Neurofeedback of Slow Cortical Potentials for Adults with Attention Deficit-/Hyperactivity Disorder

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Abstract

Introduction: During the last few years the awareness and interest in studying adults with attention deficit/hyperactivity disorder (ADHD) has increased. Symptoms of inattention, impulsivity, and hyperactivity, but also neurophysiological differences observed in children also persist into adulthood. Further, functional and structural abnormalities in the frontostriatal circuitry are still present in adulthood, as well as a general slowing of the electrical brain activity.

The altered frequency bands and also the impaired self-regulation ability reflected in slow cortical potentials (SCP) are the target of neurofeedback therapy. Neurofeedback has been applied effectively in various areas, especially in the treatment of children with ADHD. Following SCP feedback, symptom improvements and increased amplitude of the contingent negative variation (CNV) were observed in children. The CNV is a SCP reflecting attention and preparation and was found to be diminished in children with ADHD.

This study was designed to assess whether adults with ADHD differ from healthy controls in tests of attention, reaction time (RT), and CNV amplitude. Further it was assessed whether adults with ADHD were able to learn self-regulation with SCP feedback and whether this led to changes in symptomatology and neurophysiology. Unspecific effects were assessed and correlated with the outcome variables.

Methods: Twenty-one adults with ADHD (8 female) as well as 21 healthy matched controls underwent different measurements pre, midway (ADHD group only), and post treatment. Measurements included a 19-channel electroencephalogram (EEG) with a Go-No/Go CNV task, behavioural questionnaires assessing ADHD and comorbid symptoms, and a test of attention. A baseline comparison of neurophysiological and neuropsychological variables was calculated.

The ADHD group received 30 one-hour sessions of SCP feedback in which participants had to regulate the feedback object in the cued direction, up for an activation (negativation = negative potential shift) and down for deactivation (positivation = positive

potential shift). Every fifth session the ADHD group completed a questionnaire assessing unspecific treatment effects. Changes in self-rated and third-party rated ADHD symptoms, as well as CNV amplitude, were correlated with training performance and the assessed unspecific effects.

Results: Baseline differences between the ADHD and the healthy control group were confirmed for slower RT, larger RT variability, and smaller CNV amplitude.

Following SCP feedback treatment, symptoms on all ADHD and comorbid scales diminished significantly, RT decreased, and the CNV amplitude increased. However, significant correlations between the outcome variables CNV amplitude change, self-rated and third-party rated symptom reduction were not observed.

Self-regulation was achieved, however, the pattern of a main increase in positivation (and not negativation) has not been observed before. Significant correlations of training performance with symptom reduction and CNV increase were observed. Unspecific effects like patients expectancy were revealed and were significantly correlated to treatment outcome.

Discussion: Similar to children with ADHD, differences between adults with ADHD and healthy controls were confirmed. This constitutes the foundation of neurofeedback as a treatment for ADHD in adults. Not all differences were confirmed (i.e. test of attention, error rate) but this can also be due to methodological difficulties and sample size included in this pilot study.

SCP feedback led to symptom improvements over 25%, as well as decreased RT and increased CNV amplitude, both related to attentional processes. Unspecific effects were revealed through a questionnaire, but the observed behavioural changes, neurophysiological changes, and the training performance revealed specificity and effectiveness of SCP feedback in the treatment of adult ADHD.

The training data suggests that adults with ADHD are able to learn self-regulation of SCPs. However, more research is needed to confirm and explain the pattern of mainly increasing positivation. Age might be a possible mediating variable. Also methodological difficulties in data analysis might be responsible. The present study constitutes the first step towards SCP feedback being an acknowledged and recognised treatment option for adult ADHD.

Abstract German

Einführung: Erst in den letzten Jahren ist die Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) bei Erwachsenen in das Blickfeld von Klinik und Forschung geraten. Symptome der Unaufmerksamkeit, Impulsivität und Hyperaktivität sowie neuropsychologische und neurophysiologische Veränderungen werden, wie bei Kindern, auch bei Erwachsenen beobachtet. Des Weiteren finden sich auch funktionelle und strukturelle Veränderungen in frontostriatalen Schaltkreisen sowie eine generelle Verlangsamung der Gehirnaktivität.

Veränderungen der Aktivität verschiedener Frequenzbänder und die beeinträchtigte Selbstregulationsfähigkeit, welche in den langsamen kortikalen Potentialen (LP) reflektiert sind, sind Ansatzpunkte für die Neurofeedbacktherapie. Neurofeedback wurde bereits effektiv in verschiedenen Bereichen angewandt, vor allem aber bei der Behandlung von Kindern mit einer ADHS. Nach einer LP-Feedbackbehandlung wurde bei Kindern eine Reduktion der Symptome, sowie ein Anstieg der Amplitude der kontingenten negativen Variation (CNV) beobachtet. Die CNV ist ein LP, welches Aufmerksamkeit und Erwartung reflektiert. Bei Kindern mit einer ADHS wurde eine verminderte CNV-Amplitude beobachtet.

Diese Studie untersucht zum einen, ob Erwachsene mit einer ADHS sich von gesunden Personen in Aspekten der Aufmerksamkeit sowie der CNV-Amplitude unterscheiden. Zum anderen untersucht diese Studie, ob Erwachsene mit einer ADHS in der Lage sind, die LP durch ein LP-Feedback selbst zu regulieren und welchen Einfluss das auf die ADHS-Symptomatik im Verhalten sowie auf die CNV hat. Unspezifische Effekte sollen erfasst und mit den Wirkvariablen korreliert werden.

Methode: Einundzwanzig Erwachsene mit einer ADHS (8 Frauen) und 21 gematchte gesunde Probanden wurden mit verschieden Symptomfragebögen (ADHS und komorbide Störungen), Aufmerksamkeitstests und CNV-Experiment getestet. Die ADHS-Gruppe wurde vor, nach 15 Sitzungen und nach dem kompletten Neurofeedbackraining untersucht und die Kontrollgruppe an zwei Messzeitpunkten. Die Therapie um-

fasste 30 einstündige LP-Feedbacksitzungen, in welchen die Teilnehmer das Feedbackobjekt in vorgegebener Richtung auf dem Bildschirm nach oben (Aktivierung/negative Potentialverschiebung) oder unten (Deaktivierung/positive Potentialverschiebung) mussten. Die Trainingsleistung wurde mit der Veränderung der Verhaltensmaße und der CNV korreliert. Zusätzlich wurden im Verlauf der Therapie mögliche unspezifische Effekt mit einem Fragebogen erfasst und dessen Maße mit den Wirkvariablen korreliert.

Ergebnisse: Angenommene Unterschiede zwischen den ADHS Patienten und den gesunden Probanden konnten für langsamere Reaktionszeiten, erhöhte Reaktionszeitvariabilität und eine reduziert CNV-Amplitude bestätigt werden.

Nach der LP-Feedbackbehandlung wurde eine Verminderung aller ADHS und komorbider Symptome beobachtete. Des Weiteren nahm die Reaktionszeit ab und die CNV-Amplitude stieg an. Eine Korrelation zwischen der CNV-Veränderung, den selbsteingeschätzen und den fremdeingeschätzen Symptomveränderungen wurde nicht beobachtet.

