman et al. 1983). In consequence, these considerations build the background for investigating cortical inhibition in schizophrenia by transcranial magnetic stimulation.

Previous studies using the paired-pulse paradigm in schizophrenic patients revealed controversial results. While in one study reduced SICI in a small sample of unmedicated schizophrenic patients, but not in patients treated with antipsychotics compared to healthy controls could be observed (Daskalakis et al. 2002), in another study reduced SICI and increased ICF in medicated, but not in drug-naïve schizophrenic patients was found (Pascual-Leone et al. 2002). One research group observed reduced SICI in medicated schizophrenic patients compared to controls (Fitzgerald et al. 2002a) and no difference in facilitation, but could not replicate this finding in a larger sample of patients (Fitzgerald et al. 2002b). An investigation of neuroleptic-naive first-episode patients, mainly consisting of patients with disorganised schizophrenia, showed no difference in SICI or ICF compared to healthy gender and age matched control subjects (Eichhammer et al. 2004). However this sample seems not to be representative of first-episode patients, as they mostly belong to the paranoid subtype of schizophrenia.

In addition, there is some evidence that in schizophrenia patients the development of cerebral lateralization is disturbed (e.g. Crow et al. 1989). Healthy subjects may have a lower resting motor threshold (RMT) on the dominant (left) hemisphere in correlation to handedness and increased use of the dominant (right) hand (Triggs et al. 1994). Schizophrenia patients failed to show this normal laterality in physiologic differences in cortical motor representation compared to healthy controls in a previous study (Pascual-Leone et al. 2002).

In the present study first-episode patients (FE-SZ), representative for this patient group and recruited from a hospital setting with minimal exposure to antipsychotics, were measured by paired-pulse TMS to examine their cortical excitability in comparison to healthy control subjects (HC). Additionally, motor threshold in both hemispheres were compared within the subgroups.

2. Methods

2.1. Subjects

The study sample consists of 57 persons recruited at the University Hospital of the Saarland between 2003 and 2006, 29 patients with first-episode schizophrenia, all paranoid subtype, and 28 healthy control subjects. Subjects suffering from dementia, neurological illnesses, severe brain injuries or brain tumors as lifetime diagnoses were

excluded from the study. The following standardized examinations were performed on each subject: biographic interview (Bassett et al. 1993) and test of hand preference (Annett 1970). Patients underwent standardized assessment of psychopathology by PANSS-rating (Kay et al. 1987), of disease severity by clinical global impressions (CGI) (Guy and Bonato 1976) and of social functioning (GAF) (Endicott et al. 1976). The diagnosis based on a consensus of two independent psychiatrists performing SCID I and II interviews (Wittchen et al. 1997. Fydrich et al. 1997). Additionally the duration of illness (DUI), counted from the beginning of initial prodromal symptoms, the duration of psychosis (DUP), starting with the first positive symptoms belonging to the criteria of schizophrenia, and familial risk factors (psychosis in first degree relatives) were assessed. After a complete description of the study, written informed consent was obtained from each subject. The local ethic committee approved the protocol, which is in accordance with the Declaration of Helsinki.

None of the participants had a contraindication for TMS.

All 29 schizophrenic patients were treated with second generation antipsychotics (aripiprazole 2, olanzapine 18, quetiapine 2, risperidone 7, and two patients additionally treated with haloperidol) not longer than 6 weeks continuously. To compare the cumulative and daily doses of the different antipsychotics and to explore the influence of this medication on TMS parameters, chlorpromazine equivalents were calculated using suggestions of reviews and studies especially with regard to second generation antipsychotics (e.g. Woods 2003). Duration, cumulative dose and daily dose of the antipsychotic medication (expressed in chlorpromazine (CPZ) equivalents) are described in table 1. Concomitant treatment with benzodiazepines, mood stabilizers, beta-blocking agents and anticholinergics were not allowed during the last week before performing the TMS measurement.

2.2 TMS procedure

Subjects were seated in a comfortable chair with their arms supported passively. Electromyographic (EMG) recordings were made with surface electrodes from the right and left first dorsal interosseus muscle (FDI) using a commercial amplifier with a bandpass filter of 2 Hz to 10 kHz (Keypoint portable, Medtronic Co., Denmark), and each signal curve was analysed off-line and manually. Focal transcranial magnetic stimulation (TMS) was applied to the hand area of the left and right motor cortex using a figure-of-eight magnetic coil and a MagPro X 100 magnetic stimulator (Medtronic Co., Denmark). For each subject, the optimal coil position, defined as the stimulation site that produced the largest MEP at moderately suprathreshold stimulation intensities (i.e., intensities that induced MEPs of about 0.5–2.0 mV) in the resting right and left FDI muscle was determined by moving the coil in 0.5-cm steps over the presumed area of the left and

right motor cortex. The site was marked to ensure that the coil was held in the same position throughout the experiment. The coil was held tangentially on the head with the handle pointing backward and 45 degree laterally from midline that the induced current points forward and perpendicular to the central sulcus and is optimal for producing transsynaptic activation of corticospinal neurons. The resting motor threshold (RMT), expressed as a percentage of maximum stimulator output, was defined as the lowest intensity that produced a MEP of >50 μV in five out of ten trials in relaxed FDI (Ziemann et al. 1996a).

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were obtained in accordance to previously published protocols (e.g., Maeda and Pascual-Leone 2003, Eichhammer et al. 2004). The intensity of the first (conditioning) stimulus was always set at 80 % of the RMT. The second (test) stimulus was delivered at an intensity that produced MEPs averaging 0.5 - 1.5 mV in the resting FDI. Since it is known from previous studies that short ISIs (2 – 5 ms) lead to an inhibition and longer ISIs (7 – 20 ms) lead to a facilitation of the test stimulus (Kujirai et al. 1993), we used an ISI of 3 ms as inhibitory (SICI) and an ISI of 7 ms as facilitatory (ICF) paired-pulse TMS paradigm. We performed a minimum of 10 trials with each ISI and 10 trials with the test stimulus alone. The effect of the conditioning stimuli on MEP amplitude of the test stimulus was determined as the ratio of the average amplitude of the conditioned ppTMS MEP (cMEP) to the average amplitude of the unconditioned test MEP (uMEP) (Eichhammer et al. 2004).

The measurements were performed by an experienced investigator (T.W.), controlled by another experienced investigator (M.S.), and corrected for outliers and extreme values. The stimuli were ordered differently and randomly for each subject, and they were counterbalanced across groups.

2.3. Statistics

For statistical analyses SPSS for Windows 14 was used. All tests were two-tailed. Level of significance was set at $\alpha = 0.05$. Dependent variables were RMT, SICI (ISI 3 ms) and ICF (ISI 7ms) on both hemispheres. Independent variable was diagnosis (healthy controls, FE-SZ). Kolmogorov-Smirnov tests were applied to test the assumption of normal distribution for all dependent variables. As for SICI and ICF the normality assumption was violated, non-parametric tests were performed for these variables.

Oneway analysis of variance (ANOVA) was used to analyze if there were significant age differences between the two diagnostic groups. Chi^2-test on independence was performed to analyze if distribution of gender and hand difference was different between the groups.

For the control sample, correlations between age and dependent variables were computed (RMT: Pearson product moment correlations, SICI and ICF: Spearman rank correlations) and mean differences for the factor gender were analyzed (RMT: oneway

ANOVA, SICI and ICF: Mann-Whitney U-test). Since all controls were right-handers, mean differences for factor hand preference was analyzed in the FE-SZ sample (RMT: oneway ANOVA, SICI and ICF: Mann-Whitney U-test).

These preliminary calculations regulated the main analyses. For RMT analysis of covariance (ANCOVA, factor diagnosis, covariate age) was computed, since age correlated significantly with RMT. Furthermore, MANOVA with repeated measure design (within-subject factor side, between subject factor diagnosis) was performed to test the hypothesis, that in right-handed subjects RMT is lower on the left compared to the right motor cortex. For SICI and ICF variables Mann-Whitney U-test was used to analyze diagnosis differences. For the FE-SZ patients Spearman rank correlations between dependent variables and total PANSS scores, GAF, CGI, DUP and DUI were performed.

3. Results

3.1. Sociodemographic and clinical characteristics

The first-episode patients did not differ significantly in age compared to the healthy control subjects (mean age 29.8 ± 8.5 years versus 32.2 ± 7.9 years, $p = 0.28$). The percentage of male patients was higher at a trend level in the schizophrenic patient group ($p = 0.082$). While all healthy control subjects were right-handers, in the FE-SZ group 4 patients were ambidexters ($p=0.042$). No subject fulfilled the criteria for borderline or antisocial personality disorder (due to SCID II interview, DSM-IV axis II, personality disorders), which may include abnormal high impulsivity potentially linked to reduced inhibition processes. In addition no healthy control subject fulfilled the criteria of any axis II disorder.

The first-episode patients suffered from moderate to severe positive and negative symptoms according to the PANSS, accompanied by a severe degree of illness (CGI), and were severely impaired in their social functions (GAF) (for details see table 1).

More severely ill patients received higher dosages (expressed in CPZ-equivalents), as the cumulative doses correlated positively with total PANSS score ($rho = -0.65$, $p = 0.062$) at a trend level an even significantly with CGI ($rho = 0.65$, $p < 0.0005$).

3.2. Influence of sociodemographic characteristics on TMS parameters

A positive correlation was found between age and RMT on both hemispheres in the healthy control group ($r = 0.36$, $p = 0.04$, left motor cortex; $r = 0.41$, $p = 0.04$, right motor cortex). In the healthy control group a significant influence of gender on cortical facilitation (ISI 7 ms, right side) was observed (male controls displayed enhanced facilitation; $p = 0.004$). In FE-SZ, for all dependent variables no significant differences between right-handers and ambidexters were observed.

Table 1 Sociodemographic and clinical parameters

	HC (N = 28)		FE-SZ (N = 29)				
	m	**sd**	**m**	**sd**	**df**	**F**	**p**
Age (years)[a]	32.18	7.86	29.79	8.47	1, 55	1.21	0.28
DUP (weeks)	-	-	50.41	64.0	-	-	-
DUI (weeks)	-	-	183.17	157.1	-	-	-
PANSS total score	-	-	91.48	17.2	-	-	-
PANSS positive score	-	-	22.14	6.1	-	-	-
PANSS negative score	-	-	21.45	6.6	-	-	-
PANSS gen. psychop. score	-	-	47.90	9.4	-	-	-
CGI	-	-	5.96	0.6	-	-	-
GAF	-	-	28.6	10.5	-	-	-
Daily dose of antipsychotics (CPZ-equivalents)			356.2	203.7			
Duration of antipsychotic medication (days)			21.0	14.4			
Cumulative dose of antipsychotics (CPZ-equivalents)			7565.2	7886.8			

			df	**Chi²**	**p**
Gender (male/female)[b]	14 / 14	21 / 8	1	3.02	0.082
Handedness (right/left/both) [b]	28 / 0 / 0	25 / 0 / 4	1	4.15	0.042
Psychosis in first degree relatives, no. of subjects (%)	0 (0)	12 (41.3)	-	-	-

Legend:
HC = healthy controls; FE-SZ = patients with first-episode schizophrenic; m = mean; sd = standard deviation; DUP = duration of psychosis; DUI = duration of illness (including initial prodrome); PANSS = Positive and Negative Syndrome Scale; gen, psychop. = general psychopathology; CGI = Clinical Global Impressions; GAF = Global Assessment of Functioning; no. = number; df = degrees of freedom; F = F-statistics; p = probability; CPZ = chlorpromazine.

[a] Analysis of variance (ANOVA); [b] Chi-Quadrat test

3.3. Resting motor threshold (RMT)

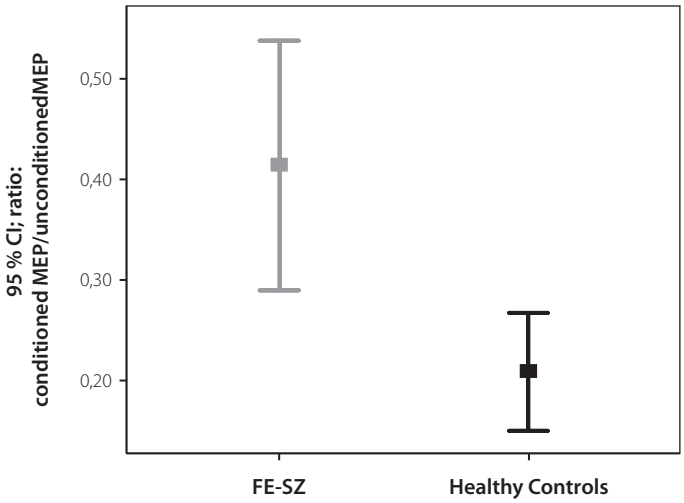
RMT was similar in first-episode patients and healthy controls on both sides (46.9 % in FE-SZ vs. 47.8 % in HC, p = 0.88 for left motor cortex and 48.3 % in FE-SZ vs. 49.6 % in HC;

p = 0.73 for right motor cortex) (for details see **table 2**). When only the right-handed subjects were included in the analysis, RMT was significantly lower on the left compared to the right motor cortex in both subgroups (p = 0.039).

3.4. Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

In first-episode patients (FE-SZ) significantly higher MEP ratios (cMEP/uMEP) were measured at the inhibitory ISI of 3 ms compared to healthy controls (HC) on left motor cortex (MEP ratio 41 % in FE-SZ vs. 21 % in HC; p = 0.017) (**figure 1),** reflecting lower SICI in the patient group. When only the right-handed FE-SZ (MEP ratio 40 %) were analyzed, the difference compared to the control group remained significant (p = 0.033). On the right motor cortex this reduced SICI in FE-SZ (ISI 3 ms) was seen at a trend level (MEP ratio 59 % in FE-SZ vs. 31 % in HC; p = 0.059).

