Transcranial direct current stimulation (tDCS) of the right inferior frontal gyrus: Towards a non-pharmacological treatment approach for children and adolescents with attention-deficit/hyperactivity disorder (ADHD)

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Abstract

Besides the core symptoms of inattention, hyperactivity, and impulsivity, ADHD is characterized by executive dysfunctions, foremost in working memory and response inhibition, which have been associated to hypoactivity of the right inferior frontal gyrus (IFG). Transcranial direct current stimulation (tDCS) is a neuromodulatory method with a good safety profile that has the potential to induce long-lasting excitability changes in targeted brain areas. Therefore, it was aimed to improve working memory and response inhibition in children and adolescents with ADHD by applying tDCS to the right IFG.

In the first step, a combined *n*-back/nogo paradigm was introduced and validated, which enabled the simultaneous and economical assessment of both executive functions in subsequent tDCS experiments. Comparisons with parallel single task versions revealed strong correlations for behavioral outcome measures as well as comparable structures of event-related potentials (ERPs). Further, the combined *n*-back/nogo task was suitable to assess ADHD related deficits in working memory, response inhibition, and attentional measures, as well as diminished ERP amplitudes of the *n*-back and the nogo P3.

In ADHD patients, tDCS was applied to the right IFG using different electrode montages, to investigate whether conventional and high definition tDCS (HD-tDCS) were effective. While conventional tDCS with large pad electrodes induces wide spread current flow patterns in the brain, HD-tDCS yields a higher focality with highest current densities occurring mainly in target brain areas. The tDCS application with both montages increased amplitudes of the P3 component and decreased N2 amplitudes during working memory trials of the *n*-back/nogo task, which indicated favorable changes in underlying higher order processing mechanisms. At the same time, behavioral performance was not generally influenced suggesting that tDCS induced neurophysiological alterations were subthreshold to translate into behavior. With this regard, both tDCS montages yielded comparable results, making HD-tDCS the favorable method as its higher precision towards the right IFG potentially reduced unintended changes in non-target brain areas.

Therefore, HD-tDCS was further investigated in a sham-controlled trial, where it was applied on five consecutive days to ADHD patients in order to induce larger and more sustainable effects. Patients received tDCS either with a current intensity of 0.5 mA or 0.25 mA depending on individual cutaneous sensitivity. In contrast to the hypothesis, no beneficial effect was found on working memory or response inhibition. However, the 0.5 mA group showed attentional improvements, indicated by reduced omission errors and reaction time variability, which were found also for non-trained transfer tasks and which were still evident at a four-month follow up assessment. In the 0.25 mA group detrimental tDCS effects were found on response inhibition. This behavioral finding of distinct tDCS effects from different current intensities was supported by EEG data of the nogo P3 component, which revealed a larger decrease in peak amplitude from baseline to post for the 0.25 mA group than for the 0.5 mA group. It was speculated that impairments after low intensity HD-tDCS resulted from an unexpected, inhibitory stimulation effect, which demonstrates the importance for research on side-effects of brain stimulation. In the future, the necessity to reduce current intensities could be avoided by using montages, which yield high focality while inducing weaker skin sensations, i.e. optimized multi-channel tDCS.

In conclusion, although tDCS of the right IFG as it was applied here could not induce enhancements of working memory and response inhibition, long-lasting beneficial effects on attention were yielded, which indicates the potential of this method, as a future non-pharmacological therapy approach for ADHD.

Zusammenfassung

Neben den Kernsymptomen Unaufmerksamkeit, Hyperaktivität und Impulsivität ist ADHS durch exekutive Dysfunktionen, insbesondere in den Bereichen Arbeitsgedächtnis und Verhaltenskontrolle, gekennzeichnet, die mit einer Unteraktivierung des rechten inferioren frontalen Gyrus (IFG) einhergehen. Die transkranielle Gleichstromstimulation (tDCS) ist eine Methode zur Neuromodulation mit gutem Sicherheitsprofil und dem Potential, langanhaltende Veränderungen der Hirnaktivität definierter Areale zu erzielen. Ziel dieser Arbeit war es, bei Kindern und Jugendlichen mit ADHS Arbeitsgedächtnis und Verhaltenskontrolle durch den Einsatz von tDCS des rechten IFG zu verbessern.

Im ersten Schritt wurde dazu ein kombiniertes *n*-back/nogo-Paradigma entwickelt und validiert, das die simultane und ökonomische Erfassung von Korrelaten dieser Exekutivfunktionen in nachfolgenden tDCS-Experimenten ermöglichte. Parallele Versionen des *n*-back und des go/nogo-Paradigmas zeigten hohe Korrelationen zum kombinierten *n*-back/nogo-Paradigma in Verhaltensmaßen sowie vergleichbare Strukturen in den ereigniskorrelierten Potentialen (EKPs). Zudem gelang es mit der kombinierten *n*-back/nogo-Aufgabe, bei ADHS-Patienten Defizite in Arbeitsgedächtnis, Verhaltenskontrolle und Aufmerksamkeit sowie verringerte EKP-Amplituden der *n*-back und der nogo-P3-Komponente nachzuweisen.

Bei ADHS-Patienten wurde tDCS des rechten IFG mittels konventioneller tDCS und hochauflösender tDCS (HD-tDCS) durchgeführt, um die Wirksamkeit beider Montagen zu beurteilen. Während konventionelle tDCS mit großen Pad-Elektroden weit verteilte Stromflussmuster im Gehirn erzeugt, erzielt HD-tDCS eine höhere Präzision. Für beide tDCS Montagen zeigte sich eine erhöhte Amplitude der P3-Komponente und eine verringerte N2-Amplitude für Arbeitsgedächtnistrials der *n*-back/nogo-Aufgabe. Allerdings fand sich keine Verbesserung in den Verhaltensmaßen der Aufgabenbearbeitung. Dies lässt darauf schließen, dass die Stimulation lediglich unterschwellige neurophysiologische Veränderungen verursachte, die sich nicht ins Verhalten übersetzten. Insgesamt lieferten beide tDCS-Montagen vergleichbare Resultate, weshalb HD-tDCS als vorteilhaftere Methode erscheint, da ihre höhere Präzision mutmaßlich unerwünschte Veränderungen in angrenzenden Hirnarealen verringern kann.

Daher wurde die HD-tDCS anschließend in einer sham-kontrollierten Studie an fünf aufeinanderfolgenden Tagen bei ADHS-Patienten angewendet, mit dem Ziel, größere und dauerhaftere Effekte zu erzielen. Die Patienten erhielten die Stimulation mit einer Stromstärke von 0,5 mA oder 0,25 mA, entsprechend der individuellen Sensibilität. Im Gegensatz zur aufgestellten Hypothese wurde dabei kein positiver Effekt auf Arbeitsgedächtnis oder Verhaltenskontrolle gefunden. Die Gruppe, die tDCS mit 0,5 mA erhielt, zeigte jedoch eine verbesserte Aufmerksamkeit in Form einer reduzierten Rate an Auslassungsfehlern und einer verringerten Reaktionszeitvariabilität. Diese wurde zudem in nicht trainierten Transferaufgaben gefunden und war noch vier Monate später nachweisbar. In der 0,25-mA-Gruppe zeigte sich eine verringerte Verhaltenskontrolle. Dieser differentielle Effekt unterschiedlicher Stromstärken auf das Verhalten wurde durch EEG-Ergebnisse der nogo-P3-Komponente gestützt. Diese zeigte in der 0,25-mA-Gruppe eine stärkere Amplitudenabnahme von der Baseline zur Post-Messung, verglichen mit der 0,5-mA-Gruppe. Es wurde gemutmaßt, dass die Beeinträchtigungen nach HD-tDCS mit niedriger Stromstärke auf einen unerwarteten, inhibitorischen Stimulationseffekt zurückzuführen seien. Dieser Befund verdeutlicht die Dringlichkeit der Erforschung von Nebenwirkungen der Hirnstimulation. Künftig könnte die Notwendigkeit einer Reduktion der Stromstärke durch den Einsatz neuerer Montagen vermieden werden, die zwar eine gute Präzision erzielen aber schwächere Hautempfindungen auslösen, beispielsweise die optimierte Multikanal-tDCS.

Zusammenfassend konnten mit der hier angewandten Stimulation des rechten IFG zwar keine Verbesserung von Arbeitsgedächtnis und Verhaltenskontrolle erreicht werden, allerdings wurden langanhaltende, positive Effekte auf die Aufmerksamkeitsleistung erzielt, was auf das Potential der Methode als zukünftigen, nicht-pharmakologischen Therapieansatz für ADHS schließen lässt.

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List of Abbreviations

ADHD	attention-deficit/hyperactivity disorder
ANOVA	analysis of variance
BOLD	blood-oxygen-level-dependent
CBCL	child behavior checklist
DLPFC	dorsolateral prefrontal cortex
EEG	electroencephalography/electroencephalogram
EOG	electrooculogram
ERP	event-related potential
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
HD	high definition
HD-tDCS	high definition transcranial direct current stimulation
IES	inverse efficiency score
IFG	inferior frontal gyrus
IQ	intelligence quotient
K-SADS-PL	schedule for affective disorders and schizophrenia for school-age children - present and lifetime version
M	mean value
MDE	minimal detectable effect
MEP	motor evoked potential
MRI	magnetic resonance imaging
ODD	oppositional defiant disorder
RI	response inhibition
ROI	region of interest
SD	standard deviation
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
tRNS	transcranial random noise stimulation
RT	reaction time
WM	working memory
YSR	youth self report

1 General Introduction

During the 1990s there was a dramatic increase in the amount of drugs prescribed to children and adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) containing the active agent methylphenidate (i.e. Ritalin®) (Ghodse, 1999). Three decades later, the number of defined daily doses seems to have reached its peak and is relatively constant in Germany since 2012 (Grimmsmann & Himmel, 2020). However, the pharmacological approach remains a central component of the therapeutic concept and since 2018, the "Level 3 guideline on the treatment of patients with ADHD" advises pharmacological therapy no longer only for severe forms of ADHD but likewise for moderate forms (DGKJP et al., 2017). This polarizing topic is critically discussed in popular science books, with authors as Gerald Hüther questioning if the administration of controlled substances to children who behave inappropriately should be socially desirable. Such voices are concerned that drug prescriptions in children mirror a growing pressure on young people for high academic performance in order to be successful in life, while individual needs are vastly ignored. However, from a scientific point of view, the key role of stimulants for the treatment of ADHD is reasonable.

Pharmacological therapy with stimulants shows the best evidence with the largest effect size of all current ADHD treatment options. If used properly, experts agree that benefits of stimulants outweigh adverse effects in most cases (DGKJP et al., 2017). Yet, pharmacological ADHD therapy is not free of side effects and therefore, many families desire non-pharmacological alternatives (Buchanan et al., 2020). A further downside of medication lays in its symptomatic treatment approach, which is not effective beyond the administration of medication (Jensen et al., 2007; Rubia, 2018). To overcome these limitations, research moves towards so-called neurotherapeutics. These are techniques that aim for a favorable impact on the brain development and thus, could have a potential rehabilitative value. A promising neurotherapeutic approach is transcranial direct current stimulation (tDCS), a non-invasive neuromodulatory method with a good safety profile and the potential to induce long-lasting changes in brain activity. Therefore, this dissertation aims to induce beneficial effects on executive functions in ADHD patients by the use of tDCS.

The thesis starts by giving a theoretical background of the topics ADHD and brain stimulation as well as on the scientific methods. Then, three experiments that form the centerpiece of this dissertation are presented. Two have been published in peer-reviewed

journals and the third has been accepted for publication. Finally, the meaning and implications of the findings will be discussed.

1.1 Attention-Deficit/Hyperactivity Disorder

The "Zappelphilipp" is a popular allegory for children with attention-deficit/hyperactivity disorder (ADHD). The famous story, published in 1844 by the German physician Heinrich Hoffmann describes a boy, who is not listening to his father while excessively fidgeting at the dinner table until he falls and tears down the tablecloth and meals making his parents furious. Since then, the disorder has gone through a history of changing names and explanatory models (Lange et al., 2010) with raising awareness among practitioners leading to an increase of its diagnostic prevalence, which is in Germany currently at 4.3% (Akmatov et al., 2018). It was as early as 1937 when the first successful attempt of stimulant treatment in children with behavioral disorders was reported, but until now, there is no curative treatment for ADHD. The related behavioral problems cause conflicts within the families and in the school. Further, children often experience rejection by peers, which results low self-esteem and a vulnerability for a variety of mental disorders (Faraone et al., 2015). This makes the investigation of effective ADHD therapies a highly relevant topic.

1.1.1 Symptoms and Diagnostics

ADHD is a neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity, and impulsivity. Inattention is defined as an increased distractibility, which makes it difficult to focus on tasks or conversations, especially over extended periods of time. The lack of organizational skills, making careless mistakes or forgetfulness are also indications of inattention. Hyperactivity expresses as excessive motor activity, such as fidgeting, running, or not remaining seated in inappropriate situations as well as excessive talking and, especially in adolescents or adults, the feeling of inner restlessness. In comparison, impulsivity manifests as impatience or interrupting during social situations (American Psychiatric Association, 2013).

Based on these core symptoms, ADHD is classified as one of three different presentations. If patients meet the criteria for either inattention or hyperactivity-impulsivity this corresponds to the predominantly inattentive or the predominantly hyperactive/impulsive presentation,

respectively. Patients that meet diagnostic criteria for both, inattention and hyperactivity-impulsivity are diagnosed with ADHD of the combined presentation.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association, 2013), at least six symptoms of inattention and/or hyperactivity and impulsivity must have persisted for a minimum of six month to a degree inconsistent with the developmental level in order to diagnose ADHD.

Inattention:

a) Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during 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 schoolwork, chores, or duties in the workplace.
e) Often has difficulty organizing tasks and activities.
f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.
g) Often loses things necessary for tasks or activities.
h) Is often easily distracted by extraneous stimuli.
i) Is often forgetful in daily activities.

Hyperactivity and impulsivity:

a) Often fidgets with or taps hands, or feet or squirms in seat.
b) Often leaves seat in situations when remaining seated is expected.
c) Often runs about or climbs in situations where it is inappropriate.
d) Often unable to play or engage in leisure activities quietly.
e) Is often „on the go“, acting as if „driven by a motor“.
f) Often talks excessively.
g) Often blurts out an answer before a question has been completed.
h) Often has difficulty waiting for his or her turn.
i) Often interrupts or intrudes on others.

In addition, the following diagnostic criteria apply:

- Several symptoms were present prior to age 12 years.

- Several symptoms are present in two or more settings, for example at home, at school, and with friends.
- Symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
- Symptoms do not occur exclusively during the course of a psychotic disorder and are not better explained by another mental disorder.

ADHD is diagnosed if all criteria are met. Depending on the number of symptoms and the degree of impairments, symptom severity is classified as mild, moderate, or severe. In mild forms of ADHD, only few symptoms in excess to those necessary to make a diagnosis are present, which cause only minor impairments, whereas in severe forms of ADHD many additional or particular severe symptoms are present resulting in marked impairments.

The differential diagnosis of ADHD is particularly important as various psychiatric disorders can underlie motoric and attentional problems, such as learning disorders, intellectual disabilities or other neurodevelopmental disorders. Oppositional defiant disorder can appear similar to ADHD because patients of both disorders often refuse doing school tasks. However, in oppositional defiant disorder this results from opposing to others, whereas ADHD patients have an aversion against tasks requiring mental effort. Intermittent explosive disorder and ADHD patients share high impulsivity, but in intermittent explosive disorder, this often expresses as serious aggressions against others, which is rather untypical in ADHD. Other important differential diagnosis for ADHD include autism spectrum disorder as well as anxiety and mood disorders. Moreover, comorbid disorders as oppositional defiant disorder and conduct disorder occur frequently in patients with ADHD (DSM-5, American Psychiatric Association, 2013).

1.1.2 Etiology

Childhood ADHD has a worldwide prevalence of about 5% and belongs therefore to the most frequent psychiatric disorders in school age children (Sayal et al., 2018). In the majority of patients, ADHD symptoms persist into adulthood causing ongoing functional impairments (Uchida et al., 2018) with a prevalence of adult ADHD ranging from 2.5 – 7.1% (Simon et al., 2009; Moulin et al., 2017). In boys, ADHD occurs 2 - 3 times more often than in girls, a ratio that is even higher in clinical samples (in Germany 3 – 4 : 1; Sayal et al., 2018). Whereas in boys oppositional defiant disorder and conduct disorder are the most common

comorbidities to ADHD, ADHD often manifests as depressive and anxiety disorders in girls, or is diagnosed as such (Martin et al., 2018).

The development of ADHD is attributed to a multifactorial interaction between genetic, environmental and psychosocial factors. ADHD is among the most heritable mental disorders with twin studies suggesting a heritability of 70 - 80%. Individuals have a five to tenfold increased risk of developing ADHD if one of their first degree relatives is affected (Faraone et al., 2015). Therefore, the key role of genetics for ADHD is indisputable but understanding the genetic complexity is challenging. More than 100 genes were found to be associated with ADHD (Hayman & Fernandez, 2018), mainly common gene variants each of a very small effect. Most ADHD risk alleles are related to processes of neurodevelopment as well as neurotransmission, especially of the dopaminergic and serotonergic systems (Akutagava-Martins et al., 2016). For example, gene variants of *DRD4* and *DRD5* encoding the expression of dopaminergic D_4 and D_5 receptors are connected to the reduced functionality of the dopaminergic system in ADHD (Sharma & Couture, 2014). Within the serotonergic system, the serotonin transporter gene *SLC6A4* and the serotonin receptor gene *HTR1B* were identified in association with ADHD. There is a genetic correlation of 0.6 between inattentive and hyperactive/impulsive ADHD symptoms indicating large portions of shared genetic variance together with domain specific fractions (Faraone et al., 2015)

Environmental and psychosocial risk factors are not specific to the development of ADHD but to psychiatric disorders in general (Faraone et al., 2015). The environment, individuals are exposed to, influences the expression of ADHD risk genes (Faraone et al., 2015), explaining 10 - 40% of the variance in the manifestation of this phenotype. Most relevant are prenatal factors including preterm birth, low birth weight, and ischemic-hypoxic events during pregnancy. Moreover, the maternal consumption of nicotine or alcohol during pregnancy belongs to the greatest risk factors, as these substances considerably impair brain development of the fetus incrementally with extent of substance exposure. Moreover, the application of medication such as antidepressants or paracetamol during pregnancy has detrimental effects on the child neurodevelopment. A further important factor is the mental health of the mother, because the risk for ADHD in the child increases with maternal stress, depression, or marital problems during pregnancy (Sciberras et al., 2017).

Besides unfavorable environmental factors, psychosocial influences can further facilitate the occurrence of ADHD. In Romanian orphans, severe cases of early maternal deprivation showed that the risk to develop ADHD symptoms increased in a dose-response relationship

with the length of the experienced deprivation (Stevens et al., 2008). Further, children in families of low social status or children in low-income families are more often diagnosed with ADHD (Sayal et al., 2018). Another factor is maternal experience indicated by the finding that children with ADHD are more probable to be the first-born child and to have a younger mother (Sciberras et al., 2017). Overall, stress could be the moderator underlying the majority of psychosocial risk factors as it was shown that the chance to develop ADHD increases with the overall number of stressful life events (Humphreys et al., 2019).

1.1.3 Pathophysiology

ADHD is characterized by complex neurobiological alterations in the brain affecting structural and functional aspects as well as neurotransmitter systems. The catecholamine hypothesis stresses the central role of dopaminergic and noradrenergic dysfunctions in the pathogenesis of ADHD (Prince, 2008). Among others, this was concluded from pharmacological research that found reduced ADHD symptoms after stimulant intake (Wu et al., 2012). However, further neurotransmitters are involved in ADHD, like serotonin and acetylcholine, which makes complex dysfunctional interactions between different neurotransmitter systems in ADHD likely (Prince, 2008).

Further, ADHD patients show a number of structural changes in the brain, including a reduced folding of the cortex associated with a diminished cortical surface area, as well as a global reduction of grey matter volume due to cortical thinning (Wolosin et al., 2009; Vilgis et al., 2016). This sums up to a total reduction of brain volume by 3 - 5% compared to healthy individuals, with a correlation between the extent of volume reduction and ADHD symptom severity (Faraone et al., 2015). The diminution of brain volume was found to be greater in the right than in the left hemisphere (Cortese & Coghill, 2018) and is most pronounced in prefrontal areas (Sharma & Couture, 2014). There, cortical thinning affects the dorsolateral prefrontal cortex, precentral areas as well as superior, medial, and ventromedial regions (Cortese & Coghill, 2018; Rubia, 2018). Of special interest in this dissertation is the volume reduction of the right inferior frontal gyrus (IFG) because it is correlated with deficits in cognitive functions in ADHD, like impaired response inhibition, increased behavioral variability and reduced processing speed (Cortese & Coghill, 2018). Besides cortical areas, further regions show a volume reduction in ADHD, like basal ganglia, limbic areas, and the cerebellum (Faraone et al., 2015; Rubia, 2018). It was suggested that structural and functional deficits in ADHD result from a maturational delay of brain development (Sripada et al.,

2014), with the prefrontal lobe showing a delayed development of cortical thickness (Shaw et al., 2006).

Structural abnormalities in ADHD are not restricted to grey matter but affect also white matter fibers impairing connectivity, which implies a disturbed integrity not of distinct regions but of entire networks. Reduced white matter volume was found for fronto-striatal, fronto-posterior, and thalamo-cortical connections as well as within the cerebellum (Nagel et al., 2011; Chen et al., 2016). Moreover, interhemispheric connectivity is reduced in ADHD with a volume reduction of the corpus callosum (Cortese & Coghill, 2018). This is reflected in a reduced functional connectivity between left and right prefrontal cortices during inhibitory tasks. During working memory and response inhibition, a reduced functional connectivity was also found between the right IFG and connected areas, including parietal and parieto-temporal cortices, basal ganglia, striatum, cingulum, and cerebellum. Interestingly, the remission of ADHD related symptoms is associated with a normalization of anatomic alterations, as reduced connectivity and cortical thinning (Cortese, 2012; Faraone et al., 2015).

Structural abnormalities associated with ADHD are reflected by functional alterations in fronto-striato-parieto-cerebellar networks that manifest mostly as reduced neural activity (Cortese, 2012; Rubia, 2018). A meta-analysis identified a number of affected regions, which showed activity reductions during inhibition tasks in the right IFG, supplementary motor area, anterior cingulate cortex, and striato-thalamic area as well as during attention tasks for the right dorsolateral prefrontal cortex, basal ganglia, thalamus, and parietal regions (Hart et al., 2013). However, somatomotor and visual areas show increased activity, which presumably reflects compensatory mechanisms resulting from diminished frontal activity (Faraone et al., 2015). Moreover, increased activity was found in the default mode network. This network is active during rest and its activity is anti-correlated with cognitive control networks during tasks. In ADHD, poor deactivation of the default mode network contributes to a reduced cognitive performance, because it competes with task associated networks (Cortese, 2012; Rubia, 2018).

In summary, ADHD is associated with alterations in widespread cortical networks affecting neurotransmitter systems, brain volume, connectivity, and neural activity, which are associated with clinical and cognitive symptoms. Brain abnormalities in ADHD are pronounced for prefrontal regions, such as the right IFG. This area shows reduced grey matter volume as well as reduced functional connectivity to connected regions and reduced neural activity during cognitive demands.

1.2 Executive Functions in ADHD

Besides the core symptoms of inattention, hyperactivity, and impulsivity, ADHD is characterized by a set of neurocognitive impairments concerning mainly executive functions (Kofler et al., 2019a). Executive functions are a group of higher-order cognitive processes that are required for self-regulation and goal-directed behavior. These include planning, set shifting, abstraction, organization, fluency, working memory, and inhibitory functions. 90% of ADHD patients show executive dysfunctions in one or more of these domains, mostly in working memory (62%) and inhibitory control (27%) (Kofler et al., 2019a).

1.2.1 Working Memory

Working memory is defined as a temporary storage to keep and manipulate information in mind in order to perform complex tasks. Working memory models assume two modality specific information stores, the visuo-spatial sketch-pad and the phonological loop. The multicomponent model of working memory further suggests an episodic buffer and a central executive. The episodic buffer is the consciously available part of working memory and the central executive controls the focus of attention to all working memory components (Baddeley, 2010). ADHD patients show impairments in all components of this working memory model, but these are most pronounced in the central executive (Rapport et al., 2008).

Working memory deficits affect the vast majority of ADHD patients and are closely associated with educational and social impairments (Rapport et al., 2013). Reading problems are very common in ADHD and seem to result partially from working memory deficits (Kofler et al., 2019b). However, in school, working memory impairments are not only associated with poor reading but also poor math performance, lower grades, and more frequent education in special classes (Fried et al., 2016). Accordingly, the degree of working memory impairments is a better predictor for school performance in patients than the severity of ADHD core symptoms (Simone et al., 2018). Moreover, working memory deficits are accompanied by a lack of organizational skills, which additionally impedes academic success (Kofler et al., 2018b). Moreover, besides educational domains, detrimental effects from working memory impairment in ADHD were also found for social interaction with peers (Kofler et al., 2011). These findings make working memory impairment a central deficit with high relevance for the quality of life in this patient group.

ADHD patients show working memory deficits in spatial and verbal working memory tasks (Gibson et al., 2011). One of the most investigated paradigms in neuroscientific working memory research is the *n*-back task. During this task, a series of stimuli is presented and participants decide for each stimulus if it was identical to the one presented a specified number *n* of trials earlier. With a higher *n*, increasing working memory demands are induced and the task becomes more demanding. There is strong evidence that ADHD patients show impaired performance during *n*-back tasks (Keage et al., 2008; Myatchin et al., 2012) with largest effect sizes during the 2-back variant (Kobel et al., 2009).

1.2.2 Response Inhibition

Response inhibition is the cognitive process to suppress predominant reactions or movements, and it is necessary for the deliberate control of behaviors towards future goals (Mullane et al., 2009). It was discussed as a primary deficit in ADHD and contains the aspects of inhibiting prepotent responses and of stopping ongoing responses (Barkley, 1997; Wodka et al., 2007). Response inhibition needs to be distinguished from interference control, which is the ability to suppress task irrelevant, competing stimuli and thus, contains a cognitive aspect of inhibition (Wöstmann et al., 2013).

ADHD related impairments in response inhibition are associated with hyperactive/impulsive as well as inattentive symptom severity (Verté et al., 2006; Bezdjian et al., 2009; Tarle et al., 2019). These deficits are detectable already in pre-school age with a predictive value for teacher ratings and ADHD diagnoses in primary school (Jacobson et al., 2018). Inhibitory problems have been associated with social impairments in ADHD patients during adolescence (Rinsky & Hinshaw, 2011). Further, reduced inhibitory functions were found in patients with addictive disorders (Smith et al., 2014) and thus, were discussed to increase the probability for drug abuse in ADHD (Groman et al., 2009). Moreover, response inhibition deficits in children with ADHD predicted later suicidal tendencies and non-suicidal self-injury (Meza et al., 2016). Therefore, inhibitory impairments in ADHD are a serious risk factor for the development of further psychiatric diseases.

Response inhibition is commonly investigated using the go/nogo paradigm. During this task, participants are instructed to react fast on pre-defined go stimuli and to withhold their reaction for nogo stimuli. Go and nogo stimuli are mostly presented in a ratio of about 80% to 20% in order to induce a prepotent response tendency for go stimuli. Using this task, response inhibition deficits in ADHD patients were repeatedly demonstrated (Fallgatter et

al., 2004; Wiersema et al., 2006; Fisher et al., 2011). A variation from the go/nogo paradigm is the stop-signal task. In this task, participants are instructed to give speeded responses, while a sudden stop-signal occurs during some trials. Thus, the task requires to stop an initiated reaction, with increasing demands on inhibitory functions for longer time intervals between stimulus and stop-signal (Janssen et al., 2015).

1.2.3 Role of the Right Inferior Frontal Gyrus

Working memory and response inhibition are related executive functions, with lower working memory capacity being associated with reduced efficiency of response inhibition (Redick et al., 2011). Accordingly, after a cognitive working memory training, transfer effects were reported to an untrained response inhibition task (Liu et al., 2017). In ADHD patients, the extent of working memory and response inhibition impairments shows medium-sized correlations (Alderson et al., 2017) but the nature of this relationship is uncertain. Burgess et al. (2011) assumed that inhibitory functions are crucial for the maintenance and retrieval of information in working memory. For ADHD, this model suggests that working memory deficits result from task-irrelevant information that was not shielded from entering working memory due to disturbed inhibition (Barkley, 1997). This assumption is supported by lifespan research, as decreasing inhibition functionality predicted progressive working memory impairments with ongoing age (Borella et al., 2008). Although the relationship between working memory and inhibitory processes is not fully understood yet, there is evidence for a common neural basis of both processes.

Executive impairments in ADHD result from complex fronto-cingulo-striato-thalamic and fronto-parieto-cerebellar dysfunctions with the prefrontal cortex playing a key role as it is involved in most networks that show altered activity patterns in ADHD during cognitive demands (Rubia, 2018). FMRI studies repeatedly demonstrated reduced prefrontal activity in ADHD during working memory and during response inhibition tasks (McCarthy et al., 2014; Norman et al., 2016; Yap et al., 2020). The investigation of brain areas that show activity during working memory as well as during response inhibition tasks, revealed the right inferior frontal gyrus (IFG) (Figure 1) suggesting that this region is involved in both cognitive functions (McNab et al., 2008). In the prefrontal system, the right IFG operates as a "brake" that implements inhibition via prefronal-basal ganglia networks (Aron et al., 2014). The right IFG shows structural as well as functional abnormalities in ADHD patients, as reduced functional connectivity to basal ganglia, parietal lobes, and cerebellum (Rubia,

2018). Further, it was demonstrated that a reduced gray matter volume of the right IFG is correlated with the extent of response inhibition deficits in ADHD patients (Depue et al., 2010). A meta-analysis showed reduced neural activity in this area during response inhibition demands in ADHD patients (Hart et al., 2013). This characteristic seems to distinguish between patients and healthy individuals, as the activity in the right IFG during a go/nogo task was successfully used to classify patients (Monden et al., 2015). Evidence for the importance of the right IFG for working memory deficits stems from patients with right frontal lesions, who manifested comparable deficits to ADHD patients not only in response inhibition but also in working memory, while patients with homologous lesions in the left frontal lobe did not. The extent of these deficits was correlated with lesion size in the right IFG (Clark et al., 2007).

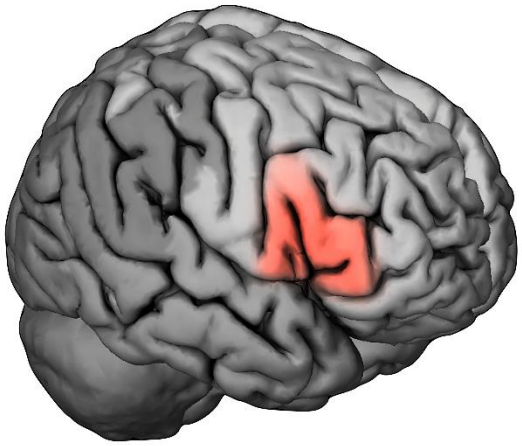

Figure 1. Right inferior frontal gyrus. Illustration of the right inferior frontal gyrus (red) in the brain. This area is of high relevance for executive dysfunctions in ADHD and shows structural as well as functional alterations in these patients[1].

After the application of methylphenidate, the right IFG is the area with the most pronounced activation increase, indicating its important role for the pharmacological success of stimulants (Rubia et al., 2014). At the same time, the connectivity of the ventrolateral prefrontal cortex was demonstrated to be increased after stimulant application, which was directly related to improved working memory performance in patients (Wong & Stevens, 2012). Different levels of right IFG activity between ADHD patients and healthy individuals cannot be explained by long-term effects of pharmacological interventions as medication naïve patients show the same pattern of right IFG hypoactivation (Rubia et al., 2005). Further evidence for the central role of right IFG underactivation stems from adult ADHD research.

[1] adapted from Brain Explorer® 2, Allen Institute

While patients with persistent ADHD symptoms into adulthood continued to show a hypoactivity in the right IFG, patients with remitted ADHD did not show right IFG abnormalities during adulthood (Szekely et al., 2017).

In summary, working memory and response inhibition deficits in ADHD are associated with the hypoactivity of prefrontal brain areas, especially of the right IFG. Executive deficits compromise the quality of life in ADHD patients and therefore, an effective treatment of this disorder should not only improve the core symptoms inattention, hyperactivity, and impulsivity but should also target executive dysfunctions. A promising therapy approach to induce cognitive improvements could be provided by methods that induce increased prefrontal activity to the right IFG.

1.3 Therapeutic Approaches in ADHD

In Germany, the "Level 3 guideline on the treatment of patients with ADHD" provides evidence-based recommendations for diagnostic and therapeutic procedures in this patient group (DGKJP et al., 2017). The treatment strategy depends on symptom severity and comorbid disorders as well as personal and environmental factors. The primary application of psychosocial interventions is advised in mild forms of ADHD and in young children, whereas severe forms of ADHD primarily require pharmacological treatment. A healthy, balanced nutrition, and regular exercise is advised as a supplementary intervention for all patients. Moreover, therapeutic approaches that target neuromodulation, as neurofeedback or non-invasive brain stimulation, increasingly draw interest as treatment options (Rubia, 2018). The following chapters describe the different therapeutic options in ADHD.

1.3.1 Pharmacological Treatment

In the therapy of ADHD, pharmacological treatment is applied depending on the participant's age, symptom severity, and the success of previous therapies. Stimulants are the first-line pharmacological treatment and include methylphenidate and the group of amphetamines (DGKJP et al., 2017). All stimulants increase the availability of dopamine and noradrenaline in prefrontal regions (Stahl, 2010) but different substances affect different parts of the catecholaminergic system (Carboni & Silvagni, 2004). Both, methylphenidate and amphetamines block the reuptake of dopamine into the neuron and therefore increase dopamine availability (Arnsten, 2011). A non-stimulant alternative is atomoxetine, which is

recommended for patients who do not respond to stimulants or who have comorbid anxiety disorders, tic disorders, or addiction (DGKJP et al., 2017). Atomoxetine blocks the reuptake of noradrenaline, which increases the concentration of dopamine and noradrenalin in the extracellular space as well (Arnsten, 2011).

Pharmacological treatment of ADHD can reduce symptoms of inattention, hyperactivity, and impulsivity (Stein et al., 2003) as well as improve executive functions (Coghill et al., 2014). Further, it was shown to have beneficial effects on the interaction within the family (Van Der Oord et al., 2008). The administration of methylphenidate is highly effective, with larger effect sizes than psychosocial treatment (Van Der Oord et al., 2008). Its duration of action can be prolonged to a maximum of 12 hours when using long-acting formulations (Brams et al., 2010).

However, stimulant-response is determined genetically (Myer et al., 2018) and thus, about 10 - 30% of patients do not respond to the treatment or are unable to tolerate side effects (Banaschewski et al., 2004). Adverse effects of methylphenidate include decreased appetite, headache, abdominal pain, sleeping problems, and increased blood pressure (Cortese et al., 2018; Storebø et al., 2018). Hence, for the reasons of insufficient effectiveness or psychological side effects, about 20% of patients cease stimulant treatment within the first year (Toomey et al., 2012). Further, families report that they refrained from pharmacological treatment because they are concerned about potential long-term side effects, mainly listing growth stunting and a risk for addiction (Ahmed et al., 2017). Unfortunately, the non-stimulant atomoxetine causes comparable side effects, as decreased appetite, weight loss, insomnia, vomiting, fatigue, and sexual dysfunction (Banaschewski et al., 2004). As a further limitation of pharmacological ADHD therapy, effects are not prolonged beyond the end of the treatment (Jensen et al., 2007; Rubia, 2018). Furthermore, dopamine transporter density adaptively increases under the long-term treatment with stimulants and thus, dose adjustment is necessary to maintain its clinical effectiveness (Fusar-Poli et al., 2012). In addition, the availability of stimulants bears a certain risk for their abuse by the patient itself or surrounding persons (Kollins, 2003). These factors may contribute to a negative attitude towards medication treatment in ADHD, which is propagated not only by patients and their families but also by some clinicians (Cortese et al., 2015). An investigation of stimulant treatment in a real-life school setting suggested that effectiveness on the every-day functional outcome is lower than usually reported in clinical studies. The authors explained this mainly

by the non-adherence in adolescents who reported very low satisfaction with pharmacological treatment (Pelham et al., 2017).

1.3.2 Psychosocial Treatment

Psychosocial treatment is the primary therapy in ADHD patients who do not receive medication, for example because they are non-responders or because they decided against it. Psychosocial interventions are defined as psychological, psychotherapeutical, and social interventions to patients and their parents with the aim to cope with ADHD related symptoms. In severe forms of ADHD, further persons in the social environment of the patient can be involved in therapy, as teachers or child care workers. For children with ADHD who are still at pre-school age, psychosocial interventions comprise parental psychoeducation and trainings to develop adequate nurturing competences to care for a child with ADHD. Additionally, child-centered trainings are applied to enhance the intensity and endurance of playing and attentional behavior. From school age on, cognitive-behavioral therapy is appropriate to train education related skills as organization, self-management, and self-instruction, but also social competence, impulse control, and emotion regulation. The psychosocial therapy in ADHD patients is usually administered in an ambulant setting but under stationary treatment can be considered for patient with severe symptom load, severe comorbid disorders, low resources in the family or adverse psychosocial conditions (DGKJP et al., 2017).

Although psychosocial therapy is well-established in the treatment of ADHD (Evans et al., 2018), a meta-analysis of Daley et al. (2014) found no evidence for beneficial effects of behavioral therapy on ADHD symptoms when the raters were blinded. It was suggested that the effectiveness of psychosocial treatment varies between patient groups and can therefore not be generalized (Evans et al., 2018). Moreover, psychosocial interventions require the willingness of the families, as they are time-consuming and rely on the repeated training of behaviors (Evans et al., 2018).