Die Selbstregulation der LP wurde gelernt, allerdings zeigen die gemittelten Trainingsdaten ein bisher noch nicht beobachtetes Muster des vorwiegenden Anstiegs der Positivierung. Unspezifische Effekte, wie z.B. die Veränderungserwartung der Patienten lagen vor. Korrelationen der Symptomreduktion, der Trainingsleistung und der CNV-Veränderung wurden beobachtet.

Diskussion: Ähnlich wie bei Kindern wurden auch zwischen Erwachsenen mit einer ADHS und gesunden Probanden Unterschiede beobachtet. Vor allem die neurophysiologischen Unterschiede bieten die Grundlage für eine Neurofeedbacktherapie. Nicht alle angenommenen Unterschiede wurden in dieser Studie bestätigt (z.B. im Aufmerksamkeitstest oder in der Fehlerrate). Dies kann u.a. durch methodische Schwierigkeiten oder der kleinen Stichprobengröße dieser Pilotstudie erklärt werden. Die LP-Feedbackbehandlung führte zu Symptomverbesserungen über 25%. Außerdem führte sie zu schnelleren Reaktionszeiten und einem Anstieg der CNV-Amplitude. Beides ist mit einer verbesserten Aufmerksamkeit assoziiert. Unspezifische Effekte wurden in den Fragebogendaten deutlich, aber die beobachteten Veränderungen auf der Verhaltensebene, in der Neurophysiologie und der Trainingsleistung zeigen eine

Spezifität und Wirksamkeit der LP-Feedbackbehandlung für Erwachsenen mit einer ADHS.

Die Trainingsdaten weisen darauf hin, dass Erwachsene mit einer ADHS die Selbstregulation von LP erlernen können. Zukünftig sollte untersucht werden, ob sich das unerwartete Muster des Positivierungsanstiegs replizieren lässt und wie es ggfs. zu erklären ist. Das Alter als Einflussvariable aber auch Alternativen in der Analysemethode sollten hier näher betrachtet werden. Unabhängig davon leistet diese Studie einen ersten Beitrag dazu, dass das LP-Feedback eine wirksame und anerkannte Behandlungsoption für Erwachsene mit einer ADHS wird.

Declaration

I hereby declare that I have produced the work entitled: "Neurofeedback of Slow Cortical Potentials for Adults with Attention Deficit-/Hyperactivity Disorder", submitted for the award of a doctorate, on my own (without external help), have used only the sources and aids indicated and have marked passages included from other works, whether verbatim or in content, as such. I swear upon oath that these statements are true and that I have not concealed anything. I am aware that making a false declaration under oath is punishable by a term of imprisonment of up to three years or by a fine.

Signed,

Kerstin Mayer

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Contents

List of Figures

List of Tables

Nomenclature

ACC Anterior Cingulate Cortex

ADHD Attention Deficit Hyperactivity Disorder

ADHD-SB Self-rated ADHD symptom scale

BDI Becks-Depression-Inventory

BSL Borderline Symptom List

CBT Cognitive Behavioural Therapy

CFT-20-R Culture Fair Test-20 Revised

CNV Contingent Negative Variation

CPT Continuous Performance Test

d2-R Test of Attention

DSM Diagnostic and Statistical Manual of Mental Disorders

EEG Electroencephalogram

EHI Edinburgh Handedness Inventory

ERP Event-Related-Potential

FEA Third-party ADHD symptom questionnaire

FERT Questionnaire assessing unspecified effects of the therapy

HASE Homburger ADHS-Skalen für Erwachsene

ICD-10 International Statistical Classification of Diseases and Related Health Problems

MRI Magnetic Resonance Imaging

NIRS Near-Infrared Spectroscopy

RT Reaction Time

RTV Reaction Time Variability

SCID-I Structured Clinical Interview for DSM-IV-TR Axis I Disorders

SCP Slow Cortical Potential

STAI-S State-Trait Anxiety Questionnaire State

STAI-S State-Trait Anxiety Questionnaire Trait

TMS Transcranial Magnetic Stimulation

WRI Wender-Reimherr Interview

WURS-K Wender Utah Rating Scale - Cildhood Symptoms

1 Introduction

The following thesis describes the first attempt to investigate the use of Slow Cortical Potential (SCP) neurofeedback as a treatment of adult attention deficit-/ hyperactivity disorder (ADHD).

In the first section of this thesis adult ADHD and its symptoms, aetiology as well as the current therapy options are described. This will highlight the need for a new treatment approach for adult ADHD. In the following chapter neurofeedback is introduced as a new treatment approach. Neurofeedback as a form of brain training has been shown to be effective in treatment of ADHD in children. The concept of this treatment is explained and neurofeedback of slow cortical potentials is described as a possible alternative treatment for adult ADHD.

The first aim of this thesis is to assess baseline differences between adults with ADHD and healthy controls in neuropsychological as well as neurophysiological parameters. The second and main aim of this thesis is to assess the effects of SCP feedback on adult ADHD symptoms, self-regulation ability, and changes in neuropsychological and neurophysiological parameters, related to possible unspecific therapy effects.

1.1 Adult ADHD

1.1.1 Prevalence, Symptoms, Diagnosis

ADHD is one of the most common psychiatric disorders of childhood. In 1902 symptoms of ADHD in children were described for the first time (Still, 1902) and mentioned

in some literature even earlier (for an overview: R. Barkley & Peters, 2012). For a long time it was thought to be a disorder of childhood and adolescence. However studies have shown that 30-65% of children with ADHD keep their symptoms into adulthood (Faraone, Biederman, & Mick, 2006).

As in children, the primary symptoms of adult ADHD include inattentiveness, impulsivity, and hyperactivity (DSM-VI-R Saß, Wittchen, & Zaudig, 2003) although symptoms of hyperactivity diminish with increasing age (R. A. Barkley, 2006). To be diagnosed symptoms have to affect at least two areas of live, like school, work or social relationships (Saß et al., 2003). ADHD is a diverse disorder with different sub-types (i.e. predominantly hyperactive, predominantly inattentive or combined type) (Saß et al., 2003). The differentiation between ADHD and ADD (attention deficit disorder) is particularly important in adults as the hyperactivity component may remit. Three types of ADHD development into adulthood are differentiated: Remission until adolescence; persistence of all symptoms or residual ADHD with diminished hyperactivity; and persistence of ADHD symptoms with comorbid psychiatric disorders as well as delinquency and substance abuse (Sobanski & Alm, 2004). Additional symptoms of adult ADHD are dysfunctional cognitions, reduced performance in educational and professional training, reduced occupational qualifications, lower social status, lower income, diminished quality of life, increased risk of accidents, increased susceptibility to crime (Schlander, Trott, & Schwarz, 2009) and a high risk of unemployment, divorce and arrest (R. A. Barkley, Fischer, Smallish, & Fletcher, 2006; Biederman & Faraone, 2006).

The comorbidity with other psychiatric disorders has been found to be as high as 65-89% including depression, anti-social personality disorder and substance abuse (for an overview: Sobanski, 2006). This indicates that a thorough diagnosis is of great importance. The International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) (1994) and the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV-TR) (2003) include criteria for the diagnosis of ADHD but only define behavioural criteria for ADHD in children.