Figure 1 Error bars for paired-pulse inhibition in diagnostic groups



First-episode patients showed significantly lower decreased MEP amplitudes (higher ratio: conditioned MEP/unconditioned MEP; mean, 95 % CI) at the inhibitory ISI of 3 ms compared to healthy controls on left motor cortex (Z = -2.39; p = 0.017; Mann-Whitney-U-test).
Abbreviations: CI = confidence interval; MEP = motor evoked potential; ISI = interstimulus interval; FE-SZ = patients with first-episode schizophrenia

For the MEP ratio of the facilitatory ISI of 7 ms (ICF) no significant differences between the two groups on both hemispheres could be observed (for details see **table 2**).

Table 2 TMS parameters

	HC (N = 28)		FE-SZ (N = 29)				
	m	**sd**	**m**	**sd**	**df**	**F**	**p**
RMT left motor cortex (%)[a]	47.82	6.5	46.93	6.9	1, 54	0.0	0.88
RMT right motor cortex (%)[a]	49.58	10,0	48.25	8.0	1, 51	0.1	0.73
					df	**Z**	**p**
ppTMS ISI 3 ms left motor cortex (ratio cMEP/uMEP)[b]	0.20	0.1	0.41	0.3	1	-2.39	0.017
ppTMS ISI 7 ms left motor cortex (ratio cMEP/uMEP) [b]	0.96	0.5	1.12	1.0	1	-0.22	0.83
ppTMS ISI 3 ms right motor cortex (ratio cMEP/uMEP) [b]	0.31	0.2	0.59	0.9	1	-1.89	0.059
ppTMS ISI 7 ms right motor cortex (ratio cMEP/uMEP) [b]	1.14	0.7	1.48	1.4	1	-0.41	0.68

Legend:
HC = healthy controls; FE-SZ = patients with first-episode schizophrenic; m = mean; sd = standard deviation; ppTMS = paired-pulse transcranial magnetic stimulation; ISI = interstimulus interval; mV = millivolt; N = number; df = degrees of freedom; F = F-statistics; Z = Z-value; p = probability; cMEP = conditioned motor evoked potential; uMEP = unconditioned motor evoked potential; RMT = resting motor threshold
[a] Analysis of covariance (ANCOVA, factor diagnosis, covariate age). percentage of maximum stimulator output
[b] Mann-Whitney-U-Test

3.5. Correlation with clinical parameters

There was a positive correlation between PANSS total score and RMT of left motor cortex (rho = 0.395, p = 0.034; Spearman rank correlations) and a negative correlation between PANSS total score and cortical inhibition (MEP ratio at 3 ms) of left motor cortex in first-episode schizophrenia (rho = -0.403; p = 0.030; Spearman rank correlations). These correlations could not be found with the PANSS positive or negative subscore, but between RMT of left motor cortex and PANSS general psychopathology (rho = 0.385, p = 0.039; Spearman rank correlations). The detected correlations remained not significant after Bonferonni correction and have to be interpreted with caution. No

other significant correlations between clinical parameters (GAF, CGI, DUP, DUI) and TMS parameters could be demonstrated.

3.6. Influence of antipsychotic medication on TMS parameters

Because the duration, cumulative dose and daily dose of the antipsychotic medication (expressed in chlorpromazine (CPZ) equivalents) were not normally distributed, we performed non-parametric correlations to assess the influence of these variables on TMS parameters. No significant correlations could be observed. At a trend level there was a positive correlation between the cumulative dosage (CPZ-equivalents) and RMT of left motor cortex (rho = 0.34, p = 0.068), and a negative correlation between the cumulative dosage (CPZ-equivalents) and the MEP ratio at ISI 7 ms (ICF) of left motor cortex (rho = -0.32, p = 0.085). There were no significant correlations of dosage (CPZ-equivalents) with RMT of right motor cortex (rho = 0.17, p > 0.2), MEP ratio at ISI 7 ms of right motor cortex (rho = 0.20, p > 0.2) or MEP ratios at ISI 3 ms of left (rho = -0.21, p > 0.2) and right motor cortex (rho = 0.01, p > 0.2).

4. Discussion

The main result of the present study is that first-episode patients demonstrated increased MEP amplitudes evoked by paired-pulse TMS at the inhibitory interstimulus interval (ISI) of 3 ms compared to healthy control subjects. No significant differences at the facilitatory ISI of 7 ms could be detected between the diagnostic groups. These findings reflect reduced short interval cortical inhibition (SICI) and no difference of intracortical facilitation (ICF) in patients with first-episode schizophrenia compared to healthy controls. Following the literature, reduced cortical inhibition in schizophrenic patients demonstrated by paired-pulse TMS is not conclusive to date. Reduced SICI was seen in a small sample of unmedicated schizophrenic patients, but not in patients treated with antipsychotics (Daskalakis et al. 2002). In another study reduced SICI and increased ICF was shown in medicated, but not in drug-naïve schizophrenic patients (Pascual-Leone et al. 2002). One research group observed reduced SICI in medicated schizophrenic patients and no difference in ICF (Fitzgerald et al. 2002a), but could not replicate this finding in a larger sample of patients (Fitzgerald et al. 2002b). The only study investigating neuroleptic-naive first-episode patients (mainly disorganized subtype) showed no difference in cortical inhibition or facilitation compared to healthy control subjects (Eichhammer et al. 2004). Differences between these study results may be partially explained by different patient populations, often consisting of multi-episode patients with chronic disease and the influence of different antipsychotic medication. Patients with first-episode schizophrenia were rarely investigated. However, although the literature is still inconsistent, our finding of reduced cortical inhibition in a large sample of medicated first-episode

patients with limited exposure to antipsychotic medication strongly supports the hypothesis that inhibitory intracortical deficits may be part of the schizophrenic pathophysiology. Several other neurophysiological studies using other tools than TMS, have provided evidence for inhibitory deficits in schizophrenia. For instance schizophrenic patients showed reduced P50 wave suppression in an auditory conditioning test paradigm (Adler et al. 1982), potentially reflecting reduced inhibition in a cortico-subcortical loop. We could not detect significant differences in ICF between medicated first-episode patients and comparable healthy control subjects. Besides reduced SICI schizophrenia patients could have presented increased ICF, but in our study this was not the case.

SICI is linked to the GABAergic system and the function of cortical GABAergic interneurons (Ziemann 2004). In healthy subjects $GABA_A$ agonists and also glutamate antagonists enhance SICI; the latter effect may be best explained through a decrease of facilitatory effects (Ziemann 2004). Recent investigations were able to segregate different GABAergic inhibitory circuits in human motor cortex and to show that SICI is probably mediated via α2- or α3-subunit rather than the α1-subunit of the $GABA_A$ receptor (Di Lazzaro et al. 2007). The α2-subunit is found only in about 15 % of cortical GABA receptors but at above 95 % of inhibitory synapses onto pyramidal neuron axon initial segments, especially in the superficial layers of the human cerebral cortex and seems to be related to higher affinity for GABA, which results in faster activation and slower deactivation times than the more common α1-subunit of the $GABA_A$ receptor (Lewis et al. 2005). On the other hand there are pharmacological studies suggesting that GABAergic activation (e.g. through benzodiazepines) mainly influence ICF rather than SICI in healthy controls (Ziemann et al. 1996b). Dopamine and noradrenaline agonists increase SICI, while dopamine antagonists like haloperidol decrease SICI (Ziemann 2004). Interestingly, the selective serotonine re-uptake inhibitor citalopram increased SICI in subjects, who were homozygotic for the long variant of the 5-HT transporter gene (Eichhammer et al. 2003). This finding suggests also an involvement of serotonine, dependent on genetic polymorphism, on cortical inhibition. On the other hand neither single nor chronic administration of paroxetine resulted in changes of SICI, but single dose of paroxetine decreased ICF, while chronic paroxetine administration enhances ICF in healthy volunteers (Gerdelat-Mas et al. 2005). This contrary effect on ICF emphasizes the different pharmacological action of a drug at cortical level depending on its acute or long-term administration. For ICF the majority of pharmacological studies on healthy subjects demonstrated a decrease of ICF by NMDA antagonists (Ziemann 2004). In contrast another study found an increase of ICF after ketamine application, a NMDA antagonist, potentially mediated by activating non-NMDA glutamatergic transmission via AMPA and kainate receptors (Di Lazzaro et al. 2003). In conclusion, our results of decreased SICI and unchanged ICF compared to healthy controls fits best to the hypothesis of GABAergic dysfunction in schizophrenia, although the dysbalance of

other neurotransmitters like glutamate, dopamine and serotonine involved in SICI reduction could not be ruled out. Nevertheless, the cited findings in healthy subjects are not necessarily comparable to the results and conditions in schizophrenia patients, and neuronal networks in schizophrenia including adaptive processes during disease course and long-term medication may be responsible for differences.

We found no significant differences in resting motor threshold (RMT) between schizophrenic patients and healthy controls. This is in line with the literature. Summing up the results of previous studies investigating RMT in schizophrenic patients, more than half of the studies (8 of 15) demonstrated no significant differences between patients and control subjects (Wobrock et al. 2007). In 3 studies a decreased RMT in schizophrenic patients was observed, as it has to be expected if reduced cortical inhibition and increased excitability of motor neurons is assumed (Abarbanel et al. 1996, Daskalakis et al 2002, Eichhammer 2004). In an other study a significant increased RMT in patients treated with antipsychotics compared to medication- free patients and normal controls was detected (Pascual-Leone et al. 2002), and in addition, a higher RMT on the left dominant hemisphere compared to the right side in medicated and unmedicated patients could be observed. This is remarkable concerning the observation that in some investigations healthy controls display a lower RMT on the left dominant side in inter-hemispheric comparison (Triggs et al. 1994). In our study we found no difference in laterality between controls and first-episode patients. In two studies investigating the effect of low frequency rTMS on RMT, in schizophrenic patients no increase of RMT was seen after rTMS compared to healthy controls (Oxley et al. 2004, Fitzgerald et al. 2004). This was discussed as reduced cortical neuroplasticity or missing cortical inhibition in schizophrenia.

In addition, we found evidence for a correlation between total symptom severity, expressed by PANSS total score and increased RMT, as well as decreased cortical inhibition. This means that reduced cortical inhibition is inversely associated with symptom severity, which seems rather contraintuitive. An explanation may be that more severely ill patients receive higher dosages of antispsychotics (CPZ-equivalents), as they did in our study, and therefore the cortical inhibition deficits could be "overcorrected". However the above mentioned negative correlation between SICI only on left motor cortex and PANSS total score could not be replicated with the PANSS positive and negative subscore. This may indicate that there is no stable correlation between symptom severity and cortical inhibition deficits at all. Furthermore, our findings of decreased cortical inhibition in schizophrenia may reflect a more general vulnerability factor (e.g. as a trait marker) than a characterization of psychopathology (e.g. as a state marker).

Our study has several limitations. First of all, antipsychotic medication could be a considerable confounding factor using TMS paradigms (Davey et al. 1997). For instance, one study found a difference in RMT between patient treated with risperidone (increased

RMT) and olanzapine (decreased RMT) (Fitzgerald et al. 2002c). We did not find a differential influence of the used antipsychotics in our patient sample. This contributes to the result of another study with healthy control subjects, where an effect on resting motor threshold (RMT) after olanzapine or haloperidol administration could not be detected (Daskalakis et al. 2003). This was explained by the fact that RMT is conventionally regarded as a measure of the membrane excitability of corticospinal neurons and interneurons in the motor cortex, increased by drugs that block voltage-gated sodium channels and not affected by drugs that alter GABA, glutamate or dopamine transmission (Di Lazarro et al. 2003, Liepert et al. 1997, Werhahn et al. 1999, Ziemann et al.1996a, Ziemann et al. 1996b, Ziemann et al. 1997, Ziemann et al. 1998) like olanzapine or haloperidol. For paired-pulse measurements, medication influencing GABA, glutamate, serotonine or dopamine transmission should be potentially relevant, because the interneuronal-pyramidal circuits are mediated via these pathways. However, according to the literature, one would expect that antipsychotics should compensate the reduced inhibition and not produce it, because there are no studies available showing increased cortical inhibition in unmedicated or medicated schizophrenia and only one study demonstrating reduced cortical inhibition exclusively in medicated patients (Pascual-Leone et al. 2002). Studies of the medication effect on cortical inhibition performed on healthy people (mostly given as single dose) do not necessarily reflect the effect of the same psychopharmacological drugs administered chronically to schizophrenic patients with a potentially different neuronal network. For future studies in schizophrenia patients it may be helpful to include other comparison groups e.g. patients with bipolar disorder treated with atypical antipsychotic drugs to control for effects of these drugs and to compare these effects with disease specific alterations.

The strength of our study is that we were able to investigate a well characterized relatively large sample of first-episode patients which seems representative for this patient group in a clinical setting. Due to disease severity and the clinical necessity for medication it was not possible to measure these patients neuroleptic-naïve.

The origin of reduced cortical inhibition measured by TMS in schizophrenia is still speculative. In one model reduced cortical inhibition in schizophrenia is explained by the assumption of a disorder of altered dopaminergic inputs from pyramidal to nonpyramidal neurons in the cortex (Benes 2000, Benes 1998). To support this hypothesis it was demonstrated that in schizophrenia dopaminergic projections to the cortex erroneously terminate on non-pyramidal cells (i.e. interneurons) to inhibit their function. Such connectivity would result in decreased activity of inhibitory interneurons and increased excitatory output in the cortex. Another explanation may be the finding of decreased numbers of (inhibitory, gabaergic) interneurons in the postmortem brains of schizophrenic patients, which could lead to reduced cortical inhibition (Benes 1991). There is an increasing literature pointing towards a GABAergic dysfunction in schizophrenia (Lewis et al. 2005). In individuals with schizophrenia an increased density of $GABA_A$

receptors was found in ligand binding studies, probably indicating a local upregulation in response to a reduction in perisomatic inhibitory input from chandelier and wide arbor neurons (Lewis et al. 2005). In post mortem studies there is convincing evidence for decreased GABA synthesis in schizophrenia with the finding of reduced glutamic acid decarboxylase (GAD67) mRNA expression in dorsolateral prefrontal cortex (Knable et al. 2002). This reduced synthesis of GABA in a parvalbumin-containing subpopulation of inhibitory GABA neurons may be caused by deficiency in signalling through tyrosine kinase receptor B, the receptor for brain-derived neurotrophic factor (BDNF) (Lewis et al. 2005). One of the consequences of reduced GABAergic transmission may be a deficit in synchronisation of pyramidal cells resulting in e.g. working memory deficits, a core syndrome of schizophrenia (Lewis et al. 2005). Our finding of reduced SICI contributes to the hypothesis of GABAergic dysfunction in schizophrenia. However, it has to be kept in mind that histopathological studies demonstrating a reduced number of GABAergic interneurons in the primary motor cortex of schizophrenia patients are not available.