1.3.3 Neurotherapeutics

Neurotherapeutic treatments aim to induce modulatory effects on pathologic brain activity. The best-established approach in ADHD is neurofeedback. During neurofeedback, patients train the regulation of neural activity as it is directly feedbacked to them, mostly in the form of a simple computer game (Arns et al., 2014). Eventually, patients learn to regulate their

brain activity without feedback and to apply it in naturalistic settings, for example during homework. Evidence-based neurofeedback protocols for ADHD include trainings of the theta/beta ratio at fronto-central regions, the sensorimotor rhythm at motor areas, and slow cortical potentials at parietal regions (DGKJP et al., 2017). Moreover, promising results were achieved by fMRI based neurofeedback training of right IFG activity (Rubia et al., 2019). Neurofeedback can be applied as an add-on treatment for children of 6 years and older (DGKJP et al., 2017). It was demonstrated to be clinically effective with medium effect sizes for inattentive and hyperactive/impulsive ADHD symptom severity (Van Doren et al., 2019). However, the effectiveness from neurofeedback remains inconclusive as it depends highly on the evaluated outcome measures. For example, it was shown that the effects are reduced to statistical trends if only blinded raters are included (Sonuga-Barke et al., 2013). Moreover, neurofeedback is tedious as it requires as much as 30 to 40 treatment sessions (Arns et al., 2014).

Another approach is the cognitive training of executive functions such as working memory and response inhibition in ADHD patients (Johnstone et al., 2010; Jones et al., 2018). Such programs are mostly applied as adaptive, computer-based trainings, which ensures the constant challenge of the patient at an adequate level of difficulty and therefore maximizes training results (Klingberg, 2010). However, the evidence for the effectiveness of working memory and response inhibition trainings is limited and a meta-analysis found only small effects on inattentive ADHD symptoms and none on hyperactive/impulsive symptoms or academic achievements (Cortese et al., 2015; Woltering et al., 2019).

The advantage of neurotherapeutic approaches is their potential to induce beneficial effects on pathologic brain developments instead of transient symptom reductions and thus, they contain a higher rehabilitative value. However, current approaches are not only effortful but also of limited effectiveness. Although neurofeedback treatments have been studied since about 50 years in ADHD (Arns et al., 2014), it is classified as “possibly efficacious” and cognitive training is classified as an “experimental treatment” (Evans et al., 2018). Therefore, the present dissertation pursues another neurotherapeutic approach: transcranial direct current stimulation (tDCS). TDCS is a neuromodulatory technique that can increase the excitability in targeted brain regions via the application of weak currents. As executive dysfunctions in ADHD are associated with a hypoactivation in prefrontal areas, tDCS is a promising tool to improve cognition by increasing neural activity in these brain regions. The high plasticity of the developing brain in children and adolescents contains the potential for

brain stimulation based interventions to effectively induce long-lasting neural changes (Castellanos & Proal, 2012).

1.4 tDCS as a Potential Therapeutic Approach in ADHD

The application of electric current in medicine reaches back to ancient Egyptians, Greeks, the Roman Empire, and Persia, where physicians treated headache and epilepsy by the use of the electric torpedo fish. In 1660, it was Otto von Guericke who invented a crank-operating generator that can be considered the first electrical stimulating device (Sarmiento et al., 2016). The earliest use of electric stimulation for the treatment of mental disorders was reported in 1804 by a nephew of Galvani. However, with the development of electro-convulsive therapy in the 1930s, the scientific focus was shifted away from weak electric currents (Stagg & Nitsche, 2011) and it was not until 1998 when Priori et al. reintroduced the transcranial electrical stimulation. Since then, Michael Nitsche and Walter Paulus investigated this technique intensively and established its modern standards. In the last 20 years, the interest in this field increased significantly, reflected by the number of tDCS studies in the database PubMed, which raised from 279 for the years 2005 - 2009 to 3739 for the years 2015 – 2019. The investigated applications reach from cognitive enhancements to the treatment of neurologic and psychiatric disorders.

1.4.1 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a technique that modulates neuronal excitability in a polarity-specific manner by the application of weak electric currents to the brain via electrodes placed on the scalp. The excitability in brain areas under the anodal electrode is increased, while brain areas under the cathode are inhibited (Nitsche & Paulus, 2001). Mostly, tDCS is applied using a battery driven stimulator and rubber electrodes with a size of 5 x 7 cm, which are placed in saline-soaked sponges (Figure 2). Current intensities of about 1 or 2 mA are generated and applied for 10 to 20 minutes to the brain. The electrode placed over the target brain area is referred to as the active electrode, whereas the second electrode serves as the reference electrode. However, the term reference implies a passive role of this electrode, although it can have an impact on the brain activity (Thair et al., 2017).

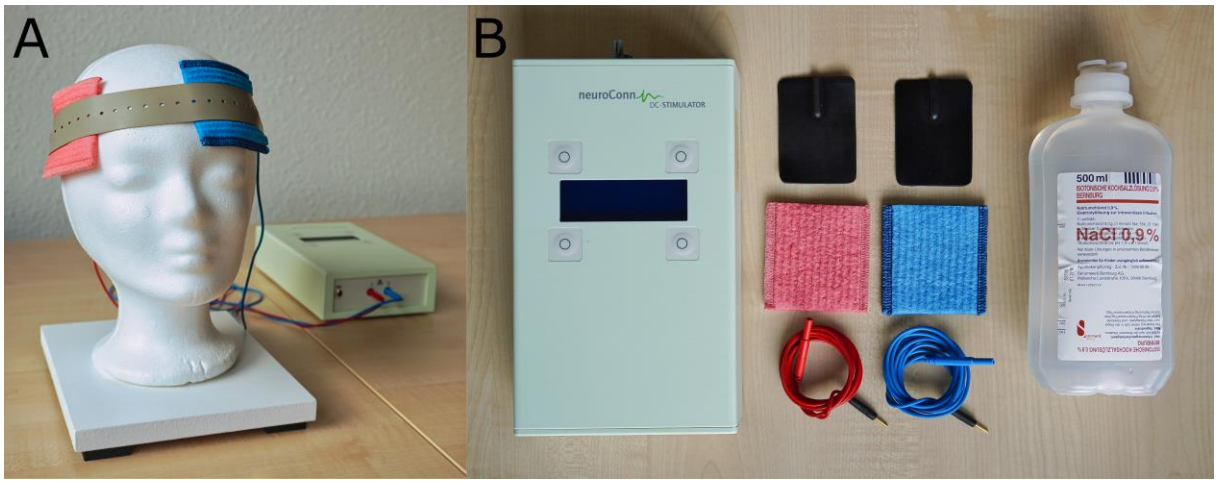

Figure 2. Transcranial stimulation device together with supplies. (A) TDCS application using a DC-stimulator and rubber electrodes, placed in saline-soaked sponges (neuroConn), **(B)** supplies for tDCS application: DC-stimulator, rubber electrodes, sponges, cables, NaCl solution (0.9%).

The application of tDCS can be associated with slight itching and tingling sensations in the skin under the electrodes, which mostly vanishes over the first minute of stimulation (Nitsche et al., 2003b). This effect is mimicked in the placebo condition of tDCS, which is called sham stimulation. During sham tDCS, stimulation is applied for a short period of time, mostly 30 seconds. Thus, participants feel the initially induced dermal sensations, while cortical excitability is not affected by this short stimulation (Nitsche & Paulus, 2000). This blinding procedure was demonstrated to have a comparable effectiveness as placebo conditions in drug trials (Brunoni et al., 2014). TDCS induced sensations are minimized by ramping currents up and down over 10 - 30 seconds in the beginning and the end of stimulation (Fertonani et al., 2015).

Beside the use of direct current in tDCS, there are other forms of transcranial electrical stimulation. During transcranial alternating current stimulation (tACS) oscillatory current is applied at given frequencies that modulate oscillatory brain activity in a frequency-specific way. Further, tDCS and tACS can be combined to oscillatory tDCS, which induces effects comparable to tACS (Herrmann et al., 2013). A further type of electrical stimulation is transcranial random noise stimulation (tRNS), where an alternating current with randomly varying intensity and frequency is applied to the brain. During this form of brain stimulation, signal intensity is increased according to the principle of stochastic resonance by adding background noise to stimulated areas, which increases excitability (Antal & Herrmann, 2016).

TDCS as well as other forms of transcranial electrical stimulation have a good safety profile, without the occurrence of severe adverse events in over 18 000 sessions (Antal et al., 2017). Although there have been two documented cases of epileptic seizures in the temporal proximity of tDCS sessions, a causality to stimulation is unlikely (Ekici, 2015; Splittgerber et al., 2020). Further, tDCS does evidently not induce oedema, changes to the blood-brain barrier, or structural changes of cerebral tissue (Nitsche et al., 2004). Current densities that can induce tissue damage in animals are at least two magnitudes higher than the current densities used in humans (Bikson et al., 2016). Common and mild adverse events associated with tDCS include tingling and burning sensations on the skin under the electrode, headache, or fatigue. However, all side effects are transient and do not require medical interventions. Furthermore, the occurrence of side effects does not differ between healthy adults and vulnerable groups as children or clinical populations (Antal et al., 2017). Still, application errors can lead to skin lesions (Wang et al., 2015), for example if the contact area between electrode and skin becomes extremely small due to misuse of the equipment. Overall, the US agency FDA classifies tDCS as non-significant risk, which means there is no reasonable expectation of a serious adverse event (Bikson et al., 2016).

1.4.2 Mechanisms of tDCS

TDCS operates as a neuromodulator that shifts resting membrane potentials and therefore changes the probability for neurons to elicit action potentials. Neurons targeted by anodal tDCS are depolarized and thus, cortical excitability is increased, whereas neurons targeted by cathodal tDCS are hyperpolarized and thus, cortical excitability is reduced (Nitsche et al., 2003a; Nitsche et al., 2005). These excitability shifts are subthreshold, which means tDCS does not directly induce action potentials (Nitsche et al., 2005). This is a central difference to transcranial magnetic stimulation (TMS), a method that triggers brain activity via the induction of electricity in brain tissue using magnetic pulses (Klomjai et al., 2015). For the systematic investigation of tDCS effects, TMS is a useful tool: Before and after tDCS applications to the primary motor cortex, TMS pulses are applied over motor areas to trigger motor evoked potentials (MEP), often targeting a hand muscle. Changes in the amplitude of MEPs after tDCS application are a reliable measure for the induced changes in cortical excitability (Nitsche & Paulus, 2001). Further, alteration in brain activity induced by tDCS are detectable as intensity changes in the BOLD signal using fMRI (Filmer et al., 2014).

TDCS modulates the resting membrane potential by affecting voltage-sensitive sodium and calcium channels (Nitsche et al., 2003a), mainly in neurons of the pyramidal tract and in interneurons (Stagg & Nitsche, 2011). Further, excitability changes are enhanced by effects on neurotransmitter systems. Pharmacological studies suggest that anodal tDCS decreases the concentration of the inhibitory neurotransmitter GABA, while cathodal tDCS decreases the concentration of the excitatory neurotransmitter glutamate (Stagg et al., 2009). TDCS induced excitability changes can be prolonged after the end of stimulation, depending on stimulation duration and intensity. A tDCS application of 10 minutes induces after-effects of about 90 minutes (Nitsche & Paulus, 2001). These prolonged effects are not explicable by shifts in resting membrane potentials, because they would not outlast the duration of polarization. Instead, in vitro experiments revealed that mechanisms of plasticity are involved (Kronberg et al., 2020). After-effects of anodal tDCS are associated with increased NMDA receptor activity and long-term potentiation (LTP), whereas cathodal after-effects result from reduced pre and post-synaptic activity causing long-term depression (LTD) and thus, reduce plasticity (Nitsche et al., 2003c; Stagg & Nitsche, 2011). Prolonged tDCS effects were further linked to serotonin and dopamine as the concentration of these neurotransmitters is critically for the outcome of stimulation (Filmer et al., 2014).

TDCS effects are not restricted to local brain regions but moreover, tDCS can modulate the functional connectivity to related areas and tDCS can influence oscillatory brain activity. Therefore, this method can induce widespread activity alterations in whole neural networks and in subcortical structures that are connected to stimulated areas (Polania et al., 2012; Filmer et al., 2014).

The current flow pattern in the brain induced by tDCS can be calculated by means of computer simulations. Such computational models are increasingly used to optimize electrode configurations for the purpose to stimulate target areas more specifically (Bikson et al., 2012). For precise modeling, current flow simulations consider individual conductivity values of different tissue types as scalp, skull, grey matter, white matter, and cerebrospinal fluid (Miranda et al., 2018). In children and adolescents, developmental aspects complicate the selection of optimal stimulation parameters. Therefore, current flow simulations are of particular interest in this field. Thinner scull and tissue lead to higher current density values in the brain of children. Consequently, the electrical field is about twice as high in 10 year old children compared to adults at equal current intensities, but with a considerable variability depending mainly on the individual head size. Moreover, different grey and white matter

distribution causes stronger tDCS effects on deeper tissue layers in children (Kessler et al., 2013). For these reasons, results from adults may not be transferable to children and tDCS montages need to take into account dosage considerations for specific age groups (Muszkat et al., 2016). In this dissertation, current flow simulations were used to find suitable tDCS montages to stimulate the right IFG in a sample of children and adolescents.

1.4.3 tDCS for the Enhancement of Cognitive Functions

Soon after the introduction of tDCS, this technique was successfully used to enhance a variety of cognitive functions, such as attention, language processing, and even complex functions as the compliance with social norms (Roy et al., 2015; Li et al., 2018; Radman et al., 2018). Moreover, researchers successfully developed clinical applications of tDCS for psychiatric and neurologic disorders as depression, schizophrenia, or stroke (Lindenmayer et al., 2019; McClintock et al., 2020; Pavlova et al., 2020), and for depression these are meanwhile offered as a treatment option in many clinics (Sauvaget et al., 2019). Still, the application of tDCS as a neuroenhancement remains controversial, mainly because frontal cortex applications produced highly variable results. In fact, one meta-analysis concluded that tDCS induces no reliable cognitive effects in healthy individuals (Horvath et al., 2015).

This can partially be attributed to the number of possible variations in tDCS parameters, like the current intensity and the duration of application. Systematic investigations of tDCS parameters stem mainly from studies in motor areas (Agboada et al., 2019; Jamil et al., 2020), since tDCS effects can be quantified more reliably for the motor cortex than for prefrontal regions. The results suggest no linear dose-response relationship, but tDCS effects rather seem to be brain state dependent (Esmaeilpour et al., 2018). This finding is associated to the methodological question of whether tDCS should be applied during a task (online) or at rest (offline). A study that compared the effects of online vs. offline tDCS on an *n*-back working memory task found better results for online tDCS one day after stimulation (Martin et al., 2014). It is likely that tDCS can yield best results in the interaction with endogenous brain mechanisms, because the method does not directly induce action potentials. Therefore, the targeted networks need to be in an activated or pre-activated state so that they can be reinforced via the excitability enhancement induced by stimulation (Gill et al., 2015).

TDCS research in healthy participants that aimed for the enhancement of working memory, applied anodal stimulation mostly to the left dorsolateral prefrontal cortex (DLPFC). However, results were heterogeneous with some studies finding beneficial effects on

working memory, while others did not find effects (Brunoni & Vanderhasselt, 2014; Hill et al., 2016; Mancuso et al., 2016). For the enhancement of response inhibition, tDCS research focused on the right IFG. It was demonstrated that anodal tDCS of the right but not of the left IFG reduced stop-signal reaction time, which is a marker for response inhibition (Jacobson et al., 2011; Cunillera et al., 2014). Further, right IFG stimulation influenced neurophysiological activity, as theta activity during resting state and the inhibitory P3 component (Jacobson et al., 2012; Cunillera et al., 2016). Moreover, repeated applications of anodal tDCS to the right IFG successively improved stop-signal reaction time over the course of four consecutive days (Ditye et al., 2012).

1.4.4 tDCS in the Developing Brain

The application of tDCS in children and adolescents is safe (Antal et al., 2017). In this age group, tDCS was investigated not only in the context of ADHD but also schizophrenia, autism, epilepsy, and further neurologic disorders with promising results (Palm et al., 2016; Rivera-Urbina et al., 2017). This makes tDCS an interesting option for the application in ADHD patients who are non-responders to medication. Moreover, in contrast to pharmacological therapy, tDCS is associated with very few side effects, which would make its application even more attractive to patients (Sierawska et al., 2019). A key advantage over pharmacological interventions would be its potential to induce long-lasting neural changes. Although the impact of a single tDCS application is transient, repeated stimulations could induce sustained effects for the duration of six or twelve months (Cohen Kadosh et al., 2010; Katz et al., 2017). Such persistent, neuroplastic effects cannot be achieved with stimulants (Rubia, 2018).

In childhood, the brain passes developmental periods with high plasticity, which makes it particularly sensitive to external stimulation. During this timeframe, tDCS could permanently influence atypical brain development in a beneficial way. At the same time, such critical periods bear the risk to induce enduring detrimental effects (Vicario & Nitsche, 2013). Therefore, in children and adolescents, tDCS must be applied with caution and the careful control for side effects should play a central role in this research field. It was suggested that tDCS could have adverse effects on other than the targeted cognitive functions by changing the balance or the coordination between brain regions (Cohen Kadosh, 2013). Further, every attempt to improve cognition should face the neuro-competition principle, which assumes that the brain has a limited capacity of resources that

must be allocated among its systems. Therefore, it seems not unlikely that stimulation induced improvements could be accompanied by downsides (Colzato et al., 2020). Indeed, tDCS induced performance decrease was found in form of a double dissociation between numerical learning and automaticity after a six-day stimulation of frontal or parietal areas, respectively (Iuculano & Cohen Kadosh, 2013). Further, bilateral tDCS of prefronal areas improved reaction times during arithmetic decisions while interference control was impaired (Sarkar et al., 2014). These findings suggests that the investigation of cognitive side effects is of particular relevance in the developing brain. However, despite risks the high neuroplasticity in the brain of children and adolescents makes tDCS a promising treatment option for ADHD as this would provide the potential to induce permanent neural changes (Rubia, 2018).

1.4.5 Previous tDCS Research in ADHD

So far, most tDCS applications in ADHD investigated the stimulation of the DLPFC. This approach resulted from the finding that the bilateral DLPFC is characterized by an underactivation in ADHD patients (McCarthy et al., 2014). Further, tDCS research from other clinical groups and healthy individuals has demonstrated enhanced cognitive performance after DLPFC stimulation, especially of the left hemisphere. Accordingly, initial tDCS studies in ADHD focused on the anodal stimulation of this brain region.

It was demonstrated that tDCS of the left DLPFC in adult ADHD patients improved impulsivity, indicated by the reduced rate of false positive errors in a continuous performance task. However, the findings from this study were inconsistent as no effects were found on a stop-signal task, another measure for impulsivity (Allenby et al., 2018). Further evidence for beneficial effects from left DLPFC stimulation stems from Nejati et al. (2017), who found reduced reaction times in a working memory task, as well as improved interference control and cognitive flexibility in children with ADHD. Moreover, improved attention and inhibitory functions were found in a further tDCS study, but without the inclusion of a sham group (Bandeira et al., 2016). Besides these effects on cognitive tasks, it was demonstrated that tDCS could improve the connectivity between the left DLPFC to associated brain areas (Cosmo et al., 2015b; Sotnikova et al., 2017). However, results from the literature do not only indicate favorable effects from left DLPFC stimulation but there are also null-findings, as in Cosmo et al. (2015a). Further, although a five-day tDCS application to the left DLPFC suggested improved clinical ADHD ratings, it had detrimental effects on

the error rate in a working memory and a response inhibition task (Soff et al., 2017; Sotnikova et al., 2017). In contrast, a further repetitive tDCS application to the left DLPFC over 10 session indicated a beneficial influence on working memory and response inhibition but the statistical methods of this paper were non-transparent (Kashani Khatib et al., 2019).

Surprisingly, positive effects on response inhibition were also demonstrated for cathodal tDCS of the left DLPFC in ADHD patients, although this stimulation has probably reduced brain activity in this area (Soltaninejad et al., 2015; Nejati et al., 2017). The authors explain this finding via interhemispheric effects, with reduced activity in left frontal areas having presumably increased activity in the homologous right frontal areas, which improved response inhibition. However, there is more evidence for positive effects from right frontal tDCS. The repeated tDCS applications over five days using a bilateral electrode configuration on DLPFC areas (right anodal, left cathodal) improved symptoms of inattention in adults with ADHD with sustained effects, still present after four weeks (Cachoeira et al., 2017). Moreover, the simultaneous application of anodal tDCS to right and left DLPFC areas with a cerebellar reference electrode reduced symptoms of hyperactivity in adult ADHD patients (Jacoby & Lavidor, 2018). Further effects from bilateral prefrontal stimulation were found on reward processing in ADHD with anodal tDCS of the right ventromedial prefrontal cortex together with cathodal tDCS of the left DLPFC reducing risky decision-making and increasing delay discounting (Nejati et al., 2020).

Besides tDCS, there are more methods of non-invasive brain stimulation, but so far, only few studies examined these in ADHD. Oscillatory tDCS of bilateral frontal cortices during early slow wave sleep was applied in children and adolescents after the encoding phase of a memory task and resulted in an improved retrieval of the learned memory content in the next morning (Prehn-Kristensen et al., 2014). Further, this stimulation approach reduced reaction times and reaction time variability during a go/nogo response inhibition task (Munz et al., 2015). Further, there were several experiments with the applications of transcranial magnetic stimulation (Rubio et al., 2016; Cao et al., 2018; Alyagon et al., 2020), transcranial alternating stimulation (Dallmer-Zerbe et al., 2020), and trigeminus nerve stimulation in ADHD (McGough et al., 2015).

So far, the results from non-invasive brain stimulation in ADHD are promising but inconsistent with most studies focusing on the left DLPFC. However, the hypoactivation of right prefrontal areas, especially of the IFG is a key aspect for ADHD related executive dysfunction, which makes this area a promising target for tDCS interventions. Nevertheless,

Breitling et al. (2016) contains the only investigation on the application of tDCS to the right IFG in ADHD patients so far. This study served as preparatory work for this dissertation and is summarized in the following section.

1.4.6 Preparatory Research

In Breitling et al. (2016) it was aimed to improve interference control in ADHD patients by stimulating the right IFG using anodal tDCS. For this purpose, tDCS was applied to children and adolescents with and without ADHD while interference control was assessed with a flanker paradigm. In this task, participants indicated the orientation of a central stimulus while congruent or incongruent distracting stimuli must be ignored. This task reliably demonstrates interference control deficits in ADHD. We expected that impaired flanker task performance in ADHD patients would improve during anodal stimulation of the right IFG.

21 children and adolescents with ADHD and 21 healthy controls in the age between 13 and 17 years participated in this study. All participants underwent anodal, cathodal, and sham tDCS sessions in counterbalanced order. Stimulation was applied over the right IFG for 20 minutes using rubber electrodes with a size of 5 x 7 cm covered in saline soaked sponges. The active electrode was placed over the EEG positon F8, which corresponds to the right IFG and the reference electrode was placed posterior to the contralateral mastoid. After five minutes of tDCS the flanker task started and for 15 minutes participants solved the task during tDCS. Furthermore, the current flow in the brain for the applied electrode montage was computer simulated.

An overall analysis of the data pointed towards positive but not significant effects of anodal tDCS on interference control in the ADHD group. Major learning effects between the first and the second experimental session occurred, which were confounded with tDCS effects. Therefore, exploratory analyses were conducted that included only the first session of each participant. Although this exploratory approach reduced the number of participants to 7 per experimental condition, it revealed reduced error rates and reaction time variability in patients who received anodal tDCS compared to the sham group (Figure 3). Thus, patients who received anodal tDCS showed a comparable flanker task performance as healthy controls. In healthy participants, there was no effect of tDCS on commission errors but reaction time variability was higher in the group that received anodal tDCS than in the sham group. Cathodal tDCS did affect neither ADHD patients nor controls.

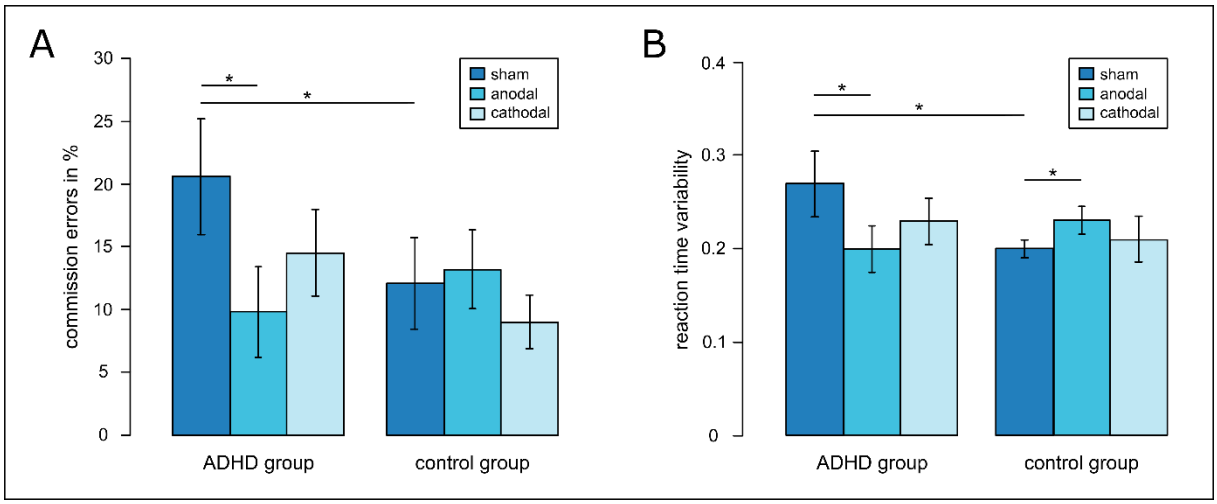

Figure 3. Effects from right IFG stimulation on interference control and RT variability. Results from tDCS over the right IFG in ADHD patients and healthy controls on **(A)** commission errors and **(B)** reaction time variability in a flanker task.

This study demonstrated that tDCS was well tolerated by children and adolescents with ADHD. Results suggested that anodal tDCS of the right IFG improved interference control in ADHD with a comparable effect size to that of methylphenidate. In healthy participants, tDCS had no beneficial but rather detrimental effects. This could be explained with an inverted U-shaped relationship between cortical activity and cognitive outcome, as it has been described for pharmacological interventions. Thus, the external modulation of cortical activity via tDCS could have interfering effects on the optimal level of brain functioning in healthy individuals.

Computer simulations of the current flow pattern in the brain are illustrated in Figure 4. Although these simulations suggest a successful targeting of the right IFG, widespread current density distributions were induced in further right frontal and temporal areas as well as in brain stem and lower cerebellum. This distributed current flow pattern resulted from large electrodes and from a not ideal placement of the reference electrode. It was placed posterior to the contralateral mastoid to avoid unintended stimulation of relevant brain areas but a placement at the contralateral orbit would have resulted in a current flow more concentrated on frontal areas.

This study demonstrated for the first time beneficial effects of anodal tDCS over the right IFG in children and adolescents with ADHD. Although conclusions from this study were limited, it provided indications that the right IFG is a promising target to induce cognitive improvements in ADHD, which should be further investigated.

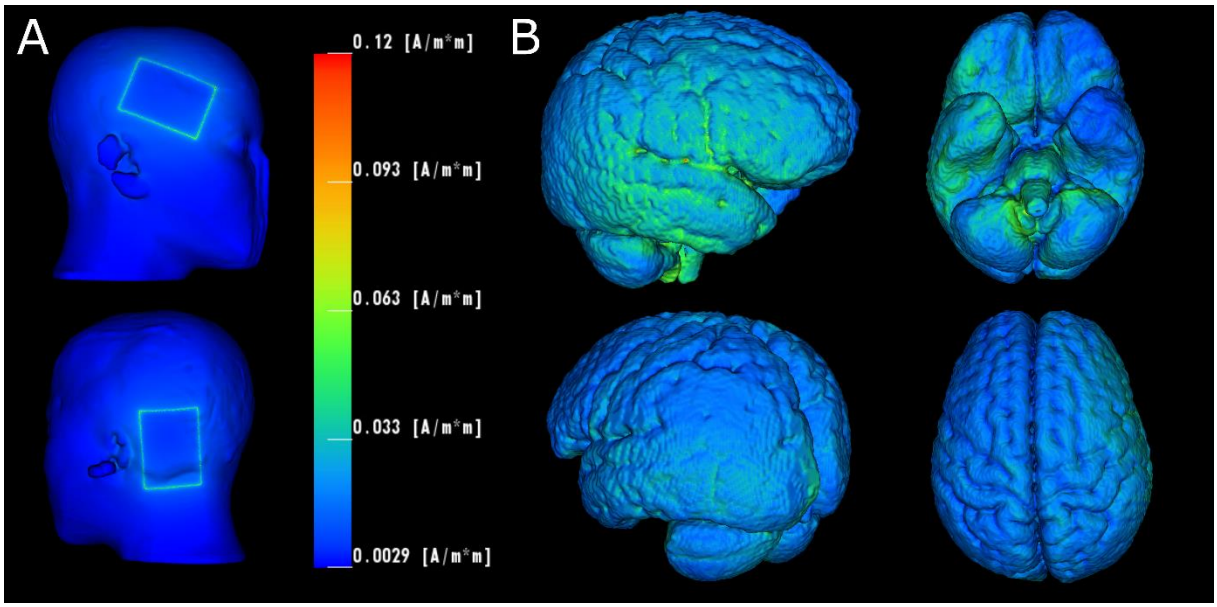

Figure 4. Electrode montage over the right IFG and current flow simulations. (A) Electrode montage and **(B)** computer simulations of the current flow pattern.

1.4.7 Improving Focality of tDCS

The successful application of tDCS crucially depends on the selection of adequate stimulation parameters. First of all, this involves the electrode montage. The optimal placement of electrodes is critical because deviations of only 5% can significantly change the current density distribution on the cortical surface (Woods et al., 2015). Therefore, the development of an electrode montage for the targeted stimulation of the right IFG was an important part of this dissertation. Conventional tDCS settings mostly use bipolar configurations of large sponge electrodes. These induce widespread current flow patterns in the brain, with the maximum current intensity being not necessarily under the active electrode (Datta et al., 2009a). But especially in the developing brain of children and adolescents with ADHD, the precise application of current to the target area is desirable because in an approach of using the lowest dose possible this should reduce the risk of inducing unintended changes in brain functioning. A possibility to overcome these limitations, is the application of an alternative, more focal stimulation method, high definition tDCS.

High definition tDCS (HD-tDCS) is the application of currents to the brain using specific arrays of small electrodes, which results in a higher focality compared to conventional bipolar configurations with large pad electrodes. Mostly, HD-tDCS is applied in a 4 x 1 ring electrode configuration of small circular electrodes with a diameter of about 1 cm (Figure 5).

In this setting, the active electrode is placed centrally and is surrounded by four reference electrodes of opposite polarity. The center electrode is placed over the target area and determines if the polarity of the stimulation setting is anodal or cathodal. This center electrode stimulates with the full current intensity, while each of the four references stimulates with one fourth of the current intensity (Villamar et al., 2013; Alam et al., 2016). During HD-tDCS, the peak current intensity is maximal in brain areas under the electrodes. Moreover, the current flow is limited to the targeted brain regions as the outer electrodes restrict spreading of currents to adjacent areas. Therefore, precision of current delivery to the brain is significantly increased compared to conventional tDCS settings (Datta et al., 2009a). HD-tDCS was demonstrated to be safe (Datta et al., 2009b) and it is tolerated well with current intensities of up to 3 mA (Reckow et al., 2018).

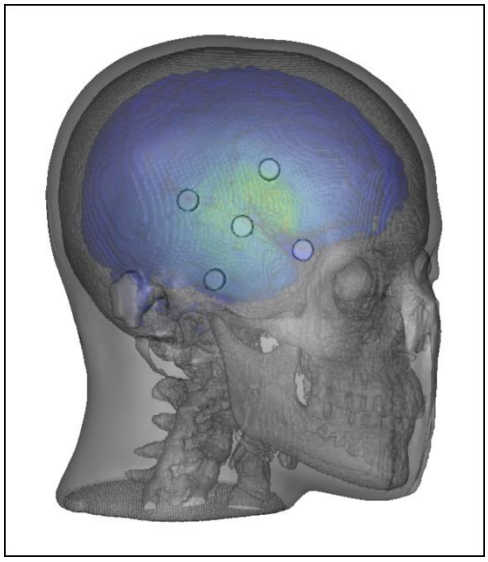

Figure 5. HD-tDCS montage in a 4 x 1 configuration. HD-tDCS montage with a 4 x 1 electrode configuration of small disc electrodes placed over the right IFG.

1.5 Aim and Outline of this Dissertation

In this dissertation, it was aimed to improve executive functions in children and adolescents with ADHD by applying tDCS to the right IFG. Besides the core symptoms of inattention, hyperactivity, and impulsivity, ADHD is characterized by executive dysfunctions, foremost in working memory and response inhibition (Kofler et al., 2019a). These cognitive deficits contribute substantially to academic underachievement, social difficulties, and an impaired quality of life, which persists into adulthood and bears an increased risk to develop further psychiatric disorders (Rinsky & Hinshaw, 2011; Fried et al., 2016; Meza et al., 2016; Thorell et

al., 2019). Pharmacological interventions belong to the first-line ADHD treatments and are highly effective (DGKJP et al., 2017). Still, they can only transiently improve ADHD symptoms without a sustained therapeutic effect, and moreover, they are associated with side effects (Storebø et al., 2018). Alternative neurotherapeutic treatments, like neuro-feedback or cognitive trainings, aim to overcome these constraints but require high effort and time, while their effectiveness is limited (Arns et al., 2014; Woltering et al., 2019). A further promising approach is tDCS, a neuromodulatory method, which has been successfully applied in various psychiatric and neurologic disorders (Fregni et al., 2020). In ADHD, this method could take beneficial influence on dysfunctional brain activity, which is a main contributor to ADHD related executive deficits (Rubia, 2018). Previous tDCS research in ADHD focused mainly on the left DLPFC (Salehinejad et al., 2019). Although this approach resulted in improvements of inhibitory functions, its effectiveness was limited and findings from different studies were inconclusive. A further promising target area for the application of tDCS is the right IFG, because reduced activity in this area has been repeatedly associated to executive dysfunctions in ADHD (Clark et al., 2007; Hart et al., 2013; Monden et al., 2015).

A preparatory tDCS study for this dissertation revealed a positive impact from right IFG stimulation on inhibitory functions in ADHD patients, encouraging further research (Breitling et al., 2016). However, compared to this study, several methodological aspects of the tDCS approach were changed. In this thesis, only anodal but not cathodal tDCS of the right IFG was applied, as it was hypothesized that performance improvements in ADHD patients would result from excitatory effects of anodal stimulation. In contrast, no positive effect is expected from an inhibiting impact on the right IFG induced by cathodal tDCS. In accordance with that, only anodal tDCS yielded performance improvements on inhibitory functions in the preparatory study. Further, in Breitling et al. (2016) current flow simulations revealed that the placement of the reference electrode was not appropriate to induce a high current density in the right IFG. In most studies that applied tDCS to the prefrontal cortex, the reference electrode was placed on the contralateral supraorbital area (Lefaucheur et al., 2017). Thus, the position of the reference electrode for the experiments of this dissertation was adjusted accordingly.

In the present thesis, three experiments were conducted with the aim to improve working memory and response inhibition in children and adolescents with ADHD via tDCS. For this purpose, in the first experiment, a combined *n*-back/nogo paradigm was introduced and validated, which contained working memory and response inhibition aspects and thus,

allowed the simultaneous and economical assessment of both executive functions. This paradigm was applied in subsequent experiments during right IFG stimulation, as an online application. This approach was chosen because online tDCS yields larger effects than offline tDCS (Martin et al., 2014), as the stimulation interacts with endogenous plasticity mechanisms (Kronberg et al., 2020).

In the second experiment, the effects of tDCS applications to the right IFG were investigated in ADHD patients, together with a methodological comparison between two electrode montages. While a conventional tDCS application with large sponge electrodes induces widespread current flow patterns in the brain, HD-tDCS allows stimulation with a better focality and it restrains the current flow to targeted areas (Datta et al., 2009a). Especially in the developing brain, the precise application of current is desirable because it could reduce the risk to induce unintended changes in non-target brain areas. The placement of this HD-tDCS montage was optimized by the use of current flow simulations. It was demonstrated that a focalized HD-tDCS application induced comparable effects to a conventional bipolar configuration.

Therefore, this HD-tDCS montage was further investigated in a repetitive application. While a single tDCS session produces only transient effects, tDCS effects can be prolonged to several months when stimulation is applied repeatedly (Katz et al., 2017). Thus, in the third experiment, tDCS was applied over the course of five consecutive days to ADHD patients in a sham-controlled trial. In this experiment, long-term effects were investigated at a four-month follow up session.

In all experiments not only ADHD patients but also age-matched healthy controls were included but did not underwent the same tDCS procedure as patients. The healthy control participants served as reference to constitute the margin of improvement that could potentially be achieved in ADHD patients.

2 General Methods

2.1 Diagnostics

The experiments in this dissertation were in accordance to the declaration of Helsinki and were approved by the local ethics committee of the Otto von Guericke University, Magdeburg. Before participating, all participants and caregivers gave their written informed assent and consent, respectively. Children and adolescents in the age between 9 and 17 years with and without ADHD were included in the experiments. They were recruited via advertisements in local newspapers, via the Department of Child and Adolescent Psychiatry and Psychotherapy of the Otto von Guericke University Magdeburg as well as via local pediatricians and child and adolescent psychotherapists.