In contrast, the Wender Utah criteria (Wender, 1995) for ADHD in adults are more specific for adult ADHD than the ICD-10 and DSM-IV-RT. They state that attentional

difficulties and persistent motor hyperactivity must be present in adults with ADHD, as well as two out of five of the following symptoms: affective liability, disorganised behaviour and inability to complete tasks, hot temper and explosive short-lived outbursts, emotional over reactivity, and impulsivity. Other diagnosis criteria according to Wender (1995) are the absence of antisocial personality disorder, the absence of signs and symptoms of schizophrenia and schizo-affective disorders and the absence of schizotypal or borderline personality disorders or traits. Associated features may include marital instability, academic and vocational success less than expected on the basis of intelligence and education, alcohol or drug abuse and addiction, atypical response to psychoactive medications, and family history of ADHD in childhood, antisocial personality disorder and Briquet's syndrome. Some of the cardinal symptoms have to be present since the age of seven which has to be assessed retrospectively through self-assessment questionnaires or family questionnaires (according to Wender (1995)). However, the Wender Utah criteria neglect patients with predominantly inattentive symptoms. The new DSM-5 (to be published in 2013) will include more specific criteria for adult ADHD, allowing for the diagnosis of a predominantly inattentive ADHD type (American Psychiatric Association, 2012).

Childhood ADHD has a cumulative incidence of 7.5% by the age of 19 years for an American population (Barbaresi, Katusic, & Colligan, 2004) and 4.8% in the age of 3 to 17 in a German population (Schlack, Kurth, & Hölling, 2008). As mentioned, 30-65% of children with ADHD keep their symptoms into adulthood (Faraone et al., 2006), which is reflected in a 4-5% prevalence of adult ADHD world-wide (Goodman & Thase, 2009). Only during the last 30 years the international scientific community started to recognise ADHD in adults (Wender, Reimherr, & Wood, 1981). In the field of psychiatry in Germany, adult ADHD receives continuously increasing interest and specific guidelines (Ebert, Krause, & Roth-Sackenheim, 2003) and diagnostic manuals (Rösler, Retz-Junginger, Retz, & Stirglitz, 2008) have been developed and adjusted. However, the field of cognitive neuroscience is still underrepresented compared to research in childhood ADHD.

1.1.2 Aetiology

The two major factors in the aetiology of ADHD are genetic and environmental.

1.1.2.1 Genetic factors

An essential genetic component in the aetiology of ADHD has been found in family, twin, adoption, and population studies. An estimated mean heritability of 76% was found in several twin studies suggesting that ADHD is one of the most heritable psychiatric disorders (Smith, Mick, & Faraone, 2009). Sobanski et al. (2004) describes two genetic types; one, in relation to dopamine in the prefrontal cortex and another in relation to noradrenalin and the posterior attention system in the parietal lobe. Dopamine was found to play a major role in ADHD. On the one hand because it has a central role in psychomotor activity and reward seeking behaviour, and on the other hand because patients with ADHD show symptom reductions during the treatment with stimulant medication.

Several molecular genetic studies of ADHD have concentrated on genes involved in dopaminergic function. Specifically, associations with ADHD have been described in both the dopamine transporter gene (DAT1) and the dopamine D4 receptor gene. Association of the dopamine transporter with ADHD is of particular importance because this site is the main target for medications like methylphenidate which is the current treatment of choice for ADHD (Dougherty, Bonab, & Spencer, 1999). Methylphenidate also targets the noradrenalin system. The assumptions that the noradrenalin system is involved in ADHD comes mainly from genetic research but is still controversial (Sobanski & Alm, 2004) and will therefore not be described.

1.1.2.2 Environmental factors

Environmental aetiologies can also contribute to the development of ADHD. Family psychosocial adversity as an accumulation of factors like severe marital discord, low social class, large family size, paternal criminality, maternal mental disorder, and foster care placement all constitute environmental risk factors for ADHD (Biederman, Milberger, & Faraone, 1995; Biederman, Petty, Clarke, Lomedico, & Faraone, 2011). Furthermore, maternal smoking during pregnancy is described as a risk factor on

multiple levels, such as intrauterine and household-level confounding effects, but also parental genotype (Langley, Heron, Smith, & Thapar, 2012).

Severe early institutional deprivation (Kreppner, O'Connor, & Rutter, 2001) can contribute to the development of ADHD and correlates with genetic risk factors (Stevens et al., 2009). Finally, secondary ADHD symptoms can develop after brain injury and stroke, especially when the dopamine-rich ventral putamen is affected (Herskovits et al., 1999; Max, Fox, & Lancaster, 2002). However, this is not ADHD according to DSM-IV-TR, ICD-10 or Wender Utah criteria.

1.1.3 Differences in brain functioning

1.1.3.1 Neuropsychological changes

The primary symptoms of ADHD are reflected in neuropsychological measures. For example, inattention is reflected in bad overall performance in the Continuous Performance Test (CPT), and impulsivity is reflected in bad performance in a Go/No-Go or inhibition task. In a meta-analytic review of 13 studies Boonstra, Oosterlaan, Sergeant and Buitelaar (2005) reported several impairments in executive functions (defined as: fluency, planning, working memory, inhibition, and set shifting) as well as in non-executive functions (defined as: speed of information processing, reaction times, and verbal memory) in adults with ADHD compared to healthy controls. Medium effects sizes have been found for decreased performance in adults with ADHD for verbal fluency, inhibition, and set shifting as well as in the non-executive functions like stability of response, word reading, colour naming, and standard error in reaction time (RT).

Most commonly in research studies, as well as clinical assessments, inattention and impulsivity are tested with the CPT or other versions of a Go-No/Go paradigm analysing RT, hit rate, and omission and commission errors. Generally, slower RTs are observed for adult ADHD compared to healthy controls (for an overview: Nigg et al., 2005), as well as increased omission errors (Ehlis, Baehne, Jacob, Herrmann, & Fallgatter, 2008; Fisher, Aharon-Peretz, & Pratt, 2011), a steeper RT decline (Dhar, Been, Minderaa, & Althaus, 2010) and overall greater RT variability (RTV) (Dhar et al., 2010; Nigg et al., 2005; Tamm et al., 2012). These impairments in executive functions

indicate that the frontostriatal/fronto-subcortical networks might be affected. However, not all studies have confirmed these results (Prox, Dietrich, Zhang, Emrich, & Ohlmeier, 2007) which has been interpreted as an indication of a better adaption of adults with ADHD over age compared to children with ADHD.

1.1.3.2 Structural and functional changes

Most knowledge concerning the neurobiology of ADHD is derived from studies of children with ADHD. The key brain abnormality involves structural and functional abnormalities in the frontostriatal circuitry (for an overview: Seidman, Valera, & Makris, 2005). As the focus of this thesis is adult ADHD only studies with adults are mentioned.

Structural brain imaging studies on adult ADHD yielded abnormalities in brain regions related to attention and executive functions compared to healthy controls. Patients with adult ADHD showed a reduced orbitofrontal volume in the left hemisphere (Hesslinger, Tebartz van Elst, Thiel, et al., 2002), and increased white matter volumes in the nucleus accumbens, as well as decreased neocortex (gray matter) in the frontal lobe and the right medial paralimbic region, specifically in the right anterior cingulate cortex (ACC) and the left superior frontal gyrus (Seidman et al., 2006). In a meta-analysis of eleven (four on adults) structural magnetic resonance imaging (MRI) studies using voxel-based morphometry mainly a volume reduction in the ACC for adults with ADHD was reported. However, the reduction in the ACC was smaller in adults that received previous pharmacological treatment with stimulants (Frodl & Skokauskas, 2012). The ACC processes and regulates emotional information between the ACC and the lateral prefrontal cortex, and seems to be involved in motor control through dense projections from the ACC to the motor cortex and spinal cord (according to Frodl and Skokauskas (2012)).