A reduced SICI detected by TMS has been found in other neuropsychiatric disorders, i.e. unipolar depression (Bajbouj et al. 2006), attention-deficit/hyperactivity disorder (ADHD) (Richter et al. 2007) or obsessive-compulsive disorder (OCD) (Greenberg et al. 2000). With regard to these findings intracortical inhibition deficits seem not specifically restricted to schizophrenia.

Future studies combining different modalities and investigational tools (e.g. TMS, event related potentials, magnetencephalography, structural and functional magnetic resonance imaging) may gain new insights in neuronal networks and either intracortical or cortico-subcortical connectivity.

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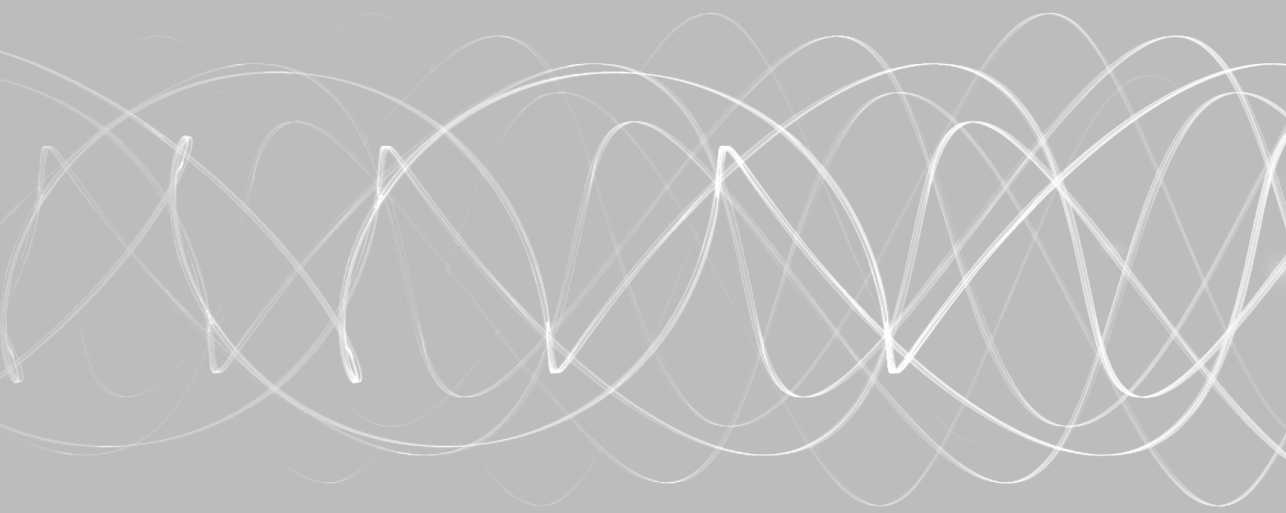

7 A similar but distinctive pattern of impaired cortical excitability in first-episode schizophrenia and ADHD

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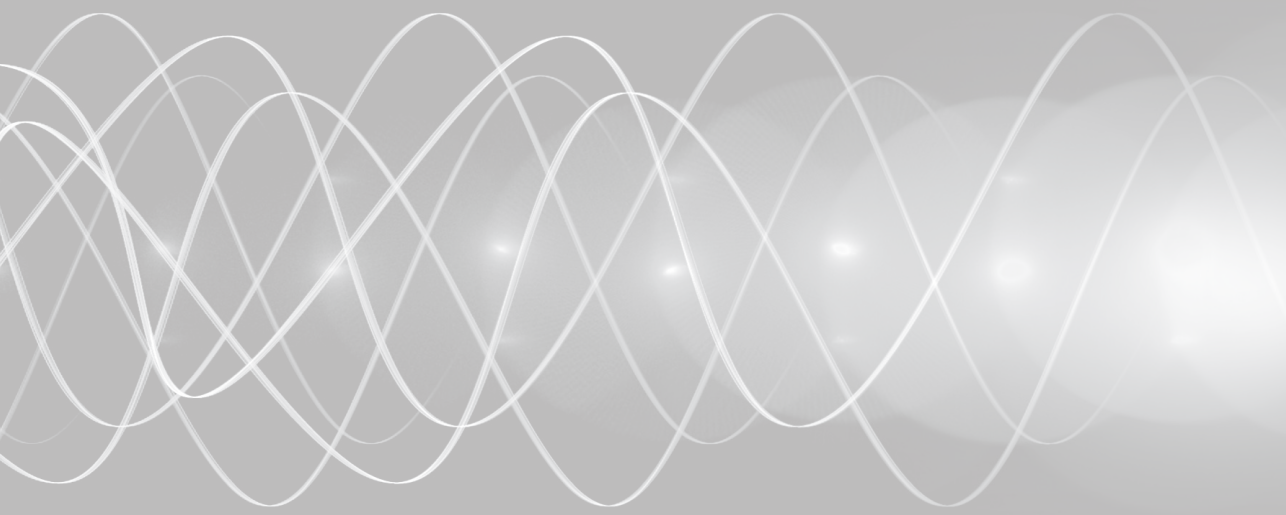


Abstract

Background: First-episode-schizophrenia (FE-SZ) and attention deficit hyperactivity disorder (ADHD) are both neuropsychiatric disorders associated with an impaired dopaminergic transmission. Though displaying different clinical phenotypes, a common pathophysiological pathway is discussed controversially. Several studies using transcranial magnetic stimulation (TMS) revealed abnormalities in human motor cortex excitability in both schizophrenia and ADHD patients. Studies on cortical excitability comparing these two diseases directly are lacking.

Method: In this study, a total of 94 subjects were analyzed. 25 FE-SZ patients were directly compared with 28 ADHD patients and 41 healthy controls (HC). We investigated cortical excitability (inhibitory and facilitatory networks) with single- and paired-pulse-TMS to the left and right motor cortex.

Results: Compared to healthy controls, FE-SZ/ADHD displayed an impaired cortical inhibition over the left hemisphere. Apart from an enhanced intracortical facilitation, FE-SZ did not differ compared to ADHD patients in the main outcome measures. Both patient groups presented a dysfunctional hemispheric pattern of cortical inhibition and facilitation in comparison with HC.

Conclusion: The results of this study indicate a pattern of cortical disinhibition and abnormal hemispheric balance of intracortical excitability networks in two different psychiatric diseases. These effects might be associated with an imbalance in GABAergic and dopaminergic transmission and might provide evidence for a common pathophysiological pathway of both diseases.

Introduction

Attention deficit hyperactivity disorder (ADHD) and schizophrenia are both heterogeneous disorders sharing a psychopathological profile of attention deficits and difficulties in social interaction. However, very perspicacious distinguishing features between these diseases are delusions, hallucinations and negative symptoms as a clinical manifestation in schizophrenia patients [1]. There is comorbidity between these diseases and retrospective studies of individuals with schizophrenia have shown a history of premorbid or concomitant ADHD [2].

With regard to the pathophysiology, both conditions are associated with a dysfunctional dopaminergic transmission of the limbic-frontal network and other midbrain structures [3,4]. An enhanced dopaminergic transmission in mesolimbic structures is associated with positive symptoms, whereas a dopaminergic underactivity in these brain structures has been linked to negative symptoms and cognitive dysfunction in schizophrenia patients. In ADHD, the pathophysiological role of the dopamine system remains elusive. Both, high midbrain dopamine activity or reduced dopamine activity are discussed to be involved in the appearance of ADHD symptoms and the discussion about hypo- or hyperdopaminergic transmission imbalance remains contradictory [4,5]. In some studies, a dopaminergic hyperfunction in the mesolimbic structures was correlated with hyperactivity and impulsivity and a dopaminergic hypofunction was found to underlie different cognitive symptoms [3,4,6-8]. Apart from dopamine, other neurotransmitter systems, especially GABAergic interneurons, are involved in the pathophysiology of these diseases [9,10].

Using paired-pulse transcranial magnetic stimulation (TMS) a reduced cortical inhibition as another common pathophysiological state was found in both diseases [11,12]. Paired-pulse TMS offers the possibility to investigate different mechanisms of cortical inhibition (short interval intracortical inhibition, SICI) and of cortical facilitation (intracortical facilitation, ICF) in the human brain [13]. SICI is discussed to be mediated by GABAergic interneurons via $GABA_A$-receptors and ICF might result from primarily glutamatergic neurotransmission [14]. Furthermore, dopaminergic neurotransmission has an impact on SICI and ICF, because dopamine agonists lead to an enhancement of SICI and ICF and dopamine antagonists reduce SICI and ICF in healthy subjects [14]. The contralateral silent period (CSP), a single-pulse TMS measure, is at least in part the result of $GABA_B$ mediated inhibitory mechanisms [15,16].

In schizophrenia patients, several TMS studies revealed abnormalities in motor-cortical excitability which have been linked to GABAergic and dopaminergic dysfunction [17-20]. Our research group has recently demonstrated a reduced SICI and a prolonged CSP in first-episode schizophrenia (FE-SZ). We hypothesized that reduced SICI points towards a $GABA_A$ deficit and the prolonged CSP may reflect compensatory increased $GABA_B$ transmission induced by hyperactivity of the dopaminergic system [11,21].

Studies with child and adult ADHD patients displayed controversial results. Three different studies found abnormal SICI and ICF in children with ADHD, which normalized after administration of a psychostimulant [22-24]. Furthermore, a reduced duration of the CSP and the ipsilateral silent period (iSP), a measure of interhemispheric connectivity, is a common finding in children with ADHD [23,24]. In adults with ADHD, two studies revealed a reduced SICI [12,25] and in another study the reduced SICI did not reach statistical significance [26]. Methodological differences in measuring and analyzing cortical excitability in adults with ADHD might be related to the negative finding of the latter study. The shift of ADHD symptoms during lifetime might be accompanied by adaptations in motor cortex excitability in some ADHD phenotypes. Furthermore, the higher variability of MEPs in ADHD might be the reason for the weak statistical significances of differences in cortical excitability between some ADHD adults and healthy controls [26]. As shown for ADHD in childhood, one study found a shortened iSP in adult ADHD, but there were no differences in CSP [27].

The present study was designed to directly compare measures of cortical excitability between ADHD and FE-SZ. To shed more light on the impact of cortical excitability on the underlying pathophysiology, 25 FE-SZ with minimal exposure to antipsychotics were compared with 28 adult ADHD patients with no psychotic or other axis I or II history and 41 healthy controls (HC). Therefore, previously and independently published samples (see materials and methods) were merged and newly analyzed towards excitability differences between schizophrenia and ADHD patients. TMS over both hemispheres was used to test parameters of cortical excitability and functional hemispheric balance (SICI, ICF, CSP and motor thresholds).

Our aim was to focus on TMS measures on transmission mechanisms related to $GABA_A$, $GABA_B$ and glutamatergic systems in order to test the hypotheses of common pathophysiological motor networks in schizophrenia and ADHD. From the background outlined above, we hypothesized that schizophrenia patients would show the most pronounced abnormality in excitability that is less evident in ADHD. Another aim was to investigate functional hemispheric asymmetry and connectivity based on measures of cortical excitability. We hypothesized that especially schizophrenia patients would show pronounced impairments in hemispheric asymmetry.

Material and Methods

Subjects

The study sample consists of 94 subjects. 28 patients with ADHD and 25 patients with FE-SZ (all paranoid subtype) from the same geographical area were recruited from inpatient and outpatient units and were compared with 41 healthy subjects. Parts of this sample have been previously published independently [11,21,25], but this study provides new data for on direct comparison of disorders, CSP in ADHD and late-ICF in first-episode

schizophrenia. Subjects with a history of dementia, neurological illnesses and severe brain injuries were excluded from the study. All subjects were right handed according to a standardized test of hand preference [28].

A clinical psychiatrist, blinded to the aims of the study, and a member of the study group (TW or MS) made a consensus diagnosis according to the German version of the Structural Clinical Interview for DSM IV [29]. Each subject underwent an assessment of disease severity (Clinical Global Impressions) [30] and an assessment of social functioning (Global Assessment of Functioning) [31].

In schizophrenia patients an assessment of psychopathology (Positive and Negative Syndrome Scale) [32], the duration of illness (DUI), counted from the beginning of initial prodromal symptoms and the duration of psychosis (DUP), counted from the onset of diagnostic/characteristic positive symptoms were evaluated according to the foregoing publication [11]. All schizophrenia patients were treated with second generation antipsychotics, but at the time of TMS measurements no patient had been treated longer than 6 weeks continuously. We calculated chlorpromazine equivalents [33] for the cumulative and daily doses of the different antipsychotics to explore the influence of this medication on the study results.

The ADHD patients (combined type) were diagnosed according to the diagnostic criteria of DSM IV (ADHD-DC: ADHD Diagnostic checklist [34]), and had used no stimulant medication before. The Wender Utah Self Rating Scale – short version (WURS-k) [35]) was used to assess childhood ADHD symptoms. Patients with the clinical diagnosis of ADHD were included in the study if the WURS-k score was at least 30, and when at least 6 of 9 items of inattention and hyperactivity/impulsivity were present. As indicators of severity of symptoms, the ADHD self-rating scale for adults (ADHD-SR) according to DSM IV [34] was used (total score: 0 to 54; attention deficit and hyperactivity/impulsivity subscores: each maximal 27). SCID-1 and 2 interviews were used to exclude further axis I and II DSM categorical diagnoses.

After a complete description of the study, written informed consent was obtained from each subject. The local ethics committee approved the protocol, which is in accordance with the Declaration of Helsinki.

