Aus dem Zentralinstitut für Seelische Gesundheit
(Direktor: Prof. Dr. Andreas Meyer-Lindenberg)
Klinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters
(Ärztlicher Direktor: Prof. Dr. Dr. Tobias Banaschewski)

Does neurofeedback training normalize reward-processing in ADHD? An ERP study

Inauguraldissertation
zur Erlangung des medizinischen Doktorgrades
der
Medizinischen Fakultät Mannheim
der Ruprecht-Karls-Universität
zu
Heidelberg

vorgelegt von
Szarah Peters

aus
Berlin
2021

Dekan: Herr Prof. Dr. med. Sergij Goerdt

Referent: Herr Prof. Dr. Dr. Tobias Banaschewski

TABLE OF CONTENTS

Page number

TABLE OF ABBREVATIONS

ACC ..... Anterior cingulate cortex

ADHD ..... Attention-Deficit/Hyperactivity Disorder

ANOVA ..... Analysis of variance

ASD ..... Autism spectrum disorder

BOLD ..... Blood-oxygen-level-dependent

CD ..... Conduct disorder

CNV ..... Contingent negative variation

DA ..... Dopamine

DISYPS ..... Diagnostik-System für psychische Störungen

DRKS ..... Deutsches Register Klinischer Studien

DSM ..... Diagnostic and Statistical Manual of Mental Disorders

ECG ..... Electrocardiogram

EEG ..... Electroencephalogram

EMG ..... Electromyogram

EOG ..... Electrooculogram

EP ..... Evoked potential

ERP ..... Event-related potential

FB-P3 ..... Feedback-P300

FERN ..... Feedback Error-Related Negativity

FMRI ..... Functional magnetic resonance imaging

FRN ..... Feedback-Related Negativity

GML ..... General linear model

ICA …….. Independent component analysis

IFC …….. Inferior frontal cortex

K-SADS-PL ……. Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime

MANOVA …….. Multivariate analysis of variance

MPH …….. Methylphenidate

MRI …… Magnetic resonance imaging

NA …….. Noradrenaline

NF …….. Neurofeedback

ODD …….. Oppositional defiant disorder

SCP …….. Slow cortical potential

SMA …… Supplementary motor area

SMR …….. Somatosensory rhythm

VS …….. Ventral striatal

WHO …… World Health Organization

LIST OF FIGURES

LIST OF TABLES

1 INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common psychiatric neurodevelopmental disorders in children and adolescents. With a worldwide prevalence of up to 5.3 % in children and adolescents, and 2.5 % in adults (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; van Hulst et al., 2017), it can be considered as a lifespan disorder. ADHD is associated with a considerable economic burden (Daley, Jacobsen, Lange, Sorensen, & Walldorf, 2019), due to increased expenses for the healthcare, educational, and justice systems (Mohr-Jensen & Steinhausen, 2016). According to the German ADHD guidelines, the first-line therapy for severely affected children above the age of six years is a pharmacotherapy with methylphenidate (MPH). However, up to 30 percent of treated patients do not respond to medication (Ogrim, Aasen, & Brunner, 2016). Furthermore, adverse events occur frequently (Cortese et al., 2013), and long-term effects remain uncertain (Banaschewski et al., 2006; Graham, 2011). Therefore, non-pharmacological treatments such as Neurofeedback (NF) have recently received increasing attention, as reflected by the considerable number of meta-analyses on this topic in the last few years. These meta-analyses suggest that NF is an effective treatment for ADHD symptoms, when rated by the parents (Riesco-Matias, Yela-Bernabe, Crego, & Sanchez-Zaballos, 2019), and findings are especially promising regarding symptoms of inattention even when raters were probably blinded (Micoulaud-Franchi et al., 2014). When following a standard training protocol while not preventing or causing a delay in another effective therapy, NF is recommended by the German ADHD Guidelines (Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Aufmerksamkeitsdefizit-/ Hyperaktivitätsstörung (ADHS) im Kindes-, Jugend- und Erwachsenenalter, Langfassung, 06.2018, available:

https://www.awmf.org/uploads/tx_szleitlinien/028-045l_S3_ADHS_2018-06.pdf; accessed on 09.10.2020). Nonetheless, further research is needed for a deeper understanding of the specific mechanisms underlying NF, which could guide the individualized treatment selection for subgroups of ADHD patients. Therefore, the aim of this thesis was to investigate specific effects of neurofeedback compared to an active control condition on clinical outcomes and neurophysiological markers of reward processing in children with ADHD.

1.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

1.1.1 Symptoms and Diagnosis

ADHD is defined by three core symptoms: attention deficit, impulsivity, and/or hyperactivity, which are age-inappropriate and often persist into adulthood. These symptoms include behaviors like failure to pay close attention to details, difficulty organizing tasks and activities, excessive talking and interrupting conversations, avoiding to engage in tasks that require sustained mental effort, fidgeting, or an inability to remain seated in appropriate situations that all occur across different settings (e.g. in school, peer group and family environments). They possibly cause significantly lower achievements in the social context/life, education, or professional career (Faraone et al., 2015). To warrant formal diagnosis of ADHD, several inattentive or hyperactive-impulsive symptoms have to be present before the age of 12 years and leading to a functional impairment according to the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5TM). Depending on the different types of symptoms being present to a different amount, different subtype presentations can be identified: If six (at least five in adults) out of nine inattentive symptoms were present for the past 6 months, diagnostic criteria for the predominantly inattentive presentation are met. Comparably, if six (at least five in adults) out of nine hyperactive-impulsive symptoms were present, diagnostic criteria for the predominantly hyperactive/impulsive presentation are met. If both criteria are fulfilled, this describes the combined type. Before the age of six, a diagnosis remains uncertain, as it is difficult to differentiate from deviations in normal development. However, if the symptoms are particularly severe, the diagnosis can be detected from the age of four. Furthermore, the severity of the disorder can be coded as mild, moderate or severe, depending on how many symptoms occur and how severe they are, whereby no

more precise specifiers are mentioned in the DSM-5TM. In addition, frequent comorbidities such as oppositional defiant disorder (ODD) and conduct disorder (CD), learning disorders, anxiety, affective disorders, and autism spectrum disorder (ASD) can be observed and may adversely affect prognosis (Antshel, Zhang-James, Wagner, Ledesma, & Faraone, 2016; Jensen & Steinhausen, 2015; Reale et al., 2017). In later adolescence and adulthood, the risk for comorbid addictive disorders and personality disorders increases (Dirks, Scherbaum, Kis, & Mette, 2017; Matthies & Philipsen, 2016; van Emmerik-van Oortmerssen et al., 2012). This includes substance abuse, but also non-substance-related dependencies such as internet addiction that have become a focus of research interest in recent years (Wang, Yao, Zhou, Liu, & Lv, 2017). Family, adoptions and twin studies were able to show that ADHD is a highly heritable disease (Faraone & Larsson, 2019), but to date causal genetic risk factors are not completely understood. A multifactorial polygenetic cause of the disorder is generally assumed. Nevertheless, a significant association between some dopaminergic, noradrenergic, and serotonergic genes and the occurrence of ADHD were recently demonstrated (Gizer, Ficks, & Waldman, 2009). But also other independent loci were significantly linked to ADHD (Drechsler et al., 2020). In summary, these factors contribute to a very heterogeneous clinical phenotype of the ADHD population.

1.1.2 Pathophysiology

The pathophysiology underlying ADHD symptomatology has been intensely studied in the last decades, but a specific pathway has not been identified yet. The behavioral symptoms described above are partly explained by impairments in executive functions, such as attentional control, inhibitory control, and working memory, which are related to altered

dopaminergic functioning (Banaschewski et al., 2005; Sagvolden, Johansen, Aase, & Russell, 2005). However, current disease models discuss distinct but at the same time coexisting neuronal alterations leading to phenotypical heterogeneity in ADHD (Sonuga-Barke, 2005). Besides alterations in executive functioning and further processes, impaired reward processing has become a focus of ADHD-research. Abnormal motivational processes linked to the fronto-ventral striatal reward circuits are discussed to be an important causal factor or pathway for ADHD in current models of the disorder (Sagvolden et al., 2005; Sonuga-Barke, 2005; Tripp & Wickens, 2008). Finally, early automatic information processing, processing speed, motor skills, and timing functions are also impaired in ADHD (Banaschewski et al., 2005).

Different methods can be used to assess structural alterations in the brain as well as neurofunctional deviations. Among the most commonly used methods are electroencephalography (EEG) and magnetic resonance imaging (MRI). EEG recordings reflect the mass action of large clusters of parallel aligned neurons that are activated simultaneously within cortical structures as well as deeper brain regions such as the brain stem. The ionic current fluctuations, which result from the polarization of neurons, are measured by electrodes placed on the scalp. Both superficial and deeper synaptic activity can be represented, and rapid as well as slow changes in electrical activity across the scalp can be reflected in a high temporal resolution in the range of milliseconds (Kappenman & Luck, 2012; Lenartowicz & Loo, 2014). Furthermore, the EEG can be assessed easily and in a completely non-invasive way. Therefore, it is especially suited for younger study populations. EEG analysis is a validated tool to observe the temporal and to a certain degree also the spatial dynamics of brain network activity in a large variety of mental states and processes. The spatial representation of the data depends on model assumptions and source geometry and leads to

lower resolution, especially for deeper brain regions (Michel & Brunet, 2019). By computing signal averages, time-locked EEG activity related to perceptual, cognitive or motor processes can be extracted (Banaschewski & Brandeis, 2007). These event-related potentials (ERPs) or evoked potentials (EP) consist of individual sequences of components that are characterized by polarity, amplitude, and latency with a constant topographical distribution of brain activation (Kappenman & Luck, 2012). On the other hand, functional magnetic resonance imaging (fMRI) offers a precise functional localization of neuronal activity using the blood-oxygen-level-dependent (BOLD) effect (Ogawa, Lee, Kay, & Tank, 1990). This technique is based on the link between neuronal activity and blood flow and uses the magnetic characteristics of oxygenated respectively deoxygenated blood. While the spatial resolution of the fMRI is very high, the hemodynamic response causes a temporal delay. Electrophysiological and functional research using brain-imaging methods such as EEG and fMRI was able to show multiple neuronal processing deficits in ADHD such as attentional processes, inhibition control, working memory, and reward processing (Drechsler et al., 2020). Inattention as one of the core symptoms of ADHD was intensively investigated using both, EEG and fMRI. EEG studies were able to show reduced amplitude of attentional and preparatory ERPs such as the Cue P3 and the contingent negative variation (CNV) in ADHD patients in comparison with typically developing children (Bluschke, Schuster, Roessner, & Beste, 2018; Cheung et al., 2017; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013; Michelini et al., 2018). For the fMRI, some studies suggest a link between attention and fronto-ventral striatal circuits (Bush, Valera, & Seidman, 2005; Paloyelis, Mehta, Kuntsi, & Asherson, 2007). A recent meta-analysis was able to show an underactivation of fronto-striatal, fronto-parietal and ventral attention networks (Rubia, 2018). But the results remain

inconclusive to date underlining the heterogeneity of the disease (Cherkasova & Hechtman, 2009; Cortese et al., 2012; Samea et al., 2019).

In addition to inattention, impaired inhibitory control was also discussed as an important pathophysiologic factor (Barkley, 1997), which leads to impulsive behavior such as interrupting conversations or hasty answers and acting. The ability to withhold a prepotent response is often used to assess inhibitory control. While increased N2 and P3 amplitudes during the NoGo compared to the Go condition are expected in Go/NoGo tasks, children with ADHD showed consistently reduced NoGo P3 activity compared to typically developing children, potentially leading to deficits in behavioral response inhibition (Albrecht et al., 2013). A reduction of the NoGo N2 amplitude, related to conflict monitoring and inhibitory processes, has been reported but is less consistent (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005; Rommel et al., 2019; Tamayo-Orrego et al., 2015). A recent meta-analysis showed that patients with ADHD exhibited on average smaller Cue-P3 amplitudes, longer Go-P3 latencies, smaller NoGO-P3 amplitudes and longer latencies, smaller CNV amplitudes, and smaller Pe amplitudes, indicating core deficits in later cognitive processing stages (Kaiser et al., 2020).

In neuroimaging studies, response inhibition was consistently associated with hypoactivation of the anterior insula, inferior frontal cortex (IFC), the anterior cingulate cortex (ACC), and the supplementary motor area (SMA) in patients with ADHD (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). In summary, to date efforts have been made predominantly to explore executive functioning in ADHD. While these findings provide insight into part of dysfunctional processes related to ADHD from a neurobiological perspective, the focus of the current thesis is on reward processing deficits as a further process implicated in ADHD, adding another important contribution to a better understanding of the complexity and heterogeneity of ADHD.

Therefore, the pathophysiology of ADHD in relation to reward processing will be discussed in more detail below.

1.1.2.1 Reward processing

Reward processing is considered as a heterogeneous construct composed of multiple different phases and psychological processes (Glazer, Kelley, Pornpattananangkul, Mittal, & Nusslock, 2018; Zhang, Li, Wang, Liu, & Zheng, 2017). It has been linked to the fronto-ventral striatal circuit (also called 'reward circuit') involving the basal ganglia, especially the ventral striatum, including the nucleus accumbens (Haber & Knutson, 2010), and cortical target regions such as the orbito-frontal cortex, medial prefrontal cortex, anterior cingulate cortex (Oldham et al., 2018). Intact reward processing is essential to make goal-oriented decisions, in other words, to receive rewards, and avoid punishment (Fareri, Martin, & Delgado, 2008). Behaviorally, ADHD patients frequently choose a smaller, immediate reward than waiting for a larger delayed reward. This phenomenon is called delay aversion and has been consistently reported in ADHD leading to, among others, impulsive decision making (Pauli-Pott & Becker, 2015; Scheres, Lee, & Sumiya, 2008; Sonuga-Barke, 2005; Sorensen et al., 2017). Current disorder models suggest abnormal motivational processes and especially deficiencies in reinforcement learning linked to the fronto-ventral striatal reward circuits to be an additional important causal factor for ADHD (Sagvolden et al., 2005). Altered reinforcement of rewarded behavior and deficient extinction of no longer rewarded behavior is proposed to lead to the above described delay aversion (Furukawa et al., 2014). Based on this approach the alternative motivational dysfunction model assumes that ADHD symptoms may also result from compromised signaling of delayed rewards instead of being caused by executive dysfunctions (Sonuga-Barke, 2005). More recent models, on the other hand, assume that there are various dysfunctions occurring at same time and in varying severity, that affect for instance the

executive functions, emotion control, sensorimotor processes and the reward system (Cortese et al., 2012; Karalunas & Nigg, 2020; Rubia, 2018).

Temporally, two stages of reward processing can be distinguished: first, the reward-anticipation phase reflecting incentive salience linked to "wanting" (e.g. motivational processes promoting the expectant attitude which influences the approach to stimuli), and second, the reward-delivery phase linked to the processing of feedback outcome associated with the "liking" of the outcome (Oldham et al., 2018). For a better understanding, several studies have investigated the neuronal basis of the different sub stages of atypical reward processing in ADHD.

1.1.2.1.1 Reward anticipation

In the reward anticipation stage the incentive salience of a stimulus is evaluated. This stage is composed of cue-evaluation, motor preparation, and feedback anticipation. In fMRI studies, the bilateral ventral striatum, pallidum, insula, thalamus, hippocampus, cingulate cortex, midbrain, motor area, and occipital areas were reliably activated during reward anticipation in healthy adolescents (Cao et al., 2018; Oldham et al., 2018) and dopamine was identified to be the principal neurotransmitter regulating reward processing (Jia et al., 2016).

Reduced ventral striatal (VS) activation during reward anticipation in ADHD is the most consistent finding (Carmona et al., 2012; Furukawa et al., 2014; Scheres, Milham, Knutson, & Castellanos, 2007; van Hulst et al., 2017), with peak activation often located in the nucleus accumbens (Akkermans et al., 2019; Mizuno et al., 2013; Stark et al., 2011). On the other hand, increased responses in the anterior cingulate, anterior frontal cortex, and cerebellum, but also ventral striatum during reward anticipation were reported in adolescents and young adults with ADHD (von Rhein et al., 2015). In addition to fMRI examinations that are characterized by a high spatial resolution helping to identify a variety of different neuro-anatomical

correlates of the reward circuit, event related potentials are used to investigate the time curse of neuronal activity during reward tasks. In simultaneous EEG and fMRI measures, the VS, the thalamus, and SMA were correlated with the CNV (Plichta et al., 2013), which is known to be attenuated in ADHD in non-incentivized trails indicating impaired cue orientation and response preparation (Albrecht et al., 2013; Banaschewski et al., 2003).

1.1.2.1.2 Reward delivery

Reward delivery has been less frequently studied and research yielded more inconsistent results in the context of ADHD. It is differentiated between the early reward impact, subsequently updating working memory, and extended affective processing of feedback information whether a reward was achieved or not (Glazer et al., 2018). Furthermore, depending on the task design, we must differentiate between win versus neutral condition and win versus loss condition (Nees et al., 2012). The bilateral ventro-medial prefrontal cortex and bilateral thalamus exhibited positive and negative activation, respectively, during reward receipt in healthy adolescents (Cao et al., 2018), likely representing the value of the reward (Oldham et al., 2018). In ADHD, some studies could show a VS hyperactivation (Furukawa et al., 2014; von Rhein et al., 2015), whereas others found no VS alteration in ADHD (Scheres et al., 2007; van Dongen et al., 2015). Furthermore, a recent study showed an underactivation to losses of the medial prefrontal cortex in a gambling task and an underactivation to wins in the left putamen/caudate during outcome evaluation relative to control subjects (Norman et al., 2018). Overall, reward delivery in ADHD has not been sufficiently investigated, so further research in this domain is urgently required.

1.1.2.2 Neurophysiological markers of reward processing

1.1.2.2.1 Reward anticipation related ERPs

1.1.2.2.1.1 CNV

The contingent negative variation (CNV) is a slow negative wave growing before movement onset. It has been related to expectation and anticipation, response and motor preparation (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). To elicit a CNV, the task design should include an external cue stimulus, indicating that a quick response is required, as a trigger (Glazer et al., 2018). In this way, the CNV can be distinguished from the "Bereitschaftspotenzial", which arises without an external stimulus before a voluntary movement (Kornhuber & Deecke, 1965).The CNV has been linked to the dopaminergic system (Linssen et al., 2011), and correlates with functional brain activity in the reward circuit including the ventral striatum, supplementary motor area, and the thalamus (Plichta et al., 2013). Previous research showed that the anticipation of a reward compared to a neutral condition induced a higher CNV amplitude (Boecker et al., 2014; Plichta et al., 2013). In ADHD, the CNV amplitude is consistently reduced across different tasks not explicitly related to reward processing (Kaiser et al., 2020). This reduction seems to be stable in time when exploring attention allocation (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010). Further, individuals with ADHD were shown to be unable to adjust the preparatory state in changed context for example during a four-choice reaction time task (Cheung et al., 2017). Nevertheless, one study showed that individuals with ADHD displayed an enhancement of the CNV amplitude to positive reinforcement (Chronaki, Soltesz, Benikos, & Sonuga-Barke, 2017). However, since this did not affect performance, the authors concluded that the increased CNV could be a marker for hyper-arousal in ADHD rather than enhanced attention.

1.1.2.2.1.2 Cue-P3

The Cue-P3 is thought to reflect the cue-evaluation (e.g. determine if a future reward is attainable or not) and is enhanced by salient cues (Broyd et al., 2012; Glazer et al., 2018; Zhang et al., 2017). It is a marker for motivated attention, stimulus-categorization processes, and updating of working memory (Polich, 2007). The Cue-P3 occurs in a time-window of 300 to 600 ms following cue onset and can be categorized as a positive centro-parietal peak. It has been linked to the VS (Pfabigan et al., 2014). In ADHD, a reduced Cue-P300-amplitude has been observed during target detection and indicating a hyporesponsiveness especially to social rewards (Sutcubasi et al., 2018; Szuromi, Czobor, Komlosi, & Bitter, 2011), while no consistent results for the latency could be demonstrated yet. Some results suggest that deviations of the Cue-P3 may be related to ADHD symptom severity in children and adolescents (Yamamuro et al., 2016). Large group differences regarding the Cue-P3 amplitude were found in adults with and without ADHD, wherefore the Cue-P3 is discussed as a potential biomarker for adult ADHD (Szuromi et al., 2011). Rosch and Hawk (2013) were able to show an enhanced Cue-P3 amplitude also in children with ADHD when receiving a reward, suggesting rewards may improve cognitive deficits in ADHD.