ADHD was diagnosed according to DSM-5 criteria. For this purpose a semi-structured interview was assessed, the German adaptation (Delmo et al., 2000) of the Schedule for affective disorders and schizophrenia for school-age children - Present and lifetime version (K-SADS-PL, Kaufmann et al, 1997). This interview was conducted with all participants with and without ADHD and separately with one of their parents. The K-SADS-PL was designed for children and adolescents and assesses via symptom-based items, the presence of psychiatric disorders and their development over lifetime.

Diagnostic information from the clinical interview was complemented with questionnaires. All parents filled in the German adaptation (Arbeitsgruppe Deutsche Child Behavior Checklist, 1993) of the Child Behavior Checklist (CBCL, Achenbach, 1991a). This questionnaire records competences as well as behavioral and emotional problems in children and adolescents between the age of 4 and 18 years. Behavioral problems are classified in different categories, as attention problems and dissocial behavior. In children of 11 years and older, the German adaptation (Arbeitsgruppe Deutsche Child Behavior Checklist, 1998) of the Youth Self-Report (YSR, Achenbach, 1991b) was additionally applied, which is the self-report equivalent to the CBCL. Further, information on handedness was assessed with the Edinburgh Handedness inventory (Oldfield, 1971).

Additionally, information on IQ, concentration, alertness, and inhibitory function was collected. The IQ was assessed using the CFT-20-R (Weiss, 2008). This culture fair test determines the fluid intelligence without the influence of socio-cultural, educational, and

ethnic factors. Concentration performance was evaluated using the d2 or the d2-R test (d2, Brickenkamp, 2002; d2-R, Brickenkamp, et al., 2010). During this paper-pencil-test, participants are instructed to speedily cross out d's with two lines while d's and p's with more or less lines act as distractors. The number of correctly and incorrectly processed items serves as a measure for concentration. Last, two subtests of the computer based test battery for attention (TAP, Zimmermann and Fimm, 2012) were applied to measure alertness and behavioral control (go/nogo). Results from these neuropsychological tests were used as supportive information for diagnostic decisions.

This diagnostic procedure that involved a clinical interview, questionnaires, and cognitive tests ensured the reliable diagnosis of ADHD and other psychiatric or neurologic disorders. It had a duration of about 1.5 hours and participants received a voucher for a local shopping center worth of 10 € for this session. For the study inclusion, ADHD patients were allowed to take stimulants as ADHD medication, but they needed to refrain from medication at least 24 hours before each experimental session. Exclusion criteria for ADHD patients were the presence of psychiatric or neurologic disorders other than oppositional defiant disorder and conduct disorder. Healthy control participants had to be free of psychiatric and neurologic disorders. Moreover, all participants with IQ values under 80 were excluded. For tDCS studies further exclusion criteria were epilepsy in a first-degree relative, cochlea implants, or cardiac pacemakers.

2.2 Transcranial Direct Current Stimulation

2.2.1 tDCS Parameters and Procedure

TDCS was applied with a battery driven direct current stimulator of the company neuroConn (Munich, Germany). This device is controlled by a programmable micro-processor, which allows for the customized adjustment of stimulation parameters. During experimental sessions, participants sat in a comfortable chair. Each session started with the placement of stimulation electrodes, which took about five to ten minutes. TDCS was applied for 20 minutes, a duration that was demonstrated to induce reliable effects on cortical excitability (Nitsche & Paulus, 2001) and to be safe (Antal et al., 2017). The stimulation started and ended with a 30 seconds ramp up and down of current, respectively, to minimize tDCS related sensations (Antal et al., 2017). The sham condition consisted of 30 seconds of stimulation in order to induce comparable sensations in sham and verum

conditions, without affecting cortical excitability (Nitsche & Paulus, 2000). All studies were conducted double blind. For this purpose, the neuroConn stimulator provides a study mode, in which verum or sham stimulation are activated using codes, while the display always indicates verum mode. For each tDCS session, participants received a 5 € voucher for a local shopping center. Two different electrode configurations were used for tDCS applications – conventional and HD-tDCS.

For conventional tDCS, two rectangular rubber electrodes with a size of 5 x 7 cm were used. The anode was placed centrally over EEG position F8 according to the International 10-20 system, which corresponds to the right IFG (Koessler et al., 2009). The cathodal reference electrode was placed on the contralateral supraorbital region. This reference placement is commonly used in tDCS of the frontal cortex and effectively induces current fields in the target region (Laakso et al., 2016). Electrodes were put in sponges soaked in saline solution with a NaCl concentration of 0.9% in order to enable current flow between electrodes and the participants head. For correct placement, the electrodes were installed under an EEG cap and electrode orientation was adjusted to EEG positions. The impedance of stimulation electrodes was kept below 15 kΩ. Current intensity was 1 mA, as this is an established value in clinical research and was demonstrated to be safe (Antal et al., 2017).

For HD-tDCS, a 4 x 1 ring configuration (Kessler et al., 2013) was used consisting of five circular Ag/AgCl-electrodes with a diameter of 1 cm. The anode was placed in the center and four cathodes were placed around it with a distance of 3 cm. The location of this ring montage was selected on the basis of current flow simulations. For this purpose, the current flow pattern for 15 different HD-tDCS montages in the area of the right IFG was computed and the montage that yielded the highest current density in the right IFG was applied in this dissertation. EEG caps that comprised the defined electrode positions were manufactured for easy electrode placement in the correct positions on the participants head. Impedances between electrodes and scalp were reduced to a value below 5 kΩ by rubbing electrolyte-gel to the skin under each electrode using a cotton swab. The center anode stimulated with a current intensity of 0.5 mA. This reduction of current intensity compared to conventional tDCS was necessary as current density on the scalp increases for smaller electrodes. For reference electrodes, current intensity was split between the four cathodes.

At the end of each study, participants filled in a safety questionnaire that assessed the following side effects during and after stimulation: pain, tingling, itching, burning, unpleasant sensations, feeling of a small electric shock, tiredness, nervousness,

concentration, phosphenes, flickering before the eyes, impaired vision, headache, vertigo, nausea, vomiting, insomnia, arousal, feeling of cold and warmth.

2.2.2 Current Flow Simulations

Computer simulations of tDCS induced current flow patterns were based on the brain atlas Pediatric Head Modeling (PHM), which includes individuals between 9 and 18 years (Song et al., 2013)[2]. Data from a 13-year old boy were used as basis of the computational model. The brain atlas fuses non-linearly registered computed tomography data with the MNI magnetic resonance imaging atlas (Fonov et al., 2011). This multimodal approach combines advantages of both imaging techniques for the accurate representation of all tissue types. Tissue segmentation of the Pediatric Head Modeling atlas was used to create a tetrahedral mesh with the software Cleaver (version 1.5.3). This mesh had more than 6 million tetrahedral nodes and 37 million elements and was employed for the bioelectric tDCS simulations. Electrodes were meshed together with head tissues as two instances of the head model. SCIRun5/BrainStimulator (SCI-Institute, 2018) was applied to set up electric boundary conditions and isotropic tissue conductivities (scalp = 0.43, skull = 0.01, cerebrospinal fluid = 1.79, gray matter = 0.33, white matter = 0.142, eye balls = 0.4, electrode saline = 1.4, internal air = 1e-6 S/m, Dannhauer et al. (2011)). The electrode contact impedance was assumed as 20 kΩ. With SCIRun5/BrainStimulator a finite element solution was computed (Dannhauer et al., 2012; Hyde et al., 2016) and the electric current density on the brain surface was visualized.

2.3 Electroencephalography

In this dissertation, tDCS induced changes of cognitive processes were not only investigated on a behavioral but on a neurophysiological level using the technique of electro-encephalography (EEG), which provides data of electrical brain activity. The main advantage of neurophysiological measures over behavior is that they allow the investigation of covert processes, like cognitive functions. In contrast, behavioral data, although of the highest relevance for the success of the intervention, are the result of a complex interplay between multiple processing steps in the brain, together with external factors. Hence, they do not allow for a reliable interpretation of changes in underlying brain activity induced by experimental manipulations. Moreover, shifts in neurophysiological activity do not necessarily result in behavioral changes and could therefore, remain undiscovered. The EEG

[2] https://home.pedeheadmod.net/display/PedVol/Pediatric+Head+Atlasses#, 19.05.2015

data assessed in the following studies provide a continuous measure of covert cognitive functions and are thus, a valuable complement to behavioral measures (Luck, 2005).

2.3.1 Principles of EEG

Electroencephalography (EEG) was invented in 1929 by Hans Berger who discovered that electrical brain activity can be measured simply by using electrodes that are placed on the scalp if the induced voltage signal is amplified. The measured activity reflects mostly postsynaptic potentials as these cause small dipoles in the extracellular space. Those dipoles occur because membrane potential changes at apical dendrites cause a negative shift of the charge at the external side of the membrane. Concurrently, the environment of basal dendrites and soma is charged positively. Hence, negative and positive charges are separated by a small distance and are therefore, forming a tiny dipole. If such dipoles of thousands or millions of neurons with the same orientation summate, they can be measured using scalp electrodes. This happens mostly in cortical pyramidal cells because of their spatial alignment perpendicular to the cortex. In neuron populations of different orientation, those potentials cancel each other out and thus, neural activity cannot be detected with EEG.

Although EEG has an outstanding temporal resolution, as electrical signals are transmitted immediately, a downside of this method is its restricted spatial resolution. Electrical currents generated in the brain spread through the tissue and expand laterally along the surface, which leads to a blurred distribution of the resulting EEG (Luck, 2005). However, spatial resolution can be improved using EEG source localization techniques, which are steadily developed further (Asadzadeh et al., 2020).

2.3.2 Event-Related Potentials

If the EEG technique is applied while an individual undergoes a controlled stimulation with repeated stimuli, for example an experimental task, the neural signal can be analyzed time-locked to specific events of sensory, cognitive, or motoric nature. Such events induce voltage fluctuations, which are called event-related potentials (ERPs). As ERPs are usually very small, they emerge only when the raw EEG signal is averaged over several trials. By doing so, neural activity not time-bound to the event as well as further noise is averaged out leaving only the ERP. Therefore, ERPs are a measure of the time-locked neural activity, which is consistently evoked by a stimulus. They can reflect mental operations during different stages of processing (Teplan, 2002).

ERP components are named after their most important characteristics, which is their polarity as well as either their position in the waveform (e.g. P3) or their latency in milliseconds (e.g. P300). Early ERP components reflect stages of sensory processing, for example the visual P1, which origins in the visual cortex. Later components as the N2 and the P3 reflect more complex processing steps (Luck, 2005) and are the focus of this dissertation as higher order cognitive functions were targeted by tDCS.

2.3.3 The N2 and the P3 Component

Working memory tasks, like the *n*-back paradigm, elicit an N2 component that peaks at centro-parietal sites (Stroux et al., 2016) and a P3 component that peaks over parietal sites (Helenius et al., 2011). The N2 seems to represent a match/mismatch process (Daffner et al., 2011), while the P3 reflects stimulus processing, evaluation, and classification, updating of mental representations in working memory, as well as the decision how to respond (Helenius et al., 2011; Kaiser et al., 2020). The amplitude size of the P3 reflects the amount of resources allocated to the working memory process (Keage et al., 2008) and thus, larger P3 amplitudes were found in individuals with better working memory (Dong et al., 2015). Paradoxically, P3 amplitudes decrease with an increasing *n* of the *n*-back task as higher working memory load results in the distribution of cognitive resources to meet task requirements (Watter et al., 2001).

The go/nogo response inhibition task elicits a frontal N2 and a fronto-central P3 component, which are both larger during nogo than during go trials (Smith et al., 2008). The nogo N2 component reflects conflict monitoring, which is considered a non-motoric subprocess of inhibition, with larger N2 amplitudes indicating better inhibitory performance (Donkers & Van Boxtel, 2004; Jonkman, 2006; Smith et al., 2008). The nogo P3 component reflects response inhibition (Donkers & Van Boxtel, 2004) and thus, is a marker for the success of motoric inhibition (Smith et al., 2008). Accordingly, larger peaks of the nogo P3 have been associated with better response inhibition performance (Donkers & Van Boxtel, 2004; Jonkman, 2006; Smith et al., 2008), while adults with high impulsivity show reduced nogo P3 amplitudes (Ruchsow et al., 2008).

In ADHD patients, P3 amplitude reductions belong to the most sensitive biomarkers for this disorder (Szuromi et al., 2011; Kaiser et al., 2020). A reduced size of the P3 has been associated with more severe ADHD symptom severity (Marquardt et al., 2018) and the P3 is

normalized by the administration of methylphenidate (Hermens et al., 2005; Shahaf et al., 2015). During working memory tasks, reduced P3 components have been associated with a diminished *n*-back performance in patients (Barry et al., 2003; Keage et al., 2008; Johnstone et al., 2013) and during the go/nogo task, reduced peaks of the P3 reflect response inhibition impairments (Johnstone et al., 2013). Further, amplitude reductions were also demonstrated for the N2 in ADHD (Barry et al., 2003), but previous research showed heterogeneous results on this component (Fallgatter et al., 2004; Shahaf et al., 2015). A recent meta-analysis by Kaiser et al. (2020) could not confirm amplitude reductions of the N2 and concluded that they exist only in a subgroup of the ADHD population.

2.3.4 EEG Procedure

For the preparation of EEG assessments in the presented experiments, participants were seated in a comfortable chair. During preparation, a movie was played, which is especially important for ADHD patients who tend to become fidgety when bored. An EEG cap (Easycap, Herrsching, Germany) was positioned on the participants head by localizing the EEG position Cz through measuring the midpoint between nasion and inion as well as between left and right pre-auricular points. Passive Ag/AgCl electrodes were placed at 21 EEG positions (Fp1, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC6, FT10, C3, Cz, C4, P7, P3, Pz, P4, P8, O1, O2) according to the International 10-20 system (Homan et al., 1987). The Ground electrode was placed at position AFz. Electrode holders for reference and EOG electrodes (electrooculogram) were attached directly to the skin after cleaning the respective areas. Linked electrodes at the left and right mastoid served as reference. Vertical and horizontal EOGs were recorded from two bipolar channels with the electrodes placed at sub and supra-orbital positions and at the outer canthi of both eyes, respectively. The space under each electrode was filled with abrasive electrolyte-gel and if necessary hair was pushed aside. By rubbing the abrasive gel on the skin with a cotton swab, the impedance between electrodes and the participants head was reduced. It was proceeded until all electrodes reached impedance values of at least below 15 kΩ, but in most cases below 10 kΩ. Overall, preparation of the EEG took approximately 30 minutes. Afterwards, the participant was instructed to sit as calm as possible during the EEG and to relax all facial muscles. Then the experiment started. Recording of EEG was conducted with a SynAmps amplifier from the company Neuroscan (Virginia, USA) with the dedicated software Acquire (version 4.1) at a sampling rate of 500 Hz. A high pass filter of 0.05 Hz, a low pass filter of 70 Hz, and a notch filter of 50 Hz were applied. Depending on the individual study, EEG was recorded during

different cognitive tasks. After the end of each session, the participant received a voucher for a local shopping center worth of 15 - 25 €.

3 Experiment 1: Economical Assessment of Working Memory and Response Inhibition in ADHD Using a Combined *n*-back/nogo Paradigm: An ERP Study

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3.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequent disorders in child and adolescent psychiatry, with a worldwide prevalence of about 3.4% (Polanczyk et al., 2015). Additional to the core symptoms of inattention, hyperactivity, and impulsivity defined in DSM-5 (American Psychiatric Association, 2013), 62% of ADHD patients are affected by significant impairments of working memory and 27% suffer from inhibitory dysfunctions (Kofler et al., 2019a). These deficits are associated with long-term consequences as academic underachievement, social problems and even addiction (Groman et al., 2009; Rinsky & Hinshaw, 2011; Simone et al., 2018). As those impairments mostly persist into adulthood (Barkley & Murphy, 2011), we emphasize that working memory and response inhibition can be essential indicators for the success of therapeutic interventions.

Therapeutic approaches that aim for the improvement of cognitive functions in ADHD include cognitive training (Johnstone et al., 2010), neurofeedback (Baumeister et al., 2018), and non-invasive brain stimulation (Salehinejad et al., 2019; Breitling et al., 2020). When evaluating the effectiveness of such interventions, the assessment of multiple cognitive functions, as working memory and response inhibition, can be necessary not only to demonstrate therapeutic success but also to detect transfer effects into other domains or to control for cognitive side effects. However, experimental settings consisting of various tasks are particularly challenging for ADHD patients who are unable to stay concentrated and calm over longer time periods (Dekkers et al., 2017). In imaging studies, this is a highly relevant obstacle because data quality is suffering when patients start to fidget or move. Thus, researchers often refrain from the assessment of multiple cognitive functions or accept

poor data quality. With this motivation, we applied the approach of merging different tasks (Ruchsow et al., 2008; Lee et al., 2010; Scharinger et al., 2015; Alderson et al., 2017) to a combined working memory and a response inhibition paradigm.

One of the most popular paradigms in working memory research is the *n*-back task. During this task, participants decide for a series of stimuli if the current stimulus is identical to the one presented a specified number *n* of trials earlier. With increasing *n* and therefore increasing working memory load, the task becomes more demanding. There is strong evidence that ADHD patients show impaired performance as well as higher reaction time and standard deviations of reaction time during *n*-back tasks (Keage et al., 2008; Myatchin et al., 2012) with largest effect sizes of impairments during the 2-back variant (Kobel et al., 2009). Response inhibition is commonly investigated using the go/nogo task. In this task, participants are instructed to react fast on pre-defined go stimuli and to withhold their reaction for nogo stimuli. Performance deficits as well as increased reaction time and standard deviations of reaction time in ADHD patients were found in this task (Fallgatter et al., 2004; Wiersema et al., 2006; Fisher et al., 2011). As neuropsychological deficits in ADHD were effectively demonstrated using 2-back and go/nogo paradigms, we combined both into the *n*-back/nogo task.

The investigation of this combined *n*-back/nogo paradigm was realized by assessing behavioral parameters and electroencephalograms (EEG) during the application of single and combined task versions. EEG analysis is optimally suited to investigate neural mechanisms underlying behavioral data. For that purpose, we focused on the following event-related potential (ERP) components as they represent the executive processes that show pathological changes in ADHD (Barry et al., 2003; Banaschewski & Brandeis, 2007).

The working memory *n*-back task evokes a P3 component that peaks at parietal sites and that is larger during *n*-back targets compared to non-targets (Watter et al., 2001). This component represents the amount of resources allocated to the working memory process (Keage et al., 2008). The P3 amplitude decreases with increasing *n* because higher working memory load results in the distribution of cognitive resources to meet task requirements (Watter et al., 2001). Furthermore, larger P3 amplitudes were found in individuals with better working memory (Dong et al., 2015). In accordance with that, ADHD patients show diminished *n*-back P3 amplitudes (Stroux et al., 2016) indicating reduced resource allocation to working memory processing (Keage et al., 2008).

The go/nogo response inhibition task elicits a frontal N2 and a fronto-central P3 component, which are both larger during nogo than during go trials (Smith et al., 2008). The nogo N2 component reflects conflict monitoring (Donkers & Van Boxtel, 2004), which is considered a non-motoric subprocess of inhibition (Smith et al., 2008). Larger N2 amplitudes and lower latencies of this component are associated with better inhibitory performance (Barry et al., 2003). In line with that, reduced peaks of the nogo N2 were found in ADHD patients, resulting from atypical inhibitory processes in frontal areas (Barry et al., 2003). However, results regarding N2 latencies in ADHD patients are inconclusive, as different studies found either reduced (Smith et al., 2004; Johnstone et al., 2009) or increased latencies (Barry et al., 2003; Fallgatter et al., 2004; Fisher et al., 2011), or found no ADHD related changes (Barry et al., 2003; Fallgatter et al., 2004). The nogo P3 component reflects response inhibition (Donkers & Van Boxtel, 2004) and is thus a marker for the success of motoric inhibition (Smith et al., 2008). Accordingly, in healthy adults with high impulsivity reduced nogo P3 amplitudes have been demonstrated (Ruchsow et al., 2008). Reduced amplitudes of the nogo P3 component are one of the most robust ERP findings in ADHD (Kaiser et al., 2020) and have been associated with response inhibition impairments in ADHD patients (Johnstone et al., 2013).

The present study aimed to validate the introduced, combined *n*-back/nogo paradigm and to demonstrate its applicability as a measurement for cognitive impairments in ADHD patients in a two-step approach. First, healthy children and adolescents performed the combined *n*-back/nogo task as well as parallel single task versions of *n*-back and go/nogo. We hypothesized that behavioral measures and ERP characteristics would be comparable between task versions. Second, ADHD patients underwent the combined *n*-back/nogo task to demonstrate similar behavioral and neurophysiological deficits as expected from established single task versions. We predicted that patients would show impaired working memory and response inhibition performance as well as reduced amplitudes of *n*-back P3, nogo N2, and nogo P3 components.

3.2 Methods

3.2.1 Participants

Fifty-nine participants aged between 9 and 16 years were recruited via the Department of Child and Adolescent Psychiatry and through advertisements in a local newspaper. Thirty-

four were diagnosed with ADHD according to DSM-5 criteria (21 combined presentation, 12 predominantly inattentive presentation, one predominantly hyperactive-impulsive presentation). Patients with comorbid psychiatric or neurologic diagnoses were excluded from the study. This also applied to dissocial disorders, because differential ERP patterns were demonstrated between patients with ADHD only and patients with comorbid diagnoses as oppositional defiant disorder or conduct disorder (Banaschewski et al., 2003). Eleven patients currently took ADHD medication but they refrained at least 24 h before the experiment. For assignment to the healthy control group, participants had to be free of psychiatric and neurologic disorders (n = 25). Trained psychologists diagnosed participants on the basis of clinical interviews, which were conducted with all participants and their parents using the German Adaptation (Delmo et al., 2000) of the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL, Kaufmann et al., 1997). As supportive diagnostic information, concentration performance was determined (d2, Brickenkamp, 2002; d2-R, Brickenkamp, et al., 2010) and behavioral problems were assessed in all participants as parent rating (Child Behavior Checklist, Achenbach, 1991), and additionally in children of 11 years and older as self-rating (Youth Self Report, Achenbach, 1991b). IQ values below 80 served as an exclusion criteria, assessed with the CFT 20-R (Weiss, 2008). Last, the Edinburgh Handedness Inventory (Oldfield, 1971) was applied. Table 1 summarizes sample characteristics and shows that ADHD and control group did not significantly differ in the proportion of females, age, intelligence or handedness (all $p \geq .085$) but in subjective and objective assessment of attentional impairments (all $p < .001$).

Table 1. Sample description of experiment 1. Sample characteristics of ADHD and control group, mean ± standard deviation, effect size Cohens *d*, *t*, and *p*-values are given.

	ADHD	controls	*t*	*p*	*d*
n	34	25	-	-	-
females in %	20.6	20.0	-	.956	-
age in years	13.15 ± 1.89	13.00 ± 2.02	-0.28	.775	0.08
ethnicity in %			-	.466	-
caucasian	91.2	96.0	-	-	-
biracial	8.8	4.0	-	-	-
diagnoses:					
ADHD combined	21	-	-	-	-
ADHD inattentive	12	-	-	-	-
ADHD hyperactive	1	-	-	-	-
current medication:					

methylphenidate	10	-	-	-	-
dexamphetamine	1	-	-	-	-
attention problems, parent rating (CBCL; *T*)	67.6 ± 8.2	54.4 ± 7.1	-6.45	< .001	1.72
attention problems, self rating (YSR; *T*)	60.9 ± 7.4	52.8 ± 4.2	-4.79	< .001	1.35
attentional performance (d2; *T*)	50.4 ± 8.8	59.7 ± 11.5	3.41	.001	0.91
IQ	102.3 ± 14.4	108.6 ± 12.6	1.75	.085	0.47
left-handed in %	2.9	8.0	-	.382	-

The study followed the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee of the Otto von Guericke University Magdeburg. All caregivers and participants gave their written informed consent and assent, respectively. Participants were reimbursed with a voucher of 15 - 20 € for a local shopping center.

3.2.2 Tasks and Procedure

The healthy control group performed single *n*-back and go/nogo task versions as well as the combined *n*-back/nogo task within one session. The order in which cognitive tasks were applied was pseudo-randomized between participants, with balanced frequency for each possible sequence. ADHD patients underwent only the combined *n*-back/nogo task. Task illustrations are provided in Figure 6. Participants were instructed to react as accurately and as fast as possible. Tasks were presented on a flat screen that had a diagonal of 61 cm using Presentation® (version 18.0, www.neurobs.com). Stimuli had a visual angle of 0.86° (height) and were presented in black on a grey background (RGB value 128). In all tasks, stimulus duration was 500 ms and participants had 2000 ms to give their response. The interstimulus interval was 2500 ms.

3.2.2.1 Single *n*-back Task

A series of capital letters was presented (A, D, E, H, I, N, R, S, T, U) and participants decided if the current stimulus was identical to the stimulus two trials earlier ($n = 2$). These target trials had a proportion of 22%. If stimuli were identical, participants pressed a button with their right hand, and if stimuli were not identical, they pressed a button with their left hand. The key assignment was the same for all participants. The task consisted of three runs that had a duration of 3.8 min each (90 trials) and that were separated by pauses of at least 30 sec. The task started with a training run of 2.5 min (40 trials) with feedback indicating right or wrong reactions. After this training, the investigator decided if the participant understood the task correctly or if the training must be repeated.

3.2.2.2 Single go/nogo Task

Participants were instructed to press a button for go trials presenting the letter O and to withhold their response for nogo trials presenting the letter X (17%). The task consisted of three runs with a duration of 4.6 min each (110 trials). It started with a short training run of 40 s (10 trials) with feedback of right or wrong reactions, which could be repeated if required.

3.2.2.3 Combined *n*-back/nogo Task

Again, letters were presented sequentially and participants decided if the present and the 2-back stimulus were identical (21%). Additionally, participants were instructed to withhold their response when the letter X appeared. Those nogo trials had a proportion of 17%. The task was composed of a random order of *n*-back sequences containing one to eleven trials (M = 5.8, SD = 3.0), with the last trial of each sequence always being a nogo trial. Participants were informed that there was never an *n*-back target trial directly after a nogo trial. The task was split into three runs with a duration of 4.6 min each (110 trials), providing an equal quantity of *n*-back target trials to the single *n*-back task. It started with a training run of 2 min (30 trials) with feedback of right or wrong reactions, which could be repeated if required.

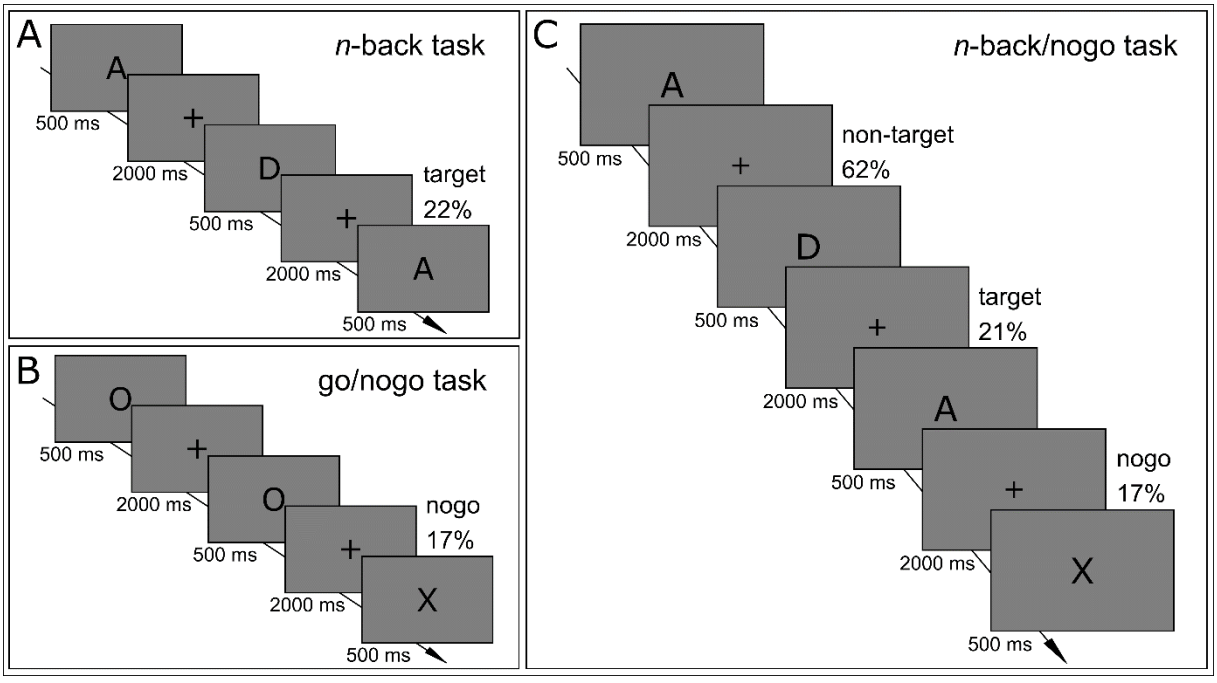

Figure 6. Cognitive tasks in experiment 1. Schematic illustrations of **(A)** single *n*-back task, **(B)** single go/nogo task, and **(C)** combined *n*-back/nogo task.

Data from ADHD patients were collected in the context of two different studies. During one study, patients performed the combined *n*-back/nogo task in the initial of several sessions for four runs while EEG was recorded (n = 24). The other was an application-oriented study, where the task was applied in one of three sessions for six runs during a placebo non-invasive brain stimulation while EEG was recorded during the last three runs (n = 10) (Breitling et al., 2020). Data from both studies indicated comparable results as shown in Supplementary Table S1.

3.2.3 EEG Recording and Analysis

EEG was recorded with a SynAmps amplifier (Neuroscan, Sterling, VA, USA) from 21 channels. For this purpose, Ag/AgCl-electrodes were placed in an EEG cap (Easycap GmbH, Herrsching, Germany), according to the International 10-20 EEG system (Fp1, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC6, FT10, C3, Cz, C4, P7, P3, Pz, P4, P8, O1, O2). The ground electrode was placed at position AFz, and the EEG was referenced to linked mastoids. Via two bipolar channels, EOG was recorded with electrodes placed at the outer canthi of both eyes and at sub- and supra-orbital positions. Impedances were kept below 15 kΩ, and data were recorded with a sampling rate of 500 Hz. A high pass filter of 0.05 Hz, a low pass filter of 70 Hz, and a notch filter of 50 Hz were applied online.

We analyzed data with EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) in the MATLAB environment (version R2013a, The MathWorks, Inc., Nattick, MA, USA). EEG data were low pass filtered offline with 30 Hz. Epochs ranging from 200 ms pre to 650 ms post-stimulus were extracted from trials with correct responses, relative to the pre-stimulus baseline. Artifactual epochs were removed in a semi-automated way. First, EEGLAB algorithms detected epochs that contained amplitudes exceeding ± 100 µV, abnormal trends exceeding 100 µV, or abnormal spectra. Afterwards, a trained investigator verified artifact detection and removed trials containing artifacts. Participants with less than ten remaining epochs were excluded from ERP analysis of the respective condition. Thus, two ADHD patients were excluded from analyses of *n*-back target trials and three from analyses of nogo trials. In the control group, 34.3 (SD = 7.7) *n*-back targets and 39.3 (SD = 6.7) nogo trials were analyzed on average in each participant for single task versions. A mean number of 48.1 (SD = 8.5) *n*-back targets and 42.0 (SD = 6.9) nogo trials of the combined *n*-back/nogo task remained in the analysis of controls. In ADHD patients, a mean of 38.4 (SD = 19.8) *n*-back targets and of 41.3 (SD = 14.7) nogo trials were analyzed on average.

ERP peak amplitudes and latencies were determined automatically with ERPLAB measurement tools. Latency ranges for ERP measurements were chosen by reference to grand average waveforms. The time window for the *n*-back P3 analysis was 275-500 ms in both, single *n*-back and combined *n*-back/nogo tasks. The nogo N2 component was analyzed at 225-350 ms in the single go/nogo task and at 250-500 ms in the combined *n*-back/nogo task. For P3 analysis in the single go/nogo task, a time window of 325-600 ms was used for nogo trials and of 225-425 ms for go trials. In the combined *n*-back/nogo task, the nogo P3 was analyzed at 425-625 ms. The *n*-back P3 component has a centro-parietal maximum (Segalowitz et al., 2001) and its analysis was, therefore, restricted to central and parietal electrode positions (C3, Cz, C4, P3, Pz, P4). Analysis of the nogo N2 component focused on frontal and central electrodes (F3, Fz, F4, C3, Cz, C4) as it has a fronto-central distribution (Smith et al., 2008). The nogo P3 was analyzed at frontal, central, and parietal positions (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4).

3.2.4 Statistics

Statistical analyses were conducted with SPSS (version 24, IBM Corp., Armonk, NY, USA). We compared sample characteristics between the control and ADHD group using independent samples *t*-tests for metric variables, and chi-square tests for dichotomous variables. Reaction times were analyzed from trials with correct responses and with a minimum reaction time of 100 ms. Working memory performance was calculated as the corrected hit rate in percent (hits targets - false positives non-targets) with higher values indicating better performance. Response inhibition performance was the inverse of nogo commission error rate (100% - false positives), thus better performance was indicated by higher values. The analyzed behavioral measures were working memory performance, response inhibition performance, omission errors, reaction time, and standard deviation of reaction times. If Levene's test for variance equality was significant, Satterthwaite approximations for the degrees of freedom are reported for *t*-tests. ERP components were characterized by peak amplitudes and latencies. These were analyzed using ANOVAs while significant main and interaction effects were further investigated via post-hoc pairwise comparisons with Bonferroni adjusted alpha levels. We applied Greenhouse Geisser corrections if assumptions of sphericity were violated. Effect sizes are reported as Cohens *d* for *t*-tests and as η^2 for ANOVAs.

3.2.4.1 Comparisons Between Single and Combined Task Versions

In the control group, behavioral measures were compared between single tasks and the combined *n*-back/nogo task using paired-samples *t*-tests. Reaction time distributions were characterized and inverse efficiency scores (IES) were determined. The IES is a measure of the speed-accuracy tradeoff, which is defined as the mean reaction time divided by the proportion of correct responses (Liesefeld & Janczyk, 2019). It indicates the reaction time corrected for the amount of errors, thus, smaller values indicate more efficient responses. The convergent validity of the introduced paradigm was investigated by calculating Pearson's *r* correlation coefficients for working memory and response inhibition performance between single and combined task versions. Further, the correlation between working memory and response inhibition within single tasks and within the combined *n*-back/nogo task were calculated to explore discriminant validity of the introduced paradigm.

For ERP analysis, first, we characterized *n*-back P3 as well as nogo N2 and P3 components within single task versions in healthy controls. For this purpose, repeated measures ANOVAs with the factors Stimulus (go vs. nogo; *n*-back target vs. non-target), Region (*n*-back P3: central vs. parietal; nogo N2: frontal vs. central; nogo P3: frontal vs. central vs. parietal) and Hemisphere (left vs. midline vs. right) were conducted for ERP characteristics. Data for the different levels of Region and Hemisphere were averaged across the following electrodes: frontal - F3, Fz, F4; central - C3, Cz, C4; parietal - P3, Pz, P4; left - F3, C3, P3; midline - Fz, Cz, Pz; right - F4, C4, P4. Second, we tested if components differed between each single task version and the combined *n*-back/nogo task, using repeated measures ANOVAs with the factors Task (single vs. combined), Region, and Hemisphere. Only main and interaction effects including the factor Task were reported for this analysis.

3.2.4.2 Comparisons Between Control and ADHD Group

Behavioral measures during the combined *n*-back/nogo task were compared between the control and ADHD group using independent-samples *t*-tests. Further, the Pearson's *r* correlation coefficient was calculated between working memory and response inhibition performance within the combined *n*-back/nogo task. ERP components were analyzed in mixed ANOVAs including the between-subjects factor Group (controls vs. ADHD) and within-subjects factors Region and Hemisphere. For this analysis, only main and interaction effects including the factor Group were reported.

3.2.4.3 Power Analysis

Post-hoc power analyses were conducted using the software G*Power version 3.1 (Faul et al., 2009) to compute the sensitivity of the present study. Given an alpha of .05 and a power of .80 the present study design allowed for the detection of medium sized effects. Minimal detectable effects for all comparisons are presented in Table 2.

Table 2. Power analysis. Minimal detectable effects (MDE) for the present study given an alpha = .05 and a power = .80, effect sizes are given as Cohens *d* for *t*-tests and as η^2 for ANOVAs.

comparison	MDE
behavioral data	
single vs. combined task	$d = 0.58$
controls vs. ADHD	$d = 0.75$
ERP data	
single vs. combined task	$\eta^2 = .078$
controls vs. ADHD:	
between subject	$\eta^2 = .098$
within subject	$\eta^2 = .035$
interaction	$\eta^2 = .035$

3.3 Results

3.3.1 Comparisons Between Single and Combined Task Versions

3.3.1.1 Behavioral Data

Comparisons between task versions indicated better performance for the combined *n*-back/nogo task compared to single task versions. So, better working memory performance was found during the combined *n*-back/nogo task than during the single *n*-back task (combined *n*-back/nogo: 73.83%, single *n*-back: 55.70%, $t(24) = 6.91$, $p < .001$, $d = 1.11$). Response inhibition performance was not significantly different between task versions (combined *n*-back/nogo: 87.44%, single go/nogo: 83.02%, $t(24) = 1.76$, $p = .091$, $d = 0.44$) Further, we found a borderline significant trend towards a reduced number of omission errors in the combined *n*-back/nogo task compared to the single *n*-back task ($t(24) = -2.04$, $p = .053$, $d = 0.43$). Reaction times and standard deviations of reaction times for the combined *n*-back/nogo task were significantly higher than for go stimuli of the single go/nogo task (all $p <$

.001, $d \geq 1.84$) and were rather comparable to the single *n*-back task (all $p \geq .338$, $d \leq 0.18$). Table 3 summarizes behavioral results.