TMS procedure

As described previously [11], subjects were seated in a comfortable reclining chair with their arms supported passively. Electromyographic (EMG) recordings from the right and left first dorsal interosseus muscle (FDI) were made with surface electrodes. Raw signals were amplified, bandpass filtered (2 Hz–10 kHz) and digitized using a commercial amplifier (Keypoint portable, Medtronic Co., Denmark). Each EMG recording was manually analyzed off-line. TMS was performed by using a MagPro X 100 magnetic stimulator (Medtronic Co., Denmark) and focal transcranial magnetic stimulation (TMS) was applied to the hand area of the left and right motor cortex with a standard figure-

of-eight magnetic coil. The optimal coil position was defined as the stimulation site that produced the largest motor evoked potential (MEP) at moderately suprathreshold stimulation intensities (i.e. intensities that induce MEPs of about 0.5–1.5 mV, SI1mV) in the resting right and left FDI muscle. The optimal position was marked to ensure that the coil was held in the correct position throughout the experiment. The coil was held tangentially to the head, with the handle pointing backwards and in an angle of 45 degrees lateral to the midline. This ensured that the induced current pointed forwards and perpendicular to the central sulcus, which is optimal for producing transsynaptic activation of corticospinal neurons. The resting motor threshold (RMT), expressed as a percentage of maximum stimulator output, was defined as the lowest intensity that produced an MEP of >50 μV in five out of ten trials in the relaxed FDI.

In accordance with standard TMS publications, SICI and ICF were obtained [13,18], setting the intensity of the conditioning stimulus at 80 % of the RMT and the test stimulus at an intensity that produced MEPs averaging 0.5 - 1.5 mV in the resting FDI. SICI/ICF were measured with interstimulus intervals (ISIs) of 3, 5, 7 and 15 ms and we performed a minimum of 8 trials with each ISI and 10 trials with the test stimulus alone. The effect of the conditioning stimulus on MEP amplitude of the test stimulus was determined as the ratio of the average amplitude of the conditioned MEP (cMEP) to the average amplitude of the unconditioned test MEP (uMEP).

CSP duration was obtained in moderately tonically active FDI (25 – 30 % of maximal contraction) by stimulating the contralateral motor cortex with intensities of 120 % and 140 % of RMT. For each intensity, 8 trials were performed and the mean CSP duration calculated. The CSP duration was defined as the time from the motor evoked potential (MEP) onset to the return of any voluntary EMG activity (absolute CSP) [36].

All measurements and clinical characterizations were performed by an experienced investigator (FE-SZ: T.W.; ADHD: M.S.), controlled by another experienced investigator FE-SZ: M.S.; ADHD: T.W.), and corrected for outliers and extreme values. The data analysis was performed by A.H., T.W., M.S. and one statistician (T.SA.).

Statistical analyses

For statistical analyses, SPSS for Windows 17.0 was used. All tests were two-tailed. Level of significance was set at $\alpha = 0.05$. Data are presented as mean ± standard deviation unless otherwise indicated. Kolmogorov-Smirnov tests were applied to test normal distribution and logarithmic transformation was used if normality assumption was violated (SICI and ICF). Independent factor was group (FE-SZ, ADHD, HC) and dependent variables were RMT, ISI (3, 5, 7, 15 ms) and CSP (intensities 120% and 140% of RMT) on both hemispheres. As initial analyses, Pearson correlations between age and dependent variables were calculated and One-way-ANOVA was performed to analyze if the factor gender influenced the dependent variables. If a significant influence of these intervening variables was found, the main analyses were adjusted for these variables.

A repeated measures multivariate analysis of variance (RM-MANOVA) with the within-subject factor "side" (left and right hemisphere) and the between-subject factor "group" (Healthy control, ADHD, FE-SZ) was initially performed. Only if this RM-MANOVA revealed a significant effect or a trend of factor "group" or "side x group" interaction , separate ANOVA's for the left and right hemisphere were performed. If appropriate, corrected Tukey´s post-hoc tests were performed to determine the differences between groups. Pearson's product moment correlations between CPZ equivalents and dependent variables were calculated for the FE-SZ.

Results

Sociodemographic and clinical characteristics, influence of intervening variables age and sex on dependent variables

There were no significant age and sex differences between groups. Schizophrenia patients presented a severe degree of illness and severe impairment of social functioning according to CGI and GAF and moderate to severe positive and negative symptoms (PANSS). ADHD patients suffered from at least moderate symptoms according to the ADHD rating score.

All schizophrenia patients received an antipsychotic medication (but no other concomitant medication, like benzodiazepines) and the dosages of daily and cumulative antipsychotic medication (expressed as CPZ equivalents) were 356.21 ± 203.65 (daily dosage) and 7565.17 ±7886.79 (cumulative dosage). ADHD patients and healthy controls were unmedicated. For details of the sociodemographic and clinical characteristics see table 1.

Except of significant correlations between age and RMT (left: $r = 0.32$, $df = 92$, $p = 0.002$; right: $r = 0.31$, $df = 92$, $p = 0.003$) there was no significant influence of age on dependent variables. From One-way-ANOVA there was no significant difference between female and male subjects for any dependent variable.

Resting motor threshold (RMT)

After adjustment for age, no statistical significant differences of RMT between groups were revealed (see table 2).

Intensity to evoke MEPs of 1mV (SI1mV)

There were no significant differences between groups (see table 2).

Table 1 Demographic and Clinical Data of Study Subjects: Interval scaled data are presented as mean ± standard deviation. Values are expressed as χ^2 statistics for categorical variables and F statistics for continuous variables

Variable	FE-SZ	ADHD	HC	Statistic	P
N	25	28	41		
Gender	18 M, 7 F	15 M, 13 F	20 M, 21 F	$\chi^2(2)=3.522$	0.17
Age (years)	29.96 ± 8.5	32.36 ± 9.1	33.37 ± 9.1	F(2, 91)=1.140	0.32
Schizophrenia patients					
PANSS positive	21.96 ± 5.7	---	---		
PANSS negative	21.76 ± 6.4	---	---		
PANSS general	48.28 ± 8.3	---	---		
PANSS total	92.00± 14.5	---	---		
CGI	5.88 ± 0.6		---		
GAF	30.0 ± 10.5		---		
CPZ1	356 ± 204		---		
CPZ2	7565 ± 7887		---		
ADHD Patients					
ADHD-SR total score	----	36.78 ± 6.3			
Attention deficit subscore	----	18.22 ± 4.6			
Subscore Impulsivity	----	10.63 ± 2.1			
Subscore Hyperactivity	----	7.93 ± 2.6			

FE-SZ: first-episode schizophrenia, ADHD: attention deficit hyperactivity disorder; HC: healthy controls; P: error probability of first kind; N, number; F, female; M, male; CGI: Clinical Global impression; GAF: Global Assessment of Functioning; CPZ1: chlorpromazine equivalents, daily dosage; CPZ2: chlorpromazine equivalents, cumulative dosage; Total and subscores ADHD-SR.

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

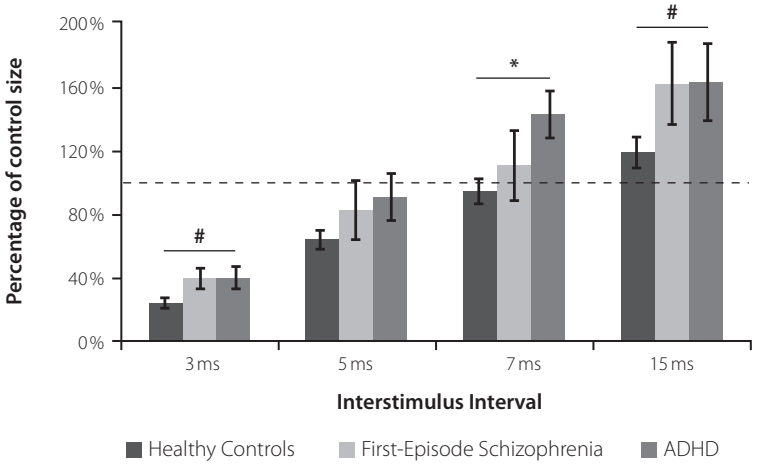
The RM-MANOVA showed a significant "side x group" interaction for ICF at 7ms ($F(2, 86) = 6.08$, $p = 0.003$) and ICF at 15ms ($F(2, 85) = 5.20$, $p = 0.007$) and a trend for the factor "group" for SICI at 3ms ($F(2, 86) = 3.04$, $p = 0.053$).

Table 2 Main outcome parameters

Variable	FE-SZ	ADHD	HC	Statistics Factor "Group" (P)
RMT left	47.68 ± 6.55	50.04 ± 6.50	47.49 ± 5.93	~
RMT right	49.00 ± 7.43	51.92 ± 8.86	48.29 ± 8.92	~
S1mV left	57.08 ± 9.31	64.79 ± 10.57	61.88 ± 10.70	~
S1mV right	59.50 ± 10.33	64.56 ± 13.35	63.65 ± 14.48	~
CSP120 left	160.82 ± 41.59	164.72 ± 33.78	133.64 ± 40.88	0.013
CSP120 right	165.04 ± 55.03	162.81 ± 43.89	166.48 ± 37.38	0.974
CSP140 left	203.89 ± 42.63	192.45 ± 46.53	172.36 ± 38.29	0.037
CSP140 right	210.38 ± 53.60	197.40 ± 57.13	186.34 ± 44.19	0.303
SICI 3ms left	39.61 ± 29.97	39.68 ± 36.95	23.90 ± 17.63	0.051
SICI 3ms right	51.11 ± 57.97	35.70 ± 32.54	32.00 ± 22.99	0.183
SICI 5ms left	82.88 ± 83.18	90.86 ± 51.28	63.86 ± 35.86	~
SICI 5ms right	86.87 ± 74.57	74.69 ± 50.88	81.48 ± 55.73	~
ICF 7ms left	110.68 ± 110.01	143.54 ± 79.73	94.35 ± 49.14	0.011
ICF 7ms right	148.23 ± 142.51	101.88 ± 58.60	113.56 ± 67.02	0.400
ICF 15ms left	162.95 ± 131.20	163.57 ± 130.08	119.18 ± 61.01	0.160
ICF 15ms right	190.86 ± 173.20	107.03 ± 67.72	146.68 ± 92.61	0.060

FE-SZ: first-episode schizophrenia, ADHD: attention deficit hyperactivity disorder; HC: healthy controls; P: error probability of first kind; RMT: resting motor threshold; S1mV: Intensity to evoke a MEP of 1 mV (peak to peak); CSP120: cortical contralateral silent period at 120% RMT; CSP140: cortical contralateral silent period at 140% RMT; SICI: Short-interval intracortical inhibition at one certain interstimulus interval (3ms, 5ms); ICF: Intracortical facilitation at a defined interstimulus interval (7ms, 15ms). Data are presented as mean ± standard deviation. Please notice that statistical analyses on SICI and ICF values were performed on log-transformed values (raw values are presented in this table). Statistics present results separately for the right and left hemisphere. ~ = RM – MANOVA did not show a side x group interaction or a group effect at least on trend level for this dependent variables, therefore no further ANOVAs were performed separately for the left and right hemisphere.

Figure 1 Relative values for paired-pulse (SICI, ICF) measures on the left hemisphere expressed as percentage change compared to the testpulse in all groups



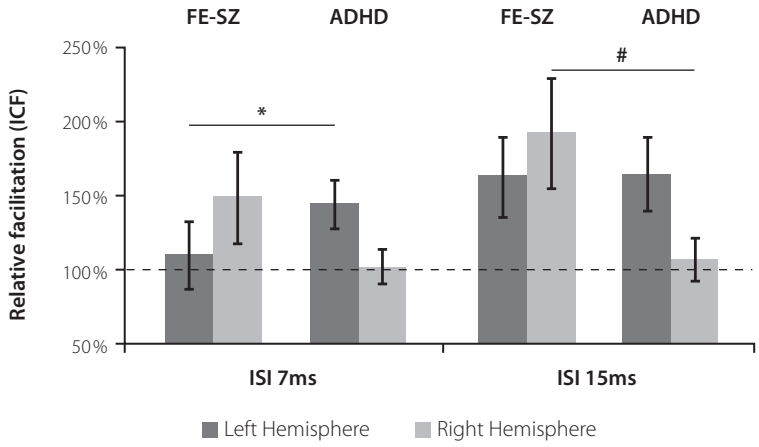
*p < 0.05 (RM-MANOVA), #0.05 ≤ p ≤ 0.060. At 3ms FE-SZ (p = 0.080) had a trend towards a reduced SICI compared to HC. ADHD patients displayed an enhanced ICF at 7ms compared to HC (p = 0.013) and to FE-SZ (p = 0.044). The numeric differences for ISI 5ms and ISI 15ms did not reach significance. Data are presented as mean ± standard error of the mean. *P* – values are corrected in accordance to Tukey´s test. Analyses were performed on logarithmic transformed data (see methods).

The subsequent ANOVA showed separately for the left hemisphere a trend for the factor group for SICI at 3ms (F (2, 90) = 3.08, p = 0.051, Tukey´s post-hoc test: trend for FE-SZ < HC (p = 0.080)) and a significant effect for ICF at 7ms (F(2, 90) = 4.76, p = 0.011, Tukey´s post-hoc test: ADHD > HC (p = 0.013), ADHD > FE-SZ (p = 0.044). ANOVA for the right hemisphere revealed a trend for ICF at 15ms (F(2, 85) = 2,92, p = 0.060, post-hoc Tukey´s test: trend for ADHD < FE-SZ (p = 0.051) (see figure 1 and 2 and table 2).