1.1.2.2.2 Feedback-related ERPs

1.1.2.2.2.1 FRN

After feedback, with a latency of 200ms, the Feedback-Related Negativity (FRN) or feedback Error-Related Negativity (fERN) is one of the earliest ERP components discriminating gains from losses. The FRN is a fronto-central peak occurring between 200 and 300 ms following feedback. It has been related to the anterior cingulate cortex (Glazer et al., 2018). In a meta-analytic review the FRN has been consistently linked to feedback-evaluation (Sambrook & Goslin, 2015). Beside the differentiation between gains and losses, it reflects the motivational salience of reward (Mei, Li, Liu, & Zheng, 2018). While some results indicate no differences between ADHD patients and typically developing children regarding the FRN (Rosch & Hawk, 2013), others show impairments in subgroups of ADHD (Bluschke et al., 2018), indicating a decreased sensitivity to punishment in primarily impulsive patients (Gong et al., 2014).

1.1.2.2.2.2 Feedback-P300 (FB-P3)

The feedback-P300 is a centro-parietal positive peak from 300 to 600 ms following a feedback stimulus. It involves attention-driven classification of salient feedback-related information such as context updating, successively integrating the information of working memory to maximize upcoming rewards (Polich, 2007), and is sensitive to reward valence (Mei et al., 2018). To our current knowledge, the brain regions linked to this component remain mainly uncertain (Glazer et al., 2018). A hyporesponsiveness to social feedback including a reduced FB-P3 was associated with hyperactivity in a healthy population (Sutcubasi et al., 2018). However, this association has not yet been confirmed in ADHD. Another recent study found no alterations of the FB-P3 in adults with ADHD (Thoma, Edel, Suchan, & Bellebaum, 2015).

1.2 Treatment of ADHD

1.2.1 Medication

Psychostimulants (methylphenidate and amphetamine preparations), atomoxetine, and guanfacine are available for the treatment of ADHD, with the former two being the first-choice drugs (Chan, Fogler, & Hammerness, 2016; Cortese et al., 2018; Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie). According to the World Health Organization (WHO), psychostimulants are substances that increase, accelerate or improve the activity of nerve cells. They can increase the performance and concentration, and can lead to euphoria in higher doses, thus there is potential for abuse and dependence (Clemow, 2017). Methylphenidate (MPH), the most commonly prescribed psychostimulant, is a dopamine (DA) and noradrenaline (NA) reuptake blocker and is thought to lead to a normalization of altered catecholamine levels in ADHD. Recently, effects of MPH on electrophysiological markers of inhibitory control (Aasen, Ogrim, Kropotov, & Brunner, 2018; Berger et al., 2018; Janssen et al., 2016), reaction time (Coghill et al., 2014), and attention (Dockree et al., 2017; Dolu et al., 2019) have been observed. MPH is approved for children above 6 years and since 2012 also for adults with ADHD in Germany. However, adverse effects occur regularly under medication. Recent reviews and meta-analyses showed that the risk ratio of serious adverse event such as arrhythmia, hypertension or increased heart rate (Liang et al., 2018) but also for non-serious adverse events such as insomnia and sleep problems, decreased appetite, abdominal pain, headache, and suppression of growth is increased in children and adolescents under medication, which often leads to withdrawal of methylphenidate (Cortese et al., 2013; Swanson et al., 2017). In order to deal well with these side effects, regular check-ups have to take place including blood pressure and pulse control as well as ECG recordings, height and

weight measurements as well as questions on eating behavior and appetite (Graham, 2011). Furthermore long-term effects and also adverse effects remain mostly unknown (Cortese et al., 2018; Fredriksen, Halmoy, Faraone, & Haavik, 2013; Hechtman & Greenfield, 2003), and even in an optimal case management, about 30 percent do not respond to stimulant medication (Ogrim et al., 2016).

1.2.1.1 Effects of medication on the reward system

Stimulant medication, the first-line pharmacotherapy for ADHD, has been shown to enhance activity in the fronto-striato-thalamo-cerebellar and parieto-temporal attention networks, to reduce hyperactivation in the orbitofrontal cortex (Rubia et al., 2009), and to increase the modulation of BOLD responses in the motivation-reward system (Newcorn et al., 2014), especially in the ventral striatum (Furukawa et al., 2019). But other studies have failed to demonstrate improved striatal activity as a consequence of stimulant medication (Schweren et al., 2017; Stoy et al., 2011). However, the supplementary motor area and dorsal anterior cingulate cortex were more activated during reward receipt after stimulant administration (Schweren et al., 2017). On the behavioral level, stimulant medication seems to reduce the preference of smaller immediate rewards over later bigger rewards (Shiels et al., 2009), and could counteract the delay aversion often observed in ADHD. Furthermore, the sensitivity to rewards could be enhanced (Mizuno et al., 2013). Lisdexamphetamine, another psychostimulant, was shown to increase the sensitivity in the reward system by modulation of BOLD responses in the caudate, when a reward was received (Newcorn et al., 2014). Furthermore, a higher accuracy during a reward task could be demonstrated in healthy young adults under medication suggesting improved efficiency of information processing in reward-motivation (Ivanov et al., 2014). While some electrophysiological markers have been studied

for the effects of medication on executive functions, the effects on electrophysiological markers of the reward system remain unknown to date.

1.2.2 A non-pharmacological treatment option: Neurofeedback

Although stimulant medication is the first line therapy for severe ADHD, there is a non-negligible high proportion of non-responders and non-serious adverse effects are frequent. Furthermore, long-term effects of pharmacotherapy remain unknown. In addition, medication is not approved under the age of 6 and there is no absolute indication for mild to moderate cases. Unfortunately, there is limited meta-analytic evidence from randomized controlled trials that non-pharmacological interventions like behavioral and parent training, cognitive training, diets, and neurofeedback are effective to improve ADHD core symptoms (Sonuga Barke et al 2013), therefore, behavioral treatments with possible long-term effects such as neurofeedback (NF) are interesting additional or alternative therapies, which directly target disorder-related neurophysiological deficits (Holtmann, Sonuga-Barke, Cortese, & Brandeis, 2014). NF represents a form of behavioral therapy using feedback of brain activity based on operant learning principles. Participants should learn to voluntarily modify specific aspects of their brain activity via trial-and-error learning. Visual and/or auditory feedback is used to represent the targeted neuronal activity measured, for example, using EEG. According to the German ADHD Guideline, there is moderate evidence for the effectiveness of NF if standard EEG-training protocols are used, but so far it is not recommended as a stand-alone treatment option, as effectiveness is not sufficiently proven. However, it could be a promising therapeutic alternative when not delaying or preventing another effective therapy. In the last years, three NF training protocols have emerged and are most commonly applied in the

treatment of ADHD: theta/beta training, somatosensory rhythm (SMR) training, and the training of slow cortical potentials (SCPs).

1.2.2.1 Theta/beta training

In the resting EEG of children with ADHD, excess frontal theta frequencies (4-7.5 Hz) on the one hand, and decreased beta frequencies (13-20 Hz) on the other have been reported (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Barry, Johnstone, & Clarke, 2003). However, these changes could not be consistently demonstrated across all ADHD subtypes (Bussalb et al., 2019; Clarke et al., 2011). The theta/beta training aims at up-regulating neurophysiological activity in the beta band and down-regulating the activity in the theta band (Gevensleben et al., 2014; Moriyama et al., 2012). The effectiveness of this training protocol has been widely studied in the past years. However, heterogeneous results have been reported. Some studies have shown clinical improvement after training in self- and parent- reported ADHD symptomatology (Arns, Heinrich, & Strehl, 2014; Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Beauregard & Levesque, 2006; Duric, Assmus, & Elgen, 2014; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2014; Rajabi, Pakize, & Moradi, 2019), that were stable over time (Gelade et al., 2018). In contrast, compared to active control conditions such as sham neurofeedback or meta-cognitive group therapy (Schonenberg et al., 2017; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2014), or to medication (Arnold, 2020; Gelade et al., 2017; Gelade et al., 2016; Janssen et al., 2016), the theta/beta training was not superior in recent studies.

1.2.2.2 SMR training

The sensorimotor rhythm (12-15Hz) training aims at increasing SMR activity, which is functionally associated with behavioral inhibition, and reducing cortical excitability (Enriquez-Geppert, Smit, Pimenta, & Arns, 2019; Gevensleben et al., 2014). In the last years, the hypothesis that, in ADHD patients with sleep problems, the SMR training could lead to stabilization in vigilance by targeting the sleep spindle circuitry, gained importance. A positive clinical outcome for this subgroup could be demonstrated (Arns, Drinkenburg, & Leon Kenemans, 2012). However, without distinguishing between ADHD patients with and without sleep problems, no additional benefit of SMR training could be shown (Bink, Bongers, Popma, Janssen, & van Nieuwenhuizen, 2016).

1.2.2.3 SCP training

During the SCP training, affected patients train self-regulation of voluntary alternation between positive and negative potential shifts and achieve a regulation of slow cortical potential shifts (Moriyama et al., 2012). This training relates to findings of reduced SCPs such as the anticipatory CNV in ADHD populations (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008). To date the efficacy of SCP training as a therapy for ADHD has been the focus of numerous studies reporting significant symptom reductions after training (Gevensleben et al., 2014; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Mayer, Wyckoff, & Strehl, 2013; Strehl et al., 2017). It has recently been shown that this effect is stable over time at least for 6 months, although the improvement was not specific NF (Aggensteiner et al., 2019). Other studies could not show any significant effect, which might be due to a small sample size or too few training sessions (Studer et al., 2014; Takahashi, Yasumura, Nakagawa, & Inagaki, 2014).

1.2.2.4 Behavioral and neurophysiological effects

In the past years, several meta-analyses investigated the effects of NF on ADHD symptomatology, showing medium-to-large effects when rated by probably non-blinded raters such as parents (Arns et al., 2009; Riesco-Matias et al., 2019; Sonuga-Barke et al., 2013). The effects are most prominent for attention deficits (Micoulaud-Franchi et al., 2014; Riesco-Matias et al., 2019), but are reduced to a trend (Sonuga-Barke et al., 2013) or eliminated when raters were probably blinded (Cortese et al., 2016). Importantly, tentative evidence in favor of NF efficacy in this meta-analysis was restricted to the above described standard protocols (Arns et al., 2014). Furthermore, changes in neuronal processing through NF training that might be associated with an improvement of ADHD symptomatology are not yet fully understood.

On an electrophysiological level, it has been shown that NF training is associated with a normalization of the theta/beta ratio (Bakhshayesh et al., 2011). On the other hand, no additional benefit of theta/sensorimotor rhythm neurofeedback over treatment as usual could be revealed in another study (Bink, van Nieuwenhuizen, Popma, Bongers, & van Boxtel, 2014, 2015). Regarding ERPs, an improvement of executive functioning was indicated by a normalization of the anticipatory CNV (Wangler et al., 2011), the N200 component, and the P300 (Arns et al., 2012; Holtmann et al., 2009) after NF training. Elsewhere, no improvement of the CNV during an attentional task could be shown (Doehnert et al., 2008). Beauregard and Levesque (2006) as well as Baumeister and colleagues (2018) have been able to show partly specific effects of NF on inhibitory control using functional magnetic resonance imaging (fMRI) but failed to show a prominent specific effect on reward processing (Baumeister et al., 2018). To our knowledge, so far, the latter was the only study to date investigating effects of NF on

reward processing in ADHD. The effects of NF on electrophysiological markers related to the reward system remain unknown, so further investigation is urgently needed.

1.2.2.5 Limitations in Neurofeedback research

Several investigations including numerous meta-analyses (Arns et al., 2009; Cortese et al., 2016; Hodgson, Hutchinson, & Denson, 2014; Riesco-Matias et al., 2019; Sonuga-Barke et al., 2013) in the last years have contributed to a better understanding of the effects of NF on ADHD symptoms. Nonetheless, inconsistent results regarding the effectiveness and the specificity of NF remain unexplained. The above mentioned three standard neurofeedback training protocols were shown to be efficacious in a number of studies, and partly specific in contrast to other types of NF-training (Enriquez-Geppert et al., 2019; Heinrich, Gevensleben, Becker, & Rothenberger, 2019). Few studies have tested different protocols within the same subjects to compare them directly to each other. Gevensleben et al. (2009) and Heinrich et al. (2019) were able to show similar improvement for theta/beta and SCP training. Some meta-analyses reported that NF is effective in treating inattention symptoms when evaluated by probably blinded raters (Hodgson et al., 2014; Micoulaud-Franchi et al., 2014; Riesco-Matias et al., 2019). Elsewhere, no increased benefit compared to the control condition could be revealed (Arnold, 2020; Cortese et al., 2016; Einarsdottir et al., 2015). While a recent meta-analysis report promising long-term effects of NF (Van Doren et al., 2019), other recent investigations failed to show superiority over a semi-active control group at a six-month follow-up (Aggensteiner et al., 2019; Arnold, 2020). Possibly, these differences can be explained by the large heterogeneity in the methodological implementation of the studies, as well as differences in sample characteristics. Various control conditions and different moderators such as age, IQ or the medication state of study subjects which are more or less thoroughly investigated have to be considered. Furthermore, unspecific effects which are

difficult to assess such as experienced self-efficacy, the patient-therapist-relationship or the expectation of the parents regarding the treatment outcome, should be taken into account (Arns et al., 2014). Some authors reduce neurofeedback training outcome to a placebo effect mainly driven by these unspecific effects (Thibault, Veissiere, Olson, & Raz, 2018). Nevertheless, these unspecific factors should be controlled for (as far as possible) via active control conditions, systematic manipulations within the study design and/or appropriate questionnaires.

1.3 Hypotheses

As discussed above, deficits in reward processing such as abnormal motivational processes and deficiencies in reinforcement learning may represent a core deficit in ADHD. Specific electrophysiological deviations related to reward anticipation were identified, such as a decreased CNV (Doehnert et al., 2013) or a decreased Cue-P3 amplitude (Szuromi et al., 2011). Neurofeedback, an alternative treatment option for ADHD, has been shown to be partly effective, but the underlying neuronal processes leading to an improvement of ADHD symptomatology are not yet fully understood. SCP-NF-training aims to train self-regulation of slow cortical potentials, such as the CNV. Exploring changes in reward-related CNV activity after treatment might allow insights into the neurophysiological mechanisms underlying NF. Thus, the aim of the current study was to investigate the effects of SCP EEG neurofeedback training on clinical outcome and neurophysiological markers of reward processing, measured through EEG, in children with ADHD. Initially planned analysis of the FRN ERP-component and the feedback-related P3 ERP-component could not be realized due to the task design and are consequently not pursued further in this work. Therefore, the following hypotheses were set.

On the neurophysiological level:

1.1. In comparison to controls, the ADHD group exhibits decreased CNV and Cue-P3 amplitudes and extended Cue-P3 latencies during reward anticipation and response preparation before training.

1.2. After the training, the NF-group in comparison to the EMG-group shows increased CNV and Cue-P3 amplitudes and shortened Cue-P3 latencies during reward anticipation.

1.3. Stimulant medication improves the decreased CNV and Cue-P3 amplitudes and extended Cue-P3 latencies in ADHD patients leading to a neuronal activity pattern similar to the healthy population.

Regarding clinical outcomes, we hypothesized that:

2. After the training, the NF-group in comparison to the EMG-group shows a greater reduction of ADHD symptoms rated by the parents.

2 MATERIAL AND METHODS

2.1 Subjects

The total sample included 24 ADHD patients (among them 6 females) from those reported in Baumeister et al (2018) and 13 controls aged between 9 and 14 years. Subjects were recruited via the outpatient clinic of the Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health Mannheim, local pediatricians and child psychiatrists.

Contra-indications for MRI measurements, as well as left-handedness, IQ below 80, insufficient German language skills, and comorbid disorders other than oppositional defiant disorder, conduct disorder or reading disorder were exclusion criteria.

All medicated participants underwent a wash out for five half-lives of the stimulant medication prior to pre- and post-intervention assessment. In the following, “medicated patient” signify previously medicated patient after the wash out.

Three children with ADHD and three controls were excluded due to excessive noise in their EEG recordings. Two ADHD participants were excluded from the analysis due to technical errors during the EEG recordings. The final sample therefore consisted of 19 subjects (thereof 4 females) and a comparison group of 10 controls (5 females). In addition, three patients did not complete the training and were excluded from the post-training analysis and pre-post comparison analysis. Due to extensive motion artifacts and technical errors another two patients had to be eliminated from the post-training analysis. A final sample of 14 training-completers (thereof 4 females) was obtained. For complete study sample characteristics, see Table 1.

All participants and their legal representatives gave written informed consent before their participation. They all had normal or corrected-to-normal vision. The proposal for the study was further approved by the Ethics Committee of the Medical Faculty of the Ruprecht-Karls-University Heidelberg and registered at the German clinical trials register *(https://drks-neu.unikl inik-freiburg.de/drks_web/), DRKS-ID: DRKS00003513.*

2.2 Psychological assessment

All participants underwent standard diagnostics with the K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime; Delmo et al. 2000) semi-structured clinical interview. The controls were screened for ADHD symptoms. The patient group had to fulfill diagnostic criteria of ADHD according to DSM-IV (American Psychiatric Association, 1994). The CBCL (Child Behavior Checklist) was used to assess the degree of comorbid symptomatology, and to exclude subthreshold symptoms of ADHD in the control group. The primary clinical outcome (see also Baumeister et al. 2018) was rated by the parents of the participants using the ADHD questionnaires of the German diagnostic system for mental disorders (DISYPS-II, Döpfner et al. 2008).

2.3 Study design

The study consisted as described by Baumeister et al. (2018) of a pre-intervention assessment, an intervention phase, and a post-intervention assessment. The healthy controls were tested only once (pre-assessment) and did not participate in any training. For the intervention phase, participants with ADHD were randomly allocated to either SCP-NF training (n = 8) or an

electromyogram feedback training (EMG, n = 6) as an active control condition. All ADHD patients participated in 20 training sessions. Each session was composed of three training blocks and one transfer block during which the feedback was not visible in half of the transfer trials. Both training types contained a token plan for successful performance and training compliance. To prevent a bias in the pre- and post-training ratings, neither participants nor parents were informed about the type of training they received (blinding).

2.4 Experimental procedures

A reward task (Boecker et al., 2014) was used based on the monetary incentive delay (MID) task as proposed by Kirsch et al. (2003) and Knutson et al. (2001), designed to capture reward anticipation and delivery. The task was adapted to simultaneous EEG-fMRI measurements. A cue signaled different types of reward conditions; either a happy smiley which meant a possible gain of money (0.50 Euro) or a scrambled smiley indicating verbal feedback ("fast reaction"). In the following, these two conditions will be called "win" and "no-win". The participants had to respond as fast as they could to a bright flash of light by pressing a button on a response device with the index finger of their right hand to win a potential reward. Following each trial, all subjects received feedback including the current account balance. Rare boost trials with the possibility to gain 2 Euros instead of 0.50 Euro to improve the motivational level of the participants were given about every eighth win trial. Each condition was presented 50 times in a pseudo-randomized order. The cue presentation was randomly varied between 3 and 5 seconds. The reaction time window was adaptive for each subject and each trial to account for inter-individual differences. The total task took approximately 15 minutes.

2.5 EEG data acquisition

In this study, EEG- and fMRI-data were recorded simultaneously. However, this work will focus only on the EEG data. The fMRI results are reported elsewhere (Baumeister et al., 2018). The EEG was continuously recorded from 60 silver/silver chloride (Ag/AgCl) electrodes within an extended 10-10 system with 2 additional electrooculogram (EOG) and 2 additional electrocardiogram (ECG) electrodes plus skin conductance as a marker of arousal using MR-compatible BrainAmp MR plus amplifier (Brain Products, Garching, Germany). Data was sampled online at 5 kHz with a 32 mV input range to facilitate fMRI gradient correction. F1 was used as recording reference while ground electrode was located at F2. Impedances were kept below 20 kΩ.

The task was presented using Presentation Software Package (Neurobehavioural Systems Inc., Albany, USA) via video goggles (Resonance Technology Inc., Northridge, USA). Response buttons (Current Designs, Philadelphia, USA) served to record the performance of participants.

2.6 EEG data analysis

2.6.1 Preprocessing of the EEG data

First, fMRI gradient and cardioballistic artifacts were eliminated using standard template subtraction procedures as proposed by the Brain Vision Analyzer 2.1. software (Brain Products, Gilching, Germany). EEG data were down-sampled to 500 Hz and low-pass filtered at 70 Hz. A conservative independent component analysis to minimize signal loss was used to remove ocular (blinks, movements) and remaining cardioballistic artifacts.