Recent imaging techniques have also revealed abnormalities in similar brain regions. For example, in an event-related functional MRI study using a Go/No-Go task participants received positive reinforcement for correct responses to Go trials and negative reinforcement to responses to NoGo trials. During these reinforcement-related processes, the ADHD group displayed less activation in the inferior frontal/orbitofrontal

cortex, hippocampus/nucleus accumbens and caudate nucleus, but more activity in the inferior frontal gyrus (Dibbets, Evers, Hurks, Marchetta, & Jolles, 2009).

Diffusion tensor imaging studies have demonstrated abnormalities in the neural network showing reduced white matter connectivity fronto-striatal (Konrad et al., 2010) and in the cingulate cortex (Makris et al., 2008). Furthermore, abnormalities in specific brain regions related to working memory have been found measuring regional cerebral blood flow (rCBF). A positron-emission-tomography (PET) study has shown reduced task-related rCBF changes in frontal and temporal regions (Schweitzer et al., 2000) and a near-infrared spectroscopy (NIRS) study has shown reduced activation in the lateral prefrontal cortex (Ehlis et al., 2008).

Thus, the observed neuropsychological and behavioural features, like inattention, impulsivity, hyperactivity, and lack of motivation in adult ADHD correlates with structural and functional abnormalities in the responsible brain areas.

1.1.3.3 Neurophysiology

Electroencephalogram (EEG) is another common imaging technique which is known for its high temporal but also poor spatial resolution. It is a popular tool in neurophysiological research due to the extreme cost effectiveness compared with other imaging techniques such as functional MRI.

Spontaneous brain activity

Analysis of the raw EEG is often performed with data derived from the resting EEG eyes closed/eyes open or an active task like the CPT. Using a Fast Fourier Transformation (FFT) different frequency bands and their individual power at the different electrode positions can be assessed.

Each frequency band is associated with a specific state of mind. Alpha (8-13 Hz) is associated with a more relaxed and calm state, but also inhibition control. Beta (13-30 Hz) is related to a state of concentration and gamma (30-100 Hz) to cross-modal sensory processing and integration of information. The slow frequency delta (1-4 Hz) is associated with slow wave sleep and theta (4-8 Hz) with drowsiness or arousal, but also inhibition of elicited responses (Niedermeyer, 1999).

Most knowledge about EEG changes in ADHD arises from childhood ADHD. An increased theta activity and theta/beta ratio is described in a large amount of research (for an overview: Clarke et al., 2008). However, recent research puts the theta/beta ratio as general maker for ADHD into question (Arns, Conners, & Kraemer, 2012; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011). A similar pattern was found in adults with ADHD. Early studies on resting EEG changes in adults with ADHD compared to healthy controls found elevated absolute and relative theta activity, comparable to studies with childhood ADHD (Bresnahan, Anderson, & Barry, 1999; Bresnahan & Barry, 2002; Bresnahan, Barry, Clarke, & Johnstone, 2006). Bresnahan et al. (2006) also found reduced global relative beta and elevated absolute delta across all electrode sites as well as reduced relative delta at the vertex. However, all three studies were limited as they only reported data for midline electrodes. In a study by Clarke et al. (2008) a global increase in relative theta was observed over all electrode sites which seemed to be the most reliable EEG marker of ADHD in eyes-closed resting EEG, independent of age. Clarke et al. (2008) also observed a global reduction in absolute delta which contradicts findings by Bresnahan et al. (2006).

Clarke at al. (2008) observed decreased midline absolute and relative beta power, although Köhler et al. (2009) could not repeat these observations. They found increased regional alpha activity in frontal, central and posterior regions similar to earlier results reported for adolescents (Lazzaro et al., 1999) and adults (Bresnahan & Barry, 2002). A brief overview about these general findings is depicted in figure 1.1.

Alpha	Beta	Theta	Delta
↑	↓	↑	↑↓

Figure 1.1: Summary of most common findings of frequency differences between healthy controls and ADHD patients, An arrow pointing up indicates observed increases in the frequency band, an arrow pointing down observed decreases.

To summarise, these differences in relative and absolute power in adults with ADHD seem to confirm a processing deficit reflected in neuropsychological variables and behaviour, described in section 1.1.3.1.

1.1.3.4 Event-Related-Potentials

Event-Related-Potentials (ERPs) are widely used to investigate the neurophysiological basis of cognitive functions. ERPs are reactions of the brain to a specific stimulus (mostly visual and auditory) or reactions in preparation of a motor or cognitive answer. ERPs are measured using averaged EEG signals locked to a specific stimulus over multiple trials (Luck, 2005).

ERPs can be divided into early and late components as well as endogenous and exogenous components. Very early components are termed exogenous as they depend on external physical characteristics during sensory processing and occur before 50 ms after the stimulus. Early ERP components are the P1, N1, P2, and N2. They are named after their polarity (Positive or Negative) and the approximate peak after the stimulus onset also called latency (e.g. 100 ms). The P1 is elicited by visual stimuli and is a mandatory sensory response which is highly dependent on the stimulus contrast whereas the auditory N1 has several distinct components and its latency can be influenced exogenously as well as endogenously through attention to the stimulus (Luck, 2005). The Contingent Negative Variation (CNV) and the P3 are examples for late ERP components, as they occur after 300 ms. They are also termed endogenous as they are dependent on internal processing factors and are not directly influenced by the physical property of the stimulus. All ERPs can be observed at specific scalp distribution in a so called topography. For example P3 is observed best at parietal central and CNV central-midline sites.

ERPs can be in experiments with healthy participants but also to investigate atypical sensory and cognitive processing in participants with a variety of disorders. ERPs have been extensively investigated in childhood ADHD (for a review see Barry, Clarke, & Johnstone, 2003).

Results of different ERP studies are difficult to compare due to the difference in the protocols used to elicit the brain response (e.g. auditory, visual or both). The protocols used in the study presented in this thesis used an auditory eyes closed task. Therefore, the following review only presents ERP studies using auditory stimuli. While many important studies have been conducted with children, the review focuses on adults, due to the relevance to this study. However, results from children are presented whenever

the body of research for adult ADHD is to small.

Early ERP components

In early ERP components differences between adult ADHD compared to healthy controls have been observed for N1, N2, and P2. N1 is sensitive to selective attention and extraction of sensory information. N2 is related to stimulus discrimination processes, being elicited by unexpected events (Näätänen & Picton, 1986), and P2 might reflect automatic stimulus discrimination or inhibits the further processing of competing information (according to Barry et al., 2009). The observed differences between adults with ADHD and healthy adults are an enhanced frontal N1 (Barry et al., 2009), but also diminished auditory N1 amplitudes (Bekker et al., 2005), globally enhanced P2, globally diminished N2 (Barry et al., 2009), increased N2 amplitudes and longer latency in N2 (Fisher et al., 2011). These differences point to an early sensory processing deficit. An overview of the general ERP findings is depicted in figure 1.2.