Table 3. Behavioral parameters of single and combined task versions. Comparisons within the healthy control group between single task versions of *n*-back and go/nogo against the combined *n*-back/nogo task, mean ± standard deviation *t* and *p*-values as well as effect sizes Cohens *d* are given.

	single task	*n*-back/nogo	*t* (24)	*p*	*d*
working memory					
performance %	55.70 ± 17.29	73.83 ± 15.39	6.91	< .001	1.11
omission errors in %	2.00 ± 2.76	1.07 ± 1.25	-2.04	.053	0.43
reaction time in ms	705 ± 189	722 ± 194	.59	.561	0.09
SD of reaction time in ms	266 ± 84	252 ± 72	-.98	.338	0.18
IES in ms	889 ± 308	826 ± 263	-1.43	.165	0.22
response inhibition					
performance in %	83.02 ± 11.59	87.44 ± 8.35	1.76	.091	0.44
omission errors in %	1.10 ± 2.59	1.07 ± 1.25	-.07	.948	0.02
reaction time in ms	421 ± 88	722 ± 194	10.30	< .001	2.00
SD of reaction time in ms	126 ± 65	252 ± 72	8.77	< .001	1.84
IES in ms	480 ± 82	820 ± 176	11.45	< .001	2.48

IES – inverse efficiency score

As reaction time measures differed significantly between single go/nogo and combined *n*-back/nogo task versions, reaction time distributions were characterized further (Figure 7). While the excess kurtosis of the reaction time distribution was at .69 for the single go/nogo task, the distribution flattened in the combined *n*-back/nogo task (excess kurtosis = -1.23) and was thus, more similar to the reaction time distribution of the single *n*-back task (excess kurtosis = -0.66). Further, while the reaction time distribution of the single go/nogo task was moderately skewed left (skewness = 0.94), reaction time distributions were approximately symmetric for the single *n*-back task (skewness = 0.33) and for the combined *n*-back/nogo task (skewness = 0.27). Moreover, regarding the IES we found no significant task difference for working memory performance (single *n*-back: 889 ms, combined *n*-back/nogo: 826 ms, $t(24) = -1.43$, $p = .165$, $d = 0.22$), but for response inhibition the IES was higher in the combined *n*-back/nogo task (820 ms) compared to the single go/nogo task (480 ms), ($t(24) = 11.45$, $p < .001$, $d = 2.48$).

Pearson's *r* correlation coefficients of behavioral measures between task versions revealed that working memory performance was highly correlated between the combined *n*-back/nogo task and the single *n*-back task ($r = .68$, $p < .001$). Further, the number of omission

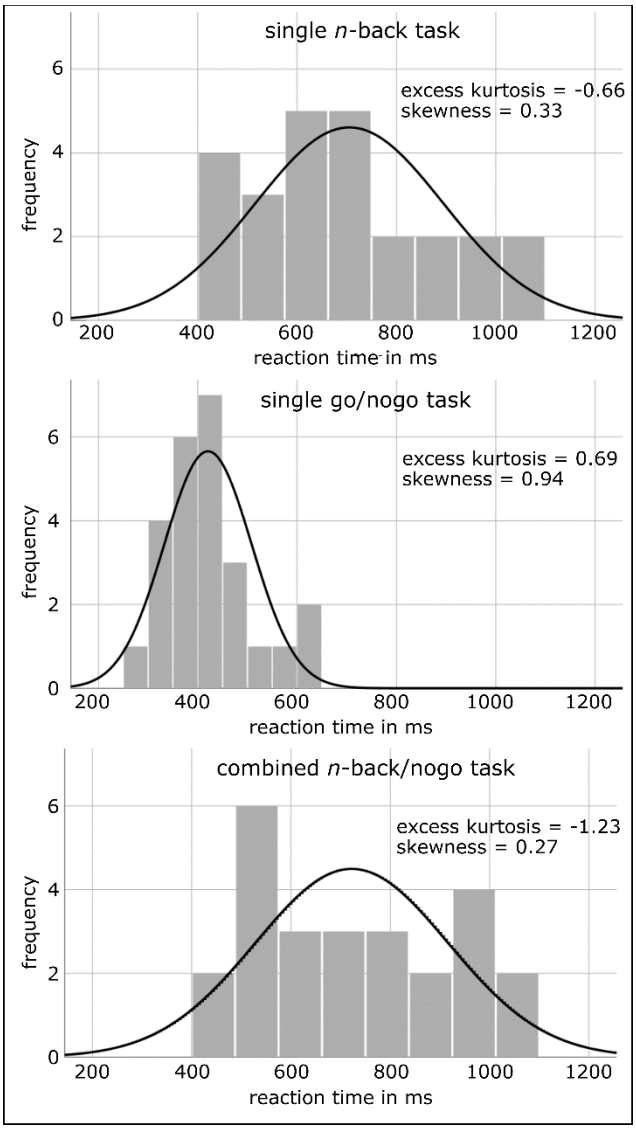

Figure 7. Reaction time distributions in single and combined task versions. Histograms of reaction time distributions in the healthy control group for different cognitive tasks, together with the illustration of a normal distribution.

errors in the combined *n*-back/nogo task was correlated to omission errors in the single *n*-back task (r = .58, p = .003) as well as in the single go/nogo task (r = .50, p = .011). Reaction times in the combined *n*-back/nogo task were correlated to reaction times in both single task versions (*n*-back: r = .72, p < .001, go/nogo: r = .70, p < .001) and the same applied for standard deviations of reaction times (*n*-back: r = .59, p = .002, go/nogo: r = .45, p = .023). For response inhibition performance, we found no significant correlation between task versions (r = .24, p = .250). However, data inspection revealed two outliers for this correlation (compare Figure 8). When the outliers were removed in an exploratory analysis, a significant correlation of r = .54, p = .007 was revealed. Unexpectedly, when exploring measures of discriminant validity, a significant correlation between working memory performance in the single *n*-back task and

response inhibition performance in the single go/nogo task was found (r = .49, p = .014). However, the same participants as above were identified as outliers and excluded for an exploratory analysis, resulting in no significant correlation (r = .18, p = .403). In the combined *n*-back/nogo task, working memory and response inhibition performance were not significantly correlated with each other (r = -.09, p = .661).

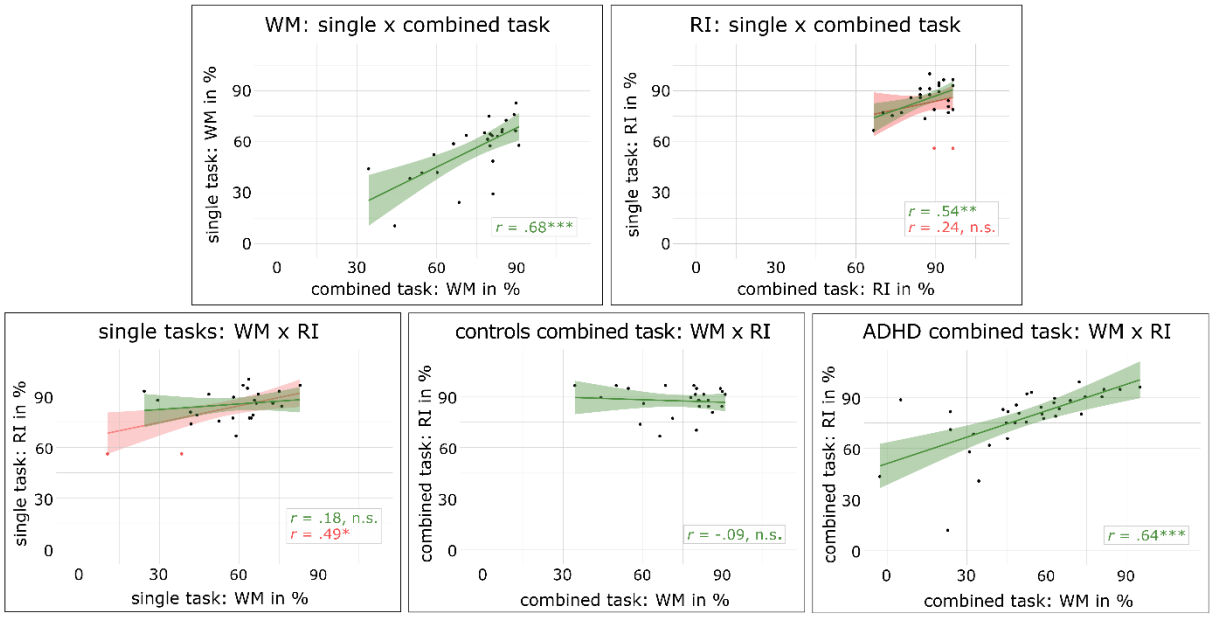

Figure 8. Convergent and discriminant validity of the *n*-back/nogo task. Scatterplots and regression lines with 95% confidence intervals are given for correlations of working memory performance (WM) and response inhibition performance (RI) in different task conditions, red lines represent the results including the two outliers that are marked as red dots, *p < .05, **p < .01, ***p < .001.

3.3.1.2 ERP Data

n-back P3. The comparison of P3 amplitudes between *n*-back targets and non-targets during the single *n*-back task revealed main effects of Stimulus (F(1, 24) = 45.54, p < .001, η^2 = .655), Region (F(1, 24) = 79.25, p < .001, η^2 = .768), Hemisphere (F(1.4, 34.0) = 6.72, p = .008, η^2 = .219), and an interaction between Stimulus and Hemisphere (F(2, 48) = 3.33, p = .044, η^2 = .122). This analysis indicated larger P3 components in response to target than to non-target stimuli and at parietal than at central electrode positions. Post-hoc tests showed larger amplitudes at midline compared to left electrode sites for target and non-target stimuli (all $p \leq .007$) while only for non-targets amplitudes were larger at right compared to left sites (p = .011). P3 amplitudes did not significantly differ between single *n*-back and combined *n*-back/nogo tasks (F(1, 24) = 0.83, p = .372, η^2 = .033).

Latency comparisons of *n*-back P3 between target and non-target trials in the single task version resulted in an interaction effect between Stimulus and Region ($F(1, 24) = 10.35$, $p = .004$, $\eta^2 = .301$), indicating higher latencies at central than parietal positions during non-target trials ($p = .007$). A further interaction between Stimulus and Hemisphere was found ($F(2, 48) = 5.41$, $p = .008$, $\eta^2 = .184$), but post-hoc tests did not reach significance. Subsequent analyses showed no latency differences between single and combined task versions ($F(1, 24) < 0.01$, $p = .964$, $\eta^2 < .001$).

nogo N2. The comparison of N2 amplitudes between go and nogo stimuli of the single go/nogo task, showed main effects of Stimulus ($F(1, 24) = 7.59$, $p = .011$, $\eta^2 = .240$) and Region ($F(1, 24) = 33.33$, $p < .001$, $\eta^2 = .581$), as well as an interaction between Region and Hemisphere ($F(2, 48) = 7.02$, $p = .002$, $\eta^2 = .226$). Hence, N2 peaks were more negative for nogo than for go stimuli and at frontal than at central electrode positions. Focusing on frontal sites, amplitudes were more negative at the midline compared to the right electrode ($p < .001$) whereas there was no difference between central sites (all $p = 1.00$). Task version did not affect N2 amplitudes ($F(1, 24) = 0.52$, $p = .479$, $\eta^2 = .021$).

During the single go/nogo task, N2 latencies were higher for nogo than for go stimuli ($F(1, 24) = 6.13$, $p = .021$, $\eta^2 = .204$), at frontal than at central electrode sites ($F(1, 24) = 4.71$, $p = .040$, $\eta^2 = .164$), and they were highest at right sites ($F(2, 48) = 4.17$, $p = .021$, $\eta^2 = .148$; post-hoc all $p \leq .046$). Latencies were increased during the combined *n*-back/nogo task in comparison to the single go/nogo task ($F(1, 24) = 40.27$, $p < .001$, $\eta^2 = .627$).

nogo P3. Comparing P3 amplitudes between stimulus types of the go/nogo task, we found main effects of Stimulus ($F(1, 24) = 43.91$, $p < .001$, $\eta^2 = .647$), Region ($F(1.5, 36.3) = 91.23$, $p < .001$, $\eta^2 = .792$), and Hemisphere ($F(1.6, 37.4) = 7.92$, $p = .003$, $\eta^2 = .248$), interactions between Stimulus and Region ($F(2, 48) = 10.80$, $p < .001$, $\eta^2 = .310$), Stimulus and Hemisphere ($F(2, 48) = 21.00$, $p < .001$, $\eta^2 = .467$), Region and Hemisphere ($F(4, 96) = 6.66$, $p < .001$, $\eta^2 = .217$), and a threefold interaction ($F(4, 96) = 6.52$, $p < .001$, $\eta^2 = .214$). Nogo stimuli elicited larger P3 components than go stimuli. This effect was greatest at central electrode positions, but was significant also at frontal and parietal sites (all $p < .001$). Generally, P3 amplitudes were largest at parietal and smallest at frontal positions (all $p < .001$). However, during nogo trials, P3 amplitudes were centro-parietally largest at midline sites (all $p \leq .026$) while during go trials P3 amplitudes were frontally, largest at the right site (all $p \leq .013$). The next comparison between single and combined task versions revealed interactions between Task and Region ($F(2, 48) = 9.95$, $p < .001$, $\eta^2 = .293$) as well as between Task, Region, and Hemisphere ($F(4, 96)$

= 3.14, p = .018, η^2 = .116), indicating larger P3 amplitudes during the combined *n*-back/nogo task at midline and right parietal electrode positions (all $p \leq .007$).

We found higher P3 latencies during nogo than during go trials ($F(1, 24) = 130.41$, $p < .001$, $\eta^2 = .845$). Further, latencies were increased in the combined *n*-back/nogo task compared to the single go/nogo task ($F(1, 24) = 84.79$, $p < .001$, $\eta^2 = .779$).

3.3.2 Comparisons Between Control and ADHD Group

3.3.2.1 Behavioral Data

As expected, group comparisons revealed that ADHD patients showed deficits in all behavioral measures during the combined *n*-back/nogo task. Working memory performance was reduced to 51.62% (controls: 73.83%, $t(57) = 4.29$, $p < .001$, $d = 1.16$), and response inhibition performance was reduced to 77.85% (controls: 87.44%, $t(49.4) = 2.74$, $p = .009$, $d = 0.69$). Moreover, patients showed more omission errors ($t(34.2) = -3.72$, $p = .001$, $d = 0.91$) as well as higher reaction times ($t(57) = -2.15$, $p = .036$, $d = 0.57$) and higher standard deviations of reaction times ($t(57) = -3.33$, $p = .002$, $d = 0.88$). Details of all comparisons are given in Table 4.

In ADHD patients, we found a significant correlation between working memory and response inhibition performance assessed with the combined *n*-back/nogo task ($r = .643$, $p < .001$). This was not associated with reported attention problems (CBCL, YSR) or attentional performance (d2, d2-R) (all $r \leq .296$, $p \geq .118$).

Table 4. Behavioral parameters in control and ADHD groups. Comparisons of behavioral data between control and ADHD group, mean ± standard deviation, *t* and *p*-values as well as effect sizes Cohens *d* are given.

	controls	ADHD	*t*	*p*	*d*
WM in %	73.83 ± 15.39	51.62 ± 22.22	$t(57.0) = 4.29$	< .001	1.16
RI in %	87.44 ± 8.35	77.85 ± 17.93	$t(49.4) = 2.74$	.009	0.69
omission errors in %	1.07 ± 1.25	7.89 ± 10.58	$t(34.2) = -3.72$	.001	0.91
reaction time in ms	722 ± 194	833 ± 197	$t(57.0) = -2.15$	.036	0.57
SD of reaction time in ms	252 ± 72	316 ± 73	$t(57.0) = -3.33$	.002	0.88

WM – working memory (performance), RI – response inhibition (performance)

3.3.2.2 ERP Data

n-back P3. In ADHD patients, diminished amplitudes of the *n*-back P3 component were found ($F(1, 55) = 4.44$, $p = .040$, $\eta^2 = .075$) but latency was not significantly different between the control and the ADHD group ($F(1, 55) = 0.28$, $p = .599$, $\eta^2 = .005$).

nogo N2. Amplitudes of the nogo N2 component did not differ between groups ($F(1, 54) = 0.95$, $p = .335$, $\eta^2 = .017$). However, ADHD patients showed delayed N2 latencies ($F(1, 54) = 6.34$, $p = .015$, $\eta^2 = .105$).

nogo P3. A main effect of Group was identified for the nogo P3 amplitude ($F(1, 54) = 11.60$, $p = .001$, $\eta^2 = .177$) indicating a reduced peak amplitude in the ADHD group. Moreover, an interaction between Group and Hemisphere was revealed ($F(2, 108) = 3.47$, $p = .035$, $\eta^2 = .060$). This indicated that controls showed largest P3 peaks at midline electrode positions (all $p \leq .001$), while in patients differences between midline and lateral electrodes were reduced but still significant (all $p \leq .020$). Further, in controls P3 peaks were larger at right compared to left electrode sites ($p = .050$) but this effect was missing in ADHD. The group analysis revealed no latency differences of the nogo P3 component ($F(1, 54) = 0.09$, $p = .761$, $\eta^2 = .002$).

ERP data are illustrated in Figure 9 and presented in Table 5 in full detail. The results of all ANOVAs are summarized in Supplementary Table S2.

3.4 Discussion

In the present study, we introduced the *n*-back/nogo paradigm that combines working memory and response inhibition aspects and hypothesized that its behavioral and ERP characteristics would be comparable to those of parallel single task versions. Contrary to our expectations, working memory performance was higher in the combined *n*-back/nogo task than in the single *n*-back task but still, both measures were highly correlated. We confirmed that response inhibition performance was similar between the combined *n*-back/nogo and the single go/nogo task version. Further, we found that reaction times and standard deviations of reaction times in the combined *n*-back/nogo task were comparable to those of the single *n*-back task but were higher than those of the single go/nogo task. As expected, the combined *n*-back/nogo paradigm demonstrated comparable ERP structures as single task versions for working memory and response inhibition task aspects. Still, we found larger

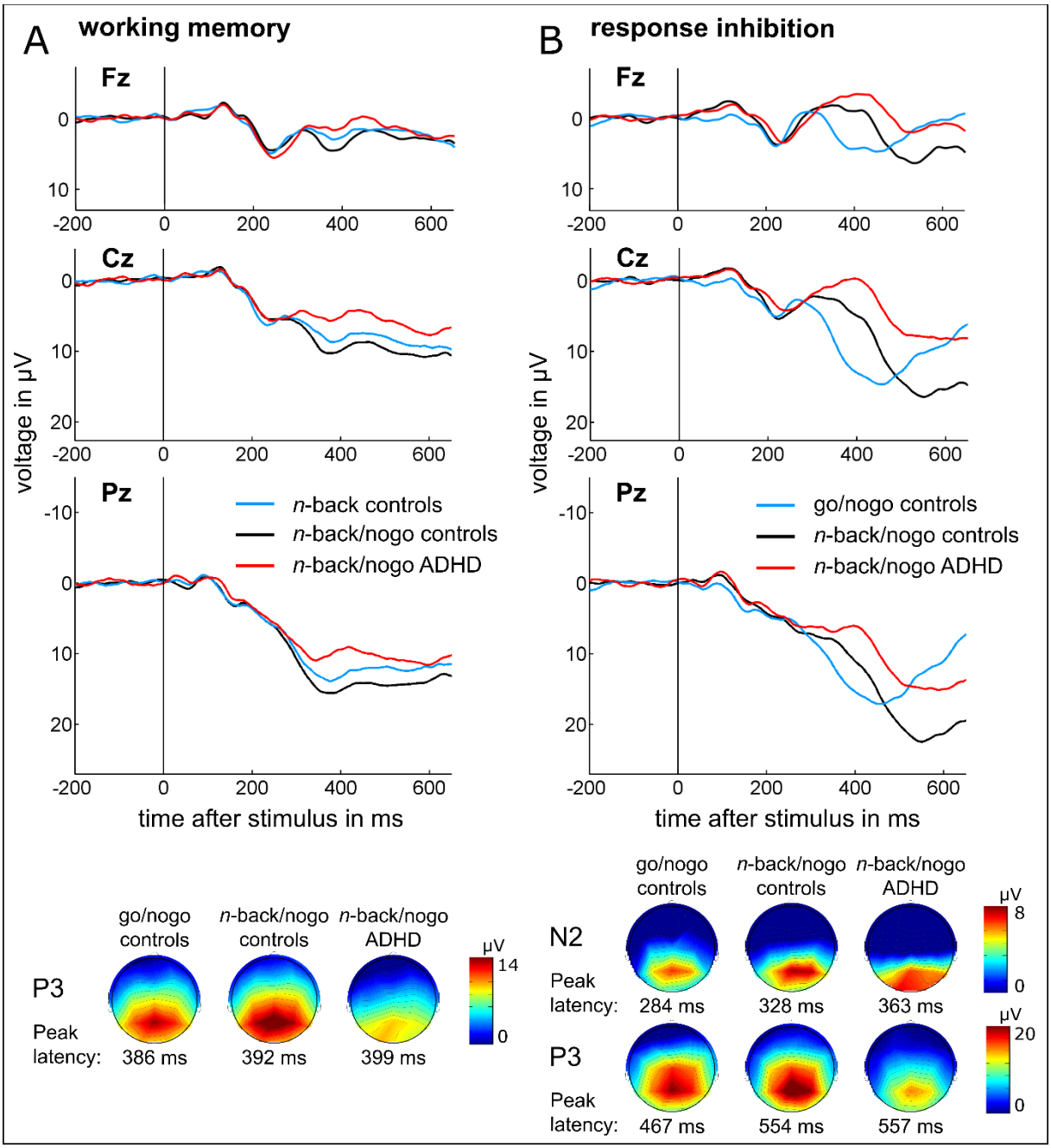

Figure 9. Averaged ERPs for single and combined task versions. Stimulus-locked, averaged ERP waveforms and topographical plots are illustrated for **(A)** *n*-back target trials of the working memory task and **(B)** nogo trials of the response inhibition task at electrode positions Fz, Cz, and Pz, topographical plots are displayed for peak latency of the respective condition and group at Pz for *n*-back and nogo P3, and at Cz for nogo N2.

Table 5. ERP data of control and ADHD groups for single and combined task versions. EEG peak amplitudes and latencies for single task versions and for the combined *n*-back/nogo task in controls and ADHD patients, mean ± standard deviation.

	amplitude in μV				latency in ms			
	controls			ADHD	controls			ADHD
	single task		*n*-back/nogo	*n*-back/nogo	single task		*n*-back/nogo	*n*-back/nogo
n-back P3	*non-target*	*target*	*target*	*target*	*non-target*	*target*	*target*	*target*
C3	5.07 ± 4.05	10.16 ± 5.16	10.26 ± 6.57	7.54 ± 5.46	406 ± 64	394 ± 66	388 ± 49	385 ± 62
Cz	5.83 ± 5.38	11.61 ± 5.92	12.31 ± 6.52	8.84 ± 5.52	417 ± 70	382 ± 58	384 ± 52	375 ± 63
C4	6.17 ± 5.27	10.76 ± 6.09	11.48 ± 5.27	9.31 ± 5.19	394 ± 74	384 ± 46	383 ± 46	377 ± 66
P3	8.55 ± 4.78	14.32 ± 6.41	15.36 ± 7.17	12.05 ± 6.61	360 ± 61	399 ± 58	390 ± 53	384 ± 58
Pz	10.80 ± 5.23	16.10 ± 6.84	17.53 ± 7.33	13.79 ± 5.71	382 ± 66	386 ± 53	392 ± 51	399 ± 65
P4	10.70 ± 4.81	15.02 ± 6.18	15.59 ± 6.17	12.77 ± 5.81	371 ± 65	386 ± 50	397 ± 58	377 ± 61
nogo N2	*go*	*nogo*	*nogo*	*nogo*	*go*	*nogo*	*nogo*	*nogo*
F3	-1.24 ± 3.95	-3.77 ± 5.67	-4.53 ± 4.92	-4.87 ± 6.05	284 ± 33	303 ± 35	374 ± 58	396 ± 54
Fz	-1.68 ± 4.32	-4.44 ± 5.89	-5.19 ± 5.23	-6.18 ± 6.83	288 ± 29	298 ± 35	358 ± 52	381 ± 58
F4	-0.39 ± 4.34	-2.52 ± 5.11	-4.51 ± 5.79	-5.88 ± 7.26	274 ± 33	289 ± 36	358 ± 51	383 ± 52
C3	2.59 ± 4.01	-0.40 ± 3.79	-0.81 ± 5.25	-2.40 ± 4.98	275 ± 36	296 ± 38	350 ± 57	381 ± 49
Cz	2.56 ± 6.31	-0.28 ± 4.93	-0.67 ± 5.69	-2.98 ± 5.87	284 ± 33	284 ± 33	328 ± 55	363 ± 55
C4	2.73 ± 4.73	-0.72 ± 4.56	-1.11 ± 5.76	-2.95 ± 5.91	269 ± 40	288 ± 37	334 ± 57	368 ± 58
nogo P3	*go*	*nogo*	*nogo*	*nogo*	*go*	*nogo*	*nogo*	*nogo*
F3	2.26 ± 4.42	7.29 ± 6.09	7.72 ± 5.70	4.42 ± 5.42	317 ± 63	438 ± 68	539 ± 52	541 ± 56
Fz	2.07 ± 4.28	8.57 ± 7.49	9.13 ± 6.70	4.19 ± 6.02	328 ± 62	443 ± 57	535 ± 49	542 ± 39
F4	4.07 ± 4.35	8.34 ± 6.81	7.99 ± 6.18	3.93 ± 6.48	317 ± 58	443 ± 61	531 ± 49	537 ± 53
C3	6.48 ± 4.70	13.20 ± 8.14	14.40 ± 7.51	8.57 ± 5.73	329 ± 54	450 ± 61	556 ± 51	557 ± 46
Cz	6.66 ± 5.44	17.76 ± 10.11	18.81 ± 8.82	10.94 ± 7.23	315 ± 61	467 ± 57	551 ± 49	550 ± 49
C4	7.38 ± 5.49	15.13 ± 8.79	16.20 ± 9.01	9.66 ± 6.33	324 ± 54	474 ± 58	553 ± 46	553 ± 46
P3	11.23 ± 5.44	15.72 ± 7.64	17.72 ± 7.40	14.00 ± 6.61	322 ± 44	461 ± 53	560 ± 46	566 ± 48
Pz	11.86 ± 6.00	19.70 ± 8.68	24.61 ± 9.45	17.70 ± 7.60	327 ± 45	467 ± 55	554 ± 46	557 ± 47
P4	11.14 ± 5.16	17.53 ± 7.58	21.42 ± 8.83	15.51 ± 7.46	316 ± 37	461 ± 55	546 ± 53	548 ± 52

nogo P3 amplitudes as well as increased nogo N2 and nogo P3 latencies for the combined task. The application of the combined paradigm in ADHD patients revealed the expected working memory and response inhibition deficits, increased omission errors, reaction times, and standard deviations of reaction time, as well as diminished *n*-back P3 and nogo P3 amplitudes. However, we found no reduction of the nogo N2 amplitude in patients.

In healthy individuals, working memory performance was found to be better during the combined *n*-back/nogo task compared to the single *n*-back task. Despite this difference in performance outcome, we argue that the combined task delivers a valid measurement of working memory, because working memory performance was highly correlated between combined and single task versions. Therefore, the improved performance outcome seems to result from a reduced difficulty of the combined paradigm. This is remarkable, as previous studies found that working memory performance decreased when inhibitory task aspects were added (Alderson et al., 2017). The performance decline that was found in prior studies resulted probably from the fact that participants were required to keep more rules in mind in order to meet task demands. However, in the present study the combination of paradigms caused a decrease in task difficulty of the working memory aspect, which we assume resulted from the introduction of nogo trials. The nogo stimuli itself were not part of the *n*-back sequence. Further, after each nogo trial a new sequence of *n*-back letters started and hence, the first two letters only needed to be encoded but not matched to previous letters (Chen et al., 2008). Thus, working memory load was reduced in this task, which could have caused the improved task performance. Generally, the 2-back paradigm is a challenging task, even for healthy individuals, indicated by a performance rate of only 56% in our study for the single task version. In ADHD patients, worse working memory performance would be expected, as in Alderson et al. (2017) who reported values as low as 27% in children with ADHD. Such low performance could cause a dramatic drop in motivation and therefore, compromise compliance if participants perceive the task as too difficult. Furthermore, we showed reduced omission errors during the combined *n*-back/nogo task compared to the single *n*-back task version, further suggesting that the difficulty during the combined task version was appropriate to induce high levels of sustained attention together with stable task performance (Thomson et al., 2015). A high number of accurate trials is needed for data analysis in neurophysiological and imaging studies. Accordingly, reduced difficulty of the combined *n*-back/nogo task should be advantageous for the investigation of populations with working memory impairments, as ADHD patients. Moreover, applications in investigations of autism spectrum disorder or young children are conceivable.

In accordance with our hypothesis, we found no difference in response inhibition performance between the single go/nogo and the combined *n*-back/nogo task. Moreover, response inhibition assessment was correlated between single and combined task versions, albeit only after the exclusion of two outliers. Although these results require a careful interpretation, we conclude that the combined *n*-back/nogo task is suitable to investigate response inhibition. Still, the analysis suggests that significant portions of variance between task versions remain unexplained. We speculate that increased reaction times in the combined *n*-back/nogo task compared to the single go/nogo task version accounted for parts of this variance. It is conceivable that slowed responses were associated with changes in stimulus processing or task strategies. For example, such effects were demonstrated in the context of a negative priming task (Mayr et al., 2006). However, it remains to be clarified how the dual-task requirements of the combined paradigm accounted for variability between task versions.

The investigation of discriminant validity in healthy participants demonstrated no correlation between measures of working memory and response inhibition within the combined *n*-back/nogo task. This matches the findings of single *n*-back and go/nogo tasks, which showed no correlation between working memory and response inhibition as well, although only after the exclusion of outliers. Thus, we assume that the combined *n*-back/nogo task was suitable to measure distinct cognitive functions instead of a general task factor.

While response inhibition performance was mostly constant between task versions, we demonstrated slowed reaction times during the combined task compared to the single go/nogo task. This was reflected by significant differences in the IES. We think the reason is that reactions during the single go/nogo task required only one-digit button presses whereas all reactions during the combined *n*-back/nogo task demanded working memory decisions. In addition, complex task demands in the combined *n*-back/nogo task have probably resulted in less automated prepotent response tendencies, leading to slower reaction times. For these reasons, it must be considered that reaction times of the combined *n*-back/nogo task are rather equivalent to such of an *n*-back than of a go/nogo task. This conclusion is further supported by the exploratory investigation of reaction time distributions that depict more similarity to the single *n*-back than to the single go/nogo task. Still, reaction time measures of the combined *n*-back/nogo task were correlated not only to those of the single *n*-back task as but also to those of the single go/nogo task. Thus, although the absolute values

differed between task versions, the relation between participants was preserved. This implies that reaction time comparisons, for example between groups of individuals or conditions, should result in the same conclusions, whether conducted with the combined *n*-back/nogo task or with a single go/nogo task, only differing in absolute values. However, this assumption needs to be validated in further investigations.

The combined *n*-back/nogo task evoked an *n*-back P3 component with similar amplitude and latency as the single *n*-back task, indicating analog working memory processing between task versions. In particular, comparability of amplitude size suggests that allocation of cognitive resources to working memory processes was similar in both tasks and therefore cognitive effort was similar between task versions (Dong et al., 2015). We stated earlier that difficulty of the working memory task aspect was lower for the combined than for the single task version. We assume that during the easier combined task version working memory processing was already at its full capacity. Hence, higher task difficulty during the single *n*-back task resulted in a ceiling effect, because no increase of cognitive engagement was possible in order to meet task demands. Instead, the performance dropped. Once again, this suggests that difficulty of the combined *n*-back/nogo task was adequate for our sample as it produced maximum cognitive engagement at a high level of performance.

The nogo N2 component that was elicited during the combined *n*-back/nogo task, had a similar peak amplitude as during the single go/nogo task, indicating similar effectiveness of conflict monitoring (Donkers & Van Boxtel, 2004; Jonkman, 2006; Smith et al., 2008). However, the nogo P3 component evoked during the combined *n*-back/nogo task had a larger peak amplitude compared to the single task version at midline and right parietal electrode positions. Topographic plots demonstrated that the nogo P3 showed a parietal distribution that was more pronounced in the right hemisphere, which corresponds to the area where differences between task versions were detected. Larger peaks of the nogo P3 have been associated with better response inhibition (Donkers & Van Boxtel, 2004; Jonkman, 2006; Smith et al., 2008). Accordingly, we assume that more resources were allocated to this process during the combined *n*-back/nogo task. We hypothesize that differences in amplitude size were associated with increased reaction times in the combined *n*-back/nogo task, because it was demonstrated that ERP responses can become more pronounced with prolonged reaction times (Mayr et al., 2006). Thus, we assume that the slowed responding allowed for the allocation of more resources to the process of response inhibition.

Increased latencies of nogo N2 and P3 components were found during the combined *n*-back/nogo task. Component latencies indicate the speed of stimulus evaluation and thus, increase with growing task-processing demands (Polich, 2007; Gajewski & Falkenstein, 2013). We therefore, assume that increased latencies of nogo related components reflect higher demands for stimulus processing linked to less automated responding during the combined task version caused by the working memory aspect. As component latencies are associated with response time (Polich, 2007), this ERP result matches behavioral findings of higher reaction times during the combined *n*-back/nogo task.

ADHD patients demonstrated impaired performance in all behavioral measures using the combined *n*-back/nogo paradigm. We showed impaired working memory and response inhibition performance in patients, as it was expected from prior research with *n*-back (Kasper et al., 2012; Myatchin et al., 2012) and go/nogo tasks (Wodka et al., 2007; Neely et al., 2017). In contrast to the healthy control group, there was a high correlation between working memory and response inhibition performance in patients, which implies that both cognitive functions were not assessed independently with the combined *n*-back/nogo task. This could not be explained with a mediation by ADHD symptom severity as we found no association with diagnostic information. However, a relation between executive deficits in working memory and response inhibition has been demonstrated in ADHD (Clark et al., 2007; Schecklmann et al., 2013), and seems to be associated specifically to an underactivation of right frontal brain regions (Clark et al., 2007). Thus, we hypothesize that the correlation between working memory and response inhibition impairments demonstrated in the present study, could reflect a general underlying deficit in executive functioning in ADHD. Still, as ADHD patients did not solve single task versions, this topic could not be explored further and our conclusions are consequently limited. As it was expected, ADHD patients showed increased numbers of omission errors, which has been associated with inattentive and hyperactive/impulsive symptom severity (Epstein et al., 2003; Bezdjian et al., 2009). Moreover, ADHD related increases in reaction times and in standard deviations of reaction time were found using the combined *n*-back/nogo task (Salum et al., 2019). We thus conclude that the introduced *n*-back/nogo task was suitable to assess executive deficits in ADHD.

Neurophysiological results from ADHD patients further reinforced this conclusion. Using the combined *n*-back/nogo task, we found diminished *n*-back P3 amplitudes in patients, as it was expected from prior research. This finding reflects ADHD related working memory deficits on a neurophysiological level (Barry et al., 2003; Keage et al., 2008; Szuromi et al.,

2011; Johnstone et al., 2013). Unexpectedly, amplitudes of the nogo N2 component did not differ between patients and controls. However, previous research showed heterogeneous results for this component (Fallgatter et al., 2004; Shahaf et al., 2015). In addition, a recent meta-analysis by Kaiser et al. (2020) could not confirm amplitude reductions for this component and concluded that reduced amplitudes of the nogo N2 could be characteristic for a subgroup of the ADHD population. Indeed, pronounced N2 reductions were found particularly in younger ADHD patients of about ten years (Johnstone et al., 2013). Thus, it is possible that we missed this effect because our sample was older. Therefore, it remains to be clarified, if the subpopulations of patients with reduced nogo N2 components would show this reduction also with the combined *n*-back/nogo task. Again, the nogo P3 component showed the expected amplitude reduction in patients reflecting ADHD related response inhibition deficits (Smith et al., 2008; Fisher et al., 2011). Regarding latency alterations of the investigated components, prior research has been inconclusive in ADHD (Fallgatter et al., 2004; Smith et al., 2008; Johnstone et al., 2009; Fisher et al., 2011). We found increased latencies of the nogo N2 in patients, which could be related to the behavioral finding of slowed reaction times (Gajewski & Falkenstein, 2013).

Two characteristics of the ADHD sample investigated in the present study are of importance for the interpretation of results, namely age and comorbidities. ADHD patients in this study had a mean age of 13 years. As cognitive impairments in ADHD and neurophysiologic correlates vary with age (Marx et al., 2010; Kaiser et al., 2020) it is possible that the sensitivity of the introduced paradigm for cognitive deficits depends on the investigated age group. Further, in this study patients with comorbid disorders were excluded, because they differ from patients with ADHD only, in cognitive and ERP profiles (Banaschewski et al., 2003; Noordermeer et al., 2015). Although this study design was favorable to reduce variability in the ADHD sample, comorbid disorders as oppositional defiant disorder and conduct disorder occur in up to half of ADHD patients (DSM-5, American Psychiatric Association, 2013). Thus, future experiments remain to demonstrate applicability of the introduced *n*-back/nogo task in ADHD samples with different characteristics.