2.6.1.1 Reward anticipation related ERPs

Then the data were re-referenced to the average reference, low-pass filtered with a cut-off of 30 Hz, and segmented into stimulus locked ERP epochs of 3500 ms starting 500 ms prior to cue onset for the CNV and of 1200 ms starting 200 ms before cue onset for the Cue-P3. In the following, the data was baseline-corrected for these intervals and remaining artifacts were removed in two steps; first they were marked by hand for exclusion to preserve as much segments as possible, then an automatic artifact rejection with a maximal allowed difference of 150 µV in the interval was used. For the conventional ERP analysis, averages of the ERP amplitude and latencies for the win and no-win condition were calculated for each participant for the Cue-P3. Furthermore, grand-averages were calculated for each condition as well as for the medication state of the participants. The CNV component was quantified at electrode CZ where the amplitude was expected to be the largest in the average, and the most prominent statistical effects were expected, within a time window of 2000-3000 ms after stimulus onset. Based on previous research, Cue-P3 peaks were identified at electrode Pz within a time window of 250-650 ms after stimulus onset. Amplitudes for both ERP components, and Cue-P3 latencies were exported for further analysis.

2.6.1.2 Feedback-related ERPs

Initially planned analysis of the FRN ERP-component and the feedback-related P3 ERP-component could not be realized due to pronounced movement artifacts in the time interval of interest. In the presented task, the movement artifact caused by the button press fell mostly in the time interval in which the feedback-related components were expected.

2.6.2 Statistical analysis of the EEG data

Further analyses were conducted using the SPSS software package (version 24, IBM Corp., Armork, NY, USA). Significance was assumed if $p < 0.05$. To test for group differences before the training a Chi-Square-test was used to investigate gender distribution and t-tests were used to investigate group differences regarding age and IQ. The same tests were used to compare the treatment groups to check for differences after randomization. Furthermore, two Chi-Square-tests were applied to investigate the treatment groups regarding symptom severity and medication state.

For both CNV and Cue-P3 amplitude as well as for the Cue-P3 latency, the following statistical evaluations were performed: to test for pre-treatment effects, general linear models (GLM) were fitted to the data. To test differences regarding ERP components multivariate analysis of variance (MANOVA) with diagnostic group (“control” or “ADHD”) as between-subjects-factor and condition (“win” or “no-win”) as within-subjects-factor was calculated using Pillai´s trace. In a second step, the same model was fitted again including only training completers in the ADHD group. To analyze the effects of training type on neurophysiological processing, repeated measures ANOVA with time (“pre” and “post”) and condition (“win” and “no-win”) as within-subjects factors, treatment group (“Neurofeedback” and “EMG”) as between-subjects factors controlled for baseline symptom severity, age and medication state was used. For post-hoc exploration of the results estimated marginal means and pairwise comparisons were calculated. Then one-way ANOVAs with diagnostic group (“controls”, “medicated ADHD patients” or “unmedicated ADHD patients”) as within-factors and one-way ANOVAs with treatment type (“Neurofeedback” and “EMG”) as within-factors were calculated, separately for the different task conditions. Tukey post hoc tests were used to compare the groups for

the the pre-training assessment (“controls”, “medicated ADHD patients” and “unmedicated ADHD patients”).

For visualization purposes paired t-tests were calculated for win vs. no-win conditions, as well as for the comparison between pre- and post-training as proposed by the Brain Vision Analyzer 2.1. For significant amplitude differences, the mean t-values were reported. Furthermore, unpaired t-tests were calculated for medicated vs unmedicated participants, as well as for the comparison between patients and controls.

2.7 Clinical outcome analysis

Treatment outcome was analyzed using SPSS. Differences between treatment types were tested using repeated measures ANOVA with the within-subjects factor time (“pre-training”, “post-training”) and the between-subjects factor treatment type (“Neurofeedback” and “EMG”) or medication status controlled in a second step for baseline symptom severity and age. Symptom severity was defined using the percentiles as “normal to slightly affected” and “moderate to severely affected”. Separate ANOVAs were performed for training type and medication status due to the small groups.

3 RESULTS

3.1 Descriptives

No significant differences between the ADHD patients and the controls regarding gender ($\chi 2$ (1) = 1.14, p = 0.29), age (t (22) = -1.6, p = 0.13) or IQ (t (22) = -0.91, p = 0.37) were identified. Overall, the IQ was above average in the whole sample, see table 1. This sample is substantially overlapping with the one described by Baumeister et al. (2018). However in the aforementioned study, simultaneous data were analyzed for fMRI outcomes, and pre-processing led to one more participant in the EMG group (Baumeister et al., 2018), see table 2 in the supplementary material.

Within the ADHD group, patients in the NF and EMG groups showed significant differences regarding age (t (12) = 2.38, p = 0.04), parent-rated ADHD symptom severity ($\chi 2$ (1) = 4.38, p = 0.04), as well as the percentage of patients taking medication ($\chi 2$ (1) = 4.38, p = 0.04). Patients in the NF group were on average older (NF: M = 12.38, *SD* = 1.3; EMG: M = 10.67, *SD* = 1.37), showed increased symptom severity (NF: M = 3.25, *SD* = 0.7; EMG: M = 1.67, *SD* = 1) and were more likely to take medication (NF = 88%; EMG = 33%) compared to the EMG group. There was no significant difference between groups regarding gender distribution ($\chi 2$ (1) = 0.01, p = 0.91) or IQ (t (12) = 1.77, p = 0.1).

Table 1. Demographic information

Participants	N	Age, M years(*SD*)	Male,%	IQ, M(*SD*)	Medication, %
ADHD baseline	19	11.8 (1.4)	79	112.4 (13.7)	68
ADHD training completers	14	11.6 (1.5)	71	112.5 (14.4)	64
ADHD NF	8	12.4 (1.3)	75	118 (14.2)	88
ADHD EMG	6	10.7 (1.4)	66	105.2 (11.1)	33
Controls	10	12.6 (1.3)	50	118.4 (17.2)	0

3.2 EEG results

3.2.1 Baseline group comparison

CNV: There was no statistically significant difference between the ADHD patients and the healthy controls regarding the CNV amplitude for any condition in the pre-treatment assessment (V = 0.025, F (2, 26) = 0.34, p = 0.72). Furthermore, no statistically significant difference could be found when only training completers and controls were compared (V = 0.02, F (2, 21) = 0.2, p = 0.82).

Cue-P3: There was neither a statistically significant difference between the Cue-P3 amplitude across all conditions in the pre-treatment assessment between the ADHD patients and the controls, V = 0.25, F (2, 21) = 0.48, p = 0.23, nor for the Cue-P3 latency, V = 0.25, F (2, 21) = 1.45, p = 0.22.

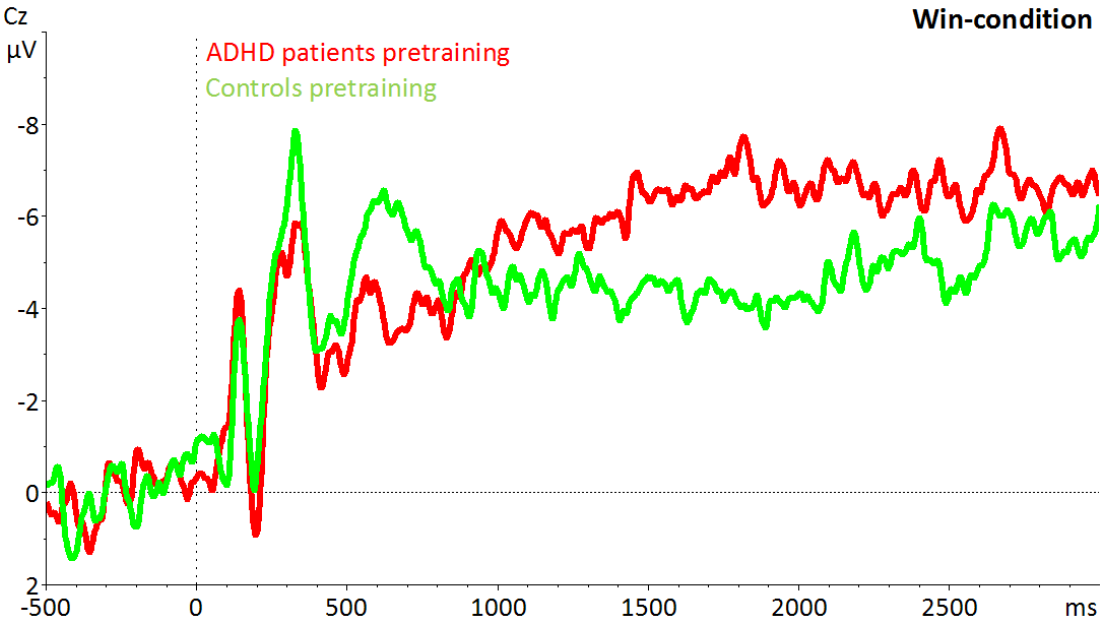


Figure 1. Visualization of the ERP results for win condition pre-training using the Brain Vision Analyzer 2.1.: Stimulus-locked ERP wave shapes in the win condition pre-training from ADHD patients (red) and controls (green).

3.2.2 Effects of treatment types

CNV: There were no significant main effects of time (F (1, 9) = 0.08, p = 0.78), treatment type (F (1, 9) = 0.4, p = 0.55) or condition (F (1, 9) = 0.3, p = 0.6) or their interactions (see Table 2).

Cue-P3: For the Cue-P3 amplitude, there were no significant main effects of time (F (1, 9) = 1.34, p = 0.28), treatment type (F (1, 9) = 0.04, p = 0.86) or condition (F (1, 9) = 0.0, p = 1.0) nor any interactions (see Table 3).

The post-hoc exploration revealed no significant treatment type effect, neither in the win condition (F (1) = 0.56, p = 0.46), nor in the no-win condition (F (1) = 0.03, p = 0.87).

For the Cue-P3 latency, there were no significant main effects of time (F (1, 9) = 1.02, p = 0.34), treatment group (F (1, 9) = 0.11, p = 0.75) or condition (F (1, 9) = 0.09, p = 0.77), and no significant time x condition x treatment group interaction (F (1, 9) = 1.11, p = 0.32*).* Regarding the control variables, there was a trend for a time x age interaction *(*F (1, 9) = 3.63, p = 0.089). When exploring this interaction, a trend for a positive correlation between age and the difference scores of the Cue-P3 latency (representing the change over time) could be shown *(*r = 0.38, p = 0.07; see supplementary figure 1). Furthermore, there was a trend for a condition x symptom severity interaction (F (1, 9) = 3.85, p = 0.081). Severely affected patients compared to moderately affected patients showed a trend for a shorter Cue-P3 latency, only in the no-win condition (severe: M = 350.1, SD = 29.85; moderate: M = 454.75, SD = 42.29; p = 0.095). The further examined interactions showed no significant effects (see Table 4).

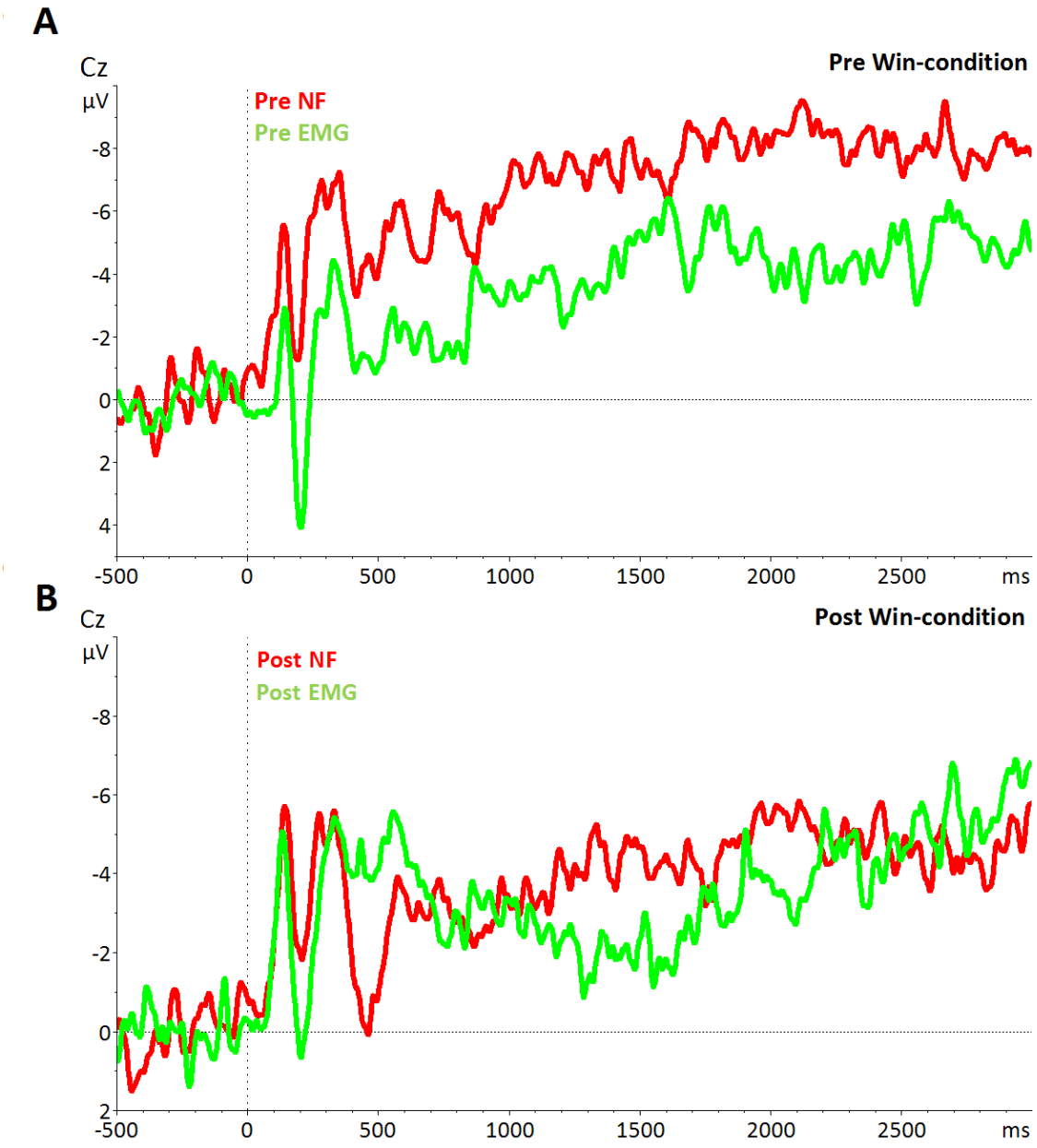


Figure 2. Visualization of the ERP results for win condition over time using the Brain Vision Analyzer 2.1. A. Stimulus-locked ERP wave shapes in the win condition pre-training from NF group (red) and EMG group (green). B. Stimulus-locked ERP wave shapes in the win condition post-training from NF group (red) and EMG group (green).

3.2.3 Effects of Medication state

3.2.3.1 Pre-treatment comparison

Demographic data: There was a trend for a difference regarding medication state between feedback types ($\chi 2$ (1) = 3.32, p = 0.069), with 88% medicated participants in the NF group and 33% medicated participants in the EMG group. Severely affected ADHD patients were more often on medication than ADHD patients with lower ADHD scores (χ2 (2) = 11.26, p = 0.004). After randomization, severely affected patients were significantly more frequent in the neurofeedback group ($\chi 2$ (1) = 4.381, p = 0.036).

CNV: No statistically significant difference in the win condition in the pre-treatment assessment between diagnostic groups could be identified by one-way ANOVA (F (2, 21) = 2.1, p = 0.15). There were no significant differences between medicated and non-medicated ADHD patients in the no-win condition (F (2, 21) = 1.1, p = 0.37).

An unpaired t-test in the Brain Vision Analyzer revealed a significantly more negative CNV only in the win condition in the pre-assessment when medicated ADHD patients (M = -9.25 µV, SD = 4.3;) are compared with non-medicated ADHD patients (M = -2 µV, SD = 6.1; t (12) = 2.62, p = 0.023; see figure 1).

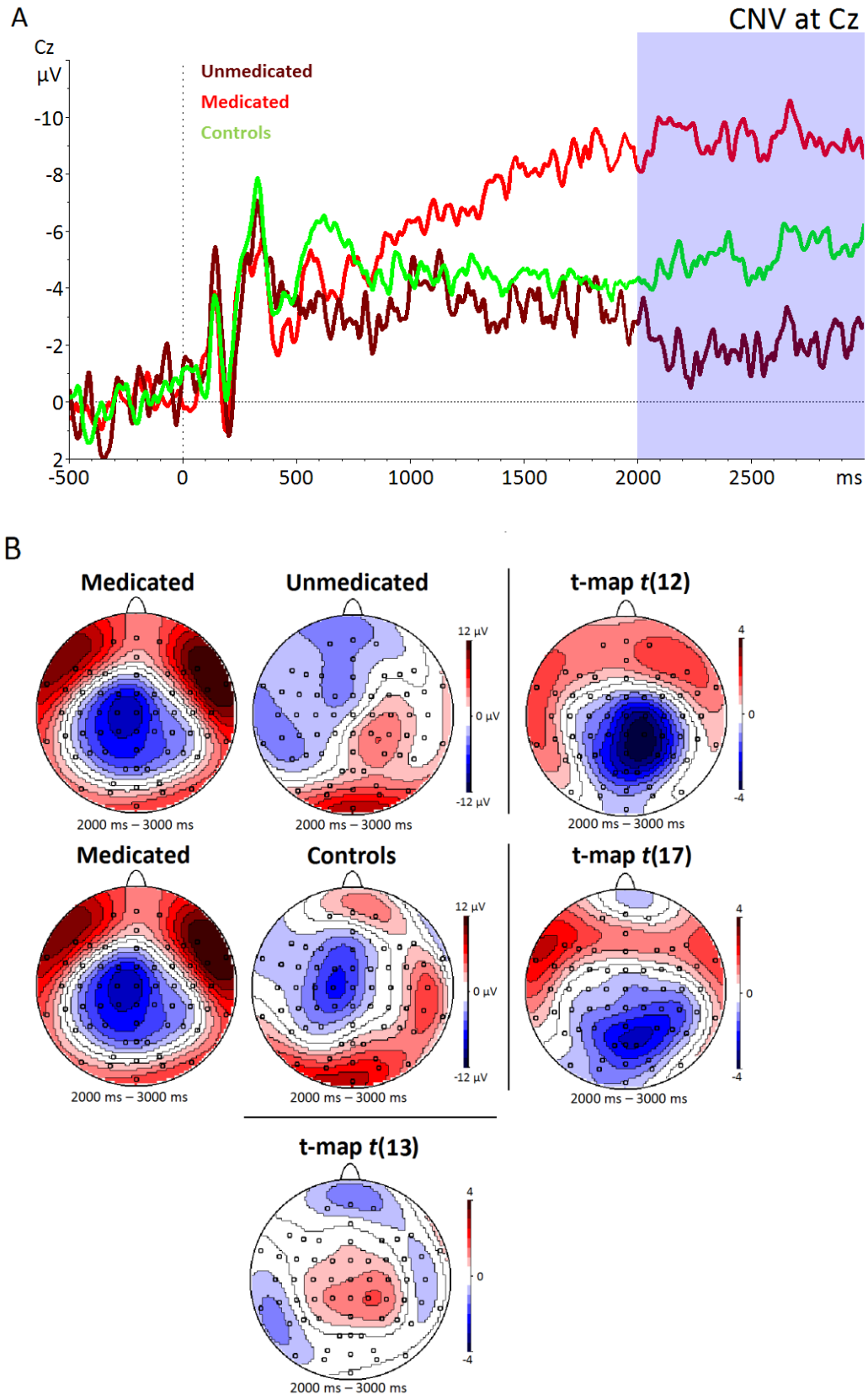


Figure 3. Visualization of the ERP results for win condition pre-training using the Brain Vision Analyzer 2.1. A. Stimulus-locked ERP wave shapes in the win condition pre-training from medicated ADHD patients (red), unmedicated ADHD patients (brown) and controls (green). B. Corresponding maps in the time range of CNV and t-maps for medication vs no medication, as well as medication vs controls and no medication vs controls comparisons.

Cue-P3: Regarding the Cue-P3 amplitude, no statistically significant difference between diagnostic groups could be determined by one-way ANOVA neither in the win condition (F (2, 21) = 1.03, p = 0.38), nor in the no-win condition (F (2, 21) = 0.6, p = 0.56). Unpaired t-tests in the Brain Vision Analyzer revealed no significant differences between the medicated and the unmedicated ADHD patients neither in the win condition (t (12) = 1.3, p = 0.219), nor in the no-win condition pre-treatment (t (12) = 0.2, p = 0.84).