Cortical Silent Period (CSP)

For CSP120, RM-MANOVA revealed a significant effect for the factor "group" (F(2, 47) = 3.84, p = 0.028) and a significant "side x group" interaction (F(2, 47) = 6.22, p = 0.004). For CSP140, RM-MANOVA showed only a significant effect for "group" (F(2, 46) = 3.36, p = 0.043), but no significant "side x group" interaction (F(2, 46) = 0.17, p = 0.84).
ANOVA separately for the left and right hemisphere showed a significant effect for the

Figure 2 Hemispheric differences of ICF at 7ms and 15ms in the FE-SZ and ADHD groups



At 7ms on the left hemisphere FE-SZ had a reduced ICF compared to ADHD ($p = 0.044$). At 15ms on the right hemisphere FE-SZ had an enhanced ICF compared to ADHD ($p = 0.051$). Analyses were performed on logarithmic transformed data (see methods). *$p < 0.05$ (RM-MANOVA), #$0.050 \leq p \leq 0.060$

factor "group" on the left hemisphere for CSP120 ($F(2, 67) = 4.61$, $p = 0.013$ (Tukey´s post-hoc tests: ADHD > HC ($p = 0.028$), FE-SZ > HC ($p = 0.042$)) (see figure 3) and CSP140 ($F(2, 63) = 3.47$, $p = 0.037$ (Tukey´s post-hoc tests: FE-SZ > HC ($p = 0.032$)), but no difference on the right hemisphere for CSP120 ($F(2, 57) = 0.03$, $p = 0.97$) and CSP 140($F(2, 55) = 1.22$, $p = 0.30$). For details see table 2.

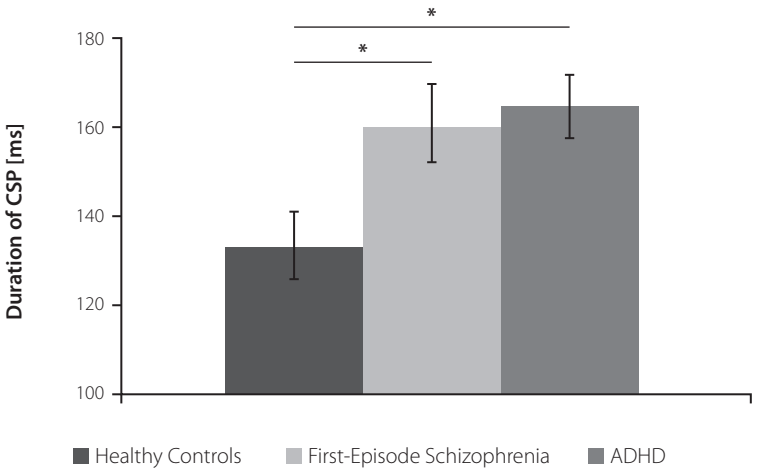
Influence of antipsychotic medication on TMS parameters

In the group of FE-SZ we did not find a significant correlation between antipsychotic medication and TMS parameters.

Discussion

Our main results are that both, FE-SZ patients and ADHD patients demonstrate a prolonged CSP and a cortical disinhibition measured by TMS-protocols compared to healthy controls (HC). Direct statistical comparison showed that both patient groups have a similarly prolonged CSP compared to HC. Furthermore, FE-SZ and ADHD patients

Figure 3 CSP120 duration on the left hemisphere in all groups



ADHD (p = 0.028) and FE-SZ (p = 0.042) present longer CSP120 duration compared to HC. ADHD and FE-SZ do not differ concerning the CSP120 duration on the left hemisphere (p = 0.950). Data are presented as mean ± standard error of the mean. *P* – values are corrected in accordance to Tukey´s test

displayed a trend towards a reduced SICI in comparison to HC. A generally enhanced ICF was found in ADHD in the left hemisphere when compared to HC. Apart from an enhanced ICF at 15 ms over the right hemisphere and reduced ICF at 7 ms over the left hemisphere, TMS measures in FE-SZ did not significantly differ from ADHD patients.

Analysis of hemispheric effects revealed significant differences between groups. Both patient groups had a significantly different pattern of the hemispheric distribution of the inhibitory CSP and facilitatory ICF compared to healthy controls. Interestingly, despite having a largely similar pattern of cortical disinhibition (CSP), a distinct hemispheric distribution of some facilitatory parameters could be detected between FE-SZ and ADHD (see figure 2).

The modified cortical excitability in both ADHD and FE-SZ compared to healthy controls and the divergent hemispheric excitability pattern in both diseases are to our knowledge new and important findings that support the idea of a common pathological pathway in brain transmission in these diseases and raise questions about functional brain asymmetry in these diseases. In order to better understand the pattern of our result some hypothetical and mechanistic explanation are provided below.

General remarks

The role of SICI and CSP in schizophrenia remains controversial. Different studies pointed towards a reduced SICI in medicated chronic schizophrenia patients [20,37,38] and FE-SZ [11], whereas other studies failed to show this difference [18,19]. CSP in medicated patients was found to be shortened [20] or prolonged [19,21,39] compared to healthy subjects. The situation for ADHD is clearer laid out. Two studies revealed a reduced SICI in adult ADHD patients [12,25], whereas in another study this could not reach statistical significance [26]. In contrast to schizophrenia patients, ADHD patients did not show a prolonged CSP compared to healthy controls in previous studies [27].

The reduced SICI and the enhanced ICF in FE-SZ and ADHD patients in our study can be considered as parameters of cortical disinhibition and might be linked to a dysfunction of the $GABA_A$ neurotransmission. The prolonged CSP in both patient groups can be best explained by an enhanced $GABA_B$ transmission [14]. To understand the relationship of different inhibitory and facilitatory pathways, the two following aspects are important.

Possible mode of action with regard to intrahemispheric and interhemispheric networks

First, it was shown that CSP and SICI have an inverse relationship and that SICI is suppressed and ICF is facilitated during CSP. SICI seems to be controlled by presynaptic $GABA_B$-receptor mediated autoinhibition on inhibitory $GABA_A$-interneurons, similar to a presynaptic autoinhibition revealed by paired intracellular recordings in slices of rat and human motor cortex [40,41]. Therefore, one explanation of our results might be that the enhanced $GABA_B$-related inhibition (CSP) and the reduced $GABA_A$-related inhibition (SICI)/enhanced glutamate-related facilitation (ICF) on the left hemisphere are interdependent and might reflect a compensatory circuit within this hemisphere [21]. However, we are not able to determine which network is dysfunctional and which network might compensate for this dysfunctionality.

Second, ADHD patients and FE-SZ presented a modified hemispheric pattern for CSP and ICF compared to healthy controls. This is of particular importance, because abnormal brain laterality is a well known finding in these diseases. Especially an atypical lateralization to the right hemisphere explored in EEG and structural MRI studies is an important finding in ADHD and schizophrenia [42-44]. It could be hypothesized that this relationship is linked to an impaired interhemispheric connectivity/inhibition (IHI). We did not investigate this in our sample. However, one study found an impaired IHI in adult ADHD patients [27] and a reduced IHI was observed in schizophrenia patients [45].

But why do FE-SZ patients differ from ADHD concerning the hemispheric distribution of ICF? We know from other studies that a cortical disinhibition of the left hemisphere (hyperexciatbility) can result in a reduced facilitation (hypoexcitability) over the contralateral right hemisphere [46-48]. To understand our findings, the cortical disinhibition in both diseases on the left hemisphere (enhanced ICF in ADHD, reduced SICI in FE-SZ compared

to HC) should be primarily taken into consideration. Therefore, we would like to hypothesize that the relatively reduced ICF in ADHD patients on the right hemisphere might compensate for the enhanced ICF on the left hemisphere. In FE-SZ this compensatory mechanisms might be impaired and this might be reflected by the relatively facilitated ICF on the right hemisphere.
In general, we would like to discuss an intrahemispheric compensatory mechanisms (reflected by CSP enhancement), which is unaffected in both patient groups and an inter-hemispheric compensatory circuit (reflected by a reduction of ICF), which seems to be exclusively active in the ADHD group.

Is there a hypothetical link to dopaminergic transmission?

It is a remarkable finding that FE-SZ and ADHD did not differ in our outcome measures, except for the aforementioned difference in ICF in both hemispheres. As hypothesized in the introduction, these diseases might share in parts a common pathophysiological pathway and one possible pathway could be associated with dysfunctional dopaminergic transmission. Drug studies in healthy subjects and research on a hypodopaminergic disease (Parkinson's disease) revealed interesting findings about the effect of dopamine on TMS parameters. The CSP was prolonged after administration of dopamine agonists (L-Dopa, Pergolide) and shortened in patients with Parkinson's disease [14,49]. Hence, the prolonged duration of the CSP over the left hemisphere might be linked with the theory of dopaminergic hyperactivity in schizophrenia and ADHD. Here, the enhanced dopaminergic input would lead to a compensatory increase of GABAergic transmission and probably cause the CSP prolongation [50]. In ADHD there is a discussion over the possibility of dopaminergic dysbalance in frontal subcortical regions. Recently, we demonstrated an improvement of SICI in ADHD with long acting methylphenidate [51]. This was interpreted as a dopamine-related response to the stimulants, possibly reflecting a complex dopaminergic-GABAergic interaction. However, with the TMS technique we are not able to determine the localization of the affected brain regions involved in dopaminergic transmission nor directly probe dopaminergic functions. Therefore, currently this theory remains speculative.

Limitations

Our comparative study has several limitations. First of all, all schizophrenia patients received antipsychotic medication, which might have an impact on the results of TMS paradigms. We did not find a correlation between CPZ equivalents on the results of the TMS measures and an influence of antipsychotic drugs on TMS measurements is discussed controversially. One recent study showed that unmedicated schizophrenia patients and patients treated with second generation antipsychotics (risperidone, olanzapine, quetiapine) had a reduced CSP and that patients treated with clozapine had significant less SICI and a longer CSP compared to healthy controls [37]. All of our

patients received second generation antipsychotic medication but, in contrast to Liu and colleagues [37] none of our patients received clozapine. Also, it is important to recognize that the schizophrenia patients in our study were at their first episode with a relatively short treatment history whereas Liu and co-authors investigated chronically ill schizophrenia patients and patients with a schizoaffective disorder. However, reviewing the literature, we would expect that antipsychotics should compensate for the reduced inhibition and not enhance it [11,14,21]. Furthermore it should be considered, that the drug naïve adult ADHD patients showed a motor disinhibition which was not present in healthy controls. Finally, there were no significant differences between ADHD and FE-SZ patients with regard to inhibitory TMS parameters. This might support the hypothesis that diminished cortical inhibition is genuine to these diseases. Nevertheless, our results in adult ADHD patients are partially in contrast with the results of two previous studies, where significant differences in SICI and CSP could not be found [26,27]. This could be due to different methodical procedures in TMS techniques as well as to divergent recruitment strategies. However, our results stay well in line with the diminished SICI seen in children and adolescents with ADHD [22,52].

Although FE-SZ and ADHD patients present a similar cortical disinhibition, we cannot rule out that different mechanisms may underlie these effects and that these are not specifically restricted to these diseases [53]. Cortical disinhibition, as revealed by TMS might reflect a general characteristic of psychiatric conditions, because different other psychiatric diseases, like depression or OCD, are known to show a cortical disinhibition [54,55].

ADHD is a dimensional diagnosis, but diagnosis of schizophrenia is based on the qualitative dimensions of symptoms. But, they still share some common executive dysfunctions (working memory, impulsivity etc.) and attention deficits, whereas the motor symptoms usually are opposite. Despite of the different subsumed pathophysiology and phenotypes, a common dopaminergic pathway has been discussed in both diseases [3,4]. However, it should be considered, that dopamine has a neuromodulatory function. The dopamine effect depends on spontaneous neuronal activity, dopamine concentration and dopaminergic sub-receptors [53]. Therefore, the transfer of our TMS-findings to the complex aspects of dopaminergic transmission mechanisms to both diseases can be done only in a limited manner. Therefore, the interpretation of our TMS results should be mainly focused on the discussed primary GABAergic transmission pathways.

Finally, it should be noted that overlapping parts of this study have been published before (see method section). However, this is the first study which directly compares cortical excitability in first-episode schizophrenia and ADHD. Furthermore, we provide new CSP data for ADHD and new late-ICF data (15 ms) for first-episode schizophrenia and we show for the first time elaborate data for functional hemispheric asymmetry measured by TMS for both diagnostic groups. A detailed discussion specific for each

diagnostic groups and focusing on effects of one hemisphere can be found in our other publications [11,21,25].

Conclusions

In conclusion, the results of our study provide evidence for a cortical disinhibition in ADHD and FE-SZ and for a common pathophysiological pathway, which might involve GABAergic, glutamatergic and dopaminergic transmission. Furthermore, we were able to present a functional hemispheric asymmetry in both diseases. This comparative work supports the idea of common pathophysiological pathways in motor excitability in schizophrenia and ADHD.