As a limitation, single task versions of *n*-back and go/nogo paradigms were applied only in healthy participants, which allows no direct conclusions on differences between task versions in ADHD and which should be addressed in future research. Further, ADHD data were pooled from the context of two different studies. However, we expect that this procedure increased variability in the data, hampering to demonstrate the expected effects.

As the results were still in line with our hypotheses, this indicates that the effects are robust under different experimental conditions. A strength of this experiment was the investigation of ADHD patients without comorbidities because this excludes confounded effects from other disorders than ADHD (Banaschewski et al., 2003).

3.4.1 Conclusions

In the present ERP study, we introduced the combined *n*-back/nogo paradigm and demonstrated its effectiveness for the assessment of working memory and response inhibition deficits in children and adolescents with ADHD on a behavioral and neurophysiological level. As both executive functions can be assessed during the same task, this paradigm provides an economical alternative to single task versions. Thus, we emphasize its relevance for research in ADHD patients and other populations who require short experimental procedures, for example in the context of developmental research with younger children and elderly people, or in clinical populations with developmental disorders. Conceivable are further applications in settings where working memory and response inhibition brain areas should be activated simultaneously, for instance in cognitive trainings or during non-invasive brain stimulation.

4 Experiment 2: Comparison Between Conventional and HD-tDCS of the Right IFG in Children and Adolescents with ADHD

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4.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) has a childhood prevalence of 7.2% and is therefore one of the most common psychiatric disorders in school age children (Thomas et al., 2015). It is characterized by age inappropriate levels of inattention, impulsivity, and hyperactivity (DSM-5, American Psychiatric Association, 2013) leading to functional and psychosocial impairments that affect school performance as well as family life (Able et al., 2007). Working memory deficits belong to the most prominent cognitive ADHD symptoms and are found in up to 98% of patients (Kasper et al., 2012). They are a better predictor than inattention or hyperactive/impulsive symptoms for academic dysfunction, grade retention, placement in special classes, and poor reading and math performance (Fried et al., 2016; Simone et al., 2018).

Working memory is defined as the temporary storage for maintaining and manipulating information. It is often investigation with the *n*-back paradigm, in which subjects have to indicate if each stimulus of a sequence matches the stimulus presented a specified number (*n*) of trials previously. ADHD patients show diminished *n*-back performance associated with reduced amplitudes of the N2 and P3 (Barry et al., 2003; Keage et al., 2008; Johnstone et al., 2013). The N2 peaks over centro-parietal sites (Stroux et al., 2016) and represents a match/mismatch process (Daffner et al., 2011). P3 peaks over parietal sites and has been associated with stimulus classification, updating of mental representations in working memory and the decision how to respond (Helenius et al., 2011). Working memory is modulated by a fronto-parietal network (Darki & Klingberg, 2015) including the inferior frontal gyrus (IFG). This region receives information from posterior association areas and organizes information held in working memory (D'esposito et al., 2000). IFG activity during

the *n*-back task is mainly bilateral (Miró-Padilla et al., 2018). But in ADHD patients, particularly the right IFG shows structural and functional changes such as reduced grey matter volume (Depue et al., 2010) and decreased activity during working memory tasks (Schweitzer et al., 2000; Valera et al., 2010).

Response inhibition is a cognitive function important to consider when understanding working memory deficits in ADHD. On a behavioral level this functions shows moderate to high correlations with working memory (Alderson et al., 2017). This is reflected on the functional level, where the right IFG was identified as a common area being active during working memory and response inhibition (McNab et al., 2008). A study from Clark et al. (2007) indicates that ADHD related deficits in both cognitive functions may stem from a common pathologic process that is driven by the underactivation of the right IFG. They showed that working memory and response inhibition performance are associated with each other in ADHD patients and in patients with right frontal lesions but not in patients with left frontal lesions. Because both functions seem to be closely intertwined, Johnstone et al. (2010) showed effectiveness for a cognitive ADHD training that combined working memory and response inhibition aspects. Accordingly, we applied a combination of both task demands for the improvement of working memory in ADHD.

Transcranial direct current stimulation (tDCS) is a method to modulate cortical excitability, which has been suggested to be of therapeutic use in ADHD (Castellanos & Proal, 2012; Muszkat et al., 2016). As a non-pharmaceutical alternative it produces less side-effects (Lee et al., 2011) and can have long-lasting effects when applied repeatedly (Cohen Kadosh et al., 2010). An important factor for the success of tDCS is the degree of activation in the target area. For prefrontal tDCS during the *n*-back task it was found that online stimulation and a difficult task (3-back task) lead to greatest performance improvements (Martin et al., 2014; Gill et al., 2015). It seems that best effects are achieved when the target brain network is in an activated or pre-activated state so that activation within the network is reinforced by the stimulation (Gill et al., 2015). In the present study design these effects were considered as stimulation was performed online. Moreover, the working memory task was enriched by inhibitory task demands to maximize involvement of the right IFG. This approach was considered most suitable for ADHD patients since increasing the difficulty of the *n*-back task could have resulted in reduced motivation or cognitive fatigue.

Studies that applied tDCS in ADHD patients have already shown beneficial effects on interference control (Breitling et al., 2016), functional connectivity (Cosmo et al., 2015b;

Sotnikova et al., 2017), different aspects of executive functions (Soltaninejad et al., 2015; Bandeira et al., 2016; Nejati et al., 2017), and general ADHD symptoms (Cachoeira et al., 2017; Soff et al., 2017). Further, oscillatory tDCS during sleep increased behavioral inhibition (Munz et al., 2015) and declarative memory (Prehn-Kristensen et al., 2014). However, none of these studies directly analyzed the underlying electrophysiology and only one focused on the stimulation of the right IFG.

All prior studies used a bipolar electrode configuration mostly with rectangular pad electrodes that had a size of 7 x 5 cm. This conventional tDCS montage is discussed critically because it induces diffuse distributions of current flow in widespread brain areas, where the largest current density might not occur directly under the electrodes (Datta et al., 2009a; Faria et al., 2011). An alternative is high definition tDCS (HD-tDCS). For HD-tDCS small disc electrodes are placed in a 4 x 1 configuration with the stimulation electrode being surrounded by four reference electrodes in a ring-like pattern (Datta et al., 2009a). In this montage current flow is restricted to the area under the electrodes, which increases precision. This ensures high current densities mainly in the target area and the risk of side effects is reduced as stimulation of non-target brain areas is kept to a minimum.

The aim of this study was to investigate whether effects of HD-tDCS and of conventional tDCS are superior to the effects of sham stimulation on working memory performance in ADHD patients. The present study is the first to apply HD-tDCS to ADHD patients and one of the first to use this method in children and adolescents. We used a within subjects design, where, in a first step, every patient underwent a training session of the cognitive task to reduce learning effects in later sessions. In the following sessions, anodal stimulation was applied to the right IFG using conventional, HD, and sham tDCS. Patients performed a 2-back task enriched with response inhibition requirements during stimulation. Current flow simulations of HD-tDCS were used to place electrodes. For conventional tDCS a bipolar setting of pad electrodes was used with the anode placed over the target area, and this montage was computer-simulated to assess the current density. EEG was recorded subsequent to tDCS, while patients still performed the cognitive task. Additionally, baseline data were assessed in a healthy control group in order to evaluate performance and neurophysiological parameters in the ADHD group. We expected that in verum tDCS conditions working memory performance would improve and that amplitudes of N2 and P3 would increase. In tDCS, as in most treatments, interindividual variability in response is high, with less than 50% responders being not unusual (Lopez-Alonso et al., 2014).

Therefore, we investigated whether individual characteristics as inattentive and hyperactive/impulsive symptom load predicted responsiveness to stimulation (Fins et al., 2017).

4.2 Methods

4.2.1 Participants

30 children and adolescents aged 10 to 16 years participated in the study. Patients were recruited via the Department of Child and Adolescent Psychiatry and control participants through advertisements in the local newspaper. All participants and their parents were interviewed using the German Adaption (Delmo et al., 2000) of the K-SADS-PL based on DSM-5 criteria (Kaufmann et al., 1997). Fifteen participants met the diagnostic criteria of ADHD. Standardized measures of intelligence (CFT 20-R; Weiss, 2008), concentration performance (d2; Brickenkamp, 2002), and handedness (Edinburgh Handedness Inventory; Oldfield, 1971) were used. In the patient group, participants with an IQ below 80 and over 130 or with psychiatric disorders others than oppositional defiant disorder or conduct disorder were excluded. Patients that were currently taking ADHD medication refrained at least 24 h before each session. Participants of the healthy control group reported no neurological or psychiatric disorders. As one ADHD patient was excluded from all data analyses, sample characteristics in Table 6 are displayed for the remaining participants. Four more patients were excluded from EEG analysis only.

The study was approved by the local ethics committee of the University of Magdeburg and followed the ethical standards of the Helsinki declaration. All participants and their parents gave written informed assent/consent before participating and none of them reported contraindications to receiving tDCS. Participants obtained a voucher in each session (15 €) for a local shopping center.

Table 6. Sample description of experiment 2. Sample characteristics, *M* and *SD*.

	ADHD	controls	*t* (*p*)
n	14	15	-
age (years)	13.3 (1.9)	13.3 (1.8)	0.13 (.896)
gender	2 females	2 females	-
combined subtype ADHD	10	-	-
primarily inattentive subtype ADHD	4	-	-

oppositional defiant disorder	3	-	-
current medication	5	-	-
Methylphenidate	4	-	-
Lisdexamfetamine	1	-	-
IQ	100.2 (11.2)	104.3 (12.0)	-0.94 (.356)
number of ADHD symptoms (K-SADS-Pl, parent rating present)	12.6 (3.7)	1.0 (2.1)	10.38 (< .001)

4.2.2 Task and Procedure

An *n*-back paradigm (*n* = 2) was used where a series of capital letters (A, D, E, H, I, N, R, S, T, U) was presented (Figure 10A). Target trials (21%) had to be identified by button press (right target, left non-target). This task was enriched by stop trials (17%) where the stimulus was an X and participants should not press any button. Afterwards, a new series of letters started. Before the beginning of the task a practice session was conducted for 1.25 min. Participants were instructed to react as fast and as accurately as possible. Stimuli were presented with the software Presentation (version 18.0, www.neurobs.com) and had a visual angle of 0.86° (height). In a pilot experiment, it was validated that the inhibitory task demands did not compromise the ERP component structure (see Supplementary Table S3).

ADHD patients underwent four sessions. In the first session they trained the task for six runs (each 4.5 minutes, 110 trials) to reduce learning effects in the following stimulation sessions. Three tDCS conditions, conventional, HD, and sham, were conducted in the following sessions in a pseudo-randomized, double blind order, separated by at least six days. After EEG and tDCS electrode placement the experiment started with 5 min of tDCS followed by another 15 min of stimulation while the task was applied (3 runs). Afterwards, the EEG recording started and the task was conducted for another 15 min. At the end of each session participants reported tDCS related skin sensations on a 5-point Likert-scale and at the end of the last session a questionnaire about tDCS side effects was filled in. Each session had a duration of about 1.5 h.

The healthy control group participated in only one session, in which the task was conducted for 15 min while recording EEG. Because of deviating procedures between patients and controls, data of both groups are not entirely comparable. Still, behavioral and neurophysiological data of healthy controls serve as reference and should constitute the margin of improvement that can potentially be achieved in ADHD patients.

4.2.3 Transcranial Direct Current Stimulation

TDCS was conducted with a battery driven DC stimulator (neuroConn, Munich, Germany). For conventional tDCS 7 x 5 cm rubber electrodes were covered with saline soaked sponges (NaCl 0.9%). The anode was placed centrally over EEG position F8, which corresponds to the right IFG (Koessler et al., 2009). The cathode was placed over the contralateral supra-orbital area. For HD-tDCS a 4 x 1 montage (Kessler et al., 2013) of small circular electrodes (diameter 1 cm) was used with the anode placed centrally. Figure 10B shows the estimated current magnitude for conventional and HD-tDCS. For details of current flow simulations of both montages and of electrode placement for HD-tDCS see 2.2.2 Current Flow Simulations. Sham tDCS was randomly applied with conventional or HD electrode setting. Current intensities were set to 1 mA for conventional and 0.5 mA for HD-tDCS to adjust for higher concentrations of current density during focal stimulation. Three patients were very sensitive to the stimulation so that current intensities were reduced by 50%. In two patients current intensities were reduced during all tDCS sessions, in one patient only current intensity of conventional tDCS was reduced. Stimulation was applied for 20 min with a 30 s ramp up and down.

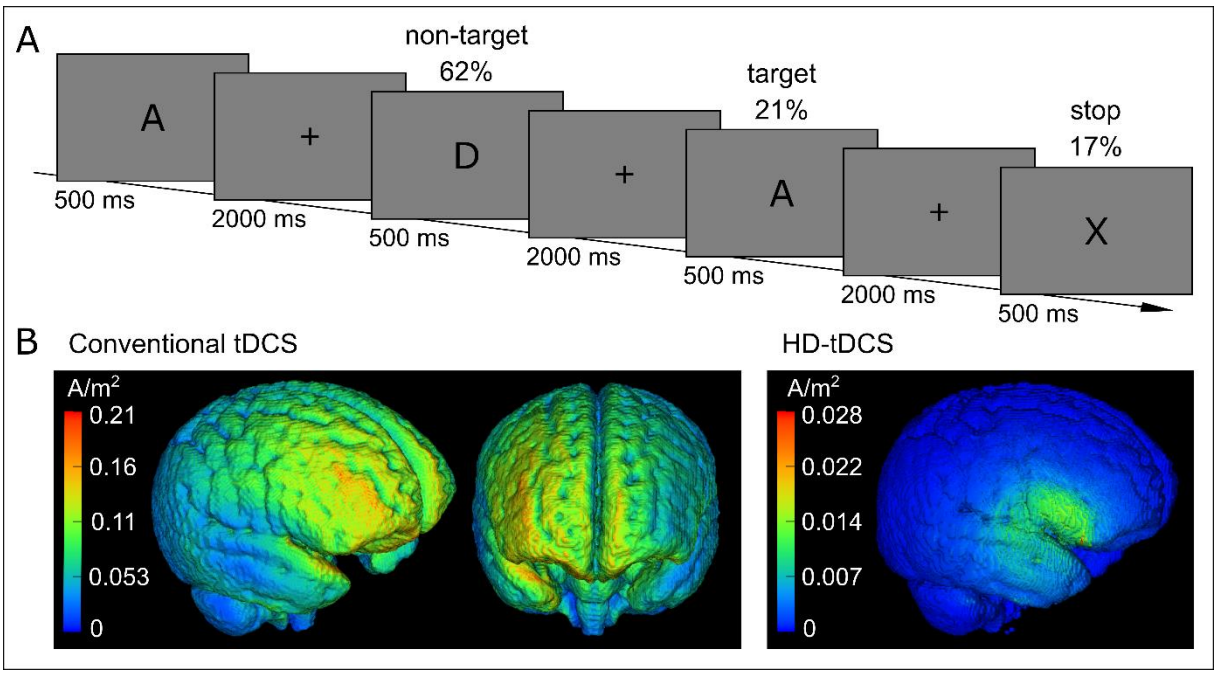

Figure 10. Cognitive task in experiment 2 and current flow simulations. (A) Schematic illustration of the modified *n*-back task, **(B)** Simulations of current flow for conventional and HD-tDCS.

4.2.4 EEG Recording and Analysis

EEG was recorded using a SynAmps amplifier (Neuroscan, Sterling, VA, USA). Data from 21 channels were measured according to the International 10-20 EEG system with Ag/AgCl-electrodes placed in a cap (Easycap GmbH, Herrsching, Germany) at positions Fp1, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC6, FT10, C3, Cz, C4, P7, P3, Pz, P4, P8, O1, and O2. Bipolar channels with electrodes placed at the outer canthi of both eyes and at sub- and supra-orbital positions were used to record electrooculograms. Signals were referenced to linked mastoid electrodes and ground electrode was at AFz. The sampling rate was 500 Hz. Data were filtered with an analog filter between 0.05 and 70 Hz and with a notch filter at 50 Hz. Impedances were kept below 15 kΩ.

EEG data were analyzed with EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) in the MATLAB environment (version R2013a, The MathWorks, Inc., Nattick, MA, USA). Data were filtered digitally with a 30 Hz low pass and split into epochs of 2000 ms. Epochs were baseline corrected relative to a time window of -200 to 0 ms. Due to extensive eye and facial movement only parietal electrodes were used for further processing. Artifact detection was applied in the time window between 0 to 700 ms. Trials with artifacts that exceeded 100 μV were removed automatically and further artifactual trials were removed by a trained person. Five ADHD patients were excluded from the EEG analysis because of low remaining trial count (less than 15 trials). Thus, a mean number of 34 *n*-back target trials was analyzed in ADHD patients and of 50 trials in healthy controls ($t(23) = -4.23$, $p < .001$). A right parietal region of interest (ROI: P4, P8) was chosen on the basis of topographic distribution of components (see Figure 11). Mean amplitudes and latencies were defined with the ERPLAB measurement tool for N2 (150-250 ms) and P3 (300-450 ms).

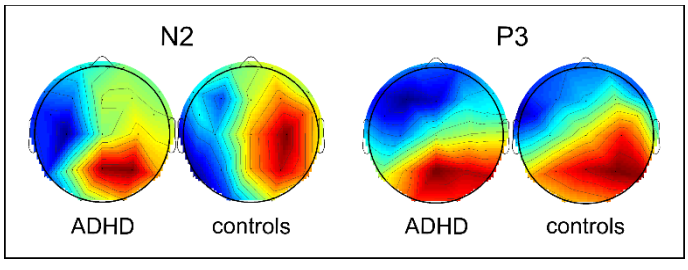

Figure 11. Topographic distribution of ERP components. Topographic plots show a right lateralization of N2 (at 220 ms) and P3 (at 320 ms) components in ADHD patients (sham session) and controls during *n*-back target trials.

4.2.5 Statistics

Working memory performance was calculated as the corrected hit rate (target hits - false alarms). One patient was excluded from behavioral data analysis because working memory performance (mean over all experimental sessions) was below two standard deviations of the group mean. Reaction times were calculated from correct trials with reaction times of 100 ms or more. Performance measures from online and offline tDCS were pooled as no interaction with tDCS condition was found (see Supplementary Table S3). Statistical evaluation was carried out in SPSS (version 24.0, IBM Corp., Armonk, NY, USA). To compare ADHD patients and healthy controls independent *t*-tests were performed. If Levene's test for equality of variances was significant, *t*-tests with a Satterthwaite approximation for the degrees of freedom were reported. For performance measures (working memory performance, misses, reaction times, standard deviation of reaction times) patients' first sessions and for ERP measures (amplitudes, latencies) patients' sham sessions were used. We point out that acquisition and trial number of ERP data in controls are not entirely comparable to ADHD patients. However, these data were used as a reference for the interpretation of ERPs in ADHD patients. ANOVAs were conducted with the factor tDCS condition (conventional vs. HD vs. sham) for performance and ERP measures to investigate effects of tDCS. When necessary, results were Greenhouse Geisser corrected. Subsequently, patients were categorized into responders and non-responders. The difference between working memory performance in verum and sham session was defined as the tDCS effect and served as an indicator for this classification. Patients with a positive difference were defined as responders, all others as non-responders. Responding rates during conventional and HD-tDCS were compared using McNemar's test for repeated measures. Finally, a regression analysis of the tDCS effect on working memory performance was calculated from the factors "number of inattentive symptoms" and "number of hyperactive/impulsive symptoms" assessed with the K-SADS-PL as well as from the factors "IQ" and "age" using the method forward.

4.3 Results

4.3.1 Behavioral Data

ADHD patients showed impaired working memory performance compared to healthy controls ($t(27) = -2.67$, $p = .013$) and responded less frequently (misses: $t(23) = 2.26$, $p = .034$). Table 7 displays the task performance.

There was no general effect of conventional or HD-tDCS on working memory performance ($F(2, 26) = 0.57$, $p = .570$) or on other task performance measures. This might be due to high variability in responsivity to tDCS between patients. On a descriptive level, variability (Figure 12) showed differences between both tDCS montages with the responder rate being higher for HD-tDCS (50% responders) than for conventional tDCS (36% responders) ($p = .50$). Thereby, all patients who responded to conventional tDCS also responded to HD-tDCS but not vice versa.

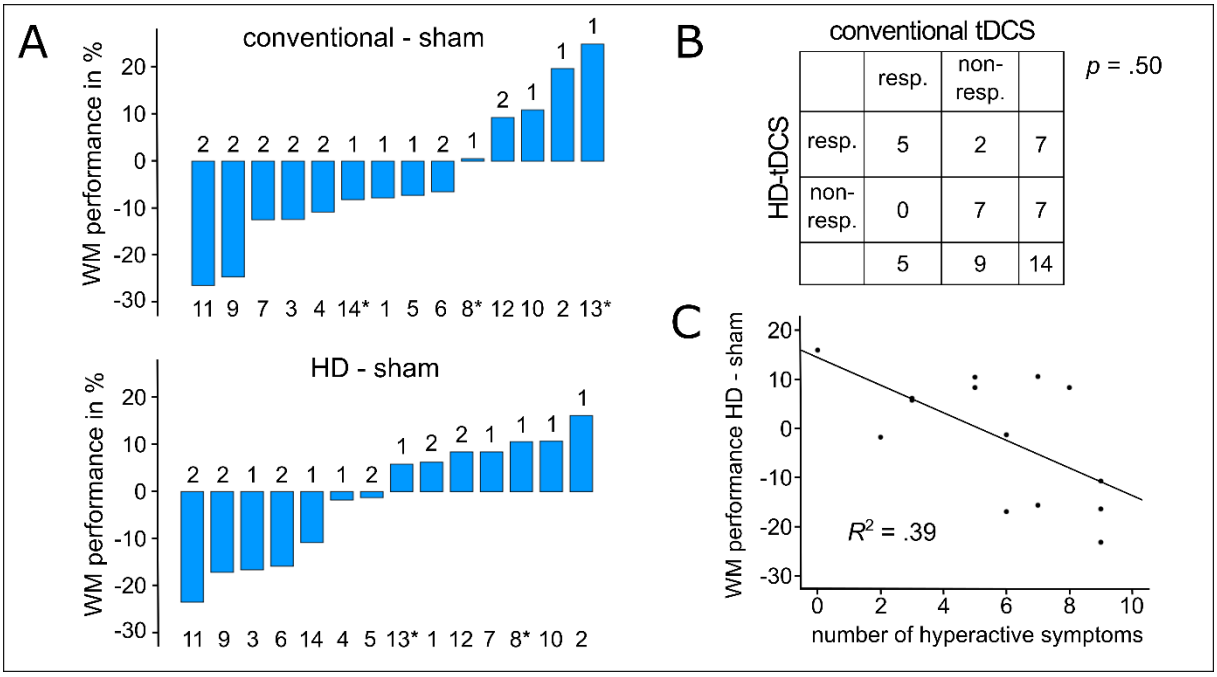

Figure 12. Interindividual variability in the response to tDCS. (A) Individual changes of working memory performance (WM) in response to conventional and HD-tDCS, positive values represent performance increase in tDCS conditions, numbers over the bars indicate if the verum tDCS condition was first or second to sham condition, numbers under the bars indicate individual patients with * specifying patients stimulated with reduced current intensities, **(B)** Number of patients that responded to stimulation for different montages, **(C)** Association between number of hyperactive ADHD symptoms and HD-tDCS induced working memory improvement.

Table 7. Behavioral results for conventional and HD-tDCS. *M* and *SD* of task performance measures in ADHD patients and controls, results of comparisons between ADHD patients (first training session) vs. controls, and within tDCS conditions (conventional vs. HD vs. sham).

	ADHD	controls	*d*	*t*	*p*	ADHD patients			η_p^2	*F*	*p*
	1st session					conventional	HD	sham			
WM[1]	58.7% (19.0%)	74.7% (12.9%)	-.985	-2.67	.013	54.3% (16.4%)	56.5% (18.2%)	57.9% (13.5%)	.042	0.57	.570
misses	2.7% (1.9%)	1.3% (1.4%)	.387	2.26	.034	3.4% (3.9%)	4.8% (4.4%)	5.8% (8.4%)	.051	0.69	.510
RT	829 ms (209 ms)	710 ms (195 ms)	.282	1.60	.122	787 ms (214 ms)	817 ms (180 ms)	785 ms (192 ms)	.100	1.44	.256
SD of RT	280 ms (79 ms)	252 ms (81 ms)	.172	0.96	.347	266 ms (78 ms)	281 ms (82 ms)	275 ms (68 ms)	.093	1.33	.282

[1] *WM – working memory*

Regression analyses were used to investigate if the number of inattentive or hyper-active/impulsive ADHD symptoms as well as IQ and age were predictors of tDCS effects. We found that for HD-tDCS the number of hyperactive/impulsive symptoms predicted the effect on working memory performance (b = -.62, $t(12)$ = -2.74, p = .018) and therefore explained a significant proportion of variance (R^2 = .39, $F(1, 12)$ = 7.50, p = .018). Thus, in individuals with fewer hyperactive/impulsive symptoms HD-tDCS had larger positive effects on working memory performance. As there was no correlation between number of hyperactive/ impulsive symptoms and working memory performance in the first training session (r = -.16, p = .578), the effect was not explained by poor baseline performance of tDCS responders. Interestingly, the effect of conventional tDCS on working memory performance was not predicted by any of the investigated factors.

4.3.2 Event-Related Potentials

Figure 13 illustrates ERP waveforms that were analyzed at a right parietal ROI (P4, P8). Over all groups and conditions, components N2 and P3 were evoked at 185 ms and at 358 ms, respectively.

Between controls and sham condition of ADHD patients there was no difference in amplitudes of N2 ($t(23)$ = -1.13, p = .271) but amplitudes of P3 were reduced in patients ($t(23)$ = -3.46, p = .002). An ANOVA (conventional vs. HD vs. sham) showed a significant difference between tDCS conditions for the N2 ($F(2, 18)$ = 7.51, p = .004). Mean amplitudes were more positive after conventional tDCS ($t(9)$ = 2.98, p = .016) and after HD-tDCS ($t(9)$ = 3.20, p = .011) compared to sham stimulation. For the P3, a significant difference between tDCS conditions was also found ($F(2, 18)$ = 8.91, p = .002). After conventional tDCS ($t(9)$ = 2.58, p = .030) and after HD-tDCS ($t(9)$ = 5.04, p = .001) amplitudes of P3 were larger compared to sham. Thus, after stimulation, working memory related ERP components in ADHD patients were more in resemblance to ERPs in healthy controls. Latencies of both components were not affected by tDCS. Mean ERP values and results of statistical comparisons are given in Table 8.

4.3.3 Side Effects

TDCS related sensations were rated with medium intensity on a 5-point Likert-scale (conventional 3.0, HD 2.8, sham 2.3; $F(2, 28)$ = 3.55, p = .043; conventional vs. sham p = .022; HD vs. sham p = .056). Patients reported the following side effects: itching 36%, pain 36%, fatigue 21%, headache 7%, phosphenes 7%.

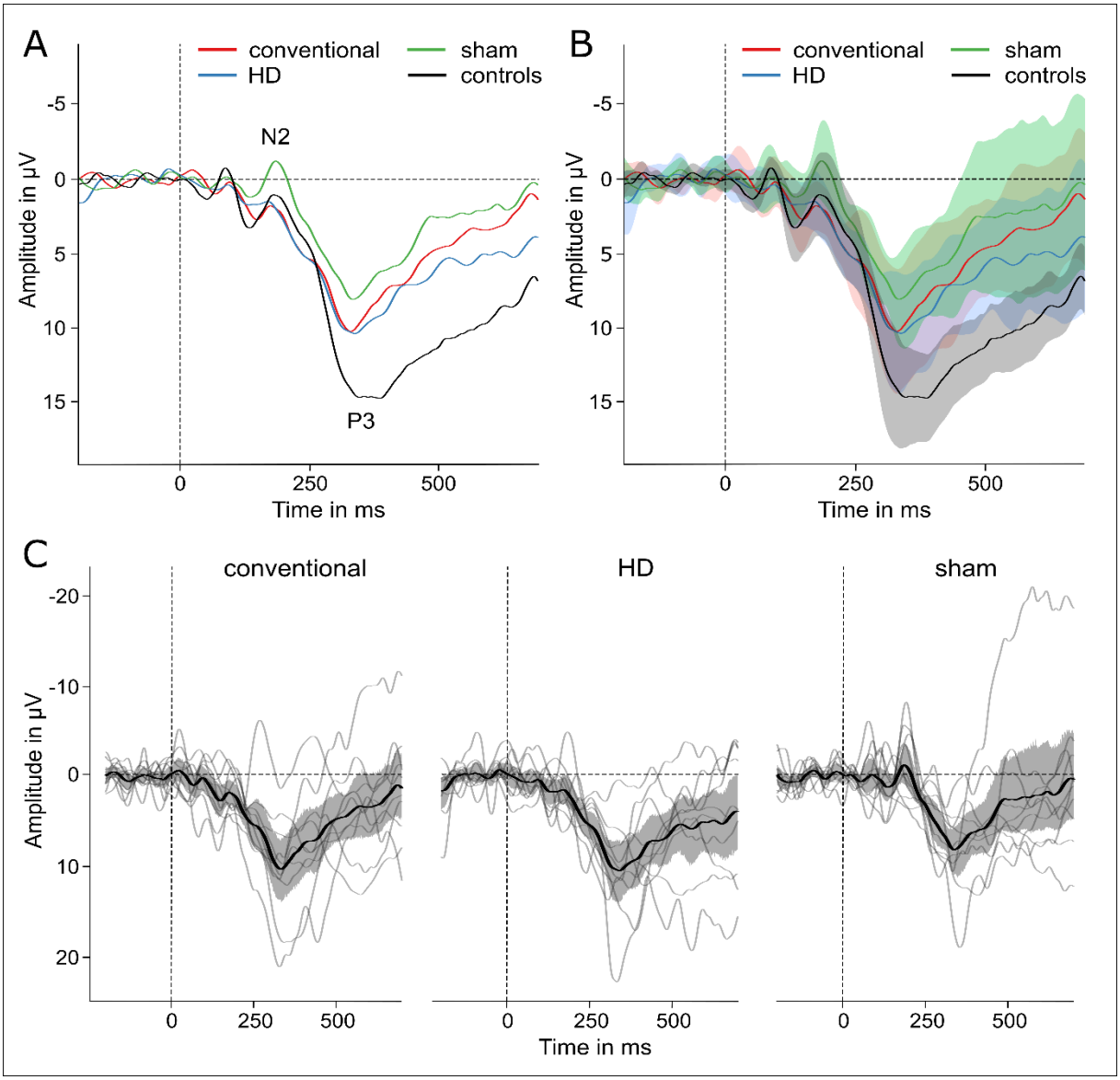

Figure 13. ERP waveforms for conventional, HD, and sham tDCS. (A) Grand average ERPs at a right parietal ROI (P4, P8) for conventional, HD, and sham tDCS in ADHD patients and healthy controls during *n*-back target trials **(B)** with their 95% confidence intervals, **(C)** EPRs of individual ADHD patients for different experimental conditions.

Table 8. ERP results for conventional and HD-tDCS. *M* and *SD* of ERP characteristics in ADHD patients and controls, results of ANOVAs and post-hoc *t*-tests between tDCS conditions (conventional vs. HD vs. sham) within ADHD patients.

	controls	ADHD patients			η_p^2	*F*	*p*	conv. vs. sham		HD vs. sham		conv. vs. HD	
		conv.	HD	sham				*t*	*p*	*t*	*p*	*t*	*p*
N2 amplitude	2.35 μV (4.80 μV)	3.16 μV (2.07 μV)	3.02 μV (1.97 μV)	0.51 μV (2.21 μV)	.455	7.51	.004	2.98	.016	3.20	.011	0.23	.821
N2 latency	191 ms (23 ms)	187 ms (27 ms)	181 ms (30 ms)	179 ms (22 ms)	.024	0.22	.804	0.67	.518	0.15	.882	0.45	.666
P3 amplitude	13.87 μV (5.36 μV)	9.14 μV (5.74 μV)	9.75 μV (4.93 μV)	7.11 μV (3.74 μV)	.497	8.91	.002	2.58	.030	5.04	.001	-0.98	.355
P3 latency	362 ms (39 ms)	350 ms (36 ms)	361 ms (47 ms)	356 ms (39 ms)	.033	0.31	.739	-0.49	.636	0.38	.713	-0.65	.531

4.4 Discussion

We investigated effects of conventional and HD-tDCS over the right IFG on working memory performance in children and adolescents with ADHD. We found increased positive values of mean amplitudes for P3 and N2 components during HD and conventional tDCS, suggesting that the underlying neurophysiological processes were more in resemblance to typically developing peers. Behavioral performance was not generally influenced by tDCS but HD-tDCS effect on working memory depended on the individual hyperactive/impulsive symptom load. Moreover, the rate of responders for HD-tDCS was at least equivalent to the responder rate for conventional tDCS.

We could show that both tDCS montages increased the amplitude of the P3. Most ERP research on P3 was done in adult ADHD patients and is therefore not entirely comparable to the present study. Still, our results are in line with a meta-analysis of Szuromi et al. (2011) finding decreased P3 amplitudes in ADHD. They stated that over a pathway which includes the lateral prefrontal cortex and the temporoparietal junction, P3 is associated with the ventral attention network. Therefore, they interpreted decreased P3 amplitudes in ADHD as a dysfunction of that network. Accordingly, increased P3 amplitudes in the verum tDCS conditions of this study suggest an enhanced function of the ventral attention network and therefore improved working memory processing in the patients. It is interesting to note that the administration of methylphenidate also increased P3 (Hermens et al., 2005). For the N2 component we found more positive values of mean amplitudes after verum tDCS, which was not in line with our hypothesis. However, this means that after stimulation N2 amplitudes were more similar to control participants, which suggests underlying neurophysiological processes became more comparable with healthy controls.

Although tDCS modulated ERP amplitudes, the primarily targeted behavioral parameter was not generally improved, which is not unusual. Often, tDCS causes changes in related parameters as reaction time (Munz et al., 2015) or network activity (Sotnikova et al., 2017). One possible explanation is that tDCS induced neurophysiological modulation can be too weak to induce behavioral effects in all individuals. Still, our ERP data indicate a positive modification of working memory processing. However, in future studies this promising approach needs to be modified in a way that induces stable improvements on a behavioral level.

Interindividual variability in response to tDCS was high, which prevented a general group effect on behavior. In fact, high variability is a frequent phenomenon in tDCS studies (Lopez-Alonso et al., 2014; Wiethoff et al., 2014). We assume that it was mainly caused by functional differences of pre-activity and excitability in relevant brain areas (Li et al., 2015) and by anatomical differences leading to varied current density distributions (Kim et al., 2014). However, when comparing both stimulation montages there was a trend towards a higher rate of responders to HD-tDCS. Furthermore, all patients that responded to conventional tDCS also responded to HD-tDCS, but not vice versa. Therefore, we consider HD-tDCS to be at least as effective as conventional tDCS.

This result is particularly remarkable as our computer simulations showed reduced average current density magnitudes of approximately 0.014 A/m^2 on the right IFG' brain surface for HD montage compared to approximately 0.14 A/m^2 for conventional tDCS (where 1 mA was injected). The current density averages differed by a factor of 10 between both montages. This discrepancy can mostly be attributed to the fact that only half (factor: 2) of the total current intensity was injected for HD-tDCS (compared to conventional tDCS), so while the anodal current intensity was 0.5 mA, the cathodal current intensity of 0.5 mA was split equally across 4 electrodes (equals to a total factor of 8). But also volume conduction properties (e.g., tissue conductivity distribution) as well as electrode placement highly influence the current density profile in the right IFG as well as the rest of the brain, whereas the latter may not have been optimal for simulating HD-tDCS to reach a similar level of current density as with conventional tDCS electrode setup. Systematically varying current intensities in future studies may provide clarity regarding this issue. To our knowledge of the literature, no computational algorithm has been proposed to search for optimal electrode scalp locations that maximizes or matches a desired current density profile in the ROI using few HD-tDCS electrodes (e.g., 4 x 1). However, for a large number of HD electrodes with fixed scalp locations, although unknown electrode current intensities, this problem can be solved (Guler et al., 2016).

Regarding ERP modulations, both tDCS montages showed similar effects but from a safety point of view HD-tDCS has some advantages. The current flow simulations shown in Figure 10B illustrate that HD-tDCS stimulated the target area with a much higher precision than conventional tDCS. HD-tDCS induced electrical current peaks in brain areas near the electrodes whereas in conventional tDCS those peaks can also be found in non-target areas in-between electrodes. Furthermore, during HD-tDCS current flow was restricted to the area

circumscribed by the electrodes, while during conventional tDCS widespread brain areas were stimulated, including the whole right frontal lobe and adjacent areas. This unnecessary stimulation of non-target brain areas enhances the risk of unintended changes in brain functions, which is of special importance in the vulnerable ADHD patient group of children and adolescents (Hameed et al., 2017). On the other hand increased precision bears the risk of missing the target area in individuals with varying neuroanatomy. But future approaches could avoid this issue by using individualized tDCS montages. A further downside of HD-tDCS is higher current density on the skin. However, current flow simulations show considerably reduced current density on the cortex during HD compared to conventional tDCS (as discussed above) while comparable effects were induced. In an approach of using the lowest dose necessary, we would expect a reduced risk of side effects by inducing less current flow in the brain. We state that it is preferable to use HD-tDCS over conventional tDCS when possible, for the reasons of higher precision and a potentially reduced dose of current in the brain while inducing similar effects.