Regarding the Cue-P3 latency, no statistically significant difference between diagnostic groups in the win condition could be determined pre-training by one-way ANOVA (F (2, 21) = 2.35, p = 0.12). There were no significant differences between medicated and non-medicated ADHD patients in the no-win condition (t (12) = 1.71, p = 0.11).

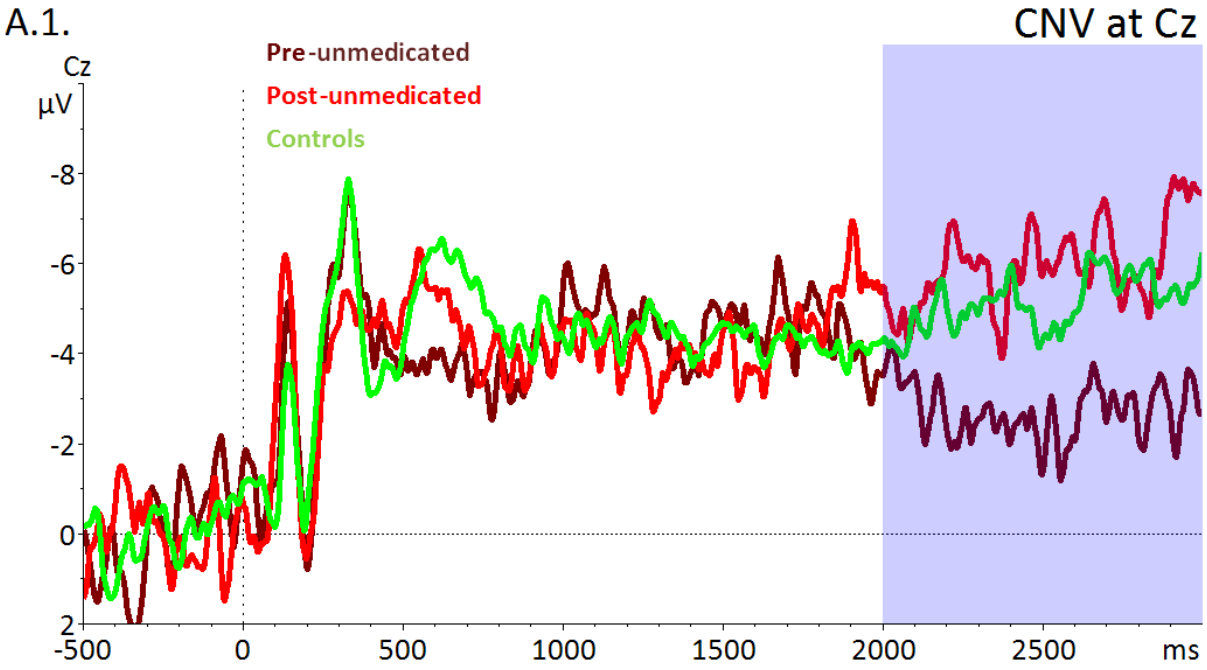
3.2.3.2 Treatment outcome analysis

CNV: The repeated measures ANOVA showed a trend for a time x medication state interaction (F (1, 9) = 4.54, p = 0.062): Descriptively, unmedicated patients showed an slightly increased CNV amplitude after the training, but this difference was statistically not significant (Pre M = -3.92, SD = 2.66; Post M = -6.63, SD= 2.68; p = 0.3), whereas medicated patients showed reduced CNV amplitudes after the training (Pre M = -8.58, SD = 1.85; Post M = -4.19, SD = 1.87; p = 0.032). Pairwise comparisons showed no significant differences between medicated and unmedicated participants, neither in the pre-training assessment (p = 0.22) nor in the post-training assessment (p = 0.52).

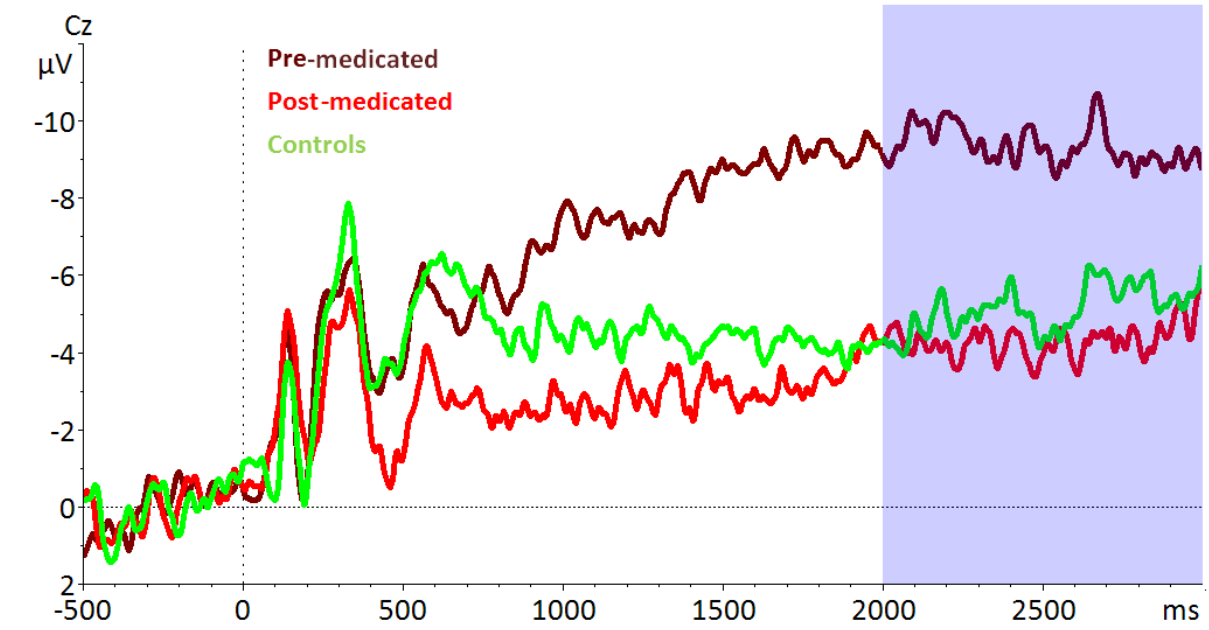
In line with these findings, analysis in the Brain Vision Analyzer also showed increased CNV amplitude after the training in unmedicated patients (t = (4) = 6.67, p = 0.003) and decreased CNV amplitudes after treatment in medicated patients (t (8) = -3.1, p = 0.015).

With a mean CNV of -4.9 µV (SD = 5.5), the non-medicated patients were approaching the values of the controls in the pre-assessment (M = -5.1 µV, SD = 8.3; see figure 2).

A.1.


CNV at Cz
Cz
µV
Pre-unmedicated
Post-unmedicated
Controls
-8
-6
-4
-2
0
2
-500
0
500
1000
1500
2000
2500
ms

A.2.


Cz
µV
Pre-medicated
Post-medicated
Controls
-10
-8
-6
-4
-2
0
2
-500
0
500
1000
1500
2000
2500
ms

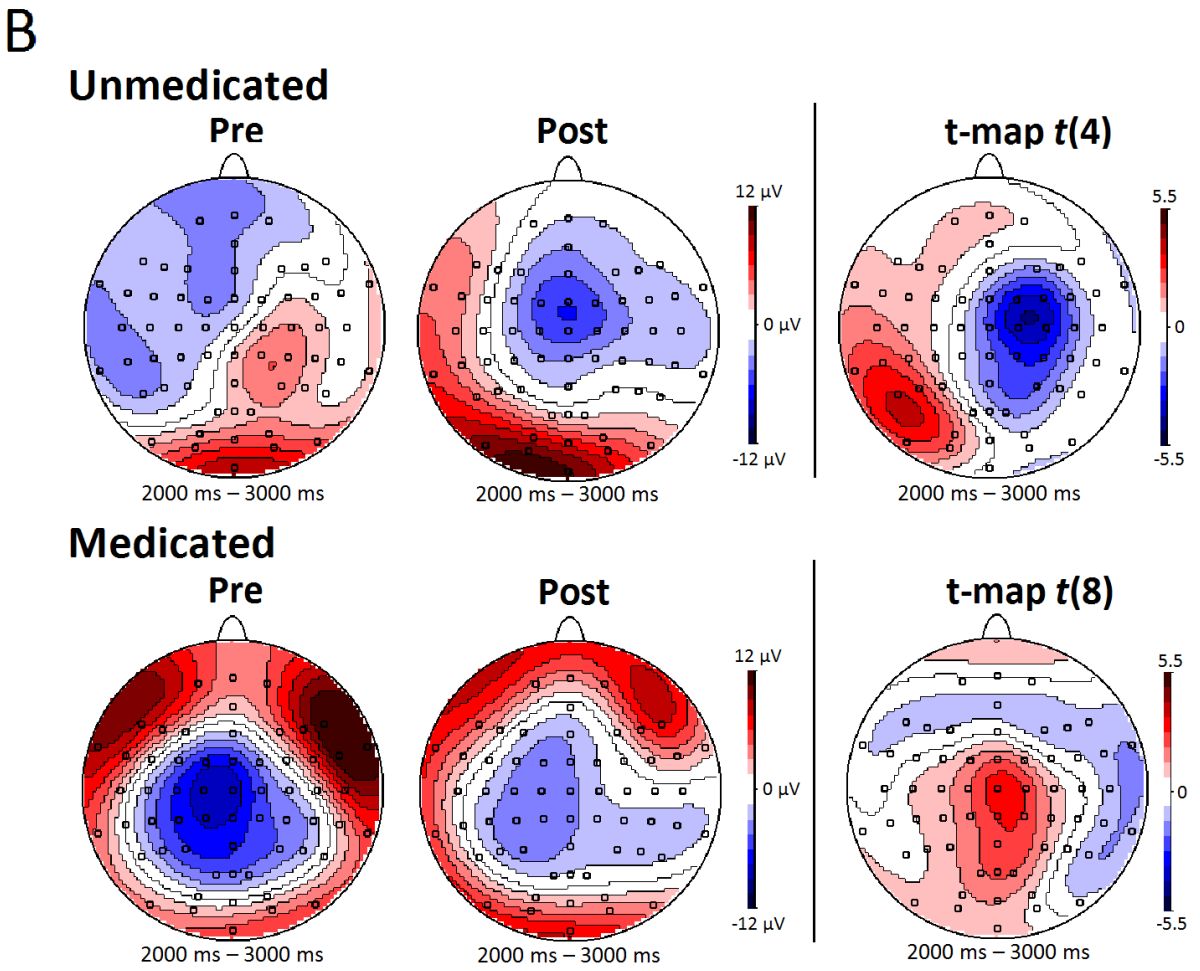


Figure 4. Visualization of the ERP results for cue win condition pre vs post training using the Brain Vision Analyzer 2.1. A.1 Stimulus-locked ERP wave shapes in the cue win condition pre- and post-training from unmedicated ADHD patients pre (brown), unmedicated ADHD patients post (red) and controls pre (green) A.2. Stimulus-locked ERP wave shapes in the cue win condition pre- and post-training from medicated ADHD patients pre (brown), medicated ADHD patients post (red) and controls pre (green). B. Corresponding maps in the time range of CNV and t-map (t-test against zero) for pre vs post training and medication state.

Cue-P3: Regarding the Cue-P3 amplitude, there was a trend for a time x condition x medication state interaction (F (1, 9) = 3.47, p = 0.096). Pairwise comparisons among the estimated marginal means showed no significant differences between medicated and unmedicated participants pre-training neither in the win condition *(*p = 0.41), nor in the no-win condition *(*p = 0.7). Comparably pairwise comparisons between medicated and unmedicated participants post-training showed no significant differences neither in the win condition (p = 0.52), nor in the no-win condition *(*p = 0.79). However, descriptively in the win condition medicated ADHD

patients had a higher Cue-P3 amplitude before training (*M* = 7.42, *SD* = 1.37) than unmedicated ADHD patients (*M* = 5.16, *SD* = 1.96), and even than healthy controls (*M* = 5.75, *SD* = 3.48) but a decreased Cue-P3 amplitude after training (*M* = 4.74, *SD* = 1.46) compared with unmedicated ADHD patients (*M* = 6.64, *SD* = 2.1; see figure 3.). An unpaired t-test in the Brain Vision Analyzer comparing the difference-scores Post- minus Pre-training of medicated and unmedicated ADHD patients revealed a trend in the win condition (*t* (10.76) = 1.85, *p* = 0,093).

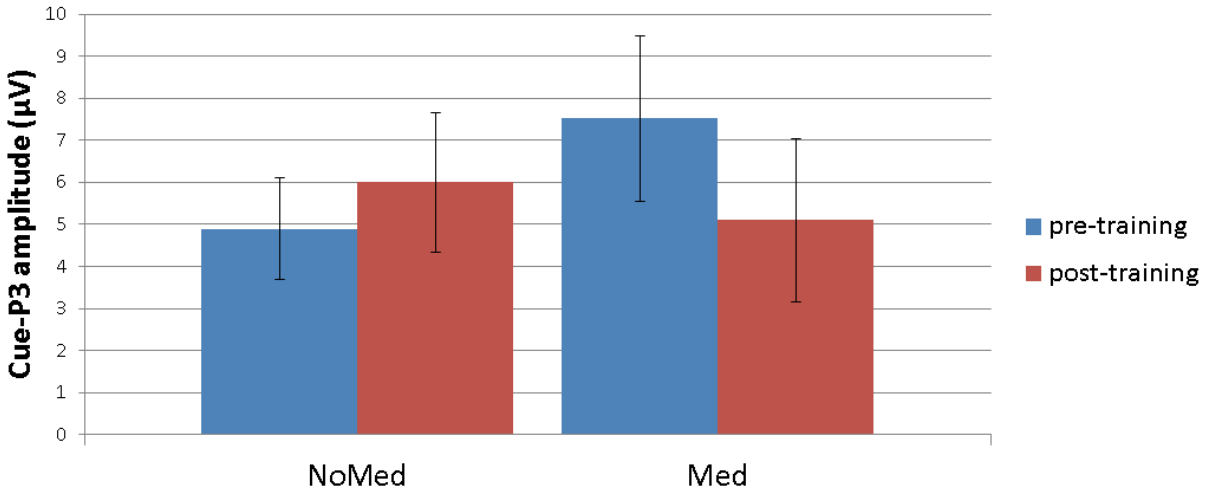


Figure 5: Mean Amplitude of Cue-P3 in the win condition over time

Regarding the Cue-P3 latency, the repeated measures ANOVA showed a trend for a time x condition x medication state interaction (*F* (1, 9) = 3.58, *p* = 0.091). Unmedicated patients showed an improved Cue-P3 latency after training in each condition with a bigger difference in the no-win condition (Pre win M = 354.87, *SD* = 50.76, Post win M = 369.28, *SD* = 58.1, *p* = 0.81; Pre no-win M = 289.82, *SD* = 50.67; Post no-win M = 418.58, *SD* = 45.1, *p* = 0.01), whereas medicated patients showed improved Cue-P3 latencies in the win- and reduced Cue-P3 latencies in the no-win-condition after training (Pre win M = 417.3, *SD* = 35.42, Post win M =

449.29, *SD* = 40.5, *p* = 0.44; Pre no-win M = 424.55, *SD* = 35.35, Post no-win M = 387.46, *SD* = 31.5, *p* = 0.22) A pairwise comparison showed a trend-level significant difference between medicated and unmedicated participants pre-training in the no-win condition (medicated no-win M = 424.55, *SD* = 35.35, unmedicated no-win M = 289.9, *SD* = 50.67, *p* = 0.079). Further comparisons provided no significant differences.

3.3 Clinical outcome

The parent rating of the global ADHD score of the DISYPS questionnaires revealed a significant time x training type interaction (*F* (1, 10) = 5.21, *p* = 0.046), with decreased scores after training (*M* = 1.12, *SD* = 0.65) compared to before training (*M* = 1.54, *SD* = 0.54) only in the NF group, but not in the EMG group (pre: *M* = 0.98, *SD* = 0.63, post: *M* = 0.95, *SD* = 0.72), similarly to the results of Baumeister et al. (2018). When controlling for age and baseline symptom severity, there were no significant main effects or interactions. Furthermore there was a significant effect of time indicating an improvement in both groups after the training (*F* (1, 8) = 6.41, *p* = 0,035), but no significant interactions regarding medication state.

4 DISCUSSION

Altered reward processing has been discussed as a core deficit in Attention-Deficit/Hyperactivity Disorder accompanied by neurophysiological alterations in the reward circuit. Contrary to our hypothesis, we did not find significant differences in ERP amplitudes or latencies of interest between patients with ADHD and controls before the training in the expected direction. Furthermore, this is in contrast to previous fMRI studies showing consistent reward-related deficits in ADHD patients (Plichta & Scheres, 2014), and previous EEG studies showing reduced CNV amplitudes in ADHD patients during non-reward related processes (for review see Kaiser et al., 2020). Our finding might be explained by findings of previous research showing elevated ERP amplitudes in ADHD patients during reinforcement compared to non-reinforced trials (Chronaki et al., 2017). According to the delay aversion hypothesis, ADHD patients are expected to be reinforced by the prospect of winning, which was also promised in half of the trials in our task design. Thus, continuous reinforcement might have normalized CNV amplitudes in our study. However, this does not explain our failure to find significant group differences in the neutral condition. Contrary to expectations, we did not find an effect of condition in the pretreatment assessment: Both patients and controls showed no differences in neurophysiological markers when comparing the win and the neutral trials. Prior studies have demonstrated elevated CNV amplitudes in the win condition using the same task in healthy adult samples (Boecker et al., 2014). The lack of condition effect in the current study might be explained by participants already performing at maximum. Another possible explanation could be linked to maturational processes with increasing age. Von Rhein (2015) examined adolescents and young adults with ADHD with a mean age of 17.7 (*SD* = 3), which showed increased neuronal responses to reward in fMRI measures.

Nevertheless Chronaki (2017) were able to show a reinforcement-related enhancement of the CNV already in an ADHD population with a mean age of 11.6 (SD= 1.6), but the authors discussed that the upregulation did not translate into improved performance and may be rather a marker for a hyper-arousal in ADHD. Furthermore contrary to the results of Plichta et al. (2012), there are some findings indicating that especially the CNV is less modulated by a possible win (Broyd et al., 2012). The authors argued that the condition effect was modulated by task design factors and influenced by personality traits such as hedonism. Another possible explanation for this might be that the patients were not sufficiently reinforced by the proposed level of monetary incentive. This is however unlikely, given that fMRI data analysis in this study has yielded a robust effect (Baumeister et al., 2018). Future research could use a varying amount of monetary rewards to understand this effect further.

Neurofeedback is a promising non-pharmacological treatment for ADHD and has been shown to be effective for inattentive symptoms (Riesco-Matias et al., 2019). But contrary to our hypotheses, the current study has been unable to demonstrate an improvement of the reward anticipation related ERP amplitudes or latencies after the treatment. In other words, regardless of the type of training, no changes in neurophysiological markers, such as the CNV and the CueP3 amplitude and latency, could be observed after the training, neither in the win nor in the non-win condition. Thus these results suggest no effect of NF on neurophysiological markers of reward processing in ADHD. This finding is only partly in line with first fMRI results investigating the effect of NF on reward processing, which indicate at least an unspecific effect of the training (Baumeister et al., 2018). In this context possible effects of group differences have to be addressed, that could have had an impact on these results. In our ADHD group, patients in the NF group were significantly older. We found that younger participants showed

a shortened Cue-P3 latency whereas older participants showed an increased latency after the training in the no win condition. In our sample were mostly included adolescents and fewer children. There is some evidence that especially the P3 component (amplitude and latency) runs through a maturational process during adolescence, indicating that typically developing children start to show a standard pattern of the P3 around age 13 comparable to healthy adults (Segalowitz & Davies, 2004). One could argue that our results might reflect this physiological maturation process. But there are still inconsistent results regarding the development of the P3 in ADHD: some findings indicate a shortened latency with increasing age (Halliday, Callaway, & Lynch, 1984), which is in contrast with our results. Others postulate that children with sensory processing disorders such as ADHD continue to process the information much longer and more intense leading to an increased P3 amplitude and latency in childhood (Davies, Chang, & Gavin, 2010). This is in contrast with the evolution we see in our results. On the behavioral level, Groeneveld et al. (2019) found greater improvements on ADHD symptoms after NF training in adults compared to children. These findings possibly indicate a maturational process of brain development, which might offer older children an advantage for NF training.