N1		**N2**		**P2**		**P3**		**CNV**
Amp	Lat	Amp	Lat	Amp	Lat	Amp	Lat	Amp
↑	↓	↑ ↓	↑	↑	↑	↓	↑	↓

Figure 1.2: Summary of most common findings of ERP differences between ADHD patients and healthy controls. Arrow up indicates a reduction in adults with ADHD; arrow down indicates an elevation in adults with ADHD. Amp = Amplitude, Lat = Latency

P3

The late ERP component P3 has been the main focus of interest for ADHD studies as the P3 is related to the allocation of attention, and its latency reflects the speed of stimulus evaluation. A P3 is elicited in an odd-ball paradigm in reaction to the deviant stimulus. In adults with ADHD a reduced P3 amplitude (Fisher et al., 2011; Szuromi, Czobor, Komlósi, & Bitter, 2010) and prolonged P3 latency (Fisher et al., 2011; McPherson & Salamat, 2004) have been observed. These abnormalities are related to attentional processing deficits.

CNV [1]

The CNV belongs to the family of slow cortical potentials. It is a slow negative shift over central sites occurring in reaction to a warning stimulus (S1) followed by an imperative

[1] The following paragraph is adopted from Mayer, Wyckoff and Strehl (2012)

stimulus (S2) which requires a response in Go- or Cue - trials. The CNV represents anticipation and/or preparation, attention, and motor preparation (Walter, 1964). The negative amplitude increases with the amount of "cognitive energy" depending on the anticipation of task performance and is therefore related to attention processes. See figure 1.3 for a CNV protocol and wave form.

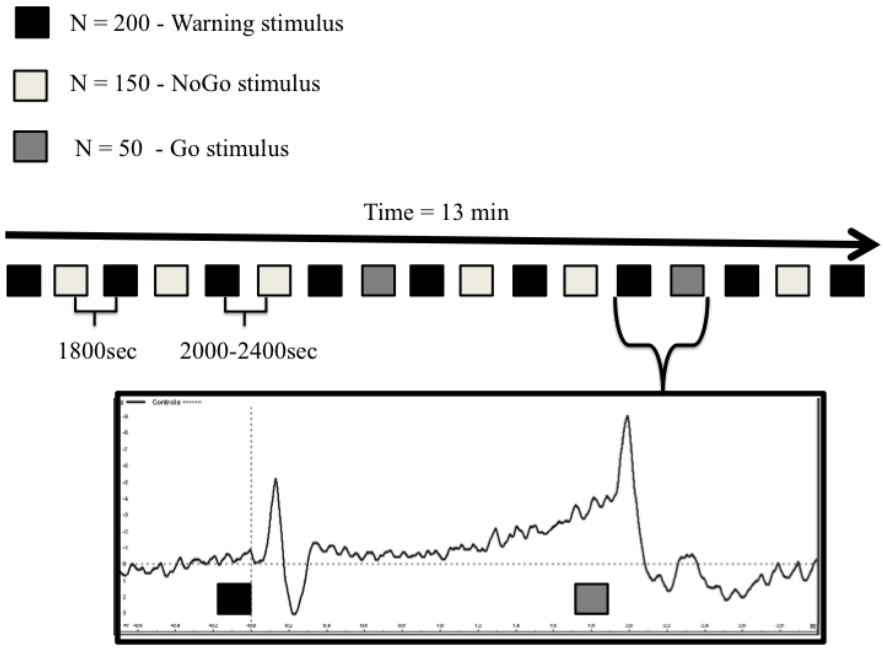

Figure 1.3: An auditory CNV example protocol with three stimuli, a warning stimulus, a NoGo stimulus and a Go stimulus. The typical CNV wave form between the warning and the Go stimulus is depicted.

A reduction in CNV amplitude has been observed for children with ADHD compared to healthy controls during cognitive preparation (Banaschewski & Brandeis, 2004; Banaschewski et al., 2003; Hennighausen, Schulte-Körne, Warnke, & Remschmidt, 2000; Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001; Sartory, Heine, Müller, & Elvermann-Hallner, 2002; van Leeuwen et al., 1998) and similarly in adults with ADHD compared to healthy controls (Dhar et al., 2010; Mayer, Wyckoff, Schulz, & Strehl, 2012; Weate et al., 1993). Dhar et al. (2010) found a tendency for healthy controls to show a larger CNV 1550-1650 ms post stimulus compared to adults with ADHD, however results did not reach statistical significance. In a study on Gilles de la Tourette Syndrome, patients with additional ADHD showed an attenuated early

CNV compared to healthy controls or Gilles de la Tourette Syndrome without ADHD (Weate et al., 1993). In a CPT Go-NoGo task McLoughlin et al. (2010) reported a reduced CNV amplitude in adults with ADHD. A negative correlation between a high CNV amplitude reflecting preparatory processes and an inhibition in response was observed. The CNV amplitude is related to conscious cognitive processes on higher processing levels (Brix, 1977). A reduced CNV amplitude might therefore reflect reduced attention, concentration, and a reduced ability to improve ones performance in high expectation and under strain (Birbaumer et al., 1990; Brix, 1977).

The findings of a decreased CNV are consistent with the model of dysfunctional regulation of energetical resources in ADHD (Sergeant, 2000, 2004), and with negative slow cortical potential shifts representing higher neural excitability (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). These findings point towards impaired excitation thresholds which may benefit from a treatment of the self-regulation ability.

1.1.4 Therapy

Common therapies for childhood ADHD include medication such as stimulants (e.g., methylphenidate) and selective norepinephrine reuptake inhibitors (e.g. atomoxetine), as well as cognitive behavioural interventions like child, family, and school oriented cognitive, behavioural, and educational interventions (Pelham & Fabiano, 2008). Generally, a multimodal treatment is recommend in clinical guidelines (Taylor et al., 2004). The number of therapy options for adults with ADHD is as limited as the research in adult ADHD. In a prevalence study conducted in the United States, it was assessed that only 11% of the adult ADHD group actually received treatment (Kessler et al., 2006).

1.1.4.1 Pharmacotherapy

According to the guidelines from the National Institute for Health & Clinical Excellence (NICE) (Graham, 2009), the first-line of treatment should be pharmacological treatment (preferably methylphenidate), unless the person prefers a psychological treatment. However, the recommended drug treatment of adult ADHD is highly dependent on the country and its laws. For example, in Germany methylphenidate for adults was only released in April 2011. Until then “off-label" medication like antide-

pressants were prescribed. Approved medications in the USA include atomoxetine, amphetamine, and methylphenidate, but this application is also mainly based on studies with children with ADHD (Wilens, Morrison, & Prince, 2011).

Stimulants like methylphenidate and amphetamine are most commonly used for treatment of ADHD. These medications increase the intrasynaptic concentration of dopamine and norepinephrine. Methylphenidate blocks the reuptake of dopamine (according to: Wilens et al., 2011). In a review of 47 studies by Wilens et al. (2011) responder rates from 25-95% are reported depending on the study. Further, they report mild to moderate side effects like headaches, dry mouth, insomnia, reduced appetite, weight loss, dysphoria, obsessiveness, and tics. Adverse cardiovascular effects such as increased systolic and diastolic blood pressure and heart rate have also been reported.