We found that effects of HD-tDCS on working memory performance depended on the hyperactive/impulsive symptom load. Patients with fewer symptoms were more likely to respond to HD-tDCS. We assume that this association was modulated by functional (Solanto et al., 2009; Orinstein & Stevens, 2014) or connectivity characteristics (Fair et al., 2012; Park et al., 2016) of ADHD patients with low hyperactivity. However, further studies that compare tDCS effects specifically between high and low hyperactive ADHD patients are necessary to draw reliable conclusions about this factor. If this association will be confirmed, it would allow for the selective use of HD-tDCS in specific individuals making tDCS more efficient by sparing patients unsuccessful stimulations. Interestingly, this relationship was not found for conventional stimulation. But causation of this montage specificity cannot to be explained with the present study as ERP results provide no indication for differential mechanisms of action.

A limitation of the study is the small sample size, especially for ERP analysis. Due to ADHD symptoms, the collection of high quality EEG data was extremely difficult resulting in a small number of analyzed trials. To account for the small sample size, confounding variables were avoided. So, participants underwent one training session in the beginning to minimize learning effects between experimental sessions. Strength of the study is the assessment of EEG data from healthy controls. Still, measurements of controls were obtained from a single session, in contrast to repeated sessions in patients. Although data acquisition differed

between groups, we assume results to be mainly comparable as it has been found earlier that the target P3 for visual stimuli does not habituate (Geisler & Polich, 1994), especially in parietal areas (Wintink et al., 2001).

4.4.1 Conclusions

We showed that HD-tDCS is at least equally suitable as conventional tDCS for the successful recruitment of the right IFG. Therefore, HD-tDCS is a safe and promising approach for modulating working memory processing in ADHD patients. Further investigations may address the question how the neurophysiological effects found here, can be extended to a stable behavioral effect. Approaches to enlarge effects could be to do repeated tDCS sessions (Ditye et al., 2012) or to apply multifocal stimulation where not only one region but a whole network can be stimulated at the same time (Fischer et al., 2017).

5 Experiment 3: Effects of a Five-Day HD-tDCS Application to the Right IFG Depend on Current Intensity: A Study in Children and Adolescents with ADHD

Carolin Breitling-Ziegler, Tino Zaehle, Christian Wellnhofer, Moritz Dannhauer, Jana Tegelbeckers, Valentin Baumann, Hans-Henning Flechtner & Kerstin Krauel. Effects of a five-day HD-tDCS application to the right IFG depend on current intensity: A study in children and adolescents with ADHD. Progress in Brain Research, 264, 117-150. DOI: 10.1016/bs.pbr.2021.01.014

5.1 Introduction

The majority of patients suffering from attention-deficit/hyperactivity disorder (ADHD) shows persistent impairments of executive functions, such as working memory and inhibitory control (Uchida et al., 2018; Kofler et al., 2019a) that are associated with poor academic achievements, social problems, and substance abuse (Groman et al., 2009; Kofler et al., 2018a; Simone et al., 2018). Even into late adulthood, these impairments significantly contribute to an impaired quality of life in these patients (Thorell et al., 2019). Although pharmacological treatment with methylphenidate successfully targets executive functioning in ADHD (Coghill et al., 2014), these stimulants are associated with side effects, such as weight loss and increased blood pressure (Cortese et al., 2018). Side effects together with subjective concerns on negative long-term consequences of medication (e.g. perception of an increased risk for drug abuse) are the main reason for non-adherence to pharmacological therapy (Ahmed et al., 2017). Thus, 20% of ADHD patients discontinue medication within the first year (Toomey et al., 2012) and desire non-pharmacological treatment approaches (Buchanan et al., 2020). Alternatives include psychosocial treatments, cognitive trainings, or neurofeedback. While achieving only small effects on symptoms (Daley et al., 2014; Cortese et al., 2015; Evans et al., 2018; Riesco-Matias et al., 2019), these treatment strategies require great effort and time from patients and practitioners. Here, transcranial direct current stimulation (tDCS) offers an alternative therapy approach that could produce long-term effects via neuroplastic mechanisms, which would be a main advantage over the transient efficiency of pharmacological treatments (Rubia, 2018).

TDCS is a non-invasive brain stimulation technique that modulates cortical excitability. For this purpose, a weak direct current is applied to the brain via electrodes placed on the scalp. The application of current can induce increased excitability in the area beneath the anode and reduced excitability in brain areas beneath the cathode (Stagg & Nitsche, 2011). Beyond excitability changes, tDCS modulates neuroplasticity of stimulated brain areas (Kronberg et al., 2020) as well as connectivity (Polania et al., 2012). An effective blinding condition can be achieved by the application of a short stimulation of about one minute in the beginning of the session to induce comparable skin sensations (Brunoni et al. 2013). TDCS was demonstrated to be safe, with only few and mild side effects, which are mostly tingling and itching skin sensations. So, it is generally tolerated well, even in children and adolescents (Antal et al., 2017).

Results from fMRI studies suggest that deficits in executive functions in ADHD stem from dysfunctions in complex fronto-cingulo-striato-thalamic and fronto-parieto-cerebellar networks (Rubia, 2018) offering potential target networks for the application of tDCS (Castellanos & Proal, 2012). The prefrontal cortex seems to be a promising target region, because it is involved in most cognitive networks that are impaired in ADHD (Hart et al., 2013; Rubia, 2018) with reduced activation in patients during tasks that demand working memory and inhibitory functions (Norman et al., 2016; Yap et al., 2020). Therefore, when prefrontal brain activity is enhanced using anodal tDCS this may improve executive functioning in children and adolescents with ADHD.

A number of controlled studies applied single sessions of prefrontal tDCS to ADHD patients. Despite some studies finding null results (Cosmo et al., 2015a; Jacoby & Lavidor, 2018), most research showed beneficial effects on inhibitory functions (Munz et al., 2015; Soltaninejad et al., 2015; Nejati et al., 2017; Allenby et al., 2018) or memory consolidation during sleep (Prehn-Kristensen et al., 2014). Further, increased connectivity of stimulated areas was demonstrated (Cosmo et al., 2015b; Sotnikova et al., 2017). A recent meta-analysis of Salehinejad et al. (2019) revealed that most ADHD studies applied stimulation to left dorsolateral prefrontal areas, resulting in overall small to medium effect sizes for the improvement of inhibitory functions (Salehinejad et al., 2019). Despite promising results from left prefrontal stimulation, we focused in previous studies on a region that has been less explored as tDCS target area in ADHD: the right inferior frontal gyrus (IFG). This brain region persistently showed structural and functional alterations in ADHD, which were associated with executive dysfunctions, especially with impaired inhibitory functions (Rubia

et al., 2005; Depue et al., 2010; Morein-Zamir et al., 2014). Right prefrontal hypoactivation successfully distinguished ADHD patients from healthy controls (Monden et al., 2015). Moreover, the right IFG is the brain area that shows the most consistent activation increase after the application of methylphenidate indicating its important role in shaping the clinical outcome in patients (Rubia et al., 2014). For these reasons, we previously applied anodal tDCS to this region and found beneficial effects in a small sample on interference control (Breitling et al., 2016) and on neurophysiological parameters suggesting enhanced central processing mechanisms (Breitling et al., 2020).

While single applications of tDCS are only of transient efficiency (Nitsche & Paulus, 2001), it was demonstrated that repeated tDCS applications of six or seven sessions can induce effects that last up to 6 or 12 months (Cohen Kadosh et al., 2010; Katz et al., 2017). This finding makes tDCS a promising approach for an effective treatment in ADHD with potential rehabilitative value (Krause & Cohen Kadosh, 2013). Until now, two studies investigated repeated applications of tDCS in ADHD for five consecutive days demonstrating promising effects on ADHD symptom severity, which were still present one to four weeks after the intervention (Cachoeira et al., 2017; Soff et al., 2017). However, in Soff et al. (2017) only a small subset of the sample could be analyzed due to carryover effects in a cross-over design. Cachoeira et al. (2017) had a larger sample of adult ADHD patients, but the evaluation of tDCS relied solely on self-rating scales. Therefore, more data on repeated tDCS applications in ADHD are required before implementing tDCS as a therapy approach in ADHD.

In most applications, tDCS has been imprecise in targeting brain areas because large sponge electrodes induced widespread current flow patterns in the brain, with the highest current density resulting not necessarily in the target area (Datta et al., 2009a; Faria et al., 2011). A method that improves focality is high definition tDCS (HD-tDCS). HD-tDCS works with a 4 x 1 ring montage consisting of five small electrodes with one stimulation electrode being surrounded by four references (Villamar et al., 2013). The setting limits the current flow in the brain to the area under the circular montage (Datta et al., 2009a). This ensures that the highest current density is induced in the target brain area, while the stimulation of non-target brain areas is kept to a minimum. In Breitling et al. (2020) we demonstrated that applying HD-tDCS to the right IFG yields comparable effects as conventional tDCS with large sponge electrodes on neurophysiological parameters.

Currently, there is a lack of understanding optimal current intensities for tDCS applications (Esmaeilpour et al., 2018), especially when it comes to children and adolescents. The current

intensity is critical with respect to the induced effects in the brain and for cutaneous sensations (Fertonani et al., 2015). It was demonstrated that on average higher current densities are induced in the cortex of children, with a significant variance between individuals depending mainly on their head size (Kessler et al., 2013). Therefore, it was suggested to reduce current intensities in children (Muszkat et al., 2016), particularly as blinding in children could be less successful due to a higher susceptibility for sensory perceptions. In the present study we aimed for the application below the individual pain threshold.

As tDCS was demonstrated to interact with endogenous plasticity mechanisms (Kronberg et al., 2020) it seems to be most effective when applied simultaneously with a cognitive task (Martin et al., 2014). ADHD related hypoactivation of the right IFG has been found mostly during tasks requiring inhibitory functions (Rubia et al., 2005; Morein-Zamir et al., 2014; Monden et al., 2015) but has also been associated with working memory deficits (Clark et al., 2007; Bayerl et al., 2010). Therefore, in order to maximize the involvement of the right IFG, we applied a cognitive task during tDCS that combined inhibitory and working memory aspects. This task merges an *n*-back task to assess verbal working memory, with aspects of a go/nogo task, commonly used to investigate response inhibition. This combined *n*-back/nogo paradigm was introduced in Breitling-Ziegler et al. (2020) for the investigation of ADHD related deficits in both executive functions. In this task, tDCS effects on event-related potentials (ERPs) have been demonstrated after right IFG stimulation in ADHD patients (Breitling et al., 2020).

Electrophysiological assessments via electroencephaolgraphy (EEG) allow the investigation of tDCS induced alterations in neural processes beyond behavioral measures. Neurophysiological investigations have the advantage that subtle alterations in neural processes can be detected, even when these do not yet translate into behavioral outcomes and therefore deliver a more comprehensive picture of tDCS induced effects. For the EEG analysis, we focused on the P3 component that reflects higher order cognitive processes such as stimulus processing, evaluation, and categorization, and also the allocation of attentional resources. During working memory requirements it indicates updating processes. P3 amplitude reductions belong to the most sensitive biomarkers for ADHD (Kaiser et al., 2020) and have been associated with ADHD symptom severity (Marquardt et al., 2018).

It was demonstrated that tDCS can induce positive transfer effects into other cognitive domains (Trumbo et al., 2016) but also negative transfer effects (impairing other cognitive

functions) (Iuculano & Cohen Kadosh, 2013; Sarkar et al., 2014). Such effects occur most probably as near transfer effects in cognitive processes closely correlated to targeted functions and that rely on shared brain regions (Von Bastian & Oberauer, 2014). Therefore, we assessed performance in two related cognitive functions, interference control and spatial working memory. Interference control was assessed using the flanker task, as task performance has been associated with the integrity of the right IFG (Luks et al., 2010) and in a small-sample study, beneficial effects on the Flanker task performance have been demonstrated after tDCS over the right IFG in ADHD patients (Breitling et al., 2016). Further, we investigated transfer effects on spatial working memory using a spanboard task. Brain activation during the spanboard task and verbal working memory tasks overlap in the right IFG (McNab et al., 2008). Besides cognitive transfer effects, we assessed tDCS related effects on ADHD symptom severity, assessed by self and parent-ratings. All assessments were repeated at a four-month follow up, to identify potential long-term effects of stimulation.

The aim of the present study was to investigate the effects of anodal HD-tDCS that was repetitively applied to the right IFG over five consecutive days in children and adolescents with ADHD. For this purpose, patients were split into two groups, who received either verum or sham tDCS. Before and after the tDCS intervention, as well as during a four-month follow up, we assessed performance and EEG data during a combined *n*-back/nogo task. We hypothesized that ADHD patients who received verum tDCS would show higher improvements of working memory, response inhibition and attention together with increased P3 amplitudes during *n*-back target and nogo trials this task compared to the group that received sham tDCS. Additionally, we performed exploratory analyses on interference control and spatial working memory in transfer tasks as well as on ADHD symptom severity ratings. Additionally to ADHD patients, we included a group of healthy control participants who underwent the same procedure as patients but received only sham tDCS. This group served to characterize the regular course of behavioral and EEG parameters over the eight experimental sessions in order to control for retest effects.

5.2 Methods

5.2.1 Participants

Children and adolescents in the age between 10 and 17 years participated in the current study. 33 of them were diagnosed with ADHD according to DSM-5 criteria (21 combined

presentation, 11 predominantly inattentive presentation, 1 predominantly hyperactive/ impulsive presentation) and 13 were healthy control participants. Children and adolescents were recruited via the Department of Child and Adolescent Psychiatry of the Otto von Guericke University Magdeburg and via advertisements in local newspapers. Diagnoses were made by experienced psychologists on the basis of clinical interviews, which were conducted with all participants of the ADHD and of the healthy control group and their parents using the German Adaptation (Delmo et al., 2000) of the Revised Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL, Kaufmann et al. 1997). Exclusion criteria for ADHD patients were comorbid psychiatric and neurologic disorders other than oppositional defiant disorder and conduct disorder. 13 ADHD patients were currently taking methylphenidate but they refrained from medication at least 24 h before each experimental session and during the five days of stimulation. Participants of the healthy control group had no psychiatric and neurologic disorders. None of the participants reported contraindications to receive tDCS. Supportive diagnostic information regarding attention problems was gathered using the Child Behavior Checklist (Achenbach, 1991a) as parent-rating. Additionally, the Youth Self Report (Achenbach, 1991b) was assessed from children and adolescents of 11 years and older. We conducted the d2 or the d2-R test of attention (Brickenkamp, 2002; Brickenkamp et al., 2010) to determine concentration performance. Further, intelligence was tested with the CFT 20-R (Weiss, 2008) with IQ values lower than 70 serving as an exclusion criterion. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

All children and adolescents and their parents gave written informed assent/consent to participate in this study in accordance with the declaration of Helsinki. After each session, participants received a voucher for a local shopping center as reimbursement, with a total value of 90 €.

5.2.2 Procedure

In the present study, participants underwent eight experimental sessions: baseline, five tDCS sessions, post, and follow up. The eight sessions within each participant were scheduled at a similar time of the day (deviation M = 0.48 h, SD = 0.46 h). Across participants the sessions took place at different day times. Figure 14 illustrates the schedule and experimental procedure.

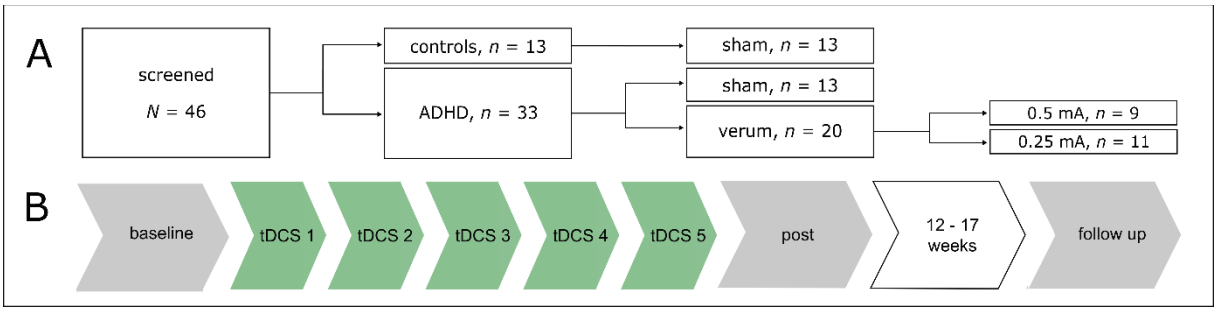

Figure 14. Group assignment and sequence of sessions in experiment 3. (A) 46 participants were included in the study, with 33 fulfilling the diagnostic criteria of ADHD, patients were randomly assigned into the sham or the verum tDCS group, patients of the verum group received either tDCS with a current intensity of 0.5 mA or 0.25 mA depending on individual dermal sensitivity to stimulation, **(B)** Experimental sessions. Each participants underwent five sessions of 20 minutes tDCS on consecutive days. In baseline, post, and four-month follow up measurements, behavioral and EEG parameters were assessed to evaluate effectiveness of stimulation.

5.2.2.1 Baseline, Post, and Follow Up Sessions

One to four days before and after the tDCS application (M = 1.72 d, SD = 0.98 d), baseline and post measurements took place. The follow up session was conducted usually after 12 to 17 weeks. Due to COVID-19 restrictions, 5 participants had delayed follow up sessions in week 19 - 23 and in 4 participants no follow up could be conducted. During baseline, post and follow up sessions, response inhibition and working memory performance was assessed via a combined *n*-back/nogo task while EEG was recorded. Afterwards, a flanker paradigm (interference control) and a span board task (spatial working memory) were conducted. Moreover, clinical self and parent-ratings via the DISYPS-II (Döpfner et al., 2008) assessed ADHD symptom severity. The DISYPS-II instructions for the post session were adapted into "rate the behavior during the last week since the start of tDCS applications" and for the follow up into "rate the behavior during the last three months". Baseline, post, and follow up sessions each had a duration of about 90 minutes.

5.2.2.2 tDCS Sessions

Each participant underwent five tDCS sessions on consecutive days (except for 2 patients that underwent 5 sessions within 6 days). ADHD patients were randomized in a double blind fashion to receive either verum or sham tDCS. Participants of the healthy control group received sham stimulation only. At the beginning of the first tDCS session, participants were familiarized with the stimulation and asked for tDCS induced skin sensations but not specifically for pain. During this procedure, 11/20 patients (55%) in the verum group and

3/13 patients (23%) in the sham group reported painful skin sensations at a current intensity of 0.5 mA. For these participants, current intensity was reduced to 0.25 mA.

During each tDCS session, participants solved the combined *n*-back/nogo task for 20 minutes while they received tDCS according to their experimental condition. TDCS related side effects were controlled with a questionnaire that assessed cutaneous sensations (pain, itching, burning) with their intensity and the presence of general symptoms (headache, vertigo, nausea, fatigue, insomnia, occurrence of phosphenes). This questionnaire was completed at the end of the last tDCS session.

5.2.3 Cognitive Tasks

All cognitive tasks were presented using the software Presentation® (www.neurobs.com) on a flat screen (diagonal 61 cm) with participants seated in a distance of about 60 cm. Stimuli were displayed in black on a grey background (RGB value 128). Task details are given in the following and are illustrated in Figure 15. All tasks started with a short training of 1 to 2.5 minutes with feedback indicating right or wrong reactions. Afterwards, the investigator decided if the participant understood the task correctly or if the training needed to be repeated.

5.2.3.1 *n*-back/nogo Task

The *n*-back/nogo paradigm is a combination from a two-back and a go-nogo task to assess response inhibition and working memory aspects (Breitling-Ziegler et al., 2020). A series of capital letters was presented (A, D, E, H, I, N, R, S, T, U) and participants decided via button press for each stimulus if it matched the stimulus presented two trials earlier (target: right hand, non-target: left hand, targets 21%). Moreover, participants were instructed to withhold their response when the stimulus was the letter "X" (17% nogo trials). Stimuli were presented with a visual angle of 0.86° (height) for a duration of 500 ms and participants had 2000 ms to give their response. The task was applied for four runs à 110 trials (duration 4.8 min) with breaks of at least 30 sec in between. Participants were instructed to give their reactions as accurately and as fast as possible.

5.2.3.2 Flanker Task

During each trial of this task, five arrows were presented with the central arrow being the target stimulus, surrounded by distractors. Participants indicated the direction of the target stimulus via button press with their right or left hand. In 50% of the trials distractors were

congruent to the target (<<<<<, >>>>>) and in 50% they were incongruent (<<><<, >><>>). Stimuli were displayed for a duration of 60 ms and participants had 1360 ms to give their response. The duration of this task was 1.75 min (52 trials). Participants were instructed to react as accurately and as fast as possible.

5.2.3.3 Spanboard Task

Participants were instructed to remember a sequence of 2 - 5 dots that appeared in a field of 4 x 4 positions (16.87° visual angle). Afterwards, this sequence was repeated backwards, either correctly or with one false position. Participants indicated via button press if the sequence was right (right hand) or false (left hand). The task had a duration of 7.3 min with 40 trials (6 x 2 dots, 14 x 3 dots, 14 x 4 dots, 6 x 5 dots). Each dot was displayed for 700 ms and participants had 1500 ms to give their response. Participants should react as correct as possible.

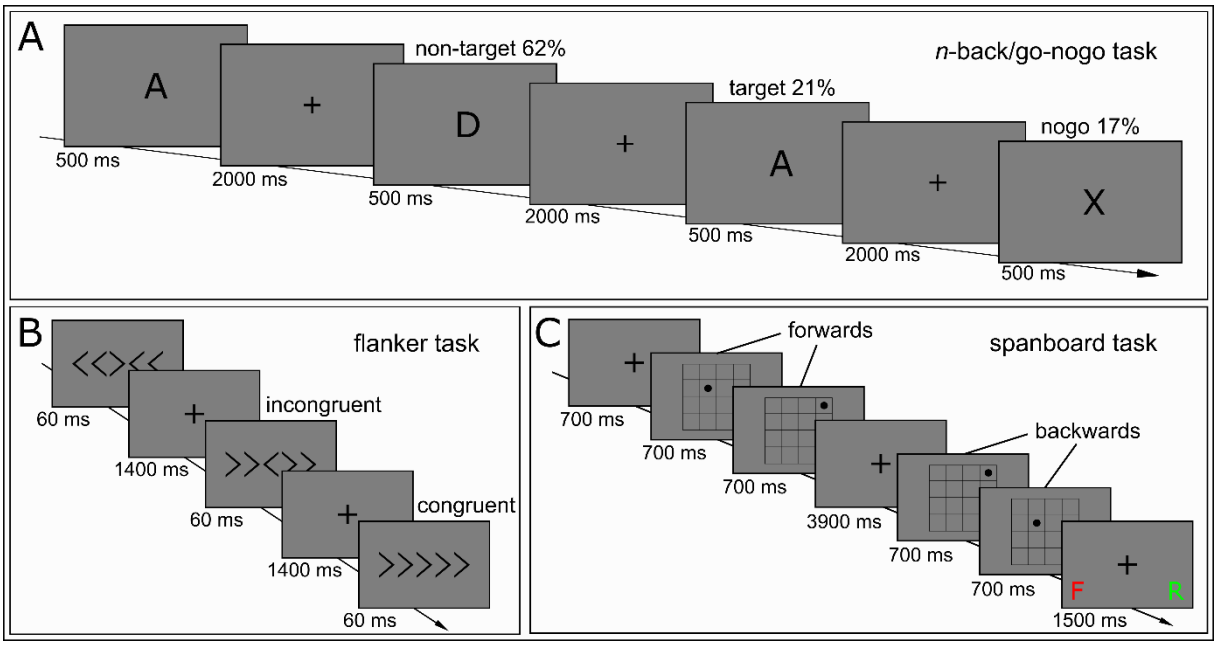

Figure 15. Cognitive tasks in experiment 3. In each session a combined *n*-back/nogo task **(A)** was applied to assess working memory and response inhibition. During baseline, post, and follow up sessions, additionally a flanker task **(B)** and a spanboard task **(C)** were applied to investigate transfer effects of stimulation.

5.2.4 Transcranial Direct Current Stimulation

HD-tDCS was applied using a battery driven DC stimulator of the company neuroConn (Munich, Germany) in a 4 x 1 ring montage. This montage induces more focalized current flow patterns in the brain compared to sponge electrodes (Datta et al., 2009a), while inducing

similar effects (Kuo et al., 2013; Breitling et al., 2020). Five circular Ag/AgCl-electrodes with a diameter of 1 cm were positioned over the right IFG, with one anode placed in the center surrounded by four cathodes in a distance of 4 cm. Electrode positions were determined on the basis of current flow simulations (Figure 16) using the software SCIRun5/BrainStimulator (SCI-Institute, 2018). Technical details of current flow simulations are given in 2.2.2 Current Flow Simulations. The electrodes were placed in an adapted EEG cap that contained the required tDCS positions. Experimental impedances were kept mostly below 5 kΩ, but at least below 15 kΩ. TDCS was applied with a current intensity of 0.5 mA (n = 9) or 0.25 mA (n = 11), depending on the individual cutaneous sensitivity to tDCS. The duration of tDCS was 20 minutes with a 30 s ramp up and down. Sham stimulation consisted of 30 s ramp up, 40 s full intensity and 30 s ramp down.

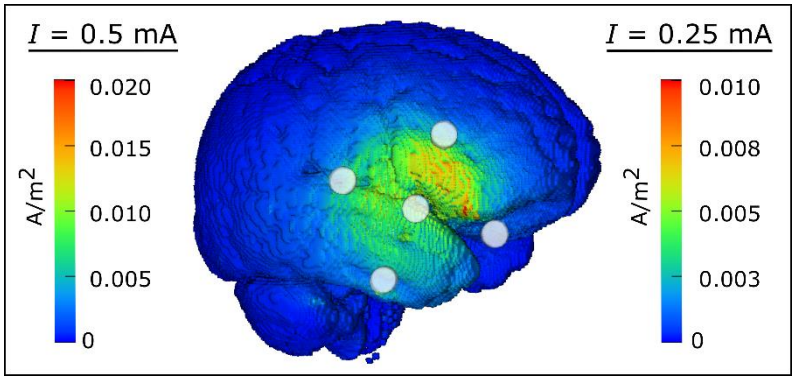

Figure 16. Current flow simulations for HD-tDCS. Visualization of the computer-simulated cortical current density distribution related to current injection through five scalp-attached electrodes that are organized in a 4 x 1 ring-like configuration when using a current intensity of I = 0.5 mA (left) and I = 0.25 mA (right). The total current intensity of the centered anodal electrode is split equally across the four surrounding, oppositely charged electrodes closing the circuit.

5.2.5 EEG Recording and Analysis

EEG was recorded with a SynAmps amplifier of the company Neuroscan (Sterling, USA). For this purpose Ag/AgCl-electrodes were placed in EEG caps (EasyCap GmbH, Herrsching, Germany) at 21 positions according to the International 10-20 EEG system (Fp1, Fp2, F7, F3, Fz, F4, F8, FT9, FC5, FC6, FT10, C3, Cz, C4, P7, P3, Pz, P4, P8, O1, O2). Horizontal and vertical electrooculograms were recorded from bipolar channels at the outer canthi of both eyes and at supra- and sub-orbital positions of the right eye. The ground electrode was placed at position AFz and linked electrodes at both mastoids served as references. The EEG was recorded with a sampling rate of 500 Hz. As online filters, a low pass filter of 70 Hz, a

high pass filter of 0.05 Hz, and a notch filter of 50 Hz were applied. Impedances were kept below 10 kΩ.

EEG data were preprocessed with EEGLAB version 2019.1 (Delorme & Makeig, 2004) in the MATLAB environment (version R2020a, The MathWorks, Inc., Nattick, MA, USA). Data were filtered digitally with a low pass filter of 30 Hz. Only trials with correct reactions were analyzed and were segmented into epochs from -200 to 750 ms, with a correction relative to the pre-stimulus-baseline. Large artifact sections were removed manually and afterwards an ICA was computed. Independent components for artifact rejection were then identified using the Multiple Artifact Rejection Algorithm (MARA), which is a machine learning algorithm based on expert ratings that is able to handle eye and muscular artifacts as well as loose electrodes (Winkler et al., 2011).

ERP characteristics were measured using ERPLAB version 7.0 (Lopez-Calderon & Luck, 2014). The latency ranges to determine peak amplitudes were chosen with regard to grand average waveforms. Peak amplitudes were analyzed for the nogo P3 at 425 - 625 ms and for the P3 during *n*-back target trials at 275 - 500 ms. All components were investigated at a parietal ROI that consisted of the electrode positions P3, Pz, and P4, because all electrodes showed a distribution with a parietal maximum (see section 5.3.5). Participants with 10 or less trials remaining in the dataset of any session were removed from the analysis. Therefore, one participant of the ADHD verum tDCS group and one participant of the control group was excluded from the analysis of nogo trials (number of analyzed trials M = 58.02, SD = 13.32). Four ADHD patients from the verum tDCS group and two of the sham group were excluded from the analysis of *n*-back target trials (number of analyzed trials M = 56.27, SD = 23.08).

5.2.6 Statistics

All statistical analyses were computed using SPSS (version 26, IBM Corp., Armonk, NY, USA). Sample characteristics and side effects were compared between groups using one-way ANOVAs with the factor Group (ADHD sham, ADHD 0.5 mA, ADHD 0.25 mA, controls) for metric variables, and chi-square tests for dichotomous variables. If an effect of Group was revealed, post-hoc tests between individual groups were reported.

5.2.6.1 *n*-back/nogo Task

The rate of commission errors during nogo trials served as an indicator for response inhibition. To assess working memory, the corrected *n*-back hit rate (hits on *n*-back targets - false alarms on *n*-back non-targets) was assessed. As measures of attention, we investigated omission errors and reaction time variability (*SD* of reaction time). Processing speed was assessed via reaction times (only trials with correct responses and with a reaction time of at least 100 ms). One participant of the control group was excluded from the analysis of nogo commission errors, because the performance was below two standard deviations of the group mean in all sessions.

The analysis was conducted using linear mixed models with the fixed factors Group (ADHD sham, ADHD verum, controls) and Session (baseline, tDCS 1, tDCS 2, tDCS 3, tDCS 4, tDCS 5, post). Individual participants and sessions were assumed as random effects with random slopes and random intercepts, with a diagonal covariance structure. Analyses were conducted with the Group ADHD sham as the reference group and the maximum likelihood estimation method was applied.

Interactions of Group x Session indicated tDCS effects. For significant interaction effects post-hoc *t*-tests of the estimated unstandardized regression coefficient *b* are reported. If this *t*-test was significant, further mixed model analyses were conducted for each individual session in comparison to baseline. Follow up data served to evaluate if induced tDCS effects persisted over a four-month-period and thus, the follow up data were compared against baseline only when there were significant tDCS effects in previous sessions.

5.2.6.2 Transfer Tasks, Clinical Assessment, Event-Related Potentials

Interference control was indicated by the flanker effect on the error rate (error rate incongruent – error rate congruent). Omission errors and reaction time variability (*SD* of reaction time) during the flanker task served as measures of attention. Reaction time during this task indicated processing speed. For the spanboard task the rate of errors indicated spatial working memory. Attention during this task was assessed via omission errors. Reaction time measures were not of interest for the spanboard task because participants were instructed to answer as correct but not as fast as possible. For the clinical assessments, all scales of the DISYPS-II questionnaire were evaluated as self and parent-ratings (ADHD total, inattention, hyperactivity, impulsivity).

Table 9. Sample description of experiment 3. Sample description, *M (± SD)*.

	ADHD sham	ADHD 0.5 mA	ADHD 0.25 mA	controls	F/χ^2 (p)
n	13	9	11	13	13
age in years	13.54 (± 1.45)	13.22 (± 2.39)	12.27 (± 1.68)	14.08 (± 2.10)	1.86 (.150)
females	15.38% (2)	11.11% (1)	36.36% (4)	23.08% (3)	2.30 (.512)
IQ	100.92 (± 13.96)	104.89 (± 20.86)	104.64 (± 13.77)	106.38 (± 6.84)	0.35 (.788)
left handed	0	11.11% (1)	0	15.38% (2)	3.66 (.301)
ADHD presentation					
- combined	46.15% (6)	66.67% (6)	81.82% (9)	-	3.32 (.190)
- inattentive	46.15% (6)	33.33% (3)	18.18% (2)	-	2.10 (.350)
- hyperactive/ impulsive	7.69% (1)	0	0	-	1.59 (.452)
comorbid ODD	15.38% (2)	11.11% (1)	18.18% (2)	-	0.19 (.908)
methylphenidate intake	38.46% (5)	55.56% (5)	27.27% (3)	-	1.67 (.435)
number of inattentive symptoms (K-SADS-PL, parent rating)	7.33 (± 2.06)	8.11 (± 1.27)	7.91 (± 1.04)	1.31 (± 2.43)	37.47 (< .001)[a]
number of hyperactive/impulsive symptoms (K-SADS-PL, parent rating)	5.67 (± 3.08)	6.11 (± 1.69)	6.64 (± 3.14)	1.00 (± 1.58)	13.25 (< .001)[b]
attention problems, parent-rating (CBCL; *T*)	70.77 (± 11.14)	68.44 (± 3.84)	67.73 (± 11.27)	52.62 (± 4.59)	11.63 (< .001)[c]
attention problems, self-rating (YSR; *T*)	63.00 (± 6.22)	62.22 (± 6.42)	62.75 (± 9.98)	52.00 (± 3.25)	5.03 (.006)[d]
attentional performance (d2/d2-R; *T*)	51.08 (± 10.89)	52.75 (± 7.44)	48.73 (± 10.87)	53.58 (± 5.78)	0.60 (.618)

[a] *ADHD 0.5 mA vs. controls: p < .001, ADHD 0.25 mA vs. controls: p < .001, ADHD sham vs. controls: p < .001*

[b] *ADHD 0.5 mA vs. controls: p < .001, ADHD 0.25 mA vs. controls: p < .001, ADHD sham vs. controls: p < .001*

[c] *ADHD 0.5 mA vs. controls: p = .004, ADHD 0.25 mA vs. controls: p = .004, ADHD sham vs. controls: p = .002*

[d] *ADHD 0.5 mA vs. controls: p < .001, ADHD 0.25 mA vs. controls: p < .001, ADHD sham vs. controls: p < .001*

Transfer tasks, clinical assessment, and ERPs were not assessed during the sessions tDCS 1 – 5. Thus, the linear mixed models included the factors Group (ADHD sham, ADHD verum, controls) and Session (baseline, post). The further procedure was analogous to the analysis of the *n*-back/nogo task.

5.3 Results

5.3.1 Sample Description

Table 9 gives the sample description for the experimental groups. The three groups of ADHD patients showed higher scores for attentional problems than healthy controls (all $p \leq .006$).

5.3.2 Side Effects

In general, tDCS was tolerated well and there was no drop out from the study. The reported side effects are given in Table 10. We found no differences in the frequency of side effects between groups (all $p \geq .203$). Although we aimed to apply tDCS below the pain threshold, a substantial proportion of patients evaluated tDCS induced skin sensations at the stimulation site as painful, when side effects were assessed after the last tDCS session. In ADHD patients, the intensity of painful sensation was rated on average as 0.94 on a 6-point likert scale (SD = 1.37), with no group differences ($F(2, 29) = 0.38$, $p = .689$) indicating successful blinding. However, 86% of individuals were willing to participate again in a tDCS study.

Table 10. Frequency of side effects. The frequency of side effects in each group was assessed with a questionnaire after the fifth session of tDCS.

	ADHD sham	ADHD 0.5 mA	ADHD 0.25 mA	controls	χ^2 (p)
painful sensations	23.1%	33.3%	63.6%	50.0%	4.61 (.203)
itching	30.8%	66.7%	36.4%	25.0%	4.31 (.230)
burning sensations	7.7%	11.1%	9.1%	0%	1.27 (.737)
headache	38.5%	22.2%	45.5%	25.0%	1.76 (.625)
vertigo	7.7%	11.1%	9.1%	0%	1.27 (.737)
nausea	7.7%	0%	0%	0%	2.52 (.472)
fatigue	46.2%	33.3%	45.5%	41.7%	0.42 (.936)
insomnia	15.4%	11.1%	9.1%	16.7%	0.37 (.946)
phosphenes	7.7%	0%	9.1%	0%	1.86 (.602)

5.3.3 *n*-back/nogo Task

5.3.3.1 Comparison ADHD Sham, ADHD Verum, Controls

The overall analysis of the *n*-back/nogo task revealed a Group effect on the corrected *n*-back hit rate ($F(2, 64.1) = 8.40$, $p = .001$) that indicated better performance in controls compared to the ADHD sham group ($t(55.1) = 3.56$, $p = .001$, $b = 23.71$). Further, Group effects of reaction time ($F(2, 79.2) = 6.71$, $p = .002$) and reaction time variability ($F(2, 65.6) = 15.31$, $p < .001$) revealed faster reaction times ($t(56.0) = -3.52$, $p = .001$, $b = -240$) with lower variability ($t(56.9) = -4.99$, $p < .001$, $b = -121$) in healthy controls compared to the ADHD sham group. No significant difference between ADHD patients and controls was found for nogo commission errors ($F(2, 62.9) = 2.91$, $p = .062$) and omission errors ($F(2, 69.0) = 2.34$, $p = .104$). Main effects of the factor Session demonstrated that over the course of the experiment, the corrected *n*-back hit rate was reduced ($F(1, 49.5) = 29.83$, $p < .001$, $b = -2.99$), omission errors increased ($F(1, 49.4) = 5.03$, $p = .029$, $b = 0.81$), and reaction time was reduced ($F(1, 46.6) = 9.15$, $p = .004$, $b = -4.54$). No main effect of Session was found for nogo commission errors or reaction time variability (all $p \geq .429$).