Since stimulant medication is the first-line therapy for ADHD (Caye, Swanson, Coghill, & Rohde, 2019), there are many studies that have examined their effects on neurophysiological markers. Many findings indicate that medication leads to a neurophysiological improvement and our results are consistent with previous literature. We were able to show that medicated patients had a significantly more negative CNV already before the training which is in line with findings of Linssen et al. (2011), who were able to show that the CNV amplitude increased depending on the dosage of methylphenidate, whereas the reaction time decreased in healthy

participants indicating greater dopamine availability in the basal ganglia. Furthermore, MPH has been shown to enhance task performance by improving efficiency of neuronal processing in reward-motivation and attention-activation systems in healthy adults (Ivanov et al., 2014). In ADHD patients, the CNV amplitude was shown to be increased by stimulant medication (MPH or dextroamphetamine, if MPH had side-effects) but only in treatment-responders (Ogrim et al., 2016), while Atomoxetine did not elicit this effect (Kratz et al., 2012). While several studies showed also an increase in the amplitude of the frontal P3 event-related component after medication intake (Dockree et al., 2017; Dolu et al., 2019; Roca, Mulas, Gandia, Ortiz-Sanchez, & Abad, 2013; Rubinson et al., 2019), the current study failed to show significant differences in Cue P3 between medicated and unmedicated ADHD patients before treatment. Recently, larger differences in the activation of the ventral striatum to cues signaling a possible reward versus neutral cues were detected when adult ADHD participants received methylphenidate compared to placebo (Furukawa et al., 2019). The authors concluded that the therapeutic effects of methylphenidate may be mediated by changes in reward processing in individuals with ADHD. On the other hand, several other studies were unable to show an improvement of striatal activation under medication (Schweren et al., 2017; Stoy et al., 2011). But the heterogeneity of the population should be taken into account when interpreting those results. As already described in the definition of DSM V, different subtypes and mixed forms can be distinguished in ADHD. Recent neurobiological models of ADHD suggest that at least three independent pathways may be involved; a dorsal fronto-striatal pathway involved in cognitive control, a ventral fronto-striatal pathway involved in reward processing and a fronto-cerebellar pathway related to temporal processing (de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012). To date, it has not been sufficiently investigated whether MPH shows the same effect strength in the different neuronal systems.

Aarts et al. (2015) showed that only subgroups of ADHD patients showed a normalized striatal response on medication. The study attributed this to genetic differences in the DAT1 gene coding for the dopamine transporter in the striatum. Patients carrying a specific allele (9R) had greater striatal responses to reward than controls, which was normalized by medication. Our findings support the idea of an improvement of the reward processing by stimulant medication.

When exploring the impact of medication use on treatment outcome in more detail, we were able to show that unmedicated patients showed a significantly more negative CNV amplitude and increased P3 amplitude after the training in the win condition. This is in line with a study by Heinrich and colleagues, who were able to demonstrate that children with ADHD had an increased CNV amplitude and decreased symptoms after SCP-NF training (Heinrich et al., 2004). In our study, we surprisingly showed a significantly reduced CNV amplitude after the training in medicated patients, in the win condition. In addition, there was a trend-level significant interaction between time, condition, and medication state for the Cue-P3 amplitude, indicating that medicated patients showed a decreased amplitude after the training, only in the win condition and independent of training type. Comparably, there was a trend-level significant interaction between time, condition, and medication state for the Cue-P3 latency, indicating that unmedicated patients showed an increased Cue-P3 latency after the training in both conditions, whereas medicated patients showed an increased latency only in the win condition. Over all, the unmedicated patients seemed to benefit more on the neurophysiological level in this study, whereas medicated patients even showed a neurophysiological deterioration after the training. In addition to the exploration of the effectiveness of the individual therapy components, the interaction of both therapies should also be examined further and to our knowledge only a few studies investigated the interaction

between medication and NF. But studies yielded inconsistent results. Several studies failed to report a greater benefit of NF in addition to pharmacological treatment. Elsewhere, there are some preliminary findings which indicate that on a behavioral level ADHD symptoms showed a greater improvement if stimulant medication and NF is combined (Duric, Assmus, Gundersen, Duric Golos, & Elgen, 2017; González-Castro, Cueli, Rodríguez, García, & Álvarez, 2016; Li, Yang, Zhuo, & Wang, 2013). The combination of NF and medication with atomoxetine did not provide any additional benefit (Azouz, Abdel-Latif, Omar, Khalil, & Abdel Maksoud, 2019; Lee & Jung, 2017). Further, a recent review and a Double-Blind Placebo-Controlled Randomized Clinical Trial reported that during NF training medication dosage could be decreased and these positive results were maintained at 6-month and at 13 month follow-up (Arnold, 2020; Razoki, 2018). Clinically, this could be very useful for ADHD patients who suffer from side-effects. We know that the frequency and intensity of side-effects augment with the dosage. Several patients have to try different drug preparations and have to be titrated carefully to find a dosage that on the one hand a sufficient improvement of symptoms is achieved and on the other hand the dosage is still tolerable regarding side-effects. For those patients, a combination of NF and medication could lead to a higher therapy-commitment. To our knowledge, this is the first study to report neurophysiological ERP data while investigating the interaction of NF and medication. So far, NF treatment has mostly been compared with medication. For example, Janssen et al. (2016) showed in a randomized controlled trial that only stimulant medication compared to NF had a specific and stronger effect on the P3 component leading to a neuropsychological improvement in response inhibition (Janssen et al., 2016). Recently, Janssen et al. (2020), showed no EEG power spectra differences at 6 months follow-up between MPH and NF and concluded that there was no specific long-term neurophysiological effects of theta/beta NF in children with ADHD. Elsewhere, increased

response speed during an oddball task, faster stop signal reaction time, and lower commission and omission error rates during a stop signal task were reported only in a medicated patient group compared to NF or an active control condition leading to the conclusion that MPH had a more positive effect on neurocognitive functioning compared to NF (Gelade et al., 2017). Also on the clinical symptom level, MPH has been shown to be superior to NF. Especially, when teacher ratings are reported in different studies (Gelade et al., 2016; Sudnawa et al., 2018). Regarding the parent ratings, the results were less conclusive. Interestingly, a recent meta-analysis reported that MPH was significantly more efficacious than NF on ADHD core symptoms, but that NF showed significantly lower dropout rates and therefore a higher therapy commitment (Yan, Wang, Yuan, & Zhang, 2019). However, the findings of the current study do not fully support previous research. Some differences regarding the study design have to be discussed. Most of the above mentioned studies used a theta/beta NF training whereas in the current study, SCP training was performed. This might have influenced the current results. Some authors have discussed that the frequency band might not be the most appropriate target for NF in ADHD (Razoki, 2018), given that ADHD is highly heterogeneous and different theta-beta ratio clusters exist in the population (Bussalb et al., 2019).

Notably, the medicated patients in the present study were still severely affected. This could have led to a greater motivation and some authors already argued that pretreatment motivation of the patients and their relatives could be a potential predictor for NF treatment response but future research in this domain is necessary (Razoki, 2018). For example, Fuchs, Birbaumer, Lutzenberger, Gruzelier, and Kaiser (2003) reported just as much behavioral improvement in the NF group as in the medication group in teacher and parent ratings, as well as an improvement on speed and accuracy in the d2 Attention Endurance Test. However these results must be interpreted with caution because, they are at odds with more recent meta-

analytic results (Riesco-Matias et al 2019). Also, in contrast to our own study, the parents could choose in which treatment group their child should be assigned to. Therefore we must assume strong motivational bias. A recent study demonstrated that SMR-NF training was effective particularly in children whose parent favored non-pharmacological treatment, but the combination of medication (here, methylphenidate) with NF was even more efficient, supporting the multimodal treatment-approach in ADHD (Pakdaman, Irani, Tajikzadeh, & Jabalkandi, 2018). Furthermore, one must assume that the efficacy of the pharmacological treatment is also influenced by unspecific factors. On the one hand, placebo effects can increase the positive treatment success. On the other hand, it must be taken into account that many parents generally refuse medication and pay close attention to side effects. It would therefore be conceivable that children in these families could experience a nocebo effect of the medication. To our knowledge, there is no sufficient investigation in this domain to date. In addition, both treatments could benefit from common unspecific effects, such as a good therapist-patient relationship.

A recent review discussed that NF may be considered a viable alternative to stimulants for a specific group of patients, especially poor responders to medication but also pointed out the need for future research with priority focus on the identification of markers that differentiate responders from non-responders (Razoki, 2018). This could also be a possible explanation for our results but response to medication before the training was not recorded in this study. This is in line with earlier observations, which identified different type of central nervous system dysfunction in good- and poor-responders to medication (Clarke, Barry, McCarthy, & Selikowitz, 2002). The authors postulated that based on the EEG profiles and the response to different medication different subgroups in the ADHD population can be identified. Ogrim et al. (2014) were able to show that the amplitude of the cue P3 component, was normal in

responders but significantly decreased in non-responders. Elsewhere, a significant increase in the P3 no-go amplitude in medication responders but not in non-responders or participants of NF training could be found (Ogrim & Hestad, 2013). The authors discussed that, for an effective NF training, a preselection might be useful but to date no criteria could be identified. Similarly, one must also take into account that there are patients who respond better or less well to NF therapy, but currently we have no evidence for single specific markers that differentiate responders from non-responders. In summary, it can be said that it would be helpful to know predictors of therapy success for both medication and NF. We are aware of a few ongoing trials further evaluating the potential predictive value of neuronal markers for the therapy response to pharmacological as well as non-pharmacological interventions (Döpfner et al., 2017; Geissler et al., 2018).

In the current study, the unmedicated patients benefited more from the NF training on the neurophysiological level, whereas the medicated patients showed deterioration on the neurophysiological level. The first point could be linked to a greater room for improvement in unmedicated patients. In children with increased levels of impairment, clinical improvement could be more apparent, whereas in children with fewer symptoms the improvement could be more subtle and more difficult to recognize for the parents. Further, not all mechanisms of action regarding medication are fully understood. In summary, our results suggest a possibly surprising negative interaction effect between NF and stimulant medication that should be further explored in future studies. Further, neurophysiological improvement may not be linked to a clinical improvement. We do not know yet how much they correlate. As proposed by Baumeister and colleagues, the neurophysiological normalization of the VS activation in medicated patients not necessarily leads to an increase in behavioral performance reflected by improvement of reaction time (Baumeister et al., 2018). Clinically, improvement regarding

symptom severity and the amelioration of the functional level prevail over the normalization of neurophysiological markers.

Regarding the clinical outcome, in the current study we were able to show, that ADHD patients in the NF group showed reduced symptom severity in parent ratings after training compared with ADHD patients in the EMG control group. This is in line with previous literature (Arns et al., 2009; Micoulaud-Franchi et al., 2014; Riesco-Matias et al., 2019; Sonuga-Barke et al., 2013) and supports conclusions from previous/other studies that report efficacy of NF. Meisel and colleagues showed that in both groups (medication or NF) an improvement of ADHD symptoms could be observed in parents and teacher ratings, but that only in the NF group a significant academic performance improvement took place (Meisel et al., 2014). Elsewhere, NF was shown to especially improve response control and inattention compared with medication (Moreno-Garcia, Meneres-Sancho, Camacho-Vara de Rey, & Servera, 2019). But we have to consider that our NF group was significantly more affected. Furthermore, clearer improvements may have led in a second step to greater positive reinforcement, like more praise for good cooperation, from the parents for the participation in therapy. This may have an influence on the parent ratings. Further projects are ongoing to investigate the effects of NF compared with medication on ADHD, including the personalization of the training protocol and improving accessibility of NF due to the opportunity to train at home (Bioulac et al., 2019). As mentioned above, for the patient and the practitioner, clinical improvement is more relevant for clinical practice than neurophysiological, especially since we do not know how much they correlate.

4.1 Limitations

Although some novel insights could be reported, some limitations have to be considered. First, only a small sample was available for the analyses after preprocessing of the data and quality control. This always harbors the risk of not being representative enough, especially since ADHD is a very heterogeneous disease. This might have led to a reduced statistical power, potentially responsible for the non-significant effects regarding the neurophysiological treatment outcome. Therefore these results need to be interpreted with caution. Next, only parent ratings were available to record clinical symptoms. Family motivation and expectations must be considered as a possible confounder in treatment outcome ratings. It is important to bear in mind the possible response-biases in the questionnaires due to those factors. We cannot rule out with certainty that the families had presumptions about the type of training their child was randomized to, even though neither the parents nor the children were informed about the treatment type. Neither the exact medication type, nor the dosage, for patients also undergoing psychopharmacological treatment was assessed. So medication effects could not be explored in more detail. Further, patients in our NF group showed a higher symptom severity score pre-training and received significantly more often medication. This could have led to different biases like more room for improvement, greater self-motivation but also an increased attention on improvement by the parents leading to rating differences. Furthermore, medicated patients were still severely affected. A possible explanation for this might be that we included patients with an important proportion of non-responders to medication. Finally, one should note that in the current study only ERPs related to reward anticipation could be investigated due to the task design, because of motion artifacts due to button press in the time interval of interest for reward delivery. Therefore, not all aspects of reward processing could be explored and data analysis was limited to reward anticipation.

4.2 Outlook

To our knowledge, the present study is the first to investigate the effects of NF on reward processing in ADHD using simultaneous fMRI/EEG data, thereby adding valuable information to the understanding of the mechanisms of action of NF. Nonetheless, further work is required to evaluate the presented effects and to further explore the here proposed hypotheses.

First of all, the study should urgently be replicated in a larger sample, because the results and interpretations discussed here are based on a small sample size. Further sufficient evidence regarding reward processing in healthy neurophysiological development, specifically in children and adolescents, is currently lacking. Therefore, a larger control group of healthy subjects and their neurophysiological development over time, especially looking at maturational processes during adolescence would be helpful. In addition, when studying NF, non-specific effects and motivational issues need to be considered. In further work, parents and children could be asked about their level of suffering and their approach towards different treatment options, to offer a better possibility to control for motivational effects. In addition, it would be interesting to depict the entire spectrum of the ADHD population and not primarily include severely affected patients to reduce the motivational bias. Furthermore, there could be more emphasis on teacher judgments for an additional and more objective assessment. Future studies should focus on a better characterization of medication intake. A more detailed assessment of medication type and dosage and, eventually, side-effects could allow for a better investigation of treatment response and interaction effects between NF and medication. In the past years some effort has been made to compare NF and medication for the treatment of ADHD, but the results are still inconsistent. In summary, it can be said that more studies are needed directly comparing standard NF-protocols with medication, including

an additional treatment group that receives both treatment types, and which use objective markers such as EEG or fMRI data to explore treatment outcome.

Another interesting topic to investigate in the future is how stable the positive effects of NF are over longer time periods. Preliminary and very promising results indicate an ongoing positive treatment effect assessed after a 6 months follow up (Aggensteiner et al., 2019; Meisel et al., 2014) and in one recent study even after a 13 months follow up (Arnold, 2020). But the named studies only focused on the clinical data exploring ADHD symptomatology via questionnaires. Therefore, it remains unclear how this ongoing positive effect of NF on a behavioral/symptom level is related to neurophysiological improvements. Overall, the relationships between the clinical measures and the neurophysiological data should be better investigated in more detail. In future work, the task design should be adjusted to investigate also the reward-related ERP components in larger studies. Exploring both, reward anticipation and delivery, will add valuable information to the understanding of reward processing in ADHD.

5 SUMMARY

Altered reward processing has been discussed as a core deficit in Attention-Deficit/Hyperactivity Disorder that has been increasingly investigated in the past years. Compared to healthy subjects, patients affected by Attention-Deficit/Hyperactivity Disorder showed reduced amplitudes of the Cue-P3 and the contingent negative variation, two event-related potentials that have been associated with reward anticipation on a neurophysiological level. Within a randomized controlled trial design, the current study investigated the effects of slow cortical potential neurofeedback on these neurophysiological indices during reward anticipation. EEG-data were recorded before and after treatment, while the participants where performing a monetary incentive delay task. After treatment, children who received neurofeedback showed reduced symptom scores in the clinical assessment. No neurophysiological change was observed after neurofeedback or electromyogram treatment. Interestingly, in the win condition, medicated patients showed a significantly increased contingent negative variation amplitude compared to unmedicated patients pre-training. After training compared to before training, they showed a less negative contingent negative variation and a reduced Cue-P3 amplitude. In contrast, unmedicated patients showed an increased contingent negative variation and CueP3 amplitude after the training.

These results suggest no specific effect of neurofeedback on reward anticipation, but point to an interaction between neurofeedback and stimulant medication. On a neurophysiological level, non-medicated patients seem to benefit more from training than medicated patients. Thus, this first study exploring the effects of neurofeedback on reward anticipation on a neurophysiological level in children suffering from Attention-Deficit/Hyperactivity Disorder offers important preliminary insights in mechanisms of action. Nonetheless, further larger

studies are needed to validate these results and to explore in more detail the interaction effects of medication and neurofeedback.

6 REFERENCES

Aarts, E., van Holstein, M., Hoogman, M., Onnink, M., Kan, C., Franke, B., . . . Cools, R. (2015). Reward modulation of cognitive function in adult attention-deficit/hyperactivity disorder: a pilot study on the role of striatal dopamine. *Behav Pharmacol, 26*(1-2), 227-240. doi:10.1097/fbp.0000000000000116

Aasen, I. E., Ogrim, G., Kropotov, J., & Brunner, J. F. (2018). Methylphenidate selectively modulates one sub-component of the no-go P3 in pediatric ADHD medication responders. *Biol Psychol, 134*, 30-38. doi:10.1016/j.biopsycho.2018.02.011

Aggensteiner, P.-M., Brandeis, D., Millenet, S., Hohmann, S., Ruckes, C., Beuth, S., . . . Holtmann, M. (2019). Slow cortical potentials neurofeedback in children with ADHD: comorbidity, self-regulation and clinical outcomes 6 months after treatment in a multicenter randomized controlled trial. *Eur Child Adolesc Psychiatr, 28*(8), 1087-1095. doi:10.1007/s00787-018-01271-8

Akkermans, S. E. A., van Rooij, D., Naaijen, J., Forde, N. J., Boecker-Schlier, R., Openneer, T. J. C., . . . Buitelaar, J. K. (2019). Neural reward processing in paediatric Tourette syndrome and/or attention-deficit/hyperactivity disorder. *Psychiatry Res Neuroimaging, 292*, 13-22. doi:10.1016/j.pscychresns.2019.08.004

Albrecht, B., Banaschewski, T., Brandeis, D., Heinrich, H., & Rothenberger, A. (2005). Response inhibition deficits in externalizing child psychiatric disorders: an ERP-study with the Stop-task. *Behav Brain Funct, 1*, 22. doi:10.1186/1744-9081-1-22

Albrecht, B., Brandeis, D., Uebel, H., Valko, L., Heinrich, H., Drechsler, R., . . . Banaschewski, T. (2013). Familiality of neural preparation and response control in childhood attention deficit-hyperactivity disorder. *Psychol Med, 43*(9), 1997-2011. doi:10.1017/s003329171200270x

Antshel, K. M., Zhang-James, Y., Wagner, K. E., Ledesma, A., & Faraone, S. V. (2016). An update on the comorbidity of ADHD and ASD: a focus on clinical management. *Expert Rev Neurother, 16*(3), 279-293. doi:10.1586/14737175.2016.1146591

Arnold, L. E., Martijn Arns, Justin Barterian, Rachel Bergman, Sarah Black, C. Keith Conners, Shea Connor. (2020). Double-Blind Placebo-Controlled Randomized Clinical Trial of Neurofeedback for Attention-Deficit/Hyperactivity Disorder With 13 Month Follow-up. *J Am Acad Child Adolesc Psychiatry*. doi:10.1016/j.jaac.2020.07.906

Arns, M., de Ridder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clin EEG Neurosci, 40*(3), 180-189. doi:10.1177/155005940904000311

Arns, M., Drinkenburg, W., & Leon Kenemans, J. (2012). The effects of QEEG-informed neurofeedback in ADHD: an open-label pilot study. *Appl Psychophysiol Biofeedback, 37*(3), 171-180. doi:10.1007/s10484-012-9191-4

Arns, M., Heinrich, H., & Strehl, U. (2014). Evaluation of neurofeedback in ADHD: the long and winding road. *Biol Psychol, 95*, 108-115. doi:10.1016/j.biopsycho.2013.11.013

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed*. Arlington, VA, US: American Psychiatric Publishing, Inc.