Noradrenergic agents like atomoxetine inhibit the presynaptic norepinephrine reuptake which results in increased norepinephrine and dopamine. Side effects are similar to stimulants but also include nausea, constipation, decreased libido, dizziness, and sweating. The last commonly used medication described by Wilens et al. (2011) are antidepressants like Bupropion, tricyclic antidepressants, and monoamine oxidase inhibitors. Those antidepressants that studies have shown to be effective in treating ADHD also work over dopaminergic and noradrenergic mechanisms and might be useful for treating comorbid depression.

1.1.4.2 Psychotherapy

There are a few studies investigating psychotherapy for adult ADHD, mostly Cognitive Behavioural Therapy (CBT). CBT includes for example dealing with procrastination, change of negative thought patterns, strategies to improve attention and memory, impulse-control skills, organisational prioritisation, time-management, planning skills, and management of comorbid problems (i.e. sleep problems, lack of emotional control or anger) (for an overview: Young & Myanthi Amarasinghe, 2010).

In a randomised controlled trial with a medication only treatment group and a medication plus CBT treatment group, the group with additional CBT demonstrated greater improvement in ADHD symptoms as well as in anxiety and depression (Safren

et al., 2005). The same superior effects of a combined treatment were reported by Bramham et al. (2009) and Rostain & Ramsay (2006).

Several studies have investigated the effect of psychotherapy without additional treatments. Hesslinger et al. (2002) found improvements on ADHD symptoms, depression, and overall personal health after structured skill-training based on Dialectic Behavioural Therapy principles. A comparison of meta-cognitive therapy and placebo-like supportive therapy in medicated and non-medicated adults showed a greater improvement of inattention for the meta-cognitive therapy group (Solanto et al., 2010). Similar results were found in a comparison of individual CBT, cognitive training, and a control group whereby the largest reductions in ADHD symptoms was observed in the CBT group (Virta et al., 2010). However, treatment related improvements on cognitive functioning could not be observed.

As mentioned, the NICE guidelines do not recommend psychotherapy as a stand alone treatment but as an addition to pharmacotherapy (Graham, 2009). But as side effects and prejudice against medication are limitations of drug treatment in adult ADHD more studies are needed to develop, improve, and prove the efficacy and long-term outcome of psychotherapy.

There is some evidence that other psychological treatments like coaching, psychoeducation or assistance with organising daily life are effective, but more research needs to be done and study designs have to be improved by including control groups, randomisation, and larger sample sizes (Graham, 2009). There are also several alternative treatments such as dietary elimination strategies, nutritional supplements, herbal and homeopathic treatments, acupuncture, biofeedback, relaxation training, hypnosis, meditation, mirror feedback, perceptual stimulation, and alternative medical treatment. Arnold (2001) identified 24 of these alternative treatments and concluded that most of the studies require more research to make any statements about their efficacy.

The appropriate treatment of ADHD in children, as well as in adults, is still a matter of debate. In regards to the growing body of research and knowledge about neurophysiological impairments in ADHD, an orientation on physiological and neurophysiological models led to a new approach to alternative treatment modules. One

of these neurophysiological oriented treatments is neurofeedback which targets the underlying neurophysiological variations in ADHD.

1.2 Neurofeedback

As highlighted in section 1.1.3.2, ADHD is characterised by structural but also functional brain activity differences. Taken together these differences represent an underarousal over frontal and central-midline cortical regions. The underarousal is reflected in an increased theta activity and a decreased beta activity as well as a decreased CNV amplitude (see section 1.1.3.4). These differences reflect impaired excitation thresholds which can be treated with a self-regulation training of the brain activity. This can be achieved through neurofeedback.

Neurofeedback is EEG-biofeedback that aims to acquire self-regulation over certain brain activity patterns. Different brain responses can be targeted depending on the disorder or desired performance enhancement. One method is the feedback and modulation of specific frequency bands. In ADHD, frequency feedback targets abnormal activity such as increased theta/beta or theta/alpha ratios, elevated relative theta power, and reduced relative alpha, and beta power in children (for an overview: Barry et al., 2003) and similar parameters in adults (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2008). This kind of neurofeedback has been effective in other disorders as well (Hammond, 2005).

A second variant of neurofeedback is feedback and self-regulation of slow cortical potentials. SCP feedback is focused on difficulties in regulation of cortical activation, and inhibition and aims to improve the self-regulation of activation and deactivation of the brain (Strehl, 2009). A detailed description follows in section 1.2.1.

The general mechanism of action in neurofeedback is feedback and operant conditioning of the specific brain pattern (Sherlin et al., 2011) (see figure 1.4 for the feedback loop). The EEG is recorded on one or more electrode position using additional electrodes as reference and ground. After processing and filtering the relevant brain activity, the signal is fed back to the participant visually on a computer screen and or auditory through music or tones. The neurofeedback therapist observes the raw EEG and the relevant activity and may additionally give verbally positive feed-

back and reinforcement. For a generalisation of behaviour so called transfer trials are

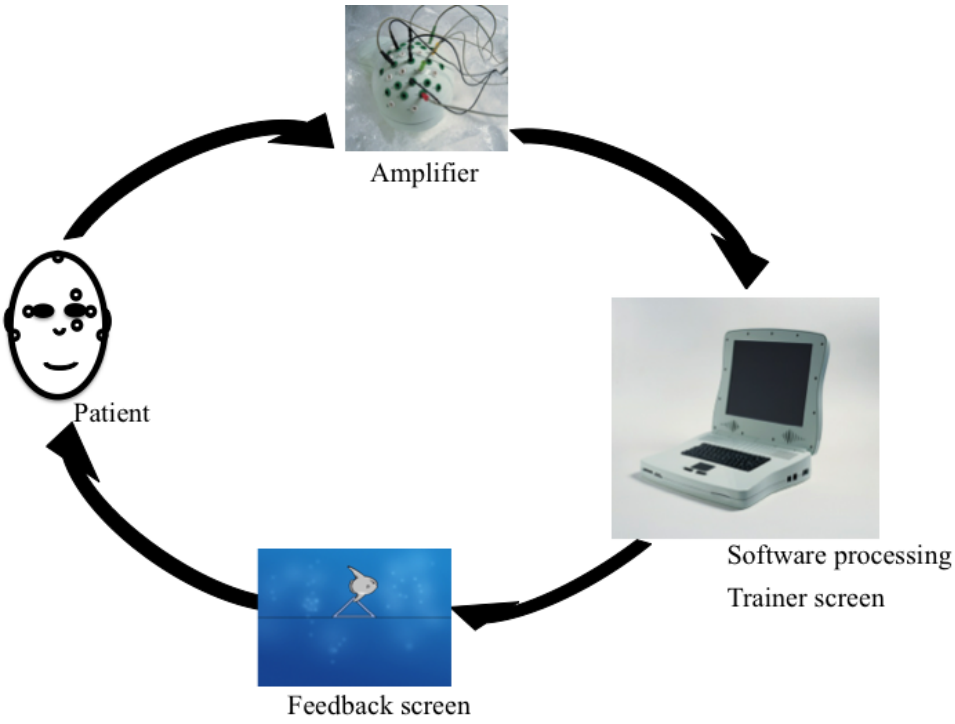

Figure 1.4: Neurofeedback loop: EEG activity gets recorded from the participant. Then is gets amplified and processed with the appropriate software to extract the desired brain activity that gets fed back to the participant. With the help of the feedback the participant can change the target brain pattern and again receives feedback about the achievement.

utilised. Transfer trials include only reinforcement but no feedback about the brain response and help using the acquired brain self-regulation in daily life. Reinforcement and reward are crucial in this process. A response-reinforcer association must be built between the reinforcement (visual or auditory feedback about the performance) and the desired specific brain behaviour response (Sherlin et al., 2011). Also, an appropriate reward needs to be established to keep the participants motivation. A vast variety of protocols, feedback screens, reinforcement options, reward schedules, and equipment is available to provide training and treatment. In the following, the rather standardised neurofeedback protocol (Mayer, Wyckoff, & Strehl, 2012), SCP feedback, will be described in detail.