A significant interaction effect for Group x Session was found on the corrected *n*-back hit rate ($F(2, 49.9) = 4.85$, $p = .012$), which indicated higher performance in controls vs. ADHD sham patients over the course of sessions ($t(49.5) = 2.31$, $p = .025$, $b = 2.54$), but there was no interaction with the verum ADHD group indicating no effect of tDCS ($t(50.2) = -0.47$, $p = .640$, $b = -0.47$). For further variables of this task, no significant interaction was revealed (all $p \geq .173$). Thus, no general effect of tDCS was detected by analysing the *n*-back/nogo task in all groups.

5.3.3.2 Comparison ADHD Sham, ADHD 0.5 mA, ADHD 0.25 mA

55% of the verum ADHD group received tDCS with a lower current intensity due to higher cutaneous sensitivity. As it was demonstrated that current intensity can affect size and duration of tDCS effects (Nitsche & Paulus, 2000) we conducted further exploratory analyses including the Groups ADHD sham, ADHD 0.5 mA, and ADHD 0.25 mA. In the following, only interaction effects are reported to investigate effectiveness of stimulation. Table 11 gives a summary of the behavioral data.

For nogo commission errors, an interaction effect between Group and Session was found ($F(2, 39.9) = 3.92$, $p = .028$). This demonstrated that nogo errors increased in the 0.25 mA

group, while errors decreased in the sham group ($t(39.9) = -2.54$, $p = .015$, $b = -2.97$). This detrimental effect was not present at the first tDCS session ($t(33) = 0.34$, $p = .735$, $b = 2.29$) but the trend started to occur at tDCS session 2 (tDCS 2: $t(33) = -1.40$, $p = .172$, $b = -4.92$, tDCS 3: $t(33) = -1.03$, $p = .311$, $b = -2.64$, tDCS 4: $t(33) = -1.70$, $p = .098$, $b = -3.25$) and became significant at tDCS session 5 ($t(33) = -2.16$, $p = .038$, $b = -3.77$). During the post session, this effect was not significant anymore ($t(33) = -1.61$, $p = .116$, $b = -2.09$) and neither during the follow up ($t(32.1) = -0.20$, $p = .840$, $b = -0.24$).

For the *n*-back hit rate we found no interaction effect ($F(2, 46.6) = 1.38$, $p = .261$).

The analysis of omission errors revealed a Group x Session effect ($F(2, 36.3) = 3.80$, $p = .032$), which indicated a reduced number of errors in the 0.5 mA ADHD group, but the direct comparison between the 0.5 mA and the sham group indicated that this was only a trend ($t(36.3) = -1.98$, $p = .055$, $b = -1.25$).

Further, there was an interaction effect for reaction time variability ($F(2, 37.8) = 3.42$, $p = .043$) indicating reduced variability in the 0.5 mA group compared to the sham group ($t(37.8) = -2.12$, $p = .041$, $b = -7.94$). This effect yielded significance for tDCS session 4, tDCS session 5, and for the post session (tDCS 1: $t(33) = -2.01$, $p = .052$, $b = -32.18$, tDCS 2: $t(33) = -1.62$, $p = .115$, $b = -18.36$, tDCS 3: $t(33) = -1.40$, $p = .170$, $b = -11.57$, tDCS 4: $t(33) = -2.84$, $p = .008$, $b = -16.13$, tDCS 5: $t(33) = -2.18$, $p = .037$, $b = -10.50$, post: $t(33) = -2.20$, $p = .035$, $b = -8.57$). Moreover, this effects was still present during the follow up ($t(29.2) = -2.21$, $p = .035$, $b = -7.83$). The described effects are illustrated in Figure 17.

For reaction times no interaction effect of Group x Session was detected ($F(2, 62.4) = 0.26$, $p = .772$).

Table 11. Effects from five-day tDCS application on the *n*-back/nogo task. Mean and standard deviations for behavioral measures of the *n*-back/nogo task during all sessions are given and significant tDCS effects are indicated.

	ADHD sham *n* = 13	ADHD 0.5 mA *n* = 9	ADHD 0.25 mA *n* = 11	controls *n* = 13
nogo commission errors in %				
baseline	23.38 (14.93)	30.85 (24.91)	26.20 (15.21)	15.02 (9.71)
tDCS session 1	17.21 (14.04)	21.64 (22.23)	17.74 (11.16)	8.66 (8.42)
tDCS session 2	15.08 (13.20)	21.21 (14.42)	27.74 (18.99)	9.76 (5.68)
tDCS session 3	17.21 (15.58)	26.71 (13.06)	27.94 (23.34)	8.88 (4.96)
tDCS session 4	15.18 (14.12)	26.19 (13.46)	30.98 (24.60)	10.86 (5.70)
tDCS session 5	18.62 (11.28)	21.64 (15.60)	40.31 (32.05)*, b	10.75 (9.80)

post	18.83 (12.73)	26.02 (18.13)	34.18 (25.81)	13.16 (9.89)
follow up[c]	17.81 (15.80)	21.11 (14.18)	20.89 (19.46)	7.68 (5.35)
corrected n-back hit rate in %				
baseline	50.75 (20.78)	43.62 (26.12)	49.46 (21.71)	74.41 (9.72)
tDCS session 1	57.11 (20.31)	43.60 (19.29)	55.07 (25.33)	81.07 (8.01)
tDCS session 2	51.73 (22.72)	44.75 (21.70)	41.09 (21.44)	79.43 (8.03)
tDCS session 3	47.91 (24.98)	40.09 (22.74)	40.47 (26.19)	79.33 (8.98)
tDCS session 4	42.60 (24.72)	36.99 (23.96)	32.82 (26.52)	78.47 (9.18)
tDCS session 5	38.34 (23.80)	35.34 (24.79)	29.76 (26.41)	72.88 (16.69)
post	38.18 (27.23)	29.70 (24.05)	28.51 (26.54)	75.96 (16.98)
follow up[c]	48.81 (26.92)	42.91 (31.22)	39.43 (25.26)	81.42 (8.49)
omission errors in %				
baseline	10.04 (9.75)	15.66 (21.69)	5.79 (6.67)	0.55 (0.67)
tDCS session 1	6.40 (9.08)	11.57 (21.43)	6.15 (8.08)	0.38 (0.47)
tDCS session 2	7.19 (6.91)	9.90 (20.52)	8.56 (10.39)	0.23 (0.42)
tDCS session 3	8.09 (9.47)	8.90 (14.24)	9.44 (9.93)	0.17 (0.21)
tDCS session 4	9.62 (9.50)	10.13 (15.62)	10.81 (12.55)	0.27 (0.46)
tDCS session 5	10.93 (11.06)	8.67 (13.48)	9.77 (11.02)	0.57 (0.83)
post	13.84 (13.79)	13.46 (16.65)	15.10 (11.24)	0.44 (0.60)
follow up[c]	8.64 (10.06)	10.36 (13.91)	6.77 (6.97)	0.27 (0.58)
reaction time variability in ms				
baseline	318 (62)	346 (62)	321 (77)	201 (58)
tDCS session 1	292 (62)	288 (56)†, [a]	299 (77)	173 (67)
tDCS session 2	305 (60)	297 (90)	310 (99)	168 (64)
tDCS session 3	302 (64)	295 (82)	313 (102)	168 (62)
tDCS session 4	316 (56)	280 (79)**, [a]	332 (104)	177 (73)
tDCS session 5	323 (65)	298 (81)*, [a]	330 (112)	174 (68)
post	334 (72)	310 (43)*, [a]	347 (113)	175 (77)
follow up[c]	298 (71)	276 (82)*, [a]	318 (73)	157 (68)
reaction time im ms				
baseline	867 (201)	787 (210)	817 (190)	625 (176)
tDCS session 1	870 (221)	788 (247)	832 (197)	576 (152)
tDCS session 2	850 (221)	756 (204)	784 (181)	544 (145)
tDCS session 3	835 (200)	706 (154)	783 (168)	528 (129)
tDCS session 4	858 (221)	689 (171)	809 (174)	541 (151)
tDCS session 5	829 (231)	729 (166)	755 (188)	525 (147)
post	850 (211)	723 (143)	790 (188)	521 (134)
follow up[c]	810 (216)	717 (179)	799 (125)	526 (127)

*†p ≤ 0.055, *p < 0.05, **p < 0.01, [a]improved, [b]impaired*

[c] ADHD 0.5 mA: n = 8, ADHD 0.25 mA: n = 8

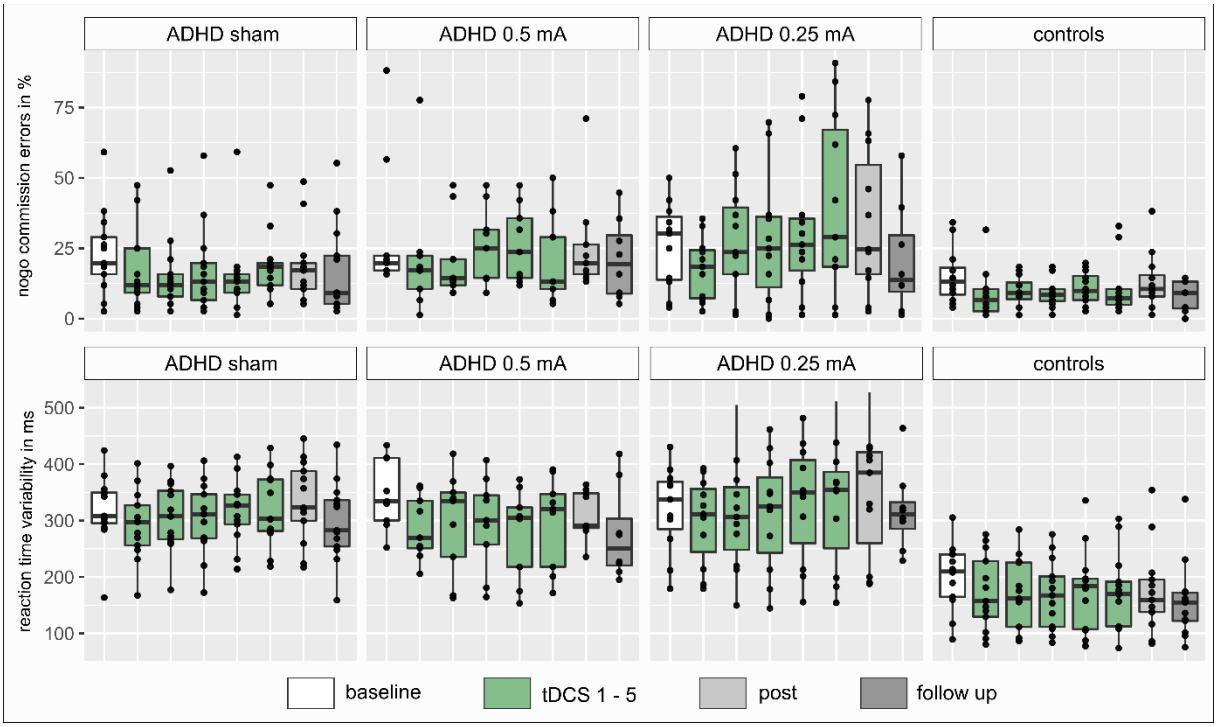

Figure 17. Nogo errors and reaction time variability for repetitive tDCS applications. Boxplots demonstrate the rate of nogo commission errors and reaction time variability (*SD* of reaction time) for different groups during all experimental sessions. Increased rates of nogo commission errors were demonstrated for 0.25 mA tDCS, while reaction time variability was reduced in the 0.5 mA tDCS group.

5.3.4 Transfer Tasks and Clinical Assessment

5.3.4.1 Flanker Task

For the flanker task, no significant Group x Session interaction was found for the flanker effect on error rate ($F(2, 33) = 0.12$, $p = .890$) and the interaction for omission errors failed to reach significance ($F(2, 33) = 2.97$, $p = .065$). Reaction time variability, however, revealed an interaction effect ($F(2, 33) = 4.89$, $p = .014$) that indicated reduced variability in the 0.5 mA compared to the sham group for the post session ($t(33) = -3.12$, $p = .004$, $b = -54.98$). During, the follow up, this effect was not significant ($t(29.7) = -1.89$, $p = .069$, $b = -17.03$). No interaction effect was found for reaction times during the flanker task ($F(2, 33) = 0.46$, $p = .633$).

5.3.4.2 Spanboard Task

For the spanboard task, no interaction was found for the error rate ($F(2, 33) = 0.86$, $p = .433$), but we observed a significant interaction effect for omission errors ($F(2, 33) = 5.91$, $p = .006$) indicating a reduced number of errors in the 0.5 mA group ($t(33) = -2.32$, $p = .027$, $b = -8.78$). This effect did not persist to the follow up session ($t(29.1) = -0.69$, $p = .498$, $b = -1.49$).

5.3.4.3 Clinical Assessment

Clinical assessments with the DISYPS-II questionnaire revealed an effect of stimulation on the self-rating of total ADHD symptoms ($F(2, 32.6) = 3.89$, $p = .031$). This indicated that symptom severity increased in the 0.5 mA group compared to the sham group ($t(32.9) = 2.22$, $p = .033$, $b = 0.45$). An analogous effect was found for hyperactivity ($F(2, 32.5) = 4.22$, $p = .023$; $t(32.7) = 2.71$, $p = .011$, $b = 0.55$). Both effects were not significant during the follow up session (total ADHD symptoms: $t(28.9) = 0.61$, $p = .546$, $b = 0.07$, hyperactivity: $t(29.0) = 0.26$, $p = .796$, $b = 0.04$). For the self-rating of inattention, there was no significant Group x Session effect ($F(2, 32.7) = 2.73$, $p = .080$). Further, self-ratings of impulsivity as well as all parent-ratings showed no effects of tDCS (all $p \geq .269$). Parents reported reduced scores on all ADHD symptom scales from baseline to the post session that did not differ between verum and sham conditions (ADHD total: $F(1, 27.5) = 11.50$, $p = .002$, $b = -0.36$, inattention: $F(1, 27.9) = 11.93$, $p = .002$, $b = -0.55$, hyperactivity: $F(1, 26.4) = 6.83$, $p = .015$, $b = -0.24$, impulsivity: $F(1, 28.1) = 6.49$, $p = .017$, $b = -0.36$). Results of transfer tasks and clinical assessments are summarized in Table 12.

Table 12. Effects from five-day tDCS on transfer tasks and clinical ratings. Mean and standard deviations for behavioral measures of the flanker and spanboard transfer tasks are given, as well as for clinical assessments with the DISYPS-II. Significant tDCS effects are indicated.

	ADHD sham *n* = 13	ADHD 0.5 mA *n* = 9	ADHD 0.25 mA *n* = 11	controls *n* = 13
Flanker task				
flanker effect on error rate in %				
baseline	14.08 (9.97)	8.76 (7.90)	11.21 (10.84)	18.93 (17.09)
post	8.85 (8.82)	5.71 (6.16)	6.92 (8.42)	14.20 (8.80)
follow up[c]	7.88 (9.35)	8.75 (8.66)	11.75 (15.59)	12.43 (10.19)
omission errors in %				
baseline	2.40 (2.86)	4.17 (6.02)	2.24 (4.20)	0.44 (1.15)
post	4.13 (4.85)	1.60 (1.74)	4.62 (7.59)	0.15 (0.53)
follow up[c]	4.13 (8.28)	8.44 (13.24)	0.78 (1.48)	0.30 (0.72)
reaction time in ms				
baseline	589 (77)	579 (120)	613 (73)	549 (35)
post	609 (109)	566 (103)	619 (79)	522 (29)
follow up[c]	600 (94)	553 (72)	571 (64)	466 (25)
reaction time variability in ms				
baseline	148 (33)	182 (38)	192 (38)	180 (10)
post	153 (57)	132 (51)**, [a]	178 (44)	157 (13)
follow up[c]	147 (44)	147 (56)	119 (27)	95 (18)
Spanboard task				

error rate in %				
baseline	25.26 (10.89)	26.39 (8.01)	25.68 (9.49)	17.29 (6.78)
post	25.00 (10.41)	21.39 (14.48)	27.37 (5.00)	14.23 (4.72)
follow up[c]	24.81 (7.39)	23.13 (9.43)	25.31 (17.55)	14.62 (6.68)
omission errors in %				
baseline	9.36 (8.09)	14.72 (14.65)	7.35 (5.31)	2.08 (2.98)
post	9.81 (10.48)	6.39 (10.47)*, [a]	12.37 (11.70)	1.54 (2.98)
follow up[c]	11.92 (14.65)	15.94 (15.98)	6.56 (6.11)	0.77 (2.14)
DISYPS-II				
self-rating ADHD total				
baseline	1.18 (0.50)	1.12 (0.48)	1.25 (0.79)	0.58 (0.37)
post	1.00 (0,60)	1.39 (0.40)*, [b]	0.96 (0.69)	0.53 (0.62)
follow up[c]	1.01 (0.57)	1.02 (0.62)	1.16 (0.55)	0.59 (0.56)
self-rating inattention				
baseline	1.37 (0.68)	1.33 (0.48)	1.34 (0.79)	0.64 (0.30)
post	1.09 (0.65)	1.50 (0.39)	0.93 (0.52)	0.60 (0.57)
follow up[c]	1.04 (0.62)	1.10 (0.51)	1.22 (0.69)	0.63 (0.48)
self-rating hyperactivity				
baseline	0.99 (0.58)	0.87 (0.51)	1.00 (0.84)	0.43 (0.42)
post	0.82 (0.63)	1.27 (0.41)*, [b]	0.87 (0.84)	0.38 (0.64)
follow up[c]	0.96 (0.60)	0.86 (0.74)	0.96 (0.42)	0.46 (0.60)
self-rating impulsivity				
baseline	1.10 (0.70)	1.08 (0.81)	1.45 (1.01)	0.83 (0.87)
post	1.13 (0.71)	1.38 (0.72)	1.18 (1.01)	0.65 (0.84)
follow up[c]	1.06 (0.63)	1.03 (0.83)	1.34 (0.78)	0.71 (0.87)
parent-rating ADHD total				
baseline	1.52 (0.78)	1.81 (0.58)	1.58 (0.47)	0.28 (0.20)
post	1.15 (0.74)	1.32 (0.63)	1.23 (0.45)	0.28 (0.38)
follow up[c]	1.08 (0.59)	1.29 (0.31)	1.12 (0.41)	0.30 (0.23)
parent-rating inattention				
baseline	2.00 (0.85)	1.93 (0.60)	1.89 (0.51)	0.37 (0.19)
post	1.44 (0.63)	1.55 (0.71)	1.49 (0.64)	0.40 (0.49)
follow up[c]	1.54 (0.69)	1.67 (0.47)	1.47 (0.51)	0.34 (0.28)
parent-rating hyperactivity				
baseline	1.02 (0.67)	1.64 (0.76)	1.03 (0.57)	0.13 (0.29)
post	0.79 (0.84)	1.03 (0.65)	0.79 (0.54)	0.09 (0.21)
follow up[c]	0.49 (0.51)	0.94 (0.36)	0.64 (0.51)	0.19 (0.32)
parent-rating impulsivity				
baseline	1.46 (1.10)	1.83 (0.84)	1.85 (0.73)	0.33 (0.41)
post	1.19 (0.94)	1.29 (1.04)	1.34 (0.63)	0.35 (0.62)
follow up[c]	1.03 (0.87)	1.05 (0.78)	1.16 (0.74)	0.40 (0.42)

*†p ≤ 0.055, *p < 0.05, **p < 0.01, [a]improved, [b]impaired*

[c] ADHD 0.5 mA: n = 8, ADHD 0.25 mA: n = 8

5.3.5 Event-Related Potentials

Successful nogo trials and *n*-back target trials elicited a P3 component with a parietal maximum (Figure 18). Over all groups, the nogo P3 component peaked at 554 ms and the *n*-back target P3 peaked at 383 ms during the baseline session.

All groups showed a reduced nogo P3 peak amplitude from baseline to post with a difference of -4.66 μV (*SD* = 5.85 μV) in the control group. While this difference (post – baseline) was -7.97 μV (*SD* = 3.48 μV) in the sham group, it was only -4.54 μV (*SD* = 5.08 μV) in the 0.5 mA group, but -9.67 μV (*SD* = 4.23 μV) in the 0.25 mA group. This resulted in a significant interaction effect between Group and Session ($F(2, 32) = 3.90$, $p = .030$). However, a direct comparison between the sham vs. 0.25 mA group revealed no effect ($t(32) = -1.04$, $p = .305$, $b = -1.70$) and the difference between the ADHD 0.5 mA group and the ADHD sham group failed to reach significance ($t(32) = 1.92$, $p = .064$, $b = 3.43$). An exploratory direct comparison between the 0.5 mA group and the 0.25 mA group was conducted, which demonstrated a larger baseline to post difference in the 0.25 mA group than in the 0.5 mA group ($t(32) = -2.78$, $p = .009$, $b = -5.12$). During the follow up session, there was no Group x Session interaction effect ($F(2, 28.1) = 0.35$, $p = .706$).

For the *n*-back target P3 amplitude, there was no interaction effect between Group and Session, indicating no significant effect of tDCS on this component ($F(2, 27) = 0.88$, $p = .427$), sham: $M = -5.52$ μV, $SD = 6.65$ μV, 0.5 mA: $M = -1.50$ μV, $SD = 4.87$ μV, 0.25 mA: $M = -3.98$ μV, $SD = 7.72$ μV, controls: $M = -3.06$ μV, $SD = 5.56$ μV).

5.4 Discussion

In the present study, children and adolescents with ADHD underwent a five-day application of HD-tDCS to the right IFG with the aim to improve response inhibition and working memory. In contrast to our hypothesis, we found no general beneficial effects on these executive functions. Although, there was overall a good compliance to the stimulation with only few and mild side effects, about half of the patients reported painful sensations when receiving tDCS at a current intensity of 0.5 mA. Thus, in this subset of patients, current intensity was reduced by 50%. This caused crucial differences in the response to stimulation. While patients in the 0.5 mA group showed improved attentional measures, the group that received stimulation with reduced intensity of 0.25 mA showed impaired response

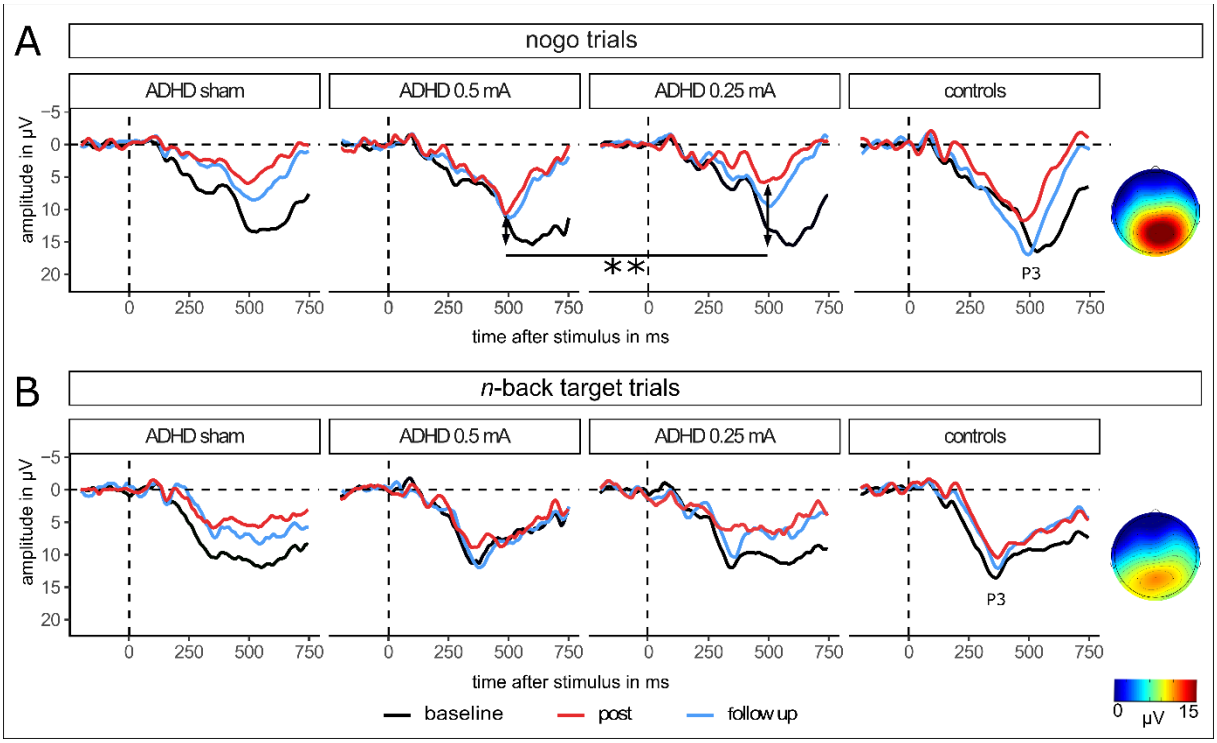

Figure 18. Averaged ERPs for repetitive tDCS applications. Averaged ERP waveforms are illustrated for a parietal ROI (P3, Pz, P4). Nogo trials **(A)** showed a significant interaction for the post - baseline difference between the ADHD 0.5 mA group and the 0.25 mA group (p = .009). No tDCS effects were detected for n-back target trials **(B)**. Topographical plots averaged over all groups are given for the baseline session at 525 ms for the nogo P3 and at 400 ms for the n-back target P3 component.

inhibition. Analogously, the investigation of neurophysiological parameters revealed opposite effects of tDCS applications with different current intensities.

We found detrimental effects of HD-tDCS with a low current intensity of 0.25 mA on response inhibition, which stands in contrast to our hypothesis as we aimed to improve this executive function by increasing excitability of the right IFG. Although anodal tDCS usually has excitatory effects on stimulated brain areas (Stagg & Nitsche, 2011), there are indications that this can be reversed when tDCS is applied with weak currents. Using the stimulation techniques transcranial alternating stimulation (tACS) and transcranial random noise stimulation (tRNS) low current intensities of 0.4 mA were demonstrated to induce cortical inhibition before switching to excitatory effects at higher current intensities (Moliadze et al., 2012). A possible explanation for this phenomenon is that varying current intensities affect different cortical systems, which changes stimulation effects fundamentally (Moliadze et al., 2012). In accordance, it was demonstrated that tDCS induces opposite effects in different cortical layers (Purpura & Mcmurtry, 1965). Unfortunately, there are only few data on this subject for anodal tDCS. However, the original data of Nitsche & Paulus (2000) show a non-

significant trend towards an inhibitory effect on the motor cortex when applying tDCS with sponge electrodes at a weak current intensity of 0.4 mA (Moliadze et al., 2012). Nevertheless, it is not entirely predictable how current intensities applied with sponge electrodes in adults translate into the application of HD-tDCS in children and adolescents, and further how stimulation effects on the motor cortex differ from those in frontal areas. Still, we speculate that the detrimental effect of low intensity HD-tDCS in the present study could result from an inhibitory stimulation effect.

An inspection of response inhibition data over the course of the five-day stimulation, revealed a cumulating effect of stimulation. While no alterations in performance occurred during initial tDCS applications, the effect became more pronounced from session to session and yielded significance at tDCS session five. This finding is in line with prior studies, demonstrating that tDCS effects cumulate when applied on a daily basis (Alonzo et al., 2012). As a positive consequence, this makes tDCS a promising tool to induce long-lasting changes in the highly plastic brain of children and adolescents (Krause & Cohen Kadosh, 2013). Then again, it bears the risk of inducing unintended and potentially harmful alterations in brain activity (Vicario & Nitsche, 2013). Fortunately, in the present study detrimental tDCS effects reduced quickly, and were not significant during post and follow up sessions. Still, the results demonstrate the utmost relevance for research on the topic of multiple tDCS session, especially in the light of a growing do-it-yourself community, which administrates stimulation without expert supervision (Wexler, 2018).

No beneficial effects of tDCS were found on response inhibition or working memory at behavioral level, with neither of the applied current intensities. It is plausible that the current intensities in the present study, with a maximum of 0.5 mA, were too low to induce positive effects. This is not unlikely because the induced current density in the brain is lower when using HD-tDCS than when using conventional sponge electrodes (Miranda et al., 2009). However, when we applied tDCS with sponge electrodes and larger current intensities in a previous study, no behavioral improvements were found for the same task either (Breitling et al., 2020). While detrimental effects on response inhibition indicated a crucial role of the right IFG for this function, no positive or negative effects were detected on working memory. This finding of a lack of tDCS induced working memory effects is in line with a meta-analysis of Salehinejad et al. (2019) that demonstrated no tDCS effects on working memory accuracy in ADHD patients as well. Moreover, two meta-analyses on tDCS in healthy individuals, demonstrated only small improvements (Mancuso et al., 2016) or mixed effects

(Hill et al., 2016) for working memory tasks. Thus, it is possible that working memory is an executive function that is difficult to improve with the method of tDCS, particularly in ADHD patients.

Although no positive tDCS effects were detected on the targeted executive functions, we found beneficial effects of 0.5 mA tDCS on measures of attention. So, reduced reaction time variability was demonstrated for the daily applied *n*-back/nogo task and also for the transfer flanker task. In the present study, reaction time variability was indicated via the standard deviation of reaction time. Although the standard deviation is positively correlated with mean reaction times (Kofler et al., 2013) the effect on variability cannot be fully explained by a confounding of both parameters as we found no tDCS induced changes in mean reaction times. This replicates a finding from Breitling et al. (2016), where beneficial effects on reaction time variability were found in a flanker task after applying single sessions of right IFG stimulation using large sponge electrodes. High levels of reaction time variability are a consistent finding in ADHD patients with larger effects sizes than for most neuropsychological ADHD markers. They are assumed to reflect lapses in sustained attention (Tamm et al., 2012) and are a specific marker for ADHD (Salum et al., 2019). Reaction time variability can be reduced by the intake of stimulants but not with behavioral ADHD therapy (Kofler et al., 2013). Thus, the tDCS induced reduction in variability indicates a beneficial influence on ADHD related processing mechanisms, reducing the level of fluctuating brain activity in patients. This variability reduction cumulated over tDCS sessions, suggesting dose-dependent effects of daily tDCS applications (Alonzo et al., 2012; Song et al., 2019). Moreover, reduced reaction time variability was still demonstrated four months after the end of tDCS sessions, which replicates results of long-lasting tDCS effects in previous studies (Cohen Kadosh et al., 2010; Katz et al., 2017). These findings are promising for the development of an tDCS based therapy approach, as it could allow the induction of large effects that are stable over longer time periods.

Furthermore, reduced rates of omission errors were detected in the 0.5 mA tDCS group during the transfer spanboard task. Omission errors are a further marker for attentional lapses (Epstein et al., 2010) and have been associated with inattentive and hyperactive/impulsive ADHD symptom severity (Epstein et al., 2003; Bezdjian et al., 2009). Therefore, reduced omission errors indicate, again, beneficial tDCS effects on attentional deficits. Effects on omission errors could not be demonstrated for the *n*-back/nogo task and for the flanker task, as these yielded only marginal significance. However, findings of

reduced omission errors together with findings from reduced reaction time variability suggest that tDCS as applied in the present study improved attention in ADHD patients.

In contrast, beneficial effects on measures of attention were not reflected by clinical assessments of ADHD symptoms via self and parent-ratings. In self-ratings of total ADHD symptoms and of hyperactive symptoms, patients reported a higher symptom severity after the applications of tDCS with a current intensity of 0.5 mA. This stands not only in contrast to attentional measures but also to previous tDCS studies that found beneficial tDCS effects on the perceived symptom load in ADHD patients and their parents (Cachoeira et al., 2017; Soff et al., 2017). The relevance of this finding remains to be explored. Parents reported a reduced ADHD symptom load in their children after tDCS interventions not only in verum tDCS groups but also in the sham group. This might reflect hopes on tDCS as a new treatment approach that could effectively reduce symptoms and further, it demonstrates the acceptance of tDCS as a potential intervention for ADHD (Buchanan et al., 2020).

EEG data revealed opposite effects of tDCS with 0.25 mA and 0.5 mA on the nogo P3, with a larger decrease of the peak amplitude from baseline to post for the 0.25 mA group than for the 0.5 mA group. A decline in P3 amplitudes was observed not only in all ADHD groups but also in healthy controls and likely reflects a habituation effect caused by repeated applications of the cognitive task (Kinoshita et al., 1996). Still, larger nogo P3 components have been associated with better inhibitory functions (Jonkman, 2006; Smith et al., 2008) and ADHD related reductions of the P3 are normalized by the intake of methylphenidate (Shahaf et al., 2015). Therefore, the group difference in P3 reduction suggests a detrimental effect of stimulation in the 0.25 mA group, compared to a beneficial effect in the 0.5 mA group. However, we emphasize that this result is based on an exploratory group comparison and that no difference to the ADHD sham group was detected. Still, a detrimental neurophysiological effect after receiving 0.25 mA tDCS is in line with the behavioral finding of increased nogo commission errors in this group and strengthens the hypothesis of an inhibitory effect of low dose stimulation. Moreover, a positive effect of 0.5 mA tDCS on the P3 component fits the finding of beneficial tDCS effects in this group that were suggested by reduced omission errors and reduced reaction time variability. No effect of stimulation was detected for the P3 component during *n*-back target trials, which stands in contrast to results from a prior experiment using an identical montage (Breitling et al., 2020). However, it must be noted that the sample size in the present study was small, increasing the risk of type II errors.

For most cognitive measures, participants showed little to no training gains over multiple task applications. Working memory performance was reduced from baseline to post and omission errors, as a measure of attention, increased, especially in ADHD patients. Training effects during repeated applications of cognitive tasks were demonstrated to depend on numerous factors as training intensity, training duration, motivational factors, and task difficulty (Von Bastian & Oberauer, 2014). We assume that motivational factors were the main contributor to the performance decay in ADHD patients as patients reported boredom to do the same task every day. Jones et al. (2015) demonstrated that more motivational task versions that included incentives led to higher benefits of tDCS on a working memory task. Therefore, increasing motivational task features could be a relevant aspect to induce stronger tDCS effects. This should be of a special relevance in ADHD patients, as they have lower levels of motivation compared to other children and adolescents (Smith & Langberg, 2018). Task engagement could be increased by using more attractive training programs with an adaptive character that include feedback (Von Bastian & Oberauer, 2014; Tricomi & Depasque, 2016).

In the present study, tDCS was applied using a 4 x 1 HD-tDCS montage. This offers the opportunity to increase focality of the stimulation by restricting the current flow to the area circumscribed by the electrode ring (Datta et al., 2009a), hereby reducing the risk of unintended changes in non-target brain regions. However, painful skin sensations at stimulated sites were reported by participants already at very low current intensities, requiring the reduction of current intensity in a subset of patients. These sensations were likely caused by high current densities on the scalp due to the small electrode size. Indeed, HD-tDCS has been found to induce higher levels of cutaneous sensations in the initial minutes of stimulation compared to conventional tDCS with sponge electrodes (Antal et al., 2017). Still, it was demonstrated to be tolerated well, even at high current intensities of 3 mA (Reckow et al., 2018). Although this result stems from elderly participants, we expected that current intensities as low as 0.5 mA would be tolerated by children and adolescents. Thus, the necessity to reduce current intensities was surprising and suggests that this montage is not appropriate for children and adolescents. An alternative is the multichannel stimulation, which yields high focality by distributing several electrodes at optimized locations on the scalp, which restricts the current intensity per electrode site (Ruffini et al., 2018).

The most important limitation of the present study is its small sample size. This is particularly problematic because the verum ADHD group was split into two groups, with

only 9 and 11 patients remaining in each. Further, the application of current intensities was not randomly assigned but depended on the individual cutaneous sensitivity. Although we did not find different characteristics between groups, confounded factors due to a self-selected sample cannot be ruled out. It would be conceivable that group differences, for example in ADHD symptoms, were confounded with the divergent performance changes between groups. Thus, we emphasize that the division into groups of different current intensities did not correspond to the originally intended study design, but was a post-hoc exploratory analysis. A further limitation was that the presented analyses were not corrected for multiple comparisons. For these reasons, the present study must be regarded as exploratory and the demonstrated findings remain to be replicated in future experiments.

5.4.1 Conclusions

The results of the current study suggest that the repetitive application of HD-tDCS to the right IFG in children and adolescents with ADHD can generate opposite effects, depending on current intensity. While stimulation with regular current intensity improved attention in ADHD patients, low-dose tDCS caused detrimental effects on response inhibition. Response inhibition impairments were detected not after one, but only after multiple stimulation sessions. Detrimental tDCS effects after repeated low-dose stimulations are a novel finding and emphasize the need for more research on repeated tDCS applications to enable a deeper understanding of stimulation mechanisms. Still, beneficial tDCS effects on attention showed a cumulative pattern over repeated stimulation sessions as well and were detectable even four months after the end of stimulation. This is a promising finding, which raises hope for the future development of tDCS-based therapy approaches that could yield sustained positive effects on ADHD symptoms.

6 General Discussion

6.1 Summary and Implications of the Findings

In the presented dissertation, the application of anodal tDCS to the right IFG was investigated in children and adolescents suffering from ADHD to target executive dysfunctions. For this purpose, a combined paradigm was introduced with the aim to reliably and economically assess behavioral and neurophysiological correlates of working memory and response inhibition. In subsequent tDCS experiments, it was intended to improve these executive functions via anodal right IFG stimulation in ADHD patients. Moreover, in order to develop an effective tDCS protocol with a low risk for side effects, a conventional tDCS application was compared to a more focal HD-tDCS montage that induced peak current densities in the targeted brain area while excluding the unintended stimulation of other regions. Then, this HD-tDCS montage was applied repetitively over five days in ADHD patients to more pronounced and longer-lasting effects. In all experiments, behavioral and neurophysiological outcome parameters were evaluated and healthy control groups were included, which allowed a systematical evaluation of tDCS induced alterations in ADHD patients. The implications of the findings are discussed in the following.