Azouz, H., Abdel-Latif, F., Omar, T., Khalil, M., & Abdel Maksoud, M. (2019). Organizational skills training or neuro-feedback, combined with pharmacotherapy in the treatment of

school-aged children with ADHD. *Atten Defic Hyperact Disord, 11*(1), S42-. doi:10.1007/s12402-019-00295-7

Bakhshayesh, A. R., Hänsch, S., Wyschkon, A., Rezai, M. J., & Esser, G. (2011). Neurofeedback in ADHD: a single-blind randomized controlled trial. *Eur Child Adolesc Psychiatr, 20*(9), 481. doi:10.1007/s00787-011-0208-y

Banaschewski, T., & Brandeis, D. (2007). Annotation: What electrical brain activity tells us about brain function that other techniques cannot tell us – a child psychiatric perspective. *J Child Psychol Psychiatry, 48*(5), 415-435. doi:10.1111/j.1469-7610.2006.01681.x

Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., & Rothenberger, A. (2003). Association of ADHD and conduct disorder--brain electrical evidence for the existence of a distinct subtype. *J Child Psychol Psychiatry, 44*(3), 356-376. doi:10.1111/1469-7610.00127

Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., . . . Taylor, E. (2006). Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. *Eur Child Adolesc Psychiatry, 15*(8), 476-495. doi:10.1007/s00787-006-0549-0

Banaschewski, T., Hollis, C., Oosterlaan, J., Roeyers, H., Rubia, K., Willcutt, E., & Taylor, E. (2005). Towards an understanding of unique and shared pathways in the psychopathophysiology of ADHD. *Dev Sci, 8*(2), 132-140. doi:10.1111/j.1467-7687.2005.00400.x

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull, 121*(1), 65-94. doi:10.1037/0033-2909.121.1.65

Barry, R. J., Johnstone, S. J., & Clarke, A. R. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. *Clin Neurophysiol, 114*(2), 184-198.

Baumeister, S., Wolf, I., Hohmann, S., Holz, N., Boecker-Schlier, R., Banaschewski, T., & Brandeis, D. (2018). The impact of successful learning of self-regulation on reward processing in children with ADHD using fMRI. *Atten Defic Hyperact Disord*. doi:10.1007/s12402-018-0269-6

Beauregard, M., & Levesque, J. (2006). Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. *Appl Psychophysiol Biofeedback, 31*(1), 3-20. doi:10.1007/s10484-006-9001-y

Berger, C., Muller-Godeffroy, J., Marx, I., Reis, O., Buchmann, J., & Duck, A. (2018). Methylphenidate promotes the interaction between motor cortex facilitation and attention in healthy adults: A combined study using event-related potentials and transcranial magnetic stimulation. *Brain Behav, 8*(12), e01155. doi:10.1002/brb3.1155

Bink, M., Bongers, I. L., Popma, A., Janssen, T. W., & van Nieuwenhuizen, C. (2016). 1-year follow-up of neurofeedback treatment in adolescents with attention-deficit hyperactivity disorder: randomised controlled trial. *BJPsych Open, 2*(2), 107-115. doi:10.1192/bjpo.bp.115.000166

Bink, M., van Nieuwenhuizen, C., Popma, A., Bongers, I. L., & van Boxtel, G. J. (2014). Neurocognitive effects of neurofeedback in adolescents with ADHD: a randomized controlled trial. *J Clin Psychiatry, 75*(5), 535-542. doi:10.4088/JCP.13m08590

Bink, M., van Nieuwenhuizen, C., Popma, A., Bongers, I. L., & van Boxtel, G. J. (2015). Behavioral effects of neurofeedback in adolescents with ADHD: a randomized

controlled trial. *Eur Child Adolesc Psychiatry, 24*(9), 1035-1048. doi:10.1007/s00787-014-0655-3

Bioulac, S., Purper-Ouakil, D., Ros, T., Blasco-Fontecilla, H., Prats, M., Mayaud, L., & Brandeis, D. (2019). Personalized at-home neurofeedback compared with long-acting methylphenidate in an european non-inferiority randomized trial in children with ADHD. *BMC Psychiatry, 19*(1), 237. doi:10.1186/s12888-019-2218-0

Bluschke, A., Schuster, J., Roessner, V., & Beste, C. (2018). Neurophysiological mechanisms of interval timing dissociate inattentive and combined ADHD subtypes. *Sci Rep, 8*(1), 2033. doi:10.1038/s41598-018-20484-0

Boecker, R., Holz, N. E., Buchmann, A. F., Blomeyer, D., Plichta, M. M., Wolf, I., . . . Laucht, M. (2014). Impact of early life adversity on reward processing in young adults: EEG-fMRI results from a prospective study over 25 years. *PLoS One, 9*(8), e104185. doi:10.1371/journal.pone.0104185

Broyd, S. J., Richards, H. J., Helps, S. K., Chronaki, G., Bamford, S., & Sonuga-Barke, E. J. S. (2012). An electrophysiological monetary incentive delay (e-MID) task: A way to decompose the different components of neural response to positive and negative monetary reinforcement. *J Neurosci Methods, 209*(1), 40-49. doi:doi.org/10.1016/j.jneumeth.2012.05.015

Bush, G., Valera, E. M., & Seidman, L. J. (2005). Functional Neuroimaging of Attention-Deficit/Hyperactivity Disorder: A Review and Suggested Future Directions. *Biol Psychiatry, 57*(11), 1273-1284. doi:doi.org/10.1016/j.biopsych.2005.01.034

Bussalb, A., Collin, S., Barthelemy, Q., Ojeda, D., Bioulac, S., Blasco-Fontecilla, H., . . . Mayaud, L. (2019). Is there a cluster of high theta-beta ratio patients in attention deficit hyperactivity disorder? *Clin Neurophysiol, 130*(8), 1387-1396. doi:10.1016/j.clinph.2019.02.021

Cao, Z., Bennett, M., Orr, C., Icke, I., Banaschewski, T., Barker, G. J., . . . Whelan, R. (2018). Mapping adolescent reward anticipation, receipt, and prediction error during the monetary incentive delay task. *Hum Brain Mapp*. doi:10.1002/hbm.24370

Carmona, S., Hoekzema, E., Ramos-Quiroga, J. A., Richarte, V., Canals, C., Bosch, R., . . . Vilarroya, O. (2012). Response inhibition and reward anticipation in medication-naïve adults with attention-deficit/hyperactivity disorder: A within-subject case-control neuroimaging study. *Hum Brain Mapp, 33*(10), 2350-2361. doi:10.1002/hbm.21368

Caye, A., Swanson, J. M., Coghill, D., & Rohde, L. A. (2019). Treatment strategies for ADHD: an evidence-based guide to select optimal treatment. *Mol Psychiatry, 24*(3), 390-408. doi:10.1038/s41380-018-0116-3

Chan, E., Fogler, J. M., & Hammerness, P. G. (2016). Treatment of Attention-Deficit/Hyperactivity Disorder in Adolescents: A Systematic Review. *JAMA, 315*(18), 1997-2008. doi:10.1001/jama.2016.5453

Cherkasova, M. V., & Hechtman, L. (2009). Neuroimaging in Attention-Deficit Hyperactivity Disorder: Beyond the Frontostriatal Circuitry. *Can J Psychiatry, 54*(10), 651-664. doi:10.1177/070674370905401002

Cheung, C. H. M., McLoughlin, G., Brandeis, D., Banaschewski, T., Asherson, P., & Kuntsi, J. (2017). Neurophysiological Correlates of Attentional Fluctuation in Attention-Deficit/Hyperactivity Disorder. *Brain Topogr, 30*(3), 320-332. doi:10.1007/s10548-017-0554-2

Chronaki, G., Soltesz, F., Benikos, N., & Sonuga-Barke, E. J. S. (2017). An electrophysiological investigation of reinforcement effects in attention deficit/hyperactivity disorder:

Dissociating cue sensitivity from down-stream effects on target engagement and performance. *Dev Cogn Neurosci, 28*, 12-20. doi:10.1016/j.dcn.2017.10.003

Clarke, A. R., Barry, R. J., Dupuy, F. E., Heckel, L. D., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2011). Behavioural differences between EEG-defined subgroups of children with Attention-Deficit/Hyperactivity Disorder. *Clin Neurophysiol, 122*(7), 1333-1341. doi:10.1016/j.clinph.2010.12.038

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2002). EEG differences between good and poor responders to methylphenidate and dexamphetamine in children with attention-deficit/hyperactivity disorder. *Clin Neurophysiol, 113*(2), 194-205. doi:doi.org/10.1016/S1388-2457(01)00736-2

Clemow, D. B. (2017). Misuse of Methylphenidate. *Curr Top Behav Neurosci, 34*, 99-124. doi:10.1007/7854_2015_426

Coghill, D. R., Seth, S., Pedroso, S., Usala, T., Currie, J., & Gagliano, A. (2014). Effects of methylphenidate on cognitive functions in children and adolescents with attention-deficit/hyperactivity disorder: evidence from a systematic review and a meta-analysis. *Biol Psychiatry, 76*(8), 603-615. doi:10.1016/j.biopsych.2013.10.005

Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A. J., Carucci, S., . . . Cipriani, A. (2018). Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry, 5*(9), 727-738. doi:10.1016/s2215-0366(18)30269-4

Cortese, S., Ferrin, M., Brandeis, D., Holtmann, M., Aggensteiner, P., Daley, D., . . . Sonuga-Barke, E. J. (2016). Neurofeedback for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials. *J Am Acad Child Adolesc Psychiatry, 55*(6), 444-455. doi:10.1016/j.jaac.2016.03.007

Cortese, S., Holtmann, M., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., . . . Sergeant, J. (2013). Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry, 54*(3), 227-246. doi:10.1111/jcpp.12036

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am J Psychiatry, 169*(10), 1038-1055. doi:10.1176/appi.ajp.2012.11101521

Daley, D., Jacobsen, R. H., Lange, A. M., Sorensen, A., & Walldorf, J. (2019). The economic burden of adult attention deficit hyperactivity disorder: A sibling comparison cost analysis. *Eur Psychiatry, 61*, 41-48. doi:10.1016/j.eurpsy.2019.06.011

Davies, P. L., Chang, W. P., & Gavin, W. J. (2010). Middle and Late Latency ERP Components Discriminate between Adults, Typical Children, and Children with Sensory Processing Disorders. *Front Integr Neurosci, 4*, 16. doi:10.3389/fnint.2010.00016

de Zeeuw, P., Weusten, J., van Dijk, S., van Belle, J., & Durston, S. (2012). Deficits in cognitive control, timing and reward sensitivity appear to be dissociable in ADHD. *PLoS One, 7*(12), e51416. doi:10.1371/journal.pone.0051416

Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie. Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) im Kindes-, Jugend- und Erwachsenenalter, Langfassung, 06.2018. Retrieved from https://www.awmf.org/uploads/tx_szleitlinien/028-045l_S3_ADHS_2018-06.pdf

Dirks, H., Scherbaum, N., Kis, B., & Mette, C. (2017). [ADHD in Adults and Comorbid Substance Use Disorder: Prevalence, Clinical Diagnostics and Integrated Therapy]. *Fortschr Neurol Psychiatr, 85*(6), 336-344. doi:10.1055/s-0043-100763

Dockree, P. M., Barnes, J. J., Matthews, N., Dean, A. J., Abe, R., Nandam, L. S., . . . O'Connell, R. G. (2017). The Effects of Methylphenidate on the Neural Signatures of Sustained Attention. *Biol Psychiatry, 82*(9), 687-694. doi:10.1016/j.biopsych.2017.04.016

Doehnert, M., Brandeis, D., Imhof, K., Drechsler, R., & Steinhausen, H. C. (2010). Mapping attention-deficit/hyperactivity disorder from childhood to adolescence--no neurophysiologic evidence for a developmental lag of attention but some for inhibition. *Biol Psychiatry, 67*(7), 608-616. doi:10.1016/j.biopsych.2009.07.038

Doehnert, M., Brandeis, D., Schneider, G., Drechsler, R., & Steinhausen, H. C. (2013). A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD). *J Child Psychol Psychiatry, 54*(3), 260-270. doi:10.1111/j.1469-7610.2012.02572.x

Doehnert, M., Brandeis, D., Straub, M., Steinhausen, H. C., & Drechsler, R. (2008). Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? *J Neural Transm (Vienna), 115*(10), 1445-1456. doi:10.1007/s00702-008-0104-x

Dolu, N., Altınkaynak, M., Güven, A., Özmen, S., Demirci, E., İzzetoğlu, M., & Pektaş, F. (2019). Effects of methylphenidate treatment in children with ADHD: A multimodal EEG/fNIRS approach. *Psychiatr Clin Psychopharmacol, 29*(3), 285-292. doi:10.1080/24750573.2018.1542779

Döpfner, M., Hautmann, C., Dose, C., Banaschewski, T., Becker, K., Brandeis, D., . . . von Wirth, E. (2017). ESCAschool study: trial protocol of an adaptive treatment approach for school-age children with ADHD including two randomised trials. *BMC Psychiatry, 17*(1), 269. doi:10.1186/s12888-017-1433-9

Drechsler, R., Brem, S., Brandeis, D., Grünblatt, E., Berger, G., & Walitza, S. (2020). ADHD: Current Concepts and Treatments in Children and Adolescents. *Neuropediatrics, 51*(5), 315-335. doi:10.1055/s-0040-1701658

Duric, N. S., Assmus, J., & Elgen, I. B. (2014). Self-reported efficacy of neurofeedback treatment in a clinical randomized controlled study of ADHD children and adolescents. *Neuropsychiatr Dis Treat, 10*, 1645-1654. doi:10.2147/ndt.s66466

Duric, N. S., Assmus, J., Gundersen, D., Duric Golos, A., & Elgen, I. B. (2017). Multimodal treatment in children and adolescents with attention-deficit/hyperactivity disorder: a 6-month follow-up. *Nord J Psychiatry, 71*(5), 386-394. doi:10.1080/08039488.2017.1305446

Einarsdottir, S., Taklo, H. M., Instebo, K., Socanski, D., Bremnes, M., & Beneventi, H. (2015). Comparison of neurofeedback training and working memory training with children who have a non-medicated ADHD. A pilot study, with neuropsychological assessment, questionnaires, and QEEG as effect measurements. *Atten Defic Hyperact Disord, 7*, S38-S39. doi:10.1007/s12402-015-0169-y

Enriquez-Geppert, S., Smit, D., Pimenta, M. G., & Arns, M. (2019). Neurofeedback as a Treatment Intervention in ADHD: Current Evidence and Practice. *Curr Psychiatry Rep, 21*(6), 46. doi:10.1007/s11920-019-1021-4

Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., . . . Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers, 1*, 15020. doi:10.1038/nrdp.2015.20

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry, 24*(4), 562-575. doi:10.1038/s41380-018-0070-0

Fareri, D. S., Martin, L. N., & Delgado, M. R. (2008). Reward-related processing in the human brain: developmental considerations. *Dev Psychopathol, 20*(4), 1191-1211. doi:10.1017/s0954579408000576

Fredriksen, M., Halmoy, A., Faraone, S. V., & Haavik, J. (2013). Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: a review of controlled and naturalistic studies. *Eur Neuropsychopharmacol, 23*(6), 508-527. doi:10.1016/j.euroneuro.2012.07.016

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback Treatment for Attention-Deficit/Hyperactivity Disorder in Children: A Comparison with Methylphenidate. *Appl Psychophysiol Biofeedback, 28*(1), 1-12. doi:10.1023/a:1022353731579

Furukawa, E., Bado, P., Tripp, G., Mattos, P., Wickens, J. R., Bramati, I. E., . . . Moll, J. (2014). Abnormal striatal BOLD responses to reward anticipation and reward delivery in ADHD. *PLoS One, 9*(2), e89129. doi:10.1371/journal.pone.0089129

Furukawa, E., da Costa, R. Q. M., Bado, P., Hoefle, S., Vigne, P., Monteiro, M., . . . Mattos, P. (2019). Methylphenidate modifies reward cue responses in adults with ADHD: An fMRI study. *Neuropharmacology, 162*, 107833. doi:10.1016/j.neuropharm.2019.107833

Geissler, J., Jans, T., Banaschewski, T., Becker, K., Renner, T., Brandeis, D., . . . Romanos, M. (2018). Individualised short-term therapy for adolescents impaired by attention-deficit/hyperactivity disorder despite previous routine care treatment (ESCAadol)—Study protocol of a randomised controlled trial within the consortium ESCAlife. *Trials, 19*(1), 254. doi:10.1186/s13063-018-2635-2

Gelade, K., Bink, M., Janssen, T. W., van Mourik, R., Maras, A., & Oosterlaan, J. (2017). An RCT into the effects of neurofeedback on neurocognitive functioning compared to stimulant medication and physical activity in children with ADHD. *Eur Child Adolesc Psychiatry, 26*(4), 457-468. doi:10.1007/s00787-016-0902-x

Gelade, K., Janssen, T. W., Bink, M., van Mourik, R., Maras, A., & Oosterlaan, J. (2016). Behavioral Effects of Neurofeedback Compared to Stimulants and Physical Activity in Attention-Deficit/Hyperactivity Disorder: A Randomized Controlled Trial. *J Clin Psychiatry, 77*(10), e1270-e1277. doi:10.4088/JCP.15m10149

Gelade, K., Janssen, T. W. P., Bink, M., Twisk, J. W. R., van Mourik, R., Maras, A., & Oosterlaan, J. (2018). A 6-month follow-up of an RCT on behavioral and neurocognitive effects of neurofeedback in children with ADHD. *Eur Child Adolesc Psychiatry, 27*(5), 581-593. doi:10.1007/s00787-017-1072-1

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., . . . Heinrich, H. (2009). Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. *Int J Psychophysiol, 74*(2), 149-157. doi:10.1016/j.ijpsycho.2009.08.005

Gevensleben, H., Kleemeyer, M., Rothenberger, L. G., Studer, P., Flaig-Rohr, A., Moll, G. H., . . . Heinrich, H. (2014). Neurofeedback in ADHD: further pieces of the puzzle. *Brain Topogr, 27*(1), 20-32. doi:10.1007/s10548-013-0285-y

Gizer, I. R., Ficks, C., & Waldman, I. D. (2009). Candidate gene studies of ADHD: a meta-analytic review. *Hum Genet, 126*(1), 51-90. doi:10.1007/s00439-009-0694-x

Glazer, J. E., Kelley, N. J., Pornpattananangkul, N., Mittal, V. A., & Nusslock, R. (2018). Beyond the FRN: Broadening the time-course of EEG and ERP components implicated in reward processing. *Int J Psychophysiol, 132*(Pt B), 184-202. doi:10.1016/j.ijpsycho.2018.02.002

Gong, J., Yuan, J., Wang, S., Shi, L., Cui, X., & Luo, X. (2014). Feedback-related negativity in children with two subtypes of attention deficit hyperactivity disorder. *PLoS One, 9*(6), e99570. doi:10.1371/journal.pone.0099570

González-Castro, P., Cueli, M., Rodríguez, C., García, T., & Álvarez, L. (2016). Efficacy of neurofeedback versus pharmacological support in subjects with ADHD. *Appl Psychophysiol Biofeedback, 41*(1), 17-25. doi:10.1007/s10484-015-9299-4

Graham, J., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., Dittmann, . (2011). European guidelines on managing adverse effects of medication for ADHD. , (1),. doi:10.1007/s00787-010-0140-6. *Eur Child Adolesc Psychiatry, 20*, 17–37.

Groeneveld, K. M., Mennenga, A. M., Heidelberg, R. C., Martin, R. E., Tittle, R. K., Meeuwsen, K. D., . . . White, E. K. (2019). Z-Score Neurofeedback and Heart Rate Variability Training for Adults and Children with Symptoms of Attention-Deficit/Hyperactivity Disorder: A Retrospective Study. *Appl Psychophysiol Biofeedback, 44*(4), 291-308. doi:10.1007/s10484-019-09439-x

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology, 35*(1), 4-26. doi:10.1038/npp.2009.129

Halliday, R., Callaway, E., & Lynch, M. (1984). Age, stimulant drug, and practice effects on P3 latency and concurrent reaction time. *Ann N Y Acad Sci, 425*, 357-361. doi:10.1111/j.1749-6632.1984.tb23556.x

Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., & Rubia, K. (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry, 70*(2), 185-198. doi:10.1001/jamapsychiatry.2013.277

Hechtman, L., & Greenfield, B. (2003). Long-term use of stimulants in children with attention deficit hyperactivity disorder: safety, efficacy, and long-term outcome. *Paediatr Drugs, 5*(12), 787-794. doi:10.2165/00148581-200305120-00002

Heinrich, H., Gevensleben, H., Becker, A., & Rothenberger, A. (2019). Effects of neurofeedback on the dysregulation profile in children with ADHD: SCP NF meets SDQ-DP - a retrospective analysis. *Psychol Med*, 1-6. doi:10.1017/s0033291718004130

Heinrich, H., Gevensleben, H., Freisleder, F. J., Moll, G. H., & Rothenberger, A. (2004). Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. *Biol Psychiatry, 55*(7), 772-775. doi:10.1016/j.biopsych.2003.11.013

Hodgson, K., Hutchinson, A. D., & Denson, L. (2014). Nonpharmacological treatments for ADHD: a meta-analytic review. *J Atten Disord, 18*(4), 275-282. doi:10.1177/1087054712444732

Holtmann, M., Grasmann, D., Cionek-Szpak, E., Hager, V., Panzner, N., Beyer, A., . . . Stadler, C. (2009). Spezifische Wirksamkeit von Neurofeedback auf die Impulsivität bei ADHS. *Kindheit und Entwicklung, 18*(2), 95-104.