1.2.1 Slow Cortical Potentials

Slow cortical potentials are very low electrical shifts in the brain activity from less than half a second upto several seconds duration after stimulus onset. They reflect the threshold regulation mechanisms of cortical activation (negative shift) and deactivation/inhibition (positive shift) (Birbaumer et al., 1990). SCPs can be described as a phasic tuning mechanism in regulation of attention (Rockstroh et al., 1993). SCPs are generated cortically and sub-cortically, involving brain stem reticular mechanisms, the thalamus and the basal ganglia. The main factor contributing to SCP recordings using EEG recordings are synaptic activities at apical dendrites in superficial layers.

SCPs are related to cognitive performance and motor actions. Negativation represents activation, increasing the firing probabilities of the underlying cortical areas, and is due to long-lasting depolarisation of superficial layer apical dendrites. A negative shift reflects provision of resources and facilitates attention as well as initiation of goal directed behaviour. This can be observed in enhanced RT, stimulus detection and short-term memory during the negative shift phase (Birbaumer et al., 1990). Positivation of SCPs represents inhibition and a decrease in firing probabilities. A positive shift reflects consumption of resources and disfacilitation of excitation thresholds. Therefore, the ability to self-regulate SCPs is important in disorders with impaired excitation thresholds like epilepsy or ADHD.

1.2.2 Slow Cortical Potential feedback

In SCP feedback, subjects learn to voluntarily generate surface-negative and surface-positive SCP-shifts over the sensorimotor cortex. The SCP-shifts are recorded and fed back to the participant, e.g. as an object moving across the screen. The SCP-shifts are represented as up and downwards directed movements of the object. An activation or negative SCP-shift is represented in an upwards movement of the object and deactivation or positive SCP-shift in a downwards movement. During the active feedback phase the participant has to direct the object reflecting the SCP-shifts in the cued direction (see figure 1.5). In successful trials the participants receives a visual reward. To generalise the regulation skills to everyday life situations, part of the treatment consists of “transfer trials” in which no visual feedback is presented during

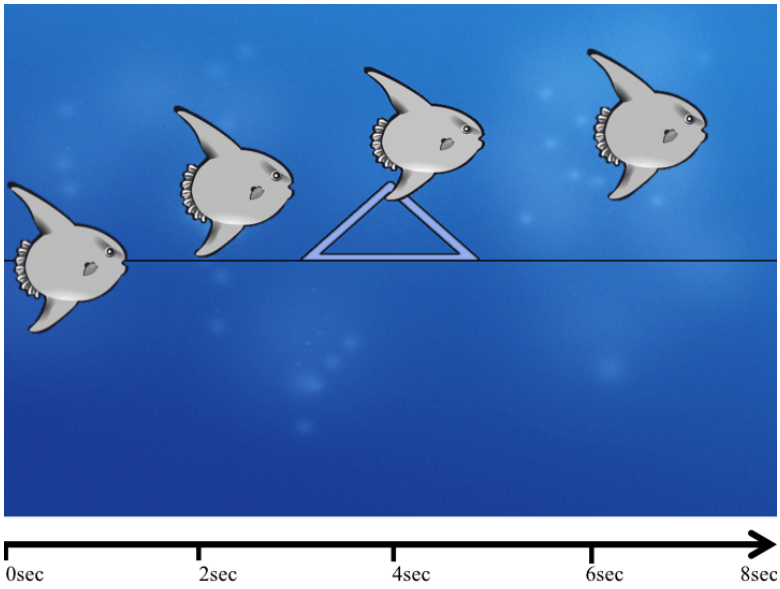

Figure 1.5: Example of the feedback screen in the activation feedback condition. The feedback object moves over the screen for 8 sec whereby the up and down direction is led though the SCP recording.

the active phase (Strehl, 2009). The visual reward stimulus was given to inform the participants whether they reached the cued brain state.

SCP feedback was originally developed for the treatment of epilepsy (Rockstroh et al., 1993). Patients with epilepsy have difficulties in regulating the excitability of neurons. Rockstroh et al. (1993) showed that patients trained to voluntarily produce negative and positive SCP shifts were able to decrease the likelihood of a seizure. The self-regulation ability and seizure reduction was replicated in a second study by Kotchoubey et al. (1999) and turned out to be stable in a six month follow-up (Kotchoubey et al., 2001).

ADHD is also a condition characterised by difficulties in regulation of cortical excitation thresholds (see section 1.1.3.4). In patients with ADHD the difficulties lie mainly in a lowered excitability, also reflected in a low skin conductance level (Satterfield & Dawson, 1971), as well as in the reduced slowing in the EEG and reduced CNV. Therefore, it is assumed that a regulation training of excitability should improve the hypoarousal observed in patients with ADHD, particularly a training of the activation through negative SCP shifts.

1.2.2.1 SCP Neurofeedback in children

To the author's knowledge, this is the first study on SCP training in adult ADHD. Therefore the results of SCP feedback on children ADHD will be described.

SCP feedback is well researched and applied in the treatment of children with ADHD (for an overview: Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Mayer, Wyckoff, & Strehl, 2012). All studies used a similar feedback protocol with only small variations in number or length of sessions, intensity of transfer training, feedback screen, token reward system or parental support.

Children learned to self-regulate their SCPs in a way that they were able to produce a differentiation between cued negativation and positivation in the feedback as well as in the transfer trials (Drechsler et al., 2007; Gani, Birbaumer, & Strehl, 2008; Strehl et al., 2006). SCP feedback was associated with symptom improvements above 25% in all published studies (Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Leins et al., 2007; Strehl et al., 2006; Wangler et al., 2011). Furthermore, a decrease in commission errors (Heinrich et al., 2004) as well as an improvement in the "Testbatterie zur Aufmerksamkeitsprüfung" (test battery for attention) (Strehl et al., 2006) and on the d2 concentration test (Drechsler et al., 2007) have been observed.

The session data of training performance correlated with symptom reduction and a predictor for clinical outcome was the ability to produce a negativation in the transfer trials (Drechsler et al., 2007; Strehl et al., 2006). In the meta-analysis of the efficacy of frequency and SCP feedback treatment in ADHD, large effect sizes for impulsivity and inattention and a medium effect size for hyperactivity were reported for frequency as well as SCP feedback (Arns, De Ridder, Strehl, Breteler, & Coenen, 2009). Moreover, long-term effects on stability of self-regulation skills, as well as attentional and behavioural improvements have been observed 6-months (Leins et al., 2007; Strehl et al., 2006) and even two years post treatment (Gani et al., 2008).