In the first experiment, the combined *n*-back/nogo paradigm was introduced that allowed the simultaneous assessment of working memory and response inhibition and thus, offered an economical alternative to applying single task versions of *n*-back and go/nogo (Breitling-Ziegler et al., 2020). This can be relevant in research on transfer effects after cognitive interventions. Although there have been dual-task applications in ADHD before, these were mostly not based on systematic validations questioning the validity of their results. For the combined *n*-back/nogo task, strong correlations with parallel single task versions of *n*-back and go/nogo were confirmed for behavioral outcome measures as well as comparable ERP structures. Most important, investigation of discriminant validity showed that the combined *n*-back/nogo paradigm assessed working memory and response inhibition as distinct cognitive functions. In ADHD patients, the combined task was suitable to detect typical behavioral impairments in working memory, response inhibition, and sustained attention via omission errors and reaction time variability, as well as related reductions of the P3 amplitude. However, the combined task version showed a better performance for the working memory aspect compared to the single *n*-back task and a reduced number of

omission errors. Still, for the examined sample of ADHD patients between 10 and 17 years this resulted in an appropriate difficulty level of the combined task that induced high levels of sustained attention together with stable task performance

With the successful validation of this paradigm, the combined *n*-back/nogo task provides an economical alternative to single task versions with relevance not only for research in ADHD patients but also other clinical populations who require short experimental procedures. Further, the validation of the combined *n*-back/nogo paradigm justified its application in the subsequent experiments of this dissertation to assess behavioral and neurophysiological correlates of working memory and response inhibition for the evaluation of tDCS effects. Moreover, the combined *n*-back/nogo task was applied with the aim to trigger right IFG activation during tDCS. This was central for the success of stimulation, because tDCS interacts with endogenous neuronal mechanisms and thus, is most effective if the targeted brain region is in an activated or pre-activated state (Kronberg et al., 2020).

In experiment 2, the effects of single tDCS applications to the right IFG were investigated in ADHD patients, together with a methodological comparison between two different electrode montages (Breitling et al., 2020). In most clinical studies, tDCS is applied in a bipolar configuration using large sponge electrodes, but such a conventional montage results in wide spread patterns of electrical fields in the brain. In contrast, HD-tDCS with a 4 x 1 configuration of small disc electrodes induces a more focused current flow with the highest current densities occurring mainly in the target brain area. ERP analyses of the *n*-back/nogo task revealed that the P3 amplitude was increased and the N2 amplitudes was decreased during working memory trials for both tDCS montages. Thus, these components were more in resemblance to typically developing peers after active stimulation, indicating favorable changes in underlying higher order processing mechanisms. At the same time, the utility of this tDCS approach for clinical applications was limited by the absence of an overall behavioral effect. It can be concluded that tDCS has induced subtle changes in brain activity, which were detectable in neurophysiological markers but were subthreshold to translate into behavior. This finding illustrates the importance to assess brain activity in tDCS research, for example via EEG, as a way to detect subtle alterations in underlying brain processes, which are too weak to be measured reliably using behavioral outcome measures. It was intended to amplify the effects of right IFG stimulation in the next step, by applying tDCS not only for a single session but repeatedly. With this approach, improvements in behavioral outcome parameters were expected.

Exploratory in-depth analyses of behavioral data from experiment 2 revealed high inter-individual differences in response to stimulation, a topic which is currently much debated. While the rate of responders to tDCS is typically around 50% (Ziemann & Siebner, 2015), intraindividual variability is much lower (Lopez-Alonso et al., 2014). It was suggested that characterizing tDCS responders could be the key to overcome the limitation of low responder rates. Once we understand, which characteristics determine the response to tDCS, adjustments could be made for non-responders to eventually turn them into responders (Fins et al., 2017). According to this idea, in experiment 2 it was investigated which characteristics distinguished between responders and non-responders, and a negative correlation was identified between the response to HD-tDCS and hyperactive symptom load. However, this finding resulted from an exploratory post-hoc analysis and remains to be replicated. Still, research showed that individual factors are highly relevant for the success of tDCS. For example, the tDCS outcome seems to be influenced by genetics (Nieratschker et al., 2015; Wiegand et al., 2016) and in patients with depression, researchers succeeded in predicting the individual success of a tDCS treatment from baseline EEG activity (Al-Kaysi et al., 2017). Such approaches will receive growing attention in the future, with the trend towards a personalized medicine of tailored therapies for individual patients.

In experiment 2, the overall induced effects of HD-tDCS were only weak, but the effectiveness of this configuration was comparable to the conventional tDCS application, indicated by a similar influence on neurophysiologial components. At the same time, current flow simulations revealed lower current densities on the cortical surface for HD-tDCS together with a much higher precision towards the target area. In contrast, conventional stimulation induced current density peaks also in non-target brain areas, which could enhance the risk for unintended changes in brain functioning. With an approach of using the lowest dose necessary in order to reduce the risk of side effects, it seemed preferable to use HD-tDCS over conventional tDCS.

Therefore, this HD-tDCS configuration was further investigated in experiment 3, where it was administered in ADHD patients over the course of five consecutive days in a sham-controlled trial while applying the *n*-back/nogo task (Breitling-Ziegler et al., accepted for publication). After the application of this stimulation protocol, positive effects manifested as a lower rate of omission errors and reduced reaction time variability, parameters which indicated enhanced effects on sustained attention. Positive effects on attention were demonstrated not only for the *n*-back/nogo task, but were confirmed also in non-trained

transfer tasks, increasing the reliability of this finding. Further, these attentional improvements showed a cumulative pattern with a tendency towards increasing effect sizes from session to session suggesting that the effectiveness of stimulation could be even further enhanced by conducting more sessions. However, it was demonstrated that five applications were sufficient to induce effects on reaction time variability that were still detectable four months after the end of the intervention. In healthy individuals, long-term effects over this period have been demonstrated before (Cohen Kadosh et al., 2010; Katz et al., 2017). However, as sustainable tDCS effects rely on dopaminergic plasticity mechanisms (Nitsche et al., 2006; Kronberg et al., 2020), it was unclear if the same applies for ADHD patients, who show dysfunctions in dopaminergic pathways (Madadi Asl et al., 2019). Therefore, this finding of long-term effects is encouraging for the further development of tDCS based therapy approaches in ADHD.

However, although tDCS yielded promising effects on attention as a core deficit in ADHD, right IFG stimulation did not generate the hypothesized improvements for behavioral measures of working memory and response inhibition. A possible explanation for the absence of these effects would be that the right IFG was not targeted successfully. Although current flow simulations indicated an appropriate placement of HD electrodes, anatomical differences presumably reduced the focality for individual patients (Laakso et al., 2015). Posner & Petersen (1990) stressed the importance of the right prefrontal cortex for attentional functions, particularly for alertness. Unspecific effects on attention as they were found in experiment 3 could thus, be explained by the stimulation of a right lateralized prefrontal attention network instead of the targeted stimulation of the right IFG.

Another option is that the right IFG does not play a key role for ADHD related executive dysfunctions, as it was considered. Research on the relationship between the hypoactivation of this brain area with response inhibition and working memory deficits stems from imaging methods, which allow mainly correlational but only restricted causal conclusions (Filmer et al., 2014). Therefore, there is no certainty that the successful excitation of the right IFG would have a positive impact on executive functioning in ADHD. Instead, other brain regions could be more productive. Most previous tDCS research in ADHD has targeted the left DLPFC with a meta-analysis of Salehinejad et al. (2019) finding small to medium sized benefits on inhibition. However, while this meta-analysis concluded on the superiority of left DLPFC over right IFG stimulation, it included only one study that investigated tDCS of the right IFG (Breitling et al., 2016). Therefore, this seems to be a premature conclusion, while right IFG

studies were still pending, with this dissertation containing the early research activities on this topic. Moreover, left DLPFC stimulation could not yield beneficial effects on accuracy in working memory tasks either (Salehinejad et al., 2019), challenging if this region is an optimal target region. Thus, to continue the research on further stimulation sites and methods in ADHD seems reasonable. It is also conceivable that best tDCS results are yielded by reinforcing network activity with the simultaneous stimulation of different target areas. Further, other methods of brain stimulation could be more successful, such as transcranial alternating current stimulation (tACS), or transcranial random noise stimulation (tRNS), a method which showed better effectiveness than tDCS on working memory enhancement in healthy individuals (Murphy et al., 2020). A further advantage of tRNS would be that this method causes weaker cutaneous sensations (Fertonani et al., 2015), which would allow for the use of higher current intensities with better tolerability in children.

An unexpected but critical finding of experiment 3 was the importance of current intensity for the direction of the induced tDCS effects. It was shown that the use of very weak current intensities of I = 0.25 mA resulted in detrimental outcomes for response inhibition performance, rather than being ineffective. This result was supported as tDCS with different current intensities induced opposite effects on the nogo P3 component, with the 0.5 mA group showing larger amplitude reductions compared to 0.25 mA. Although the explanation for this phenomenon remains speculative, in experiment 3 it was argued that anodal tDCS with low current intensity caused inhibitory instead of excitatory effects by affecting distinct cortical layers with weak electrical fields (Moliadze et al., 2012). However, independent of its principle, the finding that tDCS can induce detrimental effects, which have accumulated over repeated applications, demonstrates the high relevance for more research on side-effects of brain stimulation. Colzato et al. (2020) state that every method of neuroenhancement has to face the neuro-competition principle, which implies that cognitive enhancements are likely associated with downsides in other domains. Therefore, it would be desirable that long-term tDCS applications are monitored regularly for negative treatment outcomes, including effects on cognitive aspects. This topic becomes even more urgent in children because the developing brain goes through sensitive phases during which plasticity is particularly high and sustainable brain developments could be initiated (Vicario & Nitsche, 2013).

The reason for using very low current intensity stimulation was that some children and adolescents reported painful sensations, especially from HD-tDCS. This applied to both tDCS experiments and was attributable to the high current density on the scalp, which

resulted from the use of small disc electrodes with a diameter of only 1 cm. The experiments presented in this dissertation were the first applications of HD-tDCS in ADHD patients and one of very few applications in children. Although HD-tDCS has a decisive advantage over the use of conventional pad electrodes when it comes to focality, its practical application was restrained by painful skin sensations in the participants. Although high focality should remain the aim of tDCS electrode configurations, HD-tDCS might not be the best option to use in children. An alternative is optimized multi-channel stimulation that yields high focality by distributing several electrodes at optimized locations over the scalp, which restricts the current intensity per electrode site (Ruffini et al., 2018).

Besides the improvement of cognitive parameters, clinical ratings of ADHD symptom load are a further relevant outcome measure of tDCS. The meta-analysis by Brauer et al. (accepted for publication) evaluated such clinical effects of tDCS on the ADHD core symptoms of inattention, hyperactivity, and impulsivity and found an overall improvement of symptom severity. However, most tDCS studies did not assess clinical ratings and therefore, ADHD symptoms had to be derived from parameters that were assessed via cognitive paradigms. So, inattention was indicated by omission errors, and impulsivity was assessed via measures of response inhibition in the go/nogo or the stop-signal task. Thus, in future research a standard for the clinical evaluation of tDCS outcomes would be desirable. In experiment 3, ADHD symptoms were assessed via self and parent ratings. These revealed increased self-ratings of inattention after active stimulation, which contradicted the behavioral measures of improved attention. This finding stands in contrast to the results from Brauer et al. (accepted for publication), who showed improved attention after tDCS applications. However, most of the included studies targeted the left DLPFC and are therefore not comparable to the findings of right IFG stimulation. Thus, the origin of the negative clinical outcomes in experiment 3 remains unclear and detrimental effects of tDCS on clinical measures of ADHD symptoms must be ruled out in future studies.

The amount of reviews in the field of tDCS research in ADHD is remarkable and exceeds the number of original research articles (i.e. Palm et al., 2016; Rubio et al., 2016; Mirzaiyan et al., 2018; Cosmo et al., 2020; Salehinejad et al., 2020). Presumably, this reflects the ambivalence between a high interest in this topic, while critical voices doubt the usefulness of this approach (Filmer et al., 2020). Thus, there seems to be a desire to thoroughly inspect the existing studies in the search of new knowledge. However, although it is reasonable to

extract as much information as possible from the available research, it will not solve the main problem that more data on this topic is needed.

6.2 Limitations

The most important limitation of this dissertation is the small sample size, especially in the tDCS experiments 2 and 3, which contain 14 patients (within-subjects design) and 33 patients (between-subjects design), respectively. However, these sample sizes are comparable to those of other tDCS studies in children and adolescents with ADHD, which included between 9 and 24 patients. The small sample sizes in tDCS research result from the great effort and resources necessary for these studies in that several experimental sessions per participant are required. Further, the effort for recruitment is high, because carry-over effects do not allow for the repeated participation of the same individual in different studies without long intervals in between. From the participants' side, the realization of repeated experimental sessions requires a high compliance of the patients as well as their parents, who often accompanied their children to the research lab, and fortunately, there were very few drop-outs. Still, the involved effort set an initial barrier for the families to participate, especially for those who had little time or longer travelling distances. Moreover, participants were asked to refrain from ADHD medication during the duration of the tDCS intervention and on all days of experimental sessions. Thus, the inclusion of patients who took ADHD medication was restricted to weekends and school holidays, to avoid negative consequences from study participation on school performance. For future tDCS studies, the necessity to refrain from ADHD medication could be reconsidered, as tDCS could also be investigated as an add-on treatment to medication. This would expand the target group not only for tDCS research but also for future clinical applications. Still, in order to collect larger amounts of data on tDCS in ADHD patients, multicenter studies will be of advantage.

However, independent from these problems, small sample sizes limit the validity of experiments by reducing statistical power and thus, increasing the risk for type II errors. Moreover, among few subjects, single data points have more influence on the results, which increases the likelihood of false positive findings when exploratory analyses are applied that include more predictors than intended a priori (Forstmeier et al., 2017). A further problem concerns the EEG data. In a sample of children and adolescents with ADHD, neurophysiological data were suffering from a low signal-to-noise ratio due to a high load with motion and muscular artifacts as the patients tended to fidget during the experiment.

Therefore, more artifactual trials than usual needed to be removed and lower signal-to-noise ratios could be expected after the application of an ICA, which made the detection of effects less reliable. Therefore, although the assessment of EEG data during tDCS is a valuable method to evaluate altered brain activity, results need to be interpreted with caution.

A further limitation was that experiment 3 contained a deviation from the initial study design because different current intensities were applied between patients, with crucial consequences for the results. As this experiment was not designed to investigate the effects of current intensity, this condition was not randomly assigned to participants, but was rather determined by tDCS induced skin sensations. This procedure leaves room for alternative explanations concerning potential, systematic group differences, which were possibly associated with a sensitivity to tDCS induced sensations. In this dissertation, it was focused on transparency for the description of this a posteriori deviation from the original study design. Still, the results must be regarded as exploratory and need to be replicated. To ensure objective data interpretation in the future and to avoid publication bias in the field of tDCS, preregistering should be considered.

6.3 Outlook

The data presented in this dissertation encourage the conclusion that tDCS of the right IFG can be a promising treatment approach with the potential to promote a favorable brain development in children and adolescents with ADHD. Still, several methodological questions should be explored to optimize its results. For example, there is no consensus on the optimum current intensity. Although Agboada et al. (2019) found larger effect sizes for higher current intensities there seems to be no simple dose-response relationship (Esmaeilpour et al., 2018). Further, tDCS outcomes were demonstrated to be brain state dependent with indications for an inverted U-shaped relationship between the pre-activation of the targeted brain area and the effectiveness of stimulation (Fricke et al., 2010; Bocci et al., 2014; Gill et al., 2015). Therefore, factors that influence the level of brain activation (i.e. task difficulty, task engagement, or individual characteristics) must be taken into account, which complicates the design of universally applicable stimulation protocols. Similar to this topic, as tDCS interacts with endogenous brain mechanisms, better results from online compared to offline tDCS were found (Martin et al., 2014). However, a meta-analysis questioned this result for ADHD, because positive effects on symptom severity were only significant for studies that applied offline stimulation protocols (Brauer et al., accepted for publication).

When applying repetitive tDCS a further problem concerns the optimal inter-session-interval. Cumulated tDCS effects were demonstrated only for daily but not second daily stimulation (Alonzo et al., 2012) and data from this dissertation confirmed cumulative effects from tDCS applications over five consecutive days. However, future research needs to clarify optimal intervals for interventions over longer time periods (i.e. several months) that aim to induce durable effects. These questions need to be answered in systematic investigations to develop a standardized tDCS protocol that can be advised for clinical use in ADHD patients. Moreover, an important topic in ADHD concerns the impact from stimulant medication. While TMS research found beneficial effects from atomoxetine on the effectiveness of stimulation (Cao et al., 2018), there are no data for tDCS, although this would be highly relevant in order to develop multi-modal treatment approaches with tDCS as an add-on therapy to medication.

Interindividual variability is a great challenge in tDCS research but the individual effectiveness of stimulation has been linked directly to the magnitude of electric fields induced in the target brain region of individuals (Laakso et al., 2019). The patterns of electric fields that are induced in the human brain depend on individual anatomy with skull size and thickness, tissue layers, cerebrospinal fluid, and gyral variations accounting for variations (Li et al., 2015). Moreover, differences in functional anatomy between individuals causes further differences in the current flow (Gratton et al., 2018). For these reasons, computer-based current flow simulations, which compute the distribution of electrical fields in the brain using MRI based models, are constantly improved and can predict tDCS induced current flow patterns with a high precision. In the presented experiments, the software SCIRun5/BrainStimulator was used to create current flow simulations and to optimize electrode configurations (see Figure 19 for different software options to conduct current flow simulations). Such programs offer the possibility to optimize tDCS montages either with standardized head models or even using individual MRI data (Miranda et al., 2018). Although acquiring MRI data before applying tDCS would be expensive, the approach of individual modeling receives increasing attention among researchers, because it has the potential to boost tDCS outcomes considerably. Thus, if it can be implemented successfully, this approach will be relevant for clinical applications as well, to increase the effectiveness of tDCS based therapies.

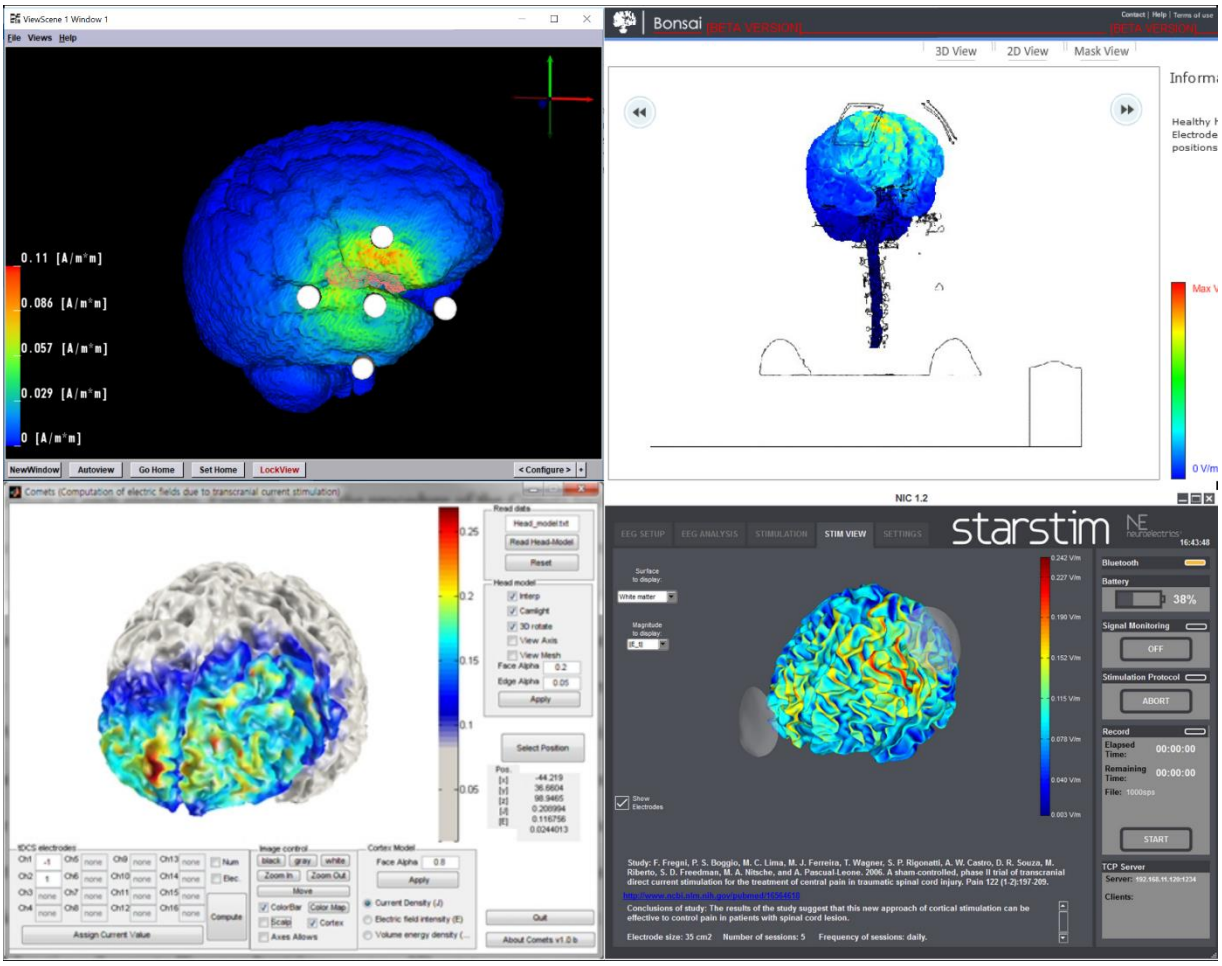

Figure 19. Software for current flow simulations. Upper left: SCIRun5/BrainStimulator (SCI-Institute, 2018), upper right: Bonsai[3], lower left: Comet[4], lower right: StimWeaver (Neuroelectrics)[5].

The results of this dissertation and of recent meta-analyses (Salehinejad et al., 2019; Westwood et al., 2020; Brauer et al., accepted for publication) suggest that tDCS applications in children and adolescents with ADHD need to be explored further before the regular use in clinical practice can be advised. Still, in Germany there are already treatment options for this method in medical practices and clinics in the form of individual health services, with the costs not being covered by the statutory health insurance[6]. Although tDCS research in this field is still at an early stage, without a sufficient proof of effectiveness in ADHD therapy,

[3] adapted from http://software.neuralengr.com/, 27.10.2020

[4] adapted from http://cone.hanyang.ac.kr/BioEST/Kor/Comets.html, 27.10.2020, Lee, C., Jung, Y.-J., Lee, S.J. & Im, C.-H. (2017). COMETS2: An advanced MATLAB toolbox for the numerical analysis of electric fields generated by transcranial direct current stimulation. *Journal of Neuroscience Methods* 277, 56-62. doi: https://doi.org/10.1016/j.jneumeth.2016.12.008.

[5] adapted from https://www.neuroelectrics.com/wiki/index.php/File:StimViewer2.png, 27.10.2020

[6] https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwjT9bmpr-PrAhVOM-wKHe5tB_AQFjADegQIAxAB&url=https%3A%2F%2Fwww.neurocaregroup.com%2Ffiles%2Fneurocare%2FDownloads%2FneuroCare_Adressen_tDCS_Klinik.pdf&usg=AOvVaw1atOD-YqUXtGoTFZSltEae, 27.10.2020

families accept such treatments and pay for it. This highlights the urgent desire for effective, non-pharmacological therapy options in ADHD, which was confirmed in the contact with families during the research for this dissertation, who were mostly open to tDCS and appreciated research efforts in this area.

Perspectively, the most practical tDCS application would be a self-administered home treatment (Sierawska et al., 2019). This would allow long-term treatments at a reasonable cost-benefit-ratio. For this purpose, engineers work on simplifying tDCS settings and develop dry electrodes for the convenient use (Khadka et al., 2018). However, home treatments will introduce new problems caused by the self-administration of stimulation, which would not occur in the laboratory. Electrode drifts of only few centimeters were demonstrated to change the effectiveness of stimulation (Woods et al., 2015) and therefore, user-friendly devices need to ensure the precise electrode placement and prevention of misuse. Still, optimism is appropriate as first studies have successfully implemented home treatments in patients with depression (Alonzo et al., 2019).

In conclusion, tDCS is an easy, cheap, and portable method to promote favorable brain activity in defined areas, with the potential to induce long-lasting changes when applied repeatedly. It has a good safety profile and thus, it is suitable for the application in children and adolescents. This makes tDCS a promising approach with a potential therapeutic value in ADHD (Muszkat et al., 2016). Although right IFG stimulation as it was applied in this dissertation could not yield the aimed enhancements of working memory and response inhibition, beneficial effect on inattention as a core symptom of ADHD were demonstrated and sustained for four months after the end of the intervention. This indicates a great potential of this approach, although several questions need to be answered before the standardized application in clinical practice should be advised. This dissertation contributed to a better understanding of right IFG stimulation in ADHD and in the long-term, it will hopefully be one piece of the puzzle towards the development of non-invasive brain stimulation as an effective, non-pharmacological treatment approach for children and adolescents with ADHD.

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Appendix

Supplementary Table S1. Results from experiment 1, separated after original studies. Comparisons between control and ADHD groups, given separately for two different studies from which ADHD data were pooled, mean ± standard deviation.

		ADHD (n = 24)			ADHD (n = 10)		
	controls	values	t	p	values	t	p
WM in %	73.83 ± 15.39	49.43 ± 22.76	$t(47.0) = 4.41$	< .001	56.87 ± 21.07	$t(33.0) = 2.65$	.012
RI in %	87.44 ± 8.35	73.52 ± 19.42	$t(31.0) = 3.24$	.003	88.25 ± 6.76	$t(33.0) = -0.27$	.788
omission errors in %	1.07 ± 1.25	10.14 ± 11.89	$t(23.5) = -3.72$	.001	2.47 ± 1.81	$t(12.6) = -2.25$	.043
reaction time in ms	722 ± 194	839 ± 206	$t(47.0) = -2.05$	.046	819 ± 182	$t(33.0) = -1.35$	.186
SD of reaction time in ms	252 ± 72	330 ± 69	$t(47.0) = -3.86$	< .001	282 ± 74	$t(33.0) = -1.09$	.284
n-back P3 amplitude at Pz in µV	17.53 ± 7.33	14.56 ± 4.77	$t(47.0) = 1.67$	.101	11.49 ± 7.83	$t(31.0) = 2.00$	.054
nogo N2 amplitude at Cz in µV	-0.67 ± 5.69	-2.76 ± 5.68	$t(45.0) = 1.26$	.215	-3.50 ± 6.66	$t(32.0) = 1.23$	.229
nogo P3 amplitude at Cz in µV	18.81 ± 8.82	12.59 ± 7.12	$t(45.0) = 2.64$	.012	6.88 ± 6.09	$t(32.0) = 3.73$	.001
n-back P3 latency at Pz in ms	392 ± 51	395 ± 69	$t(42.4) = -0.16$	.878	409 ± 56	$t(31.0) = -0.79$	.437
nogo N2 latency at Cz in ms	328 ± 55	365 ± 54	$t(45.0) = -2.36$	.023	356 ± 59	$t(32.0) = -1.30$	.204
nogo P3 latency at Cz in ms	551 ± 49	557 ± 42	$t(45.0) = -0.47$	.640	532 ± 62	$t(32.0) = 0.91$	.368

WM – working memory performance, RI – response inhibition performance

Supplementary Table S2. Overview of all ERP results of experiment 1. Results of ANOVAs for ERP analysis, *F* and *p*-values as well as effect sizes η^2 are given.

Condition / Comparison	Stimulus go vs. nogo / target vs. non-target	Task single vs. combined	Group control vs. ADHD
n-back P3 amplitude			
condition	$F(1, 24) = 45.54$, $p < .001$, $\eta^2 = .655$	$F(1, 24) = 0.83$, $p = .372$, $\eta^2 = .033$	$F(1, 55) = 4.44$, $p = .040$, $\eta^2 = .075$
region	$F(1, 24) = 79.25$, $p < .001$, $\eta^2 = .768$	-	-
hemisphere	$F(1.4, 34.0) = 6.72$, $p = .008$, $\eta^2 = .219$	-	-
condition x region	$F(1, 24) < 0.01$, $p = .966$, $\eta^2 < .001$	$F(1, 24) = 1.35$, $p = .256$, $\eta^2 = .053$	$F(1, 55) = 0.24$, $p = .624$, $\eta^2 = .004$
condition x hemisphere	$F(2, 48) = 3.33$, $p = .044$, $\eta^2 = .122$	$F(2, 48) = 0.44$, $p = .644$, $\eta^2 = .018$	$F(2, 110) = 0.77$, $p = .465$, $\eta^2 = .014$
region x hemisphere	$F(2, 48) = 1.346$, $p = .270$, $\eta^2 = .053$	-	-
condition x region x hemisphere	$F(2, 48) = 1.44$, $p = .0246$, $\eta^2 = .057$	$F(1.5, 36.9) = 1.45$, $p = .246$, $\eta^2 = .057$	$F(2, 110) = 0.14$, $p = .866$, $\eta^2 = .003$
n-back P3 latency			
condition	$F(1, 24) < 0.01$, $p = .977$, $\eta^2 < .001$	$F(1, 24) < 0.01$, $p = .964$, $\eta^2 < .001$	$F(1, 55) = 0.28$, $p = .599$, $\eta^2 = .005$
region	$F(1, 24) = 3.54$, $p = .072$, $\eta^2 = .129$	-	-
hemisphere	$F(2, 48) = 1.02$, $p = .369$, $\eta^2 = .041$	-	-
condition x region	$F(1, 24) = 10.35$, $p = .004$, $\eta^2 = .301$	$F(1, 24) = 0.21$, $p = .654$, $\eta^2 = .009$	$F(1, 55) < 0.01$, $p = .996$, $\eta^2 < .001$

condition x hemisphere	$F(2, 48) = 5.41$, $p = .008$, $\eta^2 = .184$	$F(1.6, 38.9) = 0.92$, $p = .388$, $\eta^2 = .037$	$F(2, 110) = 0.58$, $p = .561$, $\eta^2 = .010$
region x hemisphere	$F(2, 48) = 0.31$, $p = .733$, $\eta^2 = .013$	-	-
condition x region x hemisphere	$F(2, 48) = 0.61$, $p = .548$, $\eta^2 = .025$	$F(1.5, 36.4) = 0.40$, $p = .618$, $\eta^2 = .016$	$F(2, 110) = 1.63$, $p = .200$, $\eta^2 = .029$
nogo N2 amplitude			
condition	$F(1, 24) = 7.59$, $p = .011$, $\eta^2 = .240$	$F(1, 24) = 0.52$, $p = .479$, $\eta^2 = .021$	$F(1, 54) = 0.95$, $p = .335$, $\eta^2 = .017$
region	$F(1, 24) = 33.33$, $p < .001$, $\eta^2 = .581$	-	-
hemisphere	$F(2, 48) = 1.74$, $p = .186$, $\eta^2 = .068$	-	-
condition x region	$F(1, 24) = 1.03$, $p = .321$, $\eta^2 = .041$	$F(1, 24) = 1.79$, $p = .194$, $\eta^2 = .069$	$F(1, 54) = 1.21$, $p = .276$, $\eta^2 = .022$
condition x hemisphere	$F(1.6, 37.6) < 0.01$, $p = .996$, $\eta^2 < .001$	$F(2, 48) = 0.74$, $p = .481$, $\eta^2 = .030$	$F(2, 108) = 0.70$, $p = .497$, $\eta^2 = .013$
region x hemisphere	$F(2, 48) = 7.02$, $p = .002$, $\eta^2 = .226$	-	-
condition x region x hemisphere	$F(1.5, 36.8) = 0.94$, $p = .376$, $\eta^2 = .038$	$F(2, 48) = 3.05$, $p = .057$, $\eta^2 = .113$	$F(2, 108) = 0.67$, $p = .513$, $\eta^2 = .012$
nogo N2 latency			
condition	$F(1, 24) = 6.13$, $p = .021$, $\eta^2 = .204$	$F(1, 24) = 40.27$, $p < .001$, $\eta^2 = .627$	$F(1, 54) = 6.34$, $p = .015$, $\eta^2 = .105$
region	$F(1, 24) = 4.71$, $p = .040$, $\eta^2 = .164$	-	-

hemisphere	$F(2, 48) = 4.17$, $p = .021$, $\eta^2 = .148$	-	-
condition x region	$F(1, 24) = 0.03$, $p = .858$, $\eta^2 = .001$	$F(1, 24) = 2.59$, $p = .121$, $\eta^2 = .097$	$F(1, 54) = 0.84$, $p = .365$, $\eta^2 = .015$
condition x hemisphere	$F(2, 48) = 2.94$, $p = .062$, $\eta^2 = .109$	$F(2, 48) = 0.60$, $p = .552$, $\eta^2 = .024$	$F(2, 108) = 0.07$, $p = .936$, $\eta^2 = .001$
region x hemisphere	$F(2, 48) = 0.83$, $p = .442$, $\eta^2 = .033$	-	-
condition x region x hemisphere	$F(1.5, 36.4) = 0.73$, $p = .452$, $\eta^2 = .030$	$F(2, 48) = 0.18$, $p = .834$, $\eta^2 = .008$	$F(2, 108) < 0.01$, $p = .991$, $\eta^2 < .001$
nogo P3 amplitude			
condition	$F(1, 24) = 43.91$, $p < .001$, $\eta^2 = .647$	$F(1, 24) = 1.33$, $p = .260$, $\eta^2 = .053$	$F(1, 54) = 11.60$, $p = .001$, $\eta^2 = .177$
region	$F(1.5, 36.3) = 91.23$, $p < .001$, $\eta^2 = .792$	-	-
hemisphere	$F(1.6, 37.4) = 7.92$, $p = .003$, $\eta^2 = .248$	-	-
condition x region	$F(2,48) = 10.80$, $p < .001$, $\eta^2 = .310$	$F(2, 48) = 9.95$, $p < .001$, $\eta^2 = .293$	$F(2, 108) = 1.53$, $p = .222$, $\eta^2 = .027$
condition x hemisphere	$F(2, 48) = 21.00$, $p < .001$, $\eta^2 = .467$	$F(2, 48) = 1.04$, $p = .360$, $\eta^2 = .042$	$F(2, 108) = 3.47$, $p = .035$, $\eta^2 = .060$
region x hemisphere	$F(4, 96) = 6.66$, $p < .001$, $\eta^2 = .217$	-	-
condition x region x hemisphere	$F(4, 96) = 6.52$, $p < .001$, $\eta^2 = .214$	$F(4, 96) = 3.14$, $p = .018$, $\eta^2 = .116$	$F(4, 216) = 0.83$, $p = .505$, $\eta^2 = .015$

nogo P3 latency			
condition	$F(1, 24) = 130.41$, $p < .001$, $\eta^2 = .845$	$F(1, 24) = 84.79$, $p < .001$, $\eta^2 = .779$	$F(1, 54) = 0.09$, $p = .761$, $\eta^2 = .002$
region	$F(1.6,38.6) = 1.69$, $p = .201$, $\eta^2 = .066$	-	-
hemisphere	$F(2, 48) = 0.67$, $p = .518$, $\eta^2 = .027$	-	-
condition x region	$F(1.5, 36.3) = 1.61$, $p = .215$, $\eta^2 = .063$	$F(1.2, 28.3) = 0.05$, $p = .861$, $\eta^2 = .002$	$F(2, 108) = 0.09$, $p = .916$, $\eta^2 = .002$
condition x hemisphere	$F(2, 48) = 1.72$, $p = .190$, $\eta^2 = .067$	$F(1.5, 36.1) = 3.45$, $p = .055$, $\eta^2 = .126$	$F(2, 108) < 0.01$, $p = .999$, $\eta^2 < .001$
region x hemisphere	$F(4, 96) = 1.54$, $p = .197$, $\eta^2 = .060$	-	-
condition x region x hemisphere	$F(4, 96) = 1.41$, $p = .236$, $\eta^2 = .055$	$F(4, 96) = 0.38$, $p = .822$, $\eta^2 = .016$	$F(4, 216) = 0.17$, $p = .953$, $\eta^2 = .003$

Supplementary Table S3. Task performance during online and offline tDCS for experiment 2. Results of ANOVA for the task performance during (online) and after application of tDCS (offline).

		online tDCS	offline tDCS	main effect on/offline	interaction on/offline x tDCS condition
WM performance	conventional	61.6% (14.9%)	47.0% (21.6%)	$F(1, 26) = 25.06^{***}$	$F(2, 26) = 0.21$
	HD	63.5% (17.9%)	49.5% (20.5%)		
	sham	64.1% (13.5%)	46.5% (21.4%)		
misses	conventional	2.8% (4.3%)	4.1% (4.2%)	$F(1, 26) = 2.03$	$F(1.4, 18.4) = 1.96$
	HD	4.9% (6.7%)	4.7% (4.6%)		
	sham	2.9% (4.2%)	8.8% (14.9%)		
RT	conventional	791 ms (209 ms)	783 ms (225 ms)	$F(1, 26) = 1.17$	$F(1.3, 17.4) = 0.89$
	HD	831 ms (196 ms)	800 ms (170 ms)		
	sham	787 ms (189 ms)	785 ms (202 ms)		
SD of RT	conventional	259 ms (74 ms)	270 ms (85 ms)	$F(1, 26) = 6.85^{*}$	$F(1, 26) = 0.90$
	HD	266 ms (75 ms)	291 ms (90 ms)		
	sham	263 ms (69 ms)	285 ms (74 ms)		

$^{*}p \leq .05$, $^{**}p \leq .01$, $^{***}p \leq .001$

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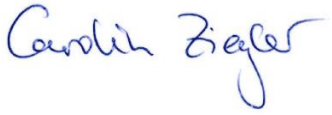

Magdeburg, 30.11.2020