Holtmann, M., Sonuga-Barke, E., Cortese, S., & Brandeis, D. (2014). Neurofeedback for ADHD: a review of current evidence. *Child Adolesc Psychiatr Clin N Am, 23*(4), 789-806. doi:10.1016/j.chc.2014.05.006

Ivanov, I., Liu, X., Clerkin, S., Schulz, K., Fan, J., Friston, K., . . . Newcorn, J. H. (2014). Methylphenidate and brain activity in a reward/conflict paradigm: Role of the insula in task performance. *Eur Neuropsychopharmacol, 24*(6), 897-906. doi:10.1016/j.euroneuro.2014.01.017

Janssen, T. W., Bink, M., Gelade, K., van Mourik, R., Maras, A., & Oosterlaan, J. (2016). A Randomized Controlled Trial Investigating the Effects of Neurofeedback,

Methylphenidate, and Physical Activity on Event-Related Potentials in Children with Attention-Deficit/Hyperactivity Disorder. *J Child Adolesc Psychopharmacol, 26*(4), 344-353. doi:10.1089/cap.2015.0144

Janssen, T. W., Geladé, K., Bink, M., van Mourik, R., Twisk, J. W. R., Maras, A., & Oosterlaan, J. (2020). Long-term effects of theta/beta neurofeedback on EEG power spectra in children with attention deficit hyperactivity disorder. *Clin Neurophysiol, 131*(6), 1332-1341. doi:10.1016/j.clinph.2020.02.020

Jensen, C. M., & Steinhausen, H. C. (2015). Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord, 7*(1), 27-38. doi:10.1007/s12402-014-0142-1

Jia, T., Macare, C., Desrivieres, S., Gonzalez, D. A., Tao, C., Ji, X., . . . Schumann, G. (2016). Neural basis of reward anticipation and its genetic determinants. *Proc Natl Acad Sci U S A, 113*(14), 3879-3884. doi:10.1073/pnas.1503252113

Kaiser, A., Aggensteiner, P. M., Baumeister, S., Holz, N. E., Banaschewski, T., & Brandeis, D. (2020). Earlier versus later cognitive event-related potentials (ERPs) in attention-deficit/hyperactivity disorder (ADHD): A meta-analysis. *Neurosci Biobehav Rev, 112*, 117-134. doi:10.1016/j.neubiorev.2020.01.019

Kappenman, E., & Luck, S. (2012). *The Oxford Handbook of Event-Related Potential Components* (P. Nahan Ed.): Oxford Library of Psychology.

Karalunas, S. L., & Nigg, J. T. (2020). Heterogeneity and Subtyping in Attention-Deficit/Hyperactivity Disorder-Considerations for Emerging Research Using Person-Centered Computational Approaches. *Biol Psychiatry, 88*(1), 103-110. doi:10.1016/j.biopsych.2019.11.002

Kirsch, P., Schienle, A., Stark, R., Sammer, G., Blecker, C., Walter, B., . . . Vaitl, D. (2003). Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study. *NeuroImage, 20*(2), 1086-1095. doi:10.1016/s1053-8119(03)00381-1

Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci, 21*(16), RC159. doi:doi: 10.1523/JNEUROSCI.21-16-j0002.2001

Kornhuber, H. H., & Deecke, L. (1965). Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. *Pflugers Arch Gesamte Physiol Menschen Tiere, 284*(1), 1-17. doi:10.1007/BF00412364

Kratz, O., Studer, P., Baack, J., Malcherek, S., Erbe, K., Moll, G. H., & Heinrich, H. (2012). Differential effects of methylphenidate and atomoxetine on attentional processes in children with ADHD: an event-related potential study using the Attention Network Test. *Prog Neuropsychopharmacol Biol Psychiatry, 37*(1), 81-89. doi:10.1016/j.pnpbp.2011.12.008

Lee, E. J., & Jung, C. H. (2017). Additive effects of neurofeedback on the treatment of ADHD: A randomized controlled study. *Asian J Psychiatr, 25*, 16-21. doi:10.1016/j.ajp.2016.09.002

Lenartowicz, A., & Loo, S. K. (2014). Use of EEG to Diagnose ADHD. *Curr Psychiatry Rep, 16*(11), 498. doi:10.1007/s11920-014-0498-0

Li, L., Yang, L., Zhuo, C. J., & Wang, Y. F. (2013). A randomised controlled trial of combined EEG feedback and methylphenidate therapy for the treatment of ADHD. *Swiss Med Wkly, 143*, w13838. doi:10.4414/smw.2013.13838

Liang, E. F., Lim, S. Z., Tam, W. W., Ho, C. S., Zhang, M. W., McIntyre, R. S., & Ho, R. C. (2018). The Effect of Methylphenidate and Atomoxetine on Heart Rate and Systolic Blood Pressure in Young People and Adults with Attention-Deficit Hyperactivity Disorder (ADHD): Systematic Review, Meta-Analysis, and Meta-Regression. *Int J Environ Res Public Health, 15*(8). doi:10.3390/ijerph15081789

Linssen, A. M., Vuurman, E. F., Sambeth, A., Nave, S., Spooren, W., Vargas, G., . . . Riedel, W. J. (2011). Contingent negative variation as a dopaminergic biomarker: evidence from dose-related effects of methylphenidate. *Psychopharmacology (Berl), 218*(3), 533-542. doi:10.1007/s00213-011-2345-x

Matthies, S., & Philipsen, A. (2016). Comorbidity of Personality Disorders and Adult Attention Deficit Hyperactivity Disorder (ADHD)--Review of Recent Findings. *Curr Psychiatry Rep, 18*(4), 33. doi:10.1007/s11920-016-0675-4

Mayer, K., Wyckoff, S. N., & Strehl, U. (2013). One size fits all? Slow cortical potentials neurofeedback: a review. *J Atten Disord, 17*(5), 393-409. doi:10.1177/1087054712468053

Mei, S., Li, Q., Liu, X., & Zheng, Y. (2018). Monetary Incentives Modulate Feedback-related Brain Activity. *Sci Rep, 8*(1), 11913. doi:10.1038/s41598-018-30294-z

Meisel, V., Servera, M., Garcia-Banda, G., Cardo, E., & Moreno, I. (2014). Reprint of "Neurofeedback and standard pharmacological intervention in ADHD: a randomized controlled trial with six-month follow-up". *Biol Psychol, 95*, 116-125. doi:10.1016/j.biopsycho.2013.09.009

Michel, C. M., & Brunet, D. (2019). EEG Source Imaging: A Practical Review of the Analysis Steps. *Front Neurol, 10*, 325. doi:10.3389/fneur.2019.00325

Michelini, G., Kitsune, V., Vainieri, I., Hosang, G. M., Brandeis, D., Asherson, P., & Kuntsi, J. (2018). Shared and Disorder-Specific Event-Related Brain Oscillatory Markers of Attentional Dysfunction in ADHD and Bipolar Disorder. *Brain Topogr, 31*(4), 672-689. doi:10.1007/s10548-018-0625-z

Micoulaud-Franchi, J. A., Geoffroy, P. A., Fond, G., Lopez, R., Bioulac, S., & Philip, P. (2014). EEG neurofeedback treatments in children with ADHD: an updated meta-analysis of randomized controlled trials. *Front Hum Neurosci, 8*, 906. doi:10.3389/fnhum.2014.00906

Mizuno, K., Yoneda, T., Komi, M., Hirai, T., Watanabe, Y., & Tomoda, A. (2013). Osmotic release oral system-methylphenidate improves neural activity during low reward processing in children and adolescents with attention-deficit/hyperactivity disorder. *Neuroimage Clin, 2*, 366-376. doi:10.1016/j.nicl.2013.03.004

Mohr-Jensen, C., & Steinhausen, H. C. (2016). A meta-analysis and systematic review of the risks associated with childhood attention-deficit hyperactivity disorder on long-term outcome of arrests, convictions, and incarcerations. *Clin Psychol Rev, 48*, 32-42. doi:10.1016/j.cpr.2016.05.002

Moreno-Garcia, I., Meneres-Sancho, S., Camacho-Vara de Rey, C., & Servera, M. (2019). A Randomized Controlled Trial to Examine the Posttreatment Efficacy of Neurofeedback, Behavior Therapy, and Pharmacology on ADHD Measures. *J Atten Disord, 23*(4), 374-383. doi:10.1177/1087054717693371

Moriyama, T. S., Polanczyk, G., Caye, A., Banaschewski, T., Brandeis, D., & Rohde, L. A. (2012). Evidence-based information on the clinical use of neurofeedback for ADHD. *Neurotherapeutics, 9*(3), 588-598. doi:10.1007/s13311-012-0136-7

Nees, F., Vollstädt-Klein, S., Fauth-Bühler, M., Steiner, S., Mann, K., Poustka, L., . . . Flor, H. (2012). A target sample of adolescents and reward processing: same neural and

behavioral correlates engaged in common paradigms? *Exp Brain Res, 223*(3), 429-439. doi:10.1007/s00221-012-3272-8

Newcorn, J., Duhoux, S., Schulz, K., Krone, B., Bedard, A. C., Pedraza, J., . . . Blair, J. (2014). Effects of lisdexamfetamine (vyvanse) on reward processing. *Biol Psychiatry, 75*(9 SUPPL. 1), 7S. doi:10.1016/j.biopsych.2014.03.014

Norman, L. J., Carlisi, C. O., Christakou, A., Murphy, C. M., Chantiluke, K., Giampietro, V., . . . Rubia, K. (2018). Frontostriatal Dysfunction During Decision Making in Attention-Deficit/Hyperactivity Disorder and Obsessive-Compulsive Disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging, 3*(8), 694-703. doi:10.1016/j.bpsc.2018.03.009

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A, 87*(24), 9868-9872. doi:10.1073/pnas.87.24.9868

Ogrim, G., Aasen, I. E., & Brunner, J. F. (2016). Single-dose effects on the P3no-go ERP component predict clinical response to stimulants in pediatric ADHD. *Clin Neurophysiol, 127*(10), 3277-3287. doi:10.1016/j.clinph.2016.07.011

Ogrim, G., & Hestad, K. A. (2013). Effects of neurofeedback versus stimulant medication in attention-deficit/hyperactivity disorder: a randomized pilot study. *J Child Adolesc Psychopharmacol, 23*(7), 448-457. doi:10.1089/cap.2012.0090

Ogrim, G., Kropotov, J., Brunner, J. F., Candrian, G., Sandvik, L., & Hestad, K. A. (2014). Predicting the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder: data from quantitative electroencephalography, event-related potentials, and a go/no-go test. *Neuropsychiatr Dis Treat, 10*, 231-242. doi:10.2147/NDT.S56600

Oldham, S., Murawski, C., Fornito, A., Youssef, G., Yucel, M., & Lorenzetti, V. (2018). The anticipation and outcome phases of reward and loss processing: A neuroimaging meta-analysis of the monetary incentive delay task. *Hum Brain Mapp, 39*(8), 3398-3418. doi:10.1002/hbm.24184

Pakdaman, F., Irani, F., Tajikzadeh, F., & Jabalkandi, S. A. (2018). The efficacy of Ritalin in ADHD children under neurofeedback training. *Neurol Sci, 39*(12), 2071-2078. doi:10.1007/s10072-018-3539-3

Paloyelis, Y., Mehta, M. A., Kuntsi, J., & Asherson, P. (2007). Functional MRI in ADHD: a systematic literature review. *Expert Rev Neurother, 7*(10), 1337-1356. doi:10.1586/14737175.7.10.1337

Pauli-Pott, U., & Becker, K. (2015). Time windows matter in ADHD-related developing neuropsychological basic deficits: A comprehensive review and meta-regression analysis. *Neurosci Biobehav Rev, 55*, 165-172. doi:10.1016/j.neubiorev.2015.04.011

Pfabigan, D. M., Seidel, E. M., Sladky, R., Hahn, A., Paul, K., Grahl, A., . . . Lamm, C. (2014). P300 amplitude variation is related to ventral striatum BOLD response during gain and loss anticipation: an EEG and fMRI experiment. *NeuroImage, 96*, 12-21. doi:10.1016/j.neuroimage.2014.03.077

Plichta, M. M., & Scheres, A. (2014). Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. *Neurosci Biobehav Rev, 38*, 125-134. doi:10.1016/j.neubiorev.2013.07.012

Plichta, M. M., Wolf, I., Hohmann, S., Baumeister, S., Boecker, R., Schwarz, A. J., . . . Brandeis, D. (2013). Simultaneous EEG and fMRI reveals a causally connected subcortical-cortical network during reward anticipation. *J Neurosci, 33*(36), 14526-14533. doi:10.1523/JNEUROSCI.0631-13.2013

Polanczyk, G. V., Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. (2014). ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol, 43*(2), 434-442. doi:10.1093/ije/dyt261

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*(10), 2128-2148. doi:10.1016/j.clinph.2007.04.019

Rajabi, S., Pakize, A., & Moradi, N. (2019). Effect of combined neurofeedback and game-based cognitive training on the treatment of ADHD: A randomized controlled study. *Appl Neuropsychol Child*, 1-13. doi:10.1080/21622965.2018.1556101

Razoki, B. (2018). Neurofeedback versus psychostimulants in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a systematic review. *Neuropsychiatr Dis Treat, 14*, 2905-2913. doi:10.2147/ndt.s178839

Reale, L., Bartoli, B., Cartabia, M., Zanetti, M., Costantino, M. A., Canevini, M. P., . . . Bonati, M. (2017). Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. *Eur Child Adolesc Psychiatry, 26*(12), 1443-1457. doi:10.1007/s00787-017-1005-z

Riesco-Matias, P., Yela-Bernabe, J. R., Crego, A., & Sanchez-Zaballos, E. (2019). What Do Meta-Analyses Have to Say About the Efficacy of Neurofeedback Applied to Children With ADHD? Review of Previous Meta-Analyses and a New Meta-Analysis. *J Atten Disord*, 1087054718821731. doi:10.1177/1087054718821731

Roca, P., Mulas, F., Gandia, R., Ortiz-Sanchez, P., & Abad, L. (2013). [Executive functioning and evoked potentials P300 pre- and post- treatment in attention deficit hyperactivity disorder]. *Rev Neurol, 56 Suppl 1*, S107-118.

Rommel, A. S., James, S. N., McLoughlin, G., Michelini, G., Banaschewski, T., Brandeis, D., . . . Kuntsi, J. (2019). Impairments in error processing and their association with ADHD symptoms in individuals born preterm. *PLoS One, 14*(4), e0214864. doi:10.1371/journal.pone.0214864

Rosch, K. S., & Hawk, L. W., Jr. (2013). The effects of performance-based rewards on neurophysiological correlates of stimulus, error, and feedback processing in children with ADHD. *Psychophysiology, 50*(11), 1157-1173. doi:10.1111/psyp.12127

Rubia, K. (2018). Cognitive Neuroscience of Attention Deficit Hyperactivity Disorder (ADHD) and Its Clinical Translation. *Front Hum Neurosci, 12*, 100. doi:10.3389/fnhum.2018.00100

Rubia, K., Halari, R., Cubillo, A., Mohammad, A. M., Brammer, M., & Taylor, E. (2009). Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task. *Neuropharmacology, 57*(7-8), 640-652. doi:10.1016/j.neuropharm.2009.08.013

Rubinson, M., Horowitz, I., Naim-Feil, J., Gothelf, D., Levit-Binnun, N., & Moses, E. (2019). Effects of methylphenidate on the ERP amplitude in youth with ADHD: A double-blind placebo-controlled cross-over EEG study. *PLoS One, 14*(5), e0217383. doi:10.1371/journal.pone.0217383

Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behav Brain Sci, 28*(3), 397-419; discussion 419-368. doi:10.1017/s0140525x05000075

Sambrook, T. D., & Goslin, J. (2015). A neural reward prediction error revealed by a meta-analysis of ERPs using great grand averages. *Psychol Bull, 141*(1), 213-235. doi:10.1037/bul0000006

Samea, F., Soluki, S., Nejati, V., Zarei, M., Cortese, S., Eickhoff, S. B., . . . Eickhoff, C. R. (2019). Brain alterations in children/adolescents with ADHD revisited: A neuroimaging meta-analysis of 96 structural and functional studies. *Neurosci Biobehav Rev, 100*, 1-8. doi:10.1016/j.neubiorev.2019.02.011

Scheres, A., Lee, A., & Sumiya, M. (2008). Temporal reward discounting and ADHD: task and symptom specific effects. *J Neural Transm (Vienna), 115*(2), 221-226. doi:10.1007/s00702-007-0813-6

Scheres, A., Milham, M. P., Knutson, B., & Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol Psychiatry, 61*(5), 720-724. doi:10.1016/j.biopsych.2006.04.042

Schonenberg, M., Wiedemann, E., Schneidt, A., Scheeff, J., Logemann, A., Keune, P. M., & Hautzinger, M. (2017). Neurofeedback, sham neurofeedback, and cognitive-behavioural group therapy in adults with attention-deficit hyperactivity disorder: a triple-blind, randomised, controlled trial. *Lancet Psychiatry, 4*(9), 673-684. doi:10.1016/s2215-0366(17)30291-2

Schweren, L. J. S., Groenman, A., von Rhein, D., Weeda, W., Faraone, S. F., Luman, M., . . . Hartman, C. A. (2017). Stimulant Treatment Trajectories Are Associated With Neural Reward Processing in Attention-Deficit/Hyperactivity Disorder. *J Clin Psychiatry, 78*(7), e790-e796. doi:10.4088/JCP.15m10624

Segalowitz, S. J., & Davies, P. L. (2004). Charting the maturation of the frontal lobe: an electrophysiological strategy. *Brain Cogn, 55*(1), 116-133. doi:10.1016/s0278-2626(03)00283-5

Shiels, K., Hawk, L. W., Reynolds, B., Mazzullo, R. J., Rhodes, J. D., Pelham, W. E., . . . Gangloff, B. P. (2009). Effects of methylphenidate on discounting of delayed rewards in attention deficit/hyperactivity disorder. *Exp Clin Psychopharmacol, 17*(5), 291-301. doi:10.1037/a0017259

Sonuga-Barke, E. J. (2005). Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry, 57*(11), 1231-1238. doi:10.1016/j.biopsych.2004.09.008

Sonuga-Barke, E. J., Brandeis, D., Cortese, S., Daley, D., Ferrin, M., Holtmann, M., . . . Sergeant, J. (2013). Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry, 170*(3), 275-289. doi:10.1176/appi.ajp.2012.12070991

Sorensen, L., Sonuga-Barke, E., Eichele, H., van Wageningen, H., Wollschlaeger, D., & Plessen, K. J. (2017). Suboptimal decision making by children with ADHD in the face of risk: Poor risk adjustment and delay aversion rather than general proneness to taking risks. *Neuropsychology, 31*(2), 119-128. doi:10.1037/neu0000297

Stark, R., Bauer, E., Merz, C. J., Zimmermann, M., Reuter, M., Plichta, M. M., . . . Herrmann, M. J. (2011). ADHD related behaviors are associated with brain activation in the reward system. *Neuropsychologia, 49*(3), 426-434. doi: 10.1016/j.neuropsychologia.2010.12.012

Stoy, M., Schlagenhauf, F., Schlochtermeier, L., Wrase, J., Knutson, B., Lehmkuhl, U., . . . Strohle, A. (2011). Reward processing in male adults with childhood ADHD--a comparison between drug-naive and methylphenidate-treated subjects. *Psychopharmacology (Berl), 215*(3), 467-481. doi:10.1007/s00213-011-2166-y

Strehl, U., Aggensteiner, P., Wachtlin, D., Brandeis, D., Albrecht, B., Arana, M., . . . Holtmann, M. (2017). Neurofeedback of Slow Cortical Potentials in Children with Attention-

Deficit/Hyperactivity Disorder: A Multicenter Randomized Trial Controlling for Unspecific Effects. *Front Hum Neurosci, 11*, 135. doi:10.3389/fnhum.2017.00135

Studer, P., Kratz, O., Gevensleben, H., Rothenberger, A., Moll, G. H., Hautzinger, M., & Heinrich, H. (2014). Slow cortical potential and theta/beta neurofeedback training in adults: effects on attentional processes and motor system excitability. *Front Hum Neurosci, 8*, 555. doi:10.3389/fnhum.2014.00555