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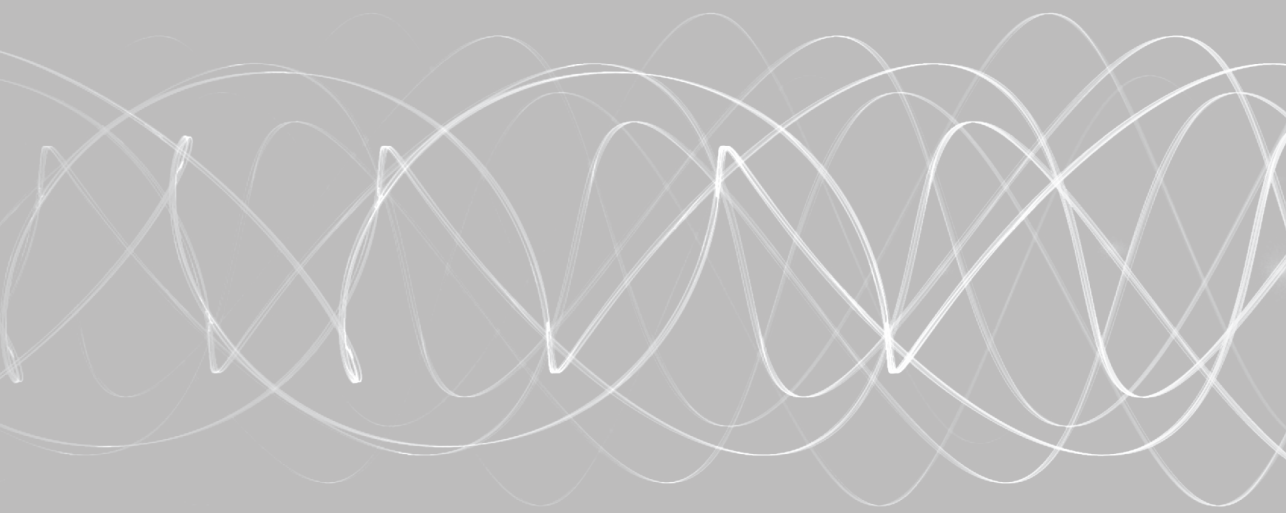
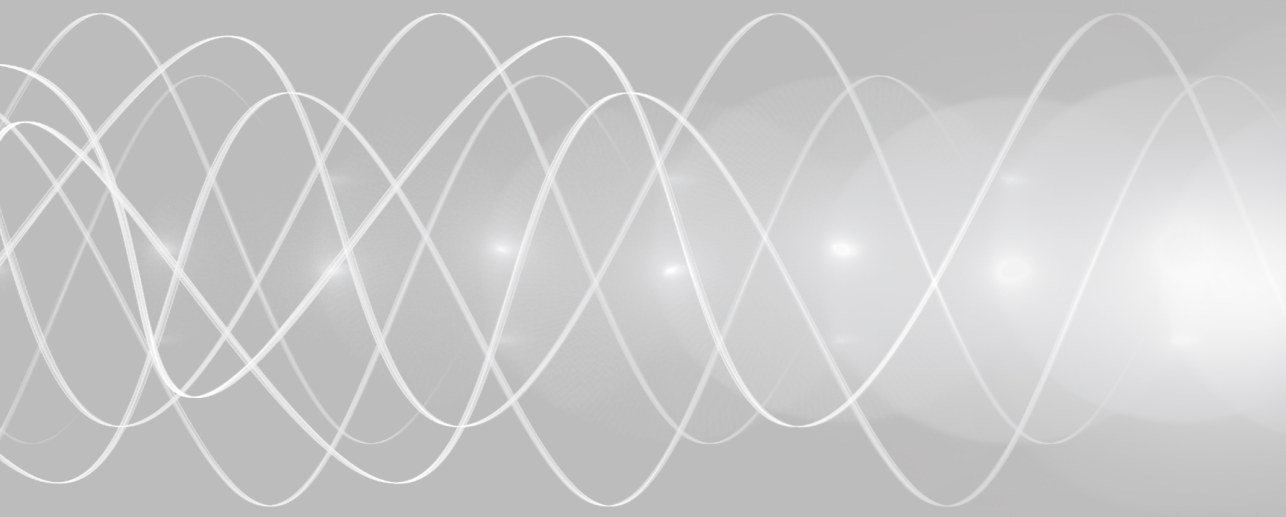


8 General discussion and conclusions



8. General discussion and conclusions

Attention Deficit/ Hyperactivity Disorder (ADHD) is characterized by shifting of symptomatology from childhood to adulthood. Especially hyperactivity and impulsivity seem to become less prominent, and disorganization dominates the symptomatic expression of attention problems (15).

To investigate the specific mechanisms leading to adult ADHD symptoms, this thesis provides evidence about the functional aspects of attention, executive and motor functions in this disorder. We assessed by functional magnetic resonance imaging (fMRI) the attention and executive brain networks in drug naive adult ADHD patients and implemented the data to the clinical phenotype (chapter 3). The motor cortex excitability and its clinical impact in adult ADHD patients was compared with healthy controls by means of the paired pulse transcranial magnetic stimulation (ppTMS) technique (chapter 4). The influence of long acting methylphenidate (LA-Mph), the standard medication for this disorder, on the motor system was assessed with this technique (chapter 5) to elucidate the underlying pathomechanisms. Motor excitability was studied in patients with schizophrenia in chapter 6 and subsequently ppTMS in ADHD and schizophrenia was compared to clarify common pathophysiological pathways and their specific components in diseases with dopaminergic dysbalances (chapter 7).

As previously delineated in chapter 1, in terms of specific aims, the main results of the thesis will be discussed. The interpretation of the studies, the clinical implications, as well as the methodological strengths and limitations including the recommendations for future research are presented, and, finally, the conclusions of the thesis are formulated.

8.1 fMRI in adult patients with ADHD

Our fMRI study with a continuous performance task paradigm showed altered activation patterns of a selective attention brain network in the fronto-striatal and parietal brain regions in adult patients with ADHD. These findings are in agreement with the existing hypotheses about the pathophysiology of ADHD. More explicitly, prefrontal cortex, anterior cingulated cortex (ACC) and striatum were implicated, that all can be considered as belonging to the frontal attentional system. In addition, the parietal lobule as part of the posterior attentional system appeared to be also hypofunctional (see overview from 89).

From the dimensional perspective, these results demonstrated that lowered activation of these distinct attention networks correlates not only with the clinical phenotype of combined type ADHD, but also with ADHD symptomatology in partially remitted patients. This leads to the hypothesis that in patients with partially remitted ADHD similar brain networks are impaired as in those with adult ADHD, combined type. Furthermore, a functional hypoactivity of several brain networks was established that could be positively related to specific ADHD symptoms: ACC to impulsivity, caudate

nuclei to attention deficits, and parietal lobule to the complete symptom profile. In contrast, the left insula was associated with hyperactivation, as reflected in clinically observed increased hyperactivity and impulsivity. The latter can be considered as a compensatory overactivation of brain regions counterbalancing the impaired networks (22,24).

Thus, the results of this study support the hypothesis that adult ADHD has to be considered as a dimensional disorder of which the severity of symptoms correlates with the degree of dysfunction in various brain networks, even in patients in whom ADHD symptoms were partially remitted after childhood. These observations in adults with ADHD are in line with those reported in younger patients and reflect pathophysiological trait characteristics of ADHD (caudate nucleus: 17, 37. ACC: 17, 38,39. Parietal lobe: 17).

8.2 ppTMS in drug naïve adult patients with ADHD versus healthy controls

No differences were found between ADHD patients and healthy controls with respect to resting motor threshold (RMT) and active motor threshold (AMT). The same holds for the stimulus response curves. Thus, no evidence could be obtained for the presence of hyperexcitability within the motor systems at the membrane level of cortical neurons in adult patients with ADHD versus healthy controls (123).

With the ppTMS technique, we found a reduced short intracortical inhibition (SICI) in adult ADHD patients as compared to controls. In the present study, no significant increase of cortical facilitation could be demonstrated. These findings are in line with a previous preliminary report on adults with ADHD (93).

With respect to the dimensional characteristics of ADHD, a positive correlation was found between inhibitory deficits (SICI) and severity of symptoms scores (Wender-Reimherr-Interview (WRI) total score and ADHD-self rating (ADHD-SR) hyperactivity and impulsivity subscores). Comparable findings were reported by Gilbert et al. (52) in Tourette patients with comorbid ADHD symptoms. In sum, the hyperactive/impulsive behaviours in adult ADHD patients are most probably linked to cortical inhibitory dysfunction.

As presented in chapter 4, SICI deficits in ADHD patients appeared to have an interhemispheric asymmetry to the left side. Comparable findings have been reported with brain imaging techniques that described hemispheric asymmetries either globally or in distinct brain areas, specifically the caudate nucleus and pallidum (8,26,27,83,109).

With respect to the SICI, several GABAergic and dopaminergic intracortical neural transmission systems have been reported to be involved (120,72,110,123). Deficits in SICI have been shown to have reliable test-retest stability in adults with ADHD (93) and little inter- and intraindividual variability (74). These observations lead to the hypothesis that attenuation of SICI results from GABAergic, glutamatergic and/or dopaminergic changes in transmission and reflects a trait marker of ADHD.

Summarizing, this is the first study with ppTMS demonstrating reduced SICI, primarily in the left hemisphere, in adult patients with ADHD. Moreover, this lowered SICI correlated with the ADHD symptom profile, in particular with disinhibited behaviours. These findings are in line with the hypothesis of neuronal motor inhibition deficits in adult ADHD. TMS, more specifically ppTMS, appeared to be an appropriate technique to investigate motor excitability in ADHD.

8.3 ppTMS effects of LA-Mph in adults with ADHD

This study (chapter 5) was performed to investigate the effects of LA-Mph – the current pharmacological treatment of ADHD - on motor excitability in adults with ADHD. Previous findings of lowered SICI in ADHD, as indicator of elevated brain motor excitability, were the rationale for this study (93,94).

Treatment with stimulants like LA-Mph should lead to normalization of elevated (lowered amplitude of) SICI. In contrast to a study with adult ADHD patients which showed no significant differences in ppTMS parameters under medication with Mph (62), Gilbert and colleagues (51,52) found an increase of amplitude of the SICI in adult patients with Tourette disorder comorbid with ADHD. Therefore, we studied the effects on ppTMS parameters in adult ADHD patients without comorbidity under stable medication with LA-Mph.

The results demonstrated no effect of LA-Mph on RMT and AMT and support the hypothesis that the compound does not directly affect membrane characteristics. These observations are in line with those reported by other investigators (ADHD children: 78,79,19; adults with ADHD: 62).

With LA-Mph in an individualized stable dose varying between 30 and 54 mg per day, a significantly reducing effect on SICI magnetically evoked potential (MEP) amplitudes was found, but not on ICF MEP amplitudes. SICI MEP amplitude appeared to be correlated with ADHD self rating scores at baseline, but not after 2 weeks of treatment. In children with ADHD, however, treatment with Mph induced significant decreases in SICI MEP amplitudes (78,19). It can, therefore, be hypothesized that the pathophysiological mechanisms, as reflected by ppTMS parameters, are present in children as well as in adults with ADHD.

In summary, the results from this study demonstrate that, like in studies with children, LA-Mph decreases SICI MEP amplitudes in adults with ADHD. A direct clinical correlation of the neurophysiological parameters with the clinical improvement of ADHD symptoms could, however, not be established.

8.4 ppTMS in adult patients with first episode schizophrenia or ADHD

ADHD and other psychiatric disorders, like schizophrenia, share attention deficits, executive dysfunctions and motor disturbances. Since the pathophysiology of schizophrenia is supposed to be related to dysbalances in dopaminergic transmission, studies with ppTMS

were performed in patients with first episode schizophrenia and adult patients with ADHD (chapters 6 and 7).

With respect to RMT in patients with first episode schizophrenia, a positive correlation was found with symptom severity as measured with the Positive and Negative Syndrome Scale (PANSS) total score, but not with the PANSS subscores. No differences in RMT could be established between patients with first episode schizophrenia and healthy controls. These results support the idea that membrane excitability is not primarily disturbed in schizophrenia.

Concerning ppTMS, increased SICI MEP amplitudes were found in patients with first episode schizophrenia. With respect to ICF, no significant differences were observed between patients and healthy controls. These findings indicate a reduced SICI, without changes in ICF in patients with first-episode schizophrenia. It can, therefore, be hypothesized that inhibitory intracortical deficits may either be involved in the pathophysiology of this disorder or serve as a vulnerability factor.

Since deficits in SICI have been demonstrated in a variety of neuropsychiatric disorders (e.g. unipolar depression: 9; ADHD: 94; obsessive compulsive disorder: 53), the ppTMS results in patients with adult ADHD were compared to those obtained in adult patients with first episode schizophrenia in order to delineate putative common psychopathological pathways.

From this comparative study using ppTMS, it appeared that patients with either first episode schizophrenia or adult ADHD patients displayed deficits in SICI and a prolonged cortical silent period (CSP) over the dominant left hemisphere. Enhancement of ICF, however, was only found in ADHD. This observation is not in line with those as reported in chapter 4, in which elevation of ICF did not reach the level of significance and may be explained from variations in the number of controls (26 vs 41). It has to be stressed, however, that elevated SICI and ICF MEP amplitudes both reflect a generally increased cortical excitability. Because SICI and ICF are thought to be primarily related to GABAergic neurotransmission (see also chapter 1.4.3), the observations in patients with first episode schizophrenia or ADHD of reduced and enhanced values for SICI and ICF, respectively, may indicate enhanced cortical disinhibition via GABAergic involvement. The prolonged CSP in both patient groups points in the same direction (121). It can, however, not be excluded that the increase of GABAergic transmission results from an enhanced compensatory dopaminergic activation in subcortical brain regions (101,104). In this respect, is could be postulated that the cortical-striatal-pallidal-thalamical-cortical loop is affected in both schizophrenia and ADHD (33,49,61,72,80). Although in patients with first episode schizophrenia and in patients with ADHD cortical disinhibition of the left hemisphere (hyperexcitability) was found, it can not be excluded that this phenomenon results from reduced facilitation (hypoexcitability) over the contralateral right hemisphere (58,108,116). Most probably, in schizophrenia, intrahemispheric and interhemispheric compensatory mechanisms are involved as reflected by CSP enhancement and ICF modulation.

In conclusion, the results of these studies support the ideas of cortical disinhibition in both ADHD and first episode schizophrenia and suggest common pathophysiological pathways related to GABAergic and dopaminergic neurotransmitter functionality.

8.5 Limitations and strengths of the studies

The fMRI technique has several techniqual limitations which are mainly related to the slow time courses of the signals which hampers stable representation of rapidly changing executive and motor functions in human beings. In addition, repeated measurements in a group of patients are warranted to get a reliable outcome. Moreover, patients must lie in a resting state without significant motor activity for about 15 minutes. These factors partly explain the inconsistency of the results in patients with psychiatric disorders, particular in whom motor disinhibition is a key symptom such as ADHD. Thus, fMRI data have to be controlled for movement artifacts which have led to a significant number of drop-outs (ca. 15%) in the data as presented in this thesis.

The main technical problem in applying TMS is the highly variable amplitude of the elicited motor signal. Therefore, averaging of the magnetically evoked potentials has to be performed in order to obtain reliable data. This specific technical limitation is particularly relevant in patients with highly increased motor activity (like in ADHD). Given this, the results of measurements in very hyperactive or restless patients had to be excluded from the data analyses.