Sudnawa, K. K., Chirdkiatgumchai, V., Ruangdaraganon, N., Khongkhatithum, C., Udomsubpayakul, U., Jirayucharoensak, S., & Israsena, P. (2018). Effectiveness of neurofeedback versus medication for attention-deficit/hyperactivity disorder. *Pediatr Int, 60*(9), 828-834. doi:10.1111/ped.13641

Sutcubasi, B., Metin, B., Tas, C., Krzan, F. K., Sarı, B. A., Ozcimen, B., & Tarhan, N. (2018). The relationship between responsiveness to social and monetary rewards and ADHD symptoms. *Cogn Affect Behav Neurosci, 18*(5), 857-868. doi:10.3758/s13415-018-0609-1

Swanson, J. M., Arnold, L. E., Molina, B. S. G., Sibley, M. H., Hechtman, L. T., Hinshaw, S. P., . . . Group, t. M. C. (2017). Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression. *J Child Psychol Psychiatry, 58*(6), 663-678. doi:10.1111/jcpp.12684

Szuromi, B., Czobor, P., Komlosi, S., & Bitter, I. (2011). P300 deficits in adults with attention deficit hyperactivity disorder: a meta-analysis. *Psychol Med, 41*(7), 1529-1538. doi:10.1017/s0033291710001996

Takahashi, J., Yasumura, A., Nakagawa, E., & Inagaki, M. (2014). Changes in negative and positive EEG shifts during slow cortical potential training in children with attention-deficit/hyperactivity disorder: a preliminary investigation. *Neuroreport, 25*(8), 618-624. doi:10.1097/wnr.0000000000000156

Tamayo-Orrego, L., Osorio Forero, A., Quintero Giraldo, L. P., Parra Sánchez, J. H., Varela, V., & Restrepo, F. (2015). Efecto diferencial del subtipo clínico en los potenciales evocados cognitivos de pacientes con déficit de atención e hiperactividad. *Rev Colomb Psiquiatr, 44*, 77-86. doi:doi.org/10.1016/j.rcp.2015.02.004

Thibault, R. T., Veissiere, S., Olson, J. A., & Raz, A. (2018). Treating ADHD With Suggestion: Neurofeedback and Placebo Therapeutics. *J Atten Disord, 22*(8), 707-711. doi:10.1177/1087054718770012

Thoma, P., Edel, M. A., Suchan, B., & Bellebaum, C. (2015). Probabilistic reward learning in adults with Attention Deficit Hyperactivity Disorder--an electrophysiological study. *Psychiatry Res, 225*(1-2), 133-144. doi:10.1016/j.psychres.2014.11.006

Tripp, G., & Wickens, J. R. (2008). Research review: dopamine transfer deficit: a neurobiological theory of altered reinforcement mechanisms in ADHD. *J Child Psychol Psychiatry, 49*(7), 691-704. doi:10.1111/j.1469-7610.2007.01851.x

van Dongen, E. V., von Rhein, D., O'Dwyer, L., Franke, B., Hartman, C. A., Heslenfeld, D. J., . . . Buitelaar, J. (2015). Distinct effects of ASD and ADHD symptoms on reward anticipation in participants with ADHD, their unaffected siblings and healthy controls: a cross-sectional study. *Mol Autism, 6*, 48. doi:10.1186/s13229-015-0043-y

Van Doren, J., Arns, M., Heinrich, H., Vollebregt, M. A., Strehl, U., & K. Loo, S. (2019). Sustained effects of neurofeedback in ADHD: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry, 28*(3), 293-305. doi:10.1007/s00787-018-1121-4

van Emmerik-van Oortmerssen, K., van de Glind, G., van den Brink, W., Smit, F., Crunelle, C. L., Swets, M., & Schoevers, R. A. (2012). Prevalence of attention-deficit hyperactivity

disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. *Drug Alcohol Depend, 122*(1-2), 11-19. doi:10.1016/j.drugalcdep.2011.12.007

van Hulst, B. M., de Zeeuw, P., Bos, D. J., Rijks, Y., Neggers, S. F., & Durston, S. (2017). Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward, irrespective of ADHD diagnosis. *J Child Psychol Psychiatry, 58*(2), 206-214. doi:10.1111/jcpp.12643

Vollebregt, M. A., van Dongen-Boomsma, M., Buitelaar, J. K., & Slaats-Willemse, D. (2014). Does EEG-neurofeedback improve neurocognitive functioning in children with attention-deficit/hyperactivity disorder? A systematic review and a double-blind placebo-controlled study. *J Child Psychol Psychiatry, 55*(5), 460-472. doi:10.1111/jcpp.12143

von Rhein, D., Cools, R., Zwiers, M. P., van der Schaaf, M., Franke, B., Luman, M., . . . Buitelaar, J. (2015). Increased neural responses to reward in adolescents and young adults with attention-deficit/hyperactivity disorder and their unaffected siblings. *J Am Acad Child Adolesc Psychiatry, 54*(5), 394-402. doi:10.1016/j.jaac.2015.02.012

Walter, W. G., Cooper, R., Aldridge, V. J., McCallum, W. C., & Winter, A. L. (1964). Contingent Negative Variation : An Electric Sign of Sensori-Motor Association and Expectancy in the Human Brain. *Nature, 203*, 380. doi:10.1038/203380a0

Wang, B. Q., Yao, N. Q., Zhou, X., Liu, J., & Lv, Z. T. (2017). The association between attention deficit/hyperactivity disorder and internet addiction: a systematic review and meta-analysis. *BMC Psychiatry, 17*(1), 260. doi:10.1186/s12888-017-1408-x

Wangler, S., Gevensleben, H., Albrecht, B., Studer, P., Rothenberger, A., Moll, G. H., & Heinrich, H. (2011). Neurofeedback in children with ADHD: Specific event-related potential findings of a randomized controlled trial. *Clin Neurophysiol, 122*(5), 942-950. doi:doi.org/10.1016/j.clinph.2010.06.036

Yamamuro, K., Ota, T., Iida, J., Nakanishi, Y., Suehiro, Y., Matsuura, H., . . . Kishimoto, T. (2016). Event-Related Potentials Correlate with the Severity of Child and Adolescent Patients with Attention Deficit/Hyperactivity Disorder. *Neuropsychobiology, 73*(3), 131-138. doi:10.1159/000444490

Yan, L., Wang, S., Yuan, Y., & Zhang, J. (2019). Effects of neurofeedback versus methylphenidate for the treatment of ADHD: systematic review and meta-analysis of head-to-head trials. *Evid Based Ment Health, 22*(3), 111-117. doi:10.1136/ebmental-2019-300088

Zhang, Y., Li, Q., Wang, Z., Liu, X., & Zheng, Y. (2017). Temporal dynamics of reward anticipation in the human brain. *Biol Psychol, 128*, 89-97. doi:doi.org/10.1016/j.biopsycho.2017.07.011

7 SUPPLEMENTARY MATERIAL

Table 2. Demographic information of the participants reported in Baumeister et al, 2018

Participants	N	Age, M years (*SD*)	Male, %	IQ, M(*SD*)	Medication, %
ADHD training completers	15	11.8 (1.5)	73	113.1 (12.8)	66
ADHF NF	8	12.4 (1.3)	75	118 (14.8)	88
ADHD EMG	7	11.1 (1.6)	71	107.6 (7.8)	42

Table 3. Supplementary results from multivariate Tests with time ("pre" and "post") and condition ("win" and "no-win") as within-subjects factors, feedback group (FB) as between-subjects factors and symptom severity (SS), IQ and medication state as covariates for the CNV amplitude.

Effect	F	Hypothesis df	Error df	Sig
time	0.08[b]	1	9	0.78
time*Feedback (FB)	0.05[b]	1	9	0.82
time*medication	4.537[b]	1	9	0.062
time*SS	0.001[b]	1	9	0.98
time*age	0.009[b]	1	9	0.93
condition	0.304[b]	1	9	0.6
condition*SS	0.442[b]	1	9	0.52
condition*age	0.373[b]	1	9	0.56
condition*medication	1.592[b]	1	9	0.24
condition*FB	0.606[b]	1	9	0.46
time*condition	0.043[b]	1	9	0.84
time*condition*SS	0.084[b]	1	9	0.78
time*condition*age	0.089[b]	1	9	0.77
time*condition*medication	0.209[b]	1	9	0.66
time*condition*FB	0.002[b]	1	9	0.97

b. Exact statistic

Table 4. Supplementary results from multivariate Tests with time ("pre" and "post") and condition ("win" and "no-win") as within-subjects factors, feedback group (FB) as between-subjects factors and symptom severity (SS), IQ and medication state as covariates for the Cue-P3 amplitude.

Effect	F	Hypothesis df	Error df	Sig
time	1.34[b]	1	9	0.28
time*Feedback (FB)	0.04[b]	1	9	0.86
time*medication	0.95[b]	1	9	0.35
time*SS	0.66[b]	1	9	0.44
time*age	2.86[b]	1	9	0.13
condition	0.00[b]	1	9	1.0
condition*SS	0.72[b]	1	9	0.42
condition*age	0.05[b]	1	9	0.83
condition*medication	0.20[b]	1	9	0.67
condition*FB	0.58[b]	1	9	0.47
time*condition	0.18[b]	1	9	0.68
time*condition*SS	0.00[b]	1	9	0.99
time*condition*age	0.45[b]	1	9	0.52
time*condition*medication	3.47[b]	1	9	0.096
time*condition*FB	0.52[b]	1	9	0.49

b. Exact statistic

Table 5. Supplementary results from multivariate Tests with time ("pre" and "post") and condition ("win" and "no-win") as within-subjects factors, feedback group (FB) as between-subjects factors and symptom severity (SS), IQ and medication state as covariates for the Cue-P3 latency.

Effect	F	Hypothesis df	Error df	Sig
Time	1,02[b]	1	9	0.34
time*Feedback (FB)	0.11[b]	1	9	0.75
time*SS	0.74[b]	1	9	0.41
time*age	3.63[b]	1	9	0.089
time*medication	2.71[b]	1	9	0.13
condition	0.094[b]	1	9	0.77
condition*SS	3.851[b]	1	9	0.081
condition*age	1.211[b]	1	9	0.3
condition*FB	0.229[b]	1	9	0.64
condition*medication	0.395[b]	1	9	0.55
time*condition	0.119[b]	1	9	0.74
time*condition*SS	1.65[b]	1	9	0.16
time*condition*age	0.018[b]	1	9	0.9
time*condition*medication	3.578[b]	1	9	0.091
time*condition*FB	1.109[b]	1	9	0.32

b. Exact statistic

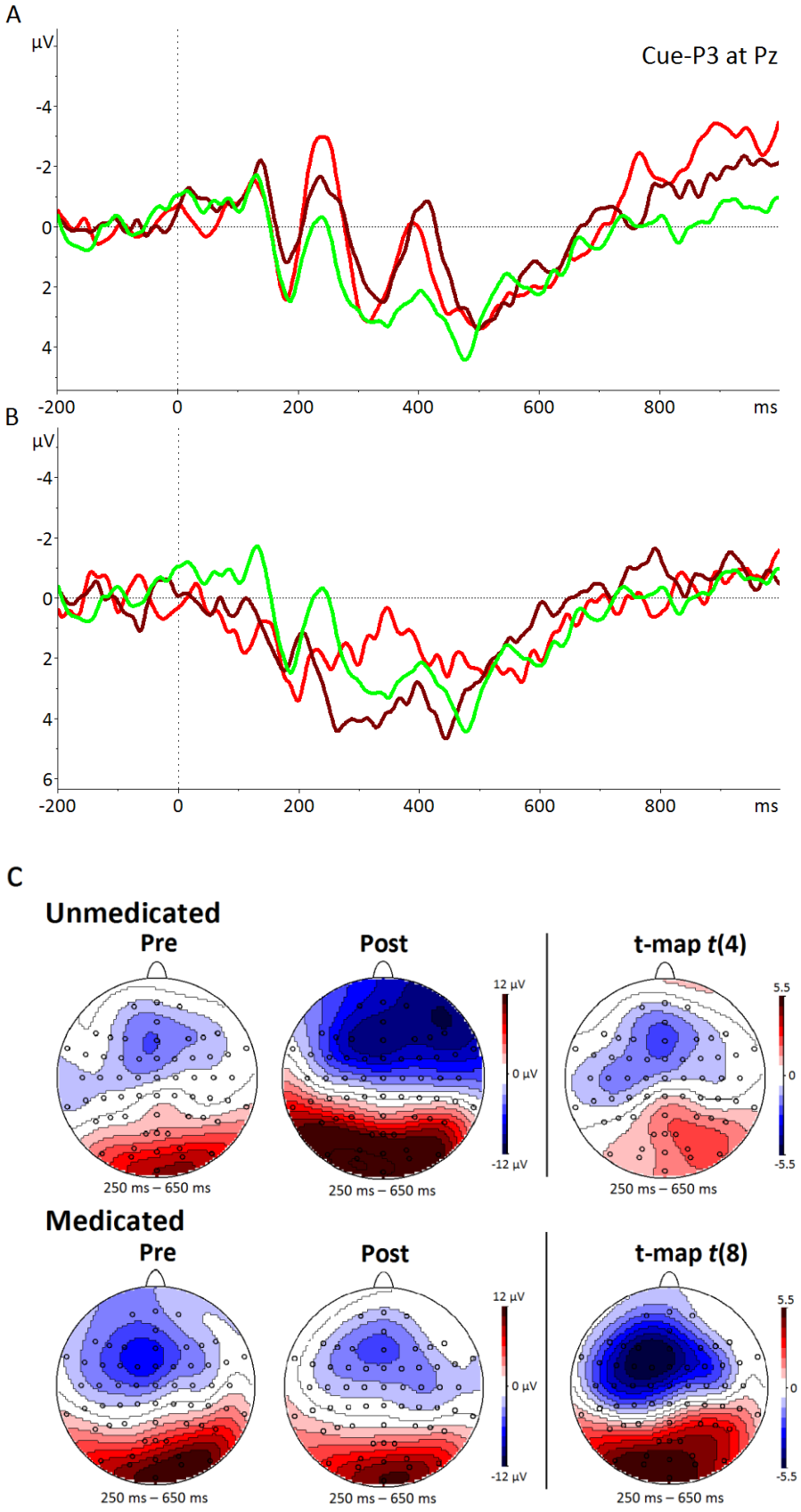
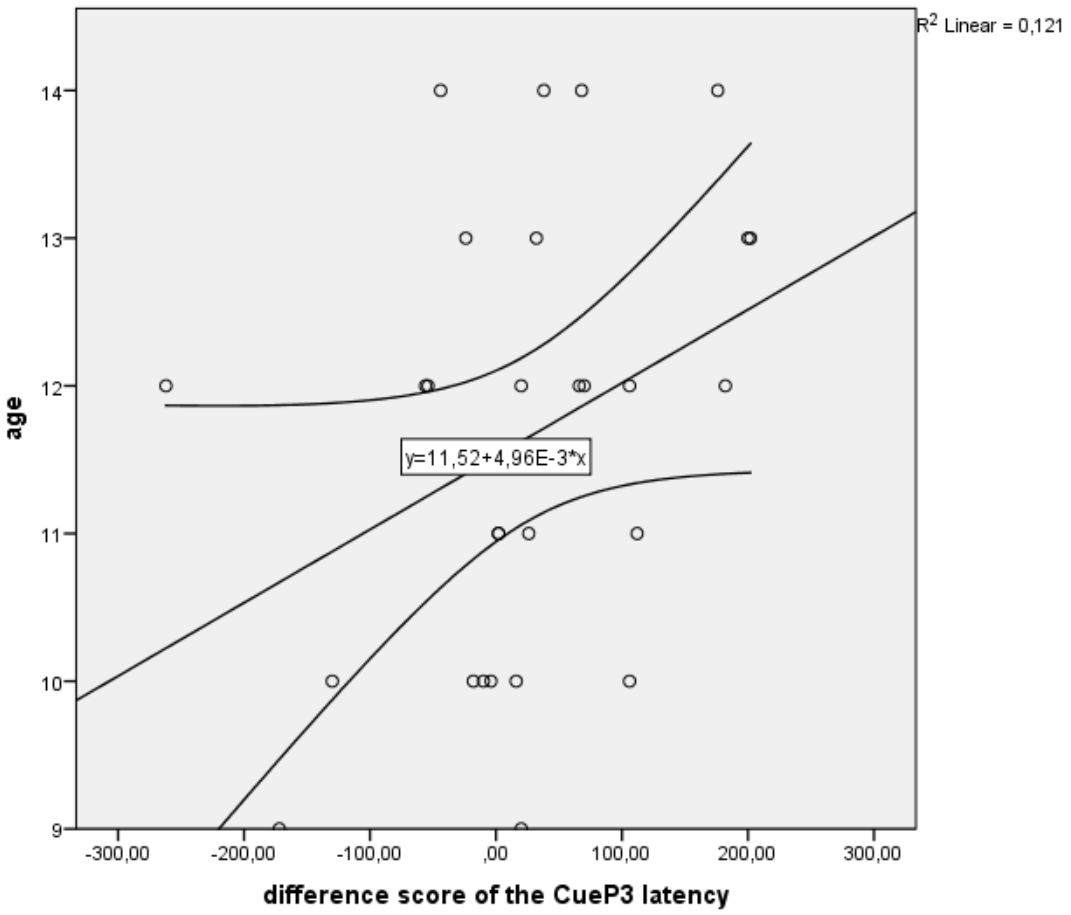


Figure 6. (Supplement) Stimulus-locked ERP waveshapes at Pz for A. medicated ADHD patients pre (red) and post training (brown) and controls (green) and B. unmedicated ADHD patients pre- (red) and post-training (brown) and controls (green) in the win condition. C. Corresponding maps in the time range of Cue-P3 and t-map (t-test against zero) for pre- vs post-training and medication state.



Graph 1. Correlation between the difference scores of the Cue-P3 latency and the age of the participants.

8 CURRICULUM VITAE

PERSONALIEN

Name und Vorname:	Peters, Szarah
Geburtsdatum:	22.08.1993
Geburtsort:	Berlin
Familienstand:	Verheiratet, 1 Kind
Vater:	Peters, Jakob
Mutter:	Peters, Judith

SCHULISCHER WERDEGANG

Sep. 2006 – Juli 2011	Besuch des Gymnasiums an der Cité Scolaire International in Grenoble, Frankreich
08.07.2011	Abschluss: Baccalauréat Général mit der Note 1,0

UNIVERSITÄRER WERDEGANG

Okt. 2011 - Sep. 2013	Medizinstudium (Vorklinik) am Universitätsklinikum Eppendorf in Hamburg

17.09.2013	Erster Abschnitt der Ärztlichen Prüfung (M1) mit der Note 3
Okt. 2013 – Okt. 2017	Medizinstudium (Klinik) am Universitätsklinikum Mannheim der Universität Heidelberg
13.10.2016	Zweiter Abschnitt der Ärztlichen Prüfung (M2) mit der Note 2
08.11.2017	Dritter Abschnitt der Ärztlichen Prüfung (M3) mit der Note 2
04.12.2017	Approbation als Ärztin

BERUFLICHER WERDEGANG

Seit Jan. 2018	Wissenschaftliche Mitarbeiterin (Doktorandin) in der AG Klinische Neurophysiologie des Kindes- und Jugendalters Und Assistenzärztin der Kinder- und Jugendpsychiatrie und Psychotherapie am Zentralinstitut für seelische Gesundheit Mannheim

Mannheim, den 22.01.2021

9 DANKSAGUNG

Zunächst möchte ich mich bei meinem Doktorvater Herrn Prof. Dr. med. Dr. rer. nat. Tobias Banaschewski für die Möglichkeit der Promotion in seiner Klinik bedanken.

Ein besonderer Dank geht an Dr. Sarah Baumeister für die umfassende Anleitung. Es war immer eine Freude mit ihr zusammen zu arbeiten und ich bin sehr dankbar von ihren klinischen, technischen und fachlichen Erfahrungen profitieren zu dürfen. Ebenfalls ganz herzlich danke ich meiner Mit-Doktorandin Anna Kaiser für die hilfreichen inhaltlichen Diskussionen, die Unterstützung und das freundschaftliche Verhältnis. Insgesamt möchte ich mich bei der AG Klinische Neurophysiologie des Kindes- und Jugendalters für das gute Arbeitsklima und die konstruktive Kritik in der Zusammenarbeit bedanken. Ich durfte in diesem Rahmen sehr viel positive Erfahrungen sammeln und hatte immer einen/eine kompetente/n Ansprechpartner/in zur Seite.

Schließlich danke ich meiner wunderbaren Frau Laura Sanchez Roman und meiner Familie Miriam, Leah, Judith und Jakob Peters dafür, dass sie mich immer unterstützt haben.