As mentioned in the discussion sections of the papers included in this thesis, the results have to be interpreted cautiously since several confounding factors were present. Apart from the technical difficulties as described above, the study groups comprised a limited number of patients only, which influenced the statistical power. Furthermore, in the study with ppTMS in patients with schizophrenia, the results may have been influenced by the use of antipsychotic medication. Finally, but relevant for all research in psychiatry, stability over time of the diagnosis and scoring instruments to assess intensity of symptoms cannot be clearly validated (e.g. the German validation of the adult ADHD scoring instruments is still going on). In this respect, it has to be stressed that the Diagnostic and Statistical Manual (DSM) is a categorical classification system and its symptom validity to establish psychiatric diagnoses is still a matter of debate. The latter has already resulted in several relevant adaptations in the subsequent issues of the DSM.

Apart from the more general remarks on the limitations of these studies, their methodical strength has also to be underlined. All but the one study with LA-Mph followed a controlled design. The age of the included patients ranged from 18 to 49 years and neither age nor intelligence influenced the stability of the neurophysiological parameters. Moreover, no relevant gender effect of the 'pure' and drug-naïve ADHD patients could be demonstrated so that 'real' ADHD pathophysiology could be studied indeed. Finally, functionality of brain mechanisms in ADHD was compared with that in

another diagnostic group, first episode schizophrenia, a disease with parallels regarding cognitive psychopathology and brain transmission mechanisms.

8.6 Clinical relevance and future outlines

As demonstrated in this thesis, the fMRI technique can be used to elegantly investigate brain networks involved in processing attention and executive brain functions. The results of the here presented studies demonstrate that the symptomatology of ADHD may persist over decades, but not always in a similar intensity and constellation. Interestingly, data from the literature indicate that alterations in the neurophysiological parameters as measured with fMRI are qualitatively rather stable over time. In other words, this functional disturbance in subcortical-cortical neuronal pathways originates from childhood and persists into adulthood irrespective the psychopathological presentation of the disorder. ADHD in adulthood can be described as an impairment of attention and executive functioning as well as motor inhibition, that may be considered as trait characteristics of the disorder. Therefore, this technique may be used in future studies to investigate putative genotype-phenotype relationships and associations between phenotypical presentations and sex and/or age. In addition, since the fMRI technique is non-invasive and can be performed repeatedly, it can be used to perform longitudinal studies aimed to detect compensatory or restorating mechanisms and effects of pharmacological interventions in individual patients with ADHD. This may ultimately lead to an endophenotypically orientated individualized diagnosis and treatment of adult patients with ADHD.

PpTMS is a non-invasive technique too by which motor functionality, related to neurotransmitter systems, can be investigated in humans. Since the magnetically evoked potential (MEP) is the result of all excitatory and inhibitory postsynaptic potentials on the motor neuroaxons, ppTMS is one of the most appropriate techniques to study overall activity of pyramidal neurons including their dynamic compensatory capacities. Given its sensitivity to pharmacological influence and its correlation with clinical phenotypes, ppTMS can be applied in follow-up treatment studies with the emphasis on the long-term effects on motor systems in adults with ADHD. As compared to the data obtained by other investigators in children with ADHD, the results of the neurophysiological parameters in the here presented studies with adult ADHD patients suggest that treatment with LA-Mph induces similar effects. This method may eventually lead to the development of "therapeutic drug monitoring" and to a better understanding of motor cortex transmission in psychiatric disorders in general.

An additional aspect to be considered is that age and gender are not of major significance in attention or motor brain network activation patterns in adults with ADHD, albeit that shifting of symptomatology occurs from childhood into adulthood (see chapter 1). Since the studies presented here were performed with drug naïve ADHD patients, the

neurophysiological parameters can be considered to reflect trait factors in ADHD patients without drug-induced variations in neuroplasticity.
Finally, in the study comparing patients with first episode schizophrenia and adults with ADHD, overlapping changes in MEP amplitudes were found which points towards a common neurobiological pathway including GABAergic and dopaminergic neurotransmitter systems and may ultimately lead to more endophenotypically orientated treatment strategies.
Future longitudinal studies are warranted to further elucidate the postulated endophenotypic trait stability of ADHD. These investigations may eventually disclose a clear genotype-phenotype relationship of ADHD and consequently a more targeted pharmacological treatment approach for this and other dopamine-related disorders or symptoms.

8.7 Conclusions

Four main conclusions can be formulated on the basis of this thesis.

The fMRI data from the controlled study demonstrated impairments of attentional and executive brain networks in adult ADHD in comparison to healthy controls. The hypoactivation in fronto-striatal and parietal brain networks correlated with the clinical ADHD symptom scores. Thus, ADHD patients used deviant brain networks via the left insula to compensate for the hypoactivation of the above mentioned attention networks.

PpTMS was used to investigate motor cortex excitability in adult patients with ADHD. The results of this controlled study showed that motor inhibition deficits localized in the left hemisphere were present in ADHD. The observed increases in inhibitory MEP amplitudes could be associated with the symptom profile.

The amplitude of the inhibitory MEP decreased during treatment with the dopamine agonistic compound LA-Mph, which suggested that dopaminergic dysfunctions are of significance in the pathophysiology of ADHD indeed.

In the controlled studies, results of ppTMS in patients with first episode schizophrenia were compared to those obtained in adult patients with ADHD. In patients from both diagnostic categories a diminished intracortical inhibition was demonstrated, especially in the left dominant hemisphere. In the right hemisphere, however, the intracortical facilitation appeared to be increased in patients with schizophrenia but not in those with ADHD. In addition, a prolonged CSP was found in both schizophrenic and ADHD patients suggesting that imbalances in GABAergic neurotransmission are also involved in the pathophysiology of motor inhibition. As a consequence, the equilibrium between

GABAergic and dopaminergic neurotransmission might be disturbed which indicates that schizophrenia and ADHD share common neurotransmitter deficits.

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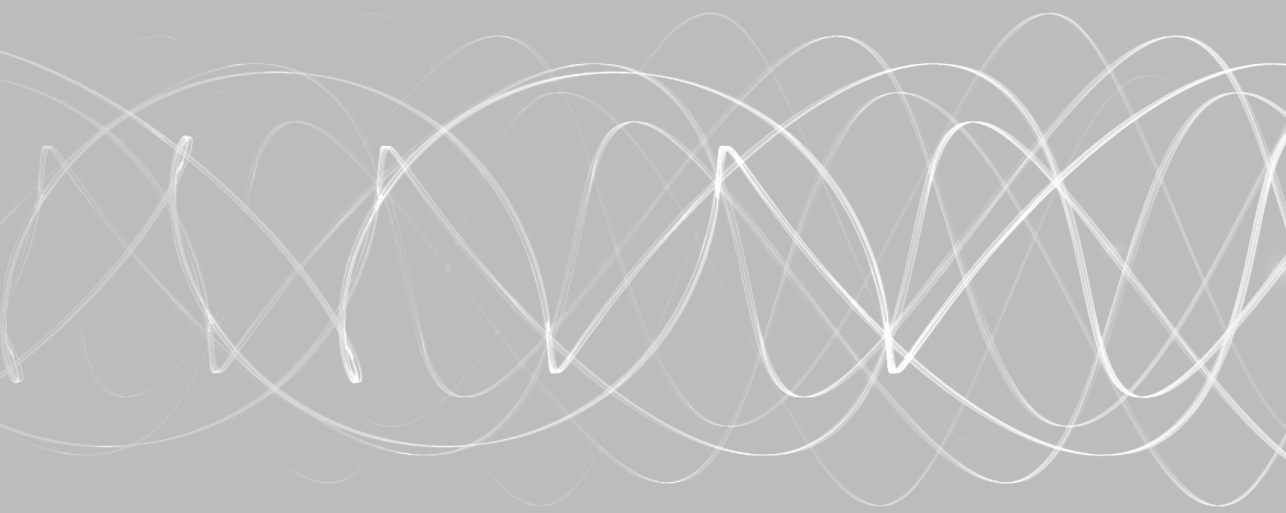

Summary

Attention Deficit/ Hyperactivity Disorder (ADHD) is characterized by a shifting of symptomatology from childhood to adulthood. Especially hyperactivity and impulsivity seem to become less prominent, and disorganization dominates the symptomatic expression of attention problems. Therefore, there is a need to investigate the pathophysiological brain mechanisms leading to ADHD symptomatology in adults and their links to the clinical phenotype. In this thesis, the functional magnetic resonance imaging (fMRI) technique was used to delineate the attention and executive impairments in ADHD. With the paired pulse transcranial magnetic stimulation (ppTMS) technique the brain motor excitability was analysed in ADHD and its modulation with the long acting stimulant methylphenidate. The comparison with patients with schizophrenia, a disorder which also includes attention deficits and motor phenomena, was included to delineate the common or distinguishing pathophysiological pathways.

First, in chapter 3 the attention network in adult ADHD patients was investigated as it still remains unclear whether ADHD psychopathology shows distinct deficits in adulthood. A total of 11 adult patients with ADHD, 8 probands with ADHD associated symptoms in childhood, and 17 controls were recruited for this event related fMRI study. With a continuous performance test (CPT) inhibitory functions were tested in the NoGo condition. It turned out that in ADHD patients not only the fronto-striatal network could be activated less, but also the posterior parietal attention system, reflecting hypofunctionality of a more broad attention network. These reduced activation patterns were similar to the patterns observed in studies with children and adolescents with ADHD. Linear regression analysis showed a correlation of reduced activities of caudate nuclei, anterior cingulate cortex as well parietal cortical structures with ADHD self-rating symptomatology. It is concluded that impairment of an array of brain regions involved in cognitive processing is present in adult patients with ADHD.

Second, motor inhibition and facilitation in adult ADHD patients was studied in chapter 4 using ppTMS. A group of 26 right handed adult ADHD patients (according to DSM-IV criteria) was investigated and compared to 26 age and sex-matched controls. In the left hemisphere, mean motor inhibition was decreased in ADHD patients as compared to controls. There were no significant differences in motor excitability concerning facilitation. Decreased motor inhibition correlated with a higher symptom score derived from the Wender Reimherr Interview and also with self rated hyperactivity/impulsivity symptoms. It was concluded that decreased motor inhibition in adult ADHD corroborates similar findings in children with ADHD and reflects disturbed impulsivity and hyperactivity on a neurophysiological level.

Third, the neurophysiological effects of long acting Methylphenidate (LA-Mph) were investigated in chapter 5 in adult patients with ADHD using ppTMS technique. Thirteen right handed adult ADHD patients were included. Measurements took place before and under treatment with LA-Mph in a stable individualized daily dose. LA-Mph significantly decreased the relative short intracortical motor inhibition (SICI) magnetically evoked potential (MEP) amplitude. The relative intracortical facilitation (ICF) MEP amplitude was not increased. The reduced relative SICI MEP amplitude with LA-Mph correlated with the improvement of the psychopathological ADHD self-rating total scores. These results demonstrate that LA-Mph significantly improves motor disinhibition in adult patients with ADHD and might have differential stabilizing effects on motor hyperexcitability.
Fourth, SICI and ICF were assessed in 29 first-episode schizophrenia patients with limited exposure to antipsychotic treatment and in 28 healthy controls in chapter 6. For SICI conditions, in patients with schizophrenia significantly higher MEP amplitudes were found from left motor cortex and, for MEPs from right motor cortex, a similar trend was observable. No difference in MEPs could be detected for ICF on either hemisphere. In addition, there was no difference in left and right resting motor threshold (RMT) comparing patients and controls. Finally, cortical excitability (inhibitory and facilitatory networks) was investigated in ADHD and schizophrenia with single- and paired-pulse-TMS to the left and right motor cortex in chapter 7. Compared to healthy controls, patients with either schizophrenia or ADHD displayed impaired cortical inhibition over the left hemisphere. Both patient groups presented a dysfunctional hemispheric pattern of cortical inhibition and facilitation in comparison with controls. These results indicate a pattern of cortical disinhibition and abnormal hemispheric balance of intracortical excitability networks in both dopamine-related diseases. These effects might be associated with an imbalance in GABAergic and dopaminergic transmission and might provide evidence for a common pathophysiological pathway of both diseases.

In chapter 8, the most important results in relation to the aims of this thesis were discussed and the conclusions were presented.

Samenvatting

Attention Deficit/ Hyperactivity Disorder (ADHD) wordt gekenmerkt door een verschuiving in de klinische symptomatologie van de kindertijd naar volwassenheid. Vooral hyperactiviteit en impulsiviteit lijken minder prominent, terwijl desorganisatie de symptomatologie van de aandachtsproblemen domineert. De onderliggende pathofysiologie is echter niet bekend. Daarom is het noodzakelijk de pathofysiologische processen in het centrale zenuwstelsel die ten grondslag liggen aan ADHD symptomen bij volwassenen te onderzoeken, alsmede de verbanden met het klinische fenotype.
In dit proefschrift werd de functionele magnetische resonantie imaging (fMRI) techniek gebruikt om de aandachts- en executieve functiestoornissen in ADHD te onderzoeken. Met de gepaarde puls transcraniële magnetische stimulatie (ppTMS) techniek werden de motorische excitabiliteit van de hersenen en de modulatie door de langwerkende afgiftevorm van methylfenidaat bij volwassen patiënten met ADHD geanalyseerd. E en vergelijkende analyse met ppTMS bij patiënten met schizofrenie, een aandoening die ook gepaard gaat met aandachtsstoornissen en psychomotorische verschijnselen, zou vervolgens de gemeenschappelijke of de te onderscheiden pathofysiologische mechanismen inzichtelijk kunnen maken.

Allereerst werden in hoofdstuk 3 de aandachtsnetwerken bij volwassen ADHD patiënten onderzocht om de mechanismen van ADHD psychopathologie in de volwassenheid aan te tonen. Een totaal van 11 volwassen patiënten met ADHD, 8 personen met aan ADHD geassocieerde symptomen in de kindertijd, en 17 controles werden gerekruteerd voor deze 'event-related' fMRI studie. Met een continue performance test (CPT) werden de inhibirende functies in de NoGo conditie getest. Bij ADHD patiënten bleek niet alleen het fronto-striatale-netwerk minder geactiveerd te worden, maar ook het posterieure pariëtale attentie systeem, ten gevolge van hypofunctionaliteit van een groter attentie netwerk. Deze verminderde activatie patronen waren vergelijkbaar met die zoals eerder gevonden in kinderen en adolescenten met ADHD. Lineaire regressie-analyses toonden een correlatie tussen verminderde activiteiten in de caudate nuclei, de anteriore cingulaire cortex en pariëtale corticale structuren en de ADHD symptomatologie op de zelfbeoordelingslijsten. Geconcludeerd wordt dat een reeks van hersengebieden die bij cognitieve verwerkingen betrokken zijn, bij volwassen patiënten met ADHD een veranderde functionele activiteit hebben.

Vervolgens werd in hoofdstuk 4 motorische inhibitie en facilitatie bij volwassen ADHD patiënten onderzocht met behulp van ppTMS. Een groep van 26 rechtshandige volwassen ADHD patiënten (volgens DSM-IV criteria) werd onderzocht en vergeleken met 26 leeftijd en geslacht gematchte controles. In de linker hersenhelft bleek de gemiddelde motorische inhibitie te zijn verminderd bij ADHD patiënten in vergelijking

met controles. Er waren geen significante verschillen in motorische excitabiliteit met betrekking tot de facilitering. Verminderde motorische inhibitie correleerde met een hogere symptoom score, zoals afgeleid van het Wender Reimherr Interview en ook met de hyperactiviteit/impulsiviteitsscores van de ADHD zelfbeoordelingslijsten.

Geconcludeerd werd dat, evenals bij kinderen met ADHD, bij volwassenen met ADHD verminderde motorische inhibitie aanwezig is. De klinische symptomatologie van de impulsiviteit en hyperactiviteit sluit bij volwassenen met ADHD aan op de neurofysiologisch meetbare disinhibite.

Daarna werden in hoofdstuk 5 de neurofysiologische effecten van langwerkend methylfenidaat (LA-Mph) bij volwassen patiënten met ADHD onderzocht met behulp van de ppTMS techniek. Dertien rechtshandige volwassen ADHD-patiënten werden gerecruteerd. Metingen vonden plaats vóór en tijdens de behandeling met LA-Mph in een stabiele individuele dagelijkse dosering. LA-Mph verminderde significant de relatieve korte intracorticale motorische inhibitorische (SICI) magnetisch evoked potential (MEP) amplitude. De relatieve intracorticale faciliterende (ICF) MEP amplitudes waren niet verhoogd. De verminderde relatieve SICI MEP amplitude met LA-Mph correleerde met een verbetering van de ADHD symptomen, zoals vastgelegd met de totaal scores op zelfbeoordelingslijsten. Deze resultaten tonen aan dat LA-Mph de motorische disinhibitie bij volwassen patiënten met ADHD significant verbetert en een gedifferentieerd stabiliserend effect heeft op de motorische hyperexcitabiliteit.

In hoofdstuk 6 werden SICI en ICF geanalyseerd in 29 eerste episode schizofrenie patiënten met een beperkte blootstelling aan antipsychotische behandeling en bij 28 gezonde controlepersonen. Voor de conditie SICI werden bij patiënten met schizofrenie significant hogere MEP amplitudes gevonden van de linker motorische cortex. Een soortgelijke trend werd ook voor de rechter motorische cortex gevonden. Geen verschil van MEP kon worden gedetecteerd in de ICF van beide hemisferen. Daarnaast was er geen verschil in de motorische drempel in rust (RMT) tussen patiënten en controles.

Tot slot werd in hoofdstuk 7 met behulp van single- en gepaarde puls-TMS de corticale excitabiliteit (inhiberende en faciliterende netwerken) over de linker en rechter motorische cortex onderzocht bij patienten met ADHD of schizofrenie. In vergelijking met gezonde controles vertoonden de patiënten met schizofrenie of ADHD een verminderde corticale inhibitie over de linker hemisfeer. In vergelijking met controles toonden beide groepen patiënten een disfunctioneel hemisferisch patroon van corticale inhibitie en facilitatie. Deze resultaten wijzen op een patroon van corticale desinhibitie en abnormale hemisferische balans van intracorticale excitabiliteit van neuronale netwerken in deze dopamine-gerelateerde ziekten. Deze effecten zijn

waarschijnlijk gerelateerd aan een disbalans in GABA-erge en dopaminerge neurotransmissie en wijzen op een gemeenschappelijke pathofysiologische factor.

In hoofdstuk 8 worden de belangrijkste resultaten met betrekking tot de doelstellingen van dit proefschrift besproken en de conclusies gepresenteerd.

Zusammenfassung

Die Aufmerksamkeits-Defizit/ Hyperaktivitätsstörung (ADHS) ist durch eine klinische Symptomverlagerung von der Kindheit zum Erwachsenenalter charakterisiert.

Besonders Hyperaktivität und Impulsivität scheinen im Laufe der Zeit weniger prominent zu werden, währenddessen die Desorganisation symptomatisch für die Aufmerksamkeitsprobleme wird. Diese Aspekte unterstreichen die Notwendigkeit, die pathophysiologischen Mechanismen des Gehirns zu untersuchen, die zur ADHS Symptomatik bei Erwachsenen führen und die Zusammenhänge zum klinischen Phänotyp zu verdeutlichen. In dieser Arbeit wurde die funktionelle Magnetresonanztomographie (fMRI) angewandt, um die Aufmerksamkeits- und exekutiven Störungen bei ADHS darzustellen. Mit der transkraniellen Doppelpuls-Magnetstimulation (ppTMS) wurde die motorische Erregbarkeit des Gehirns bei ADHS inklusive deren Modulation mit der lang wirksamen Applikationsform des Stimulans Methylphenidat untersucht. Der Vergleich mittels ppTMS mit Patienten mit Schizophrenie, einer Krankheit, die auch Aufmerksamkeitsstörungen und psychomotorische Phänomene aufweist, könnte die Abgrenzung von gemeinsamen oder unterschiedlichen pathophysiologischen Vorgängen ermöglichen.

Zunächst wurden in Kapitel 3 die Aufmerksamkeitsnetzwerke bei erwachsenen ADHS-Patienten untersucht, zumal unklar war, ob die ADHS-Psychopathologie relevante funktionelle Defizite im Erwachsenenalter aufzeigt. Insgesamt 11 erwachsene Patienten mit ADHS, 8 Probanden mit ADHS-assoziierten Symptomen in der Kindheit, und 17 Kontrollprobanden wurden für diese ereigniskorrelierte fMRI-Studie rekrutiert. Mit einem Continuous Performance-Test (CPT) wurden die inhibitorischen Funktionen in der NoGo Bedingung untersucht. Es stellte sich heraus, dass bei ADHS-Patienten nicht nur die fronto-striatalen Netzwerke weniger aktiviert wurden, sondern auch die posterioren Aufmerksamkeitssysteme, was auf Hypofunktionalität breiter Aufmerksamkeitsnetzwerke hindeutet. Diese reduzierten Aktivierungsmuster ähnelten den Mustern aus Studien mit Kindern und Jugendlichen mit ADHS. Die lineare Regressionsanalyse zeigte eine Korrelation von reduzierter Aktivität des Nucleus caudatus, anterioren cingulären Cortex als auch parietaler kortikaler Strukturen mit der Symptomatologie der ADHS-Selbstbeurteilungsskalen. Es wurde daraus gefolgert, dass Beeinträchtigungen einer Reihe von Hirnregionen bestehen, die mit der kognitiven Verarbeitung, bei erwachsenen Patienten mit ADHS vergesellschaftet sind.

Zweitens, motorische Inhibition und Fazilitation wurden bei erwachsenen ADHS-Patienten in Kapitel 4 mit Hilfe der ppTMS untersucht. Die physiologischen Parameter von 26 rechtshändigen erwachsenen ADHS-Patienten (nach DSM-IV) wurden mit denen

von 26 Alters- und Geschlechts-gematchten Kontrollen verglichen. In der linken Hemisphäre, war die gemittelte motorische Inhibition bei den ADHS-Patienten im Vergleich zu den Kontrollen vermindert. Es gab keine signifikanten Unterschiede in der motorischen Erregbarkeit im Bezug auf die Fazilitation. Die verminderte motorische Inhibition korrelierte mit einem höheren Symptom-Score aus dem Wender Reimherr Interview und auch mit den Hyperaktivitäts-/ Impulsivitätsscores der ADHS-Selbsteinschätzungsskalen. Es konnte festgestellt werden, dass die verminderte motorische Inhibition bei erwachsenen ADHS-Patienten ähnliche Befunde erbrachte, die bei Kindern mit ADHS beschrieben wurden. Störungen der Impulsivität und Hyperaktivität spiegeln sich somit auf neurophysiologischer Ebene wider.

Drittens, wurden die neurophysiologischen Auswirkungen von lang wirksamem Methylphenidat (LA-Mph) in Kapitel 5 bei erwachsenen Patienten mit ADHS mit der ppTMS Technik untersucht. Dreizehn rechtshändige erwachsene ADHS-Patienten wurden in diese Studie eingeschlossen. Die Messungen fanden vor und während der Behandlung mit einer stabilen individuellen Tagesdosis LA-Mph statt. LA-Mph verringerte signifikant die relative, kurze intrakortikale motorische inhibitorische (SICI) magnetisch evozierte Potential-(MEP) Amplitude. Die relative intrakortikale Fazilitations (ICF)- MEP Amplitude wurde nicht erhöht. Die Verringerung der relativen SICI MEP Amplitude mit LA-MPH korrelierte mit der Verbesserung des psychopathologischen ADHD-Self-Rating-Gesamtscores. Diese Ergebnisse zeigen, dass LA-Mph deutlich die motorische Dysinhibition bei erwachsenen Patienten mit ADHS verbessert und eine differentielle stabilisierende Wirkung auf die motorische Übererregbarkeit haben könnte.

Viertens, SICI und ICF wurden in Kapitel 6 bei 29 ersterkrankten Schizophrenie-Patienten mit begrenzter Exposition mit antipsychotischer Behandlung und bei 28 gesunden Kontrollpersonen untersucht. Für die SICI-Bedingungen wurden bei den Patienten mit Schizophrenie deutlich höhere MEP-Amplituden im linken motorischen Kortex gefunden. Ein ähnlicher Trend war bei den Patienten im rechtshemispärischen motorischen Kortex zu beobachten. Kein Unterschied in den MEPs konnte für die ICF auf beiden Hemisphären nachgewiesen werden. Darüber hinaus ergaben sich im links- und rechtshemisphärischen Vergleich der motorischen Schwellen in Ruhe (RMT) von Patienten und Kontrollen keine Abweichungen. Schließlich wurde in Kapitel 7 die kortikale Erregbarkeit (inhibitorische und fazilitatorische Kreisläufe) bei ADHS und Schizophrenie mit single- und paired-pulse-TMS am linken und rechten motorischen Kortex untersucht. Im Vergleich zu gesunden Kontrollpersonen, wiesen Patienten mit Schizophrenie oder ADHS Verminderungen der kortikalen Inhibition über der linken Hemisphäre auf. Beide Patientengruppen präsentierten ein dysfunktionales Hemisphärenmuster der kortikalen Inhibition und Fazilitation im Vergleich zu Kontrollen. Diese

Ergebnisse zeigen ein Muster der kortikalen Enthemmung und abnormen hemisphärischen Balance der Erregbarkeit intrakortikaler Netzwerke in beiden dopaminergen Erkrankungen auf. Solche Effekte könnten mit einem Ungleichgewicht der GABAergen und dopaminergen Transmission in Verbindung gebracht werden und könnten auf einen gemeinsamen pathophysiologischen Weg der beiden Erkrankungen deuten.

In Kapitel 8 wurden die wichtigsten Ergebnisse in Bezug auf die Fragestellungen dieser Arbeit diskutiert und die Schlussfolgerungen präsentiert.

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List of publications

Alkomiet Hasan*, Marc Schneider*, Thomas Schneider-Axmann, Diane Ruge, Wolfgang Retz, Michael Rösler, Peter Falkai, Thomas Wobrock (2012) A similar but distinctive pattern of impaired cortical excitability in first-episode schizophrenia and ADHD. Accepted in Neuropsychobiology.

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STELLINGEN

Behorende bij het proefschrift van Marc Schneider

1. Bij ADHD bij volwassenen vinden zich stoornissen bij hersenen attentie netwerken die betrokken zijn bij de verwerking van eenvoudige signalen en ook van signal conflicten. (Dit proefschrift)
2. Aandachtstekort en hyperactiviteit/impulsiviteit zijn geassocieerd met verminderde activatie van de neuronale circuits behorende bij attentie en motoriek. (Dit proefschrift)
3. Volwassenen met ADHD vertonen verminderde activatie van fronto-striatale en parietale hersengebieden in vergelijking met gezonde controles; deze verminderde activatie correleert met de klinische symptomatologie. (Dit proefschrift)
4. Verhoogde motorische excitabiliteit van de hersenen bij patiënten met ADHD is zichtbaar in de linker hemisfeer en correleert met het klinische fenotype. (Dit proefschrift)
5. Een behandeling met Methylfenidaat vermindert de symptomen van ADHD en normaliseert de verlaagde inhibitie van het motorische neurotransmissie systeem. (Dit proefschrift)
6. Bij patiënten met ADHD en schizofrenie wordt een hemisferische disbalans in de motorische excitabiliteit gevonden, hetgeen duidt op een mogelijke gemeenschappelijke pathofysiologische betrokkenheid van dopaminerge en GABAerge neurotransmissie systemen bij deze beide ziektebeelden. (Dit proefschrift)
7. There are no such things as applied sciences, only applications of science. (Louis Pasteur 1822-1895)
8. Human affairs are so obscure and various that nothing can be clearly known. (Desiderius Erasmus 1469-1536)
9. Auf dem Wege in die Irre ist der Rückschritt Fortschritt. (Josef Viktor Stummer 1910-1981)
10. Soms kan het zeer handig zijn, tijdens het eten van een kogelvis in een Japaans restaurant een pijlgif kikker in de buurt te hebben.
11. Essence of science. You first think of something that might be true - then you look to see if it is, and generally it isn't. (Bertrand Russell 1872-1970)