1.2.2.2 Effects on neurophysiological parameters

Besides the observed improvements in behaviour ratings and psychometric test measures, neurofeedback leads to changes in EEG parameters and even neuroplastic

changes. Neuroplastic changes were observed in healthy adults after alpha reduction neurofeedback which led to sustained changes in motor cortex excitability tested with transcranial magnetic stimulation (TMS) (Ros, Munneke, Ruge, Gruzelier, & Rothwell, 2010), as well as an increase in connectivity within the salience network (dorsal anterior cingulate focus) tested with functional MRI (Ros et al., 2012). This indicates that neurofeedback may be able to directly influence brain plasticity. Similar neurophysiological changes following neurofeedback can be observed in EEG and ERP parameters. The presentation of results will be focused on changes following SCP feedback.

Resting EEG

Changes of resting EEG following SCP feedback have been observed and reported in several studies. A trend of decreased theta/beta ratio at Cz, usually related to theta/beta frequency training, was reported in children with ADHD-combined type following SCP feedback (Doehnert, Brandeis, & Straub, 2008). Further midline central alpha band increases were observed and found to be related to hyperactivity and impulsivity behavioural outcome (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Wangler et al., 2011). However, these changes in the resting EEG were only observed in ADHD subgroups (e.g. combined type) or as a trend rather than statistically significant.

P3

Increases in P3 have been mainly related to theta/beta feedback (Egner & Gruzelier, 2001). In healthy students an increase in P3 was observed after beta feedback, which was attributed to higher general background excitation (Egner & Gruzelier, 2001, 2004). Kropotov et al. (2005) described a P3 increase in a Go/No-Go task for children with ADHD who were considered good performers following a relative beta feedback protocol. However, Wangler et al. (2011) found an increase of cue-P300 after SCP feedback but a decrease of the target-P300 after theta/beta feedback. They commented that the increase of cue-P300 after SCP feedback might indicate an allocation of more attentional resources to process more salient stimuli, and they related the decrease of the target-P300 after theta/beta feedback to an adaption process.

CNV

The strong relationship between SCPs and CNV led to the assumption that SCP feedback may change the CNV amplitude. Furthermore, the observation that children with ADHD show a reduced CNV amplitude made it plausible to use SCP feedback as a treatment for ADHD.

Two studies have found the expected increase in CNV amplitude following SCP feedback (Gevensleben, Moll, & Heinrich, 2010; Heinrich et al., 2004; Wangler et al., 2011). Heinrich et al. (2004) were the first to investigate the effect SCP feedback on CNV amplitude and found an increased CNV amplitude after treatment compared to a waiting-list group. In a comparison of theta/beta frequency feedback and SCP feedback for children with ADHD, Wangler et al. (2011) found an increase of the CNV amplitude in cue trials only after SCP feedback. In addition, children with a higher CNV at baseline showed a greater improvement on behaviour ratings from their parents. Wangler et al. (2011) noted that children were initially able to recruit more resources, which helped them accomplish the transfer into daily life better. Children with a smaller baseline CNV had to build up this resource first and might need more training or time to reach the same results. It was suggested that the baseline CNV might be an indicator for the number of neurofeedback sessions needed (Wangler et al., 2011).

In one study these results could not be confirmed (Doehnert et al., 2008). A significant reduction in CNV during a CPT following SCP feedback was observed. The authors attributed this to the difficulty to transfer the learned self-regulation to the monotone and long CPT task and highlight motivational problems in the task performance. They suggested that ADHD patients were especially challenged in this monotone test due to the motivation deficit in ADHD.

1.2.2.3 Neurofeedback studies in adults

There are only two published studies concerning neurofeedback in adults with ADHD. One study reports a single case of a 16 year old boy with behavioural problems receiving 30 sessions of theta/alpha feedback (Butnik, 2005). The effects were described as gradual and continued improved attention and academic performance. The partici-

pant described that he gained a sense of control over his attention and improved his motivation.

The other published research on neurofeedback as a treatment for adults with ADHD is a preliminary study of the full results presented in this thesis. This preliminary study reported improvements in ADHD symptoms as well as in depression scores and a trend of an increased CNV after 15 sessions of SCP feedback for ten patients (Mayer, Wyckoff, Schulz, & Strehl, 2012).

1.2.3 Unspecific effects

Unspecific effects of a treatment or placebo effects are always present in any treatment. Most commonly, a placebo is an inert medication which is used in clinical trials and double blind study designs to test the efficacy of a medication. A placebo is not a substance itself but rather the social circumstances that suggest a treatment. Thus, a placebo can be a sham psychotherapy, or even just rituals, words, meanings or symbols (Benedetti, Carlino, & Pollo, 2010). The important element is the suggestion of clinical benefit, raising expectations about therapeutic benefit or reward in the person receiving the placebo (Price, Finniss, & Benedetti, 2008). These expectations as well as a combination of pavlovian or operant conditioning and social learning mediate the placebo effect as a multifaceted phenomena with a psychobiological basis (Benedetti et al., 2010).

These unspecific effects add to the treatment specific effects and can constitute up to 80% of the clinical outcome (Hammond, 2011). In developing and testing a new treatment, investigators attempt to test the specificity of the new treatment, using methods like clinical trials, double or triple blind studies, shame conditions or assessments of the mediating components like expectations etc.

Neurofeedback studies have been criticised for not disentangling specific and unspecific effects. This is mostly due to a lack of appropriate study designs which made it impossible to separate specific from unspecific effects (Vaque & Hammond, 2002). To investigate how efficacious and specific a treatment is a double-blind-study design is essential (Vaque & Hammond, 2002). However, the use of this study design has found to be challenging in neurofeedback studies. Lofthouse et al. (2011) describe,

that triple and double blind studies cannot be conducted in psychotherapy as well as in neurofeedback as the therapist needs to know what the treatment includes or which EEG parameters to feed back. Sham neurofeedback, which would control well for unspecific effects, is rarely used due to technological and ethical reasons (Lofthouse et al., 2011). Another reason for a less complex study design is often simply a lack of resources in equipment or staff to conduct such a study.

Due to these limitations there is a need for other ways to control for unspecific effects. Vollmann et al. (2009) developed a questionnaire (Fragebogen zur Erfassung relevanter Therapiebedingungen - FERT) for the assessment of relevant therapy settings and general active factors of psychotherapy. The author identified six factors as critical general unspecific factors in all psychotherapies. These factors are: patients treatment expectations, goodness of fit between patient and therapist, therapeutic relationship, professional competence of the therapist, persuasiveness of the therapist, and willingness of the patient to engage in the therapy. The questionnaire of Vollmann assesses these unspecific effects and makes it possible to account and control for them, compare different treatment groups and observe the development over time.

Finally, another approach to account for unspecific effects in neurofeedback is a correlation between neurofeedback training performance and behavioural, as well as neurophysiological changes, as mentioned by Leins (2004). Leins (2004) suggested that this method could differentiate behavioural- cognitive changes due to successful learning and its related EEG changes from changes due to unspecific effects without changes in brain activity. This method was already recommended by Lubar (1997). He stated that if the participant cannot learn how to change the trained brain activity, the neocortical dynamics as well as the thalamocortical dynamics will not change. Thus, only a correlation of training performance, behavioural changes, and brain activity changes can show specific effects.

1.3 Objectives

The appropriate treatment of ADHD in children as well as in adults is still a matter of debate. In regards to the growing body of research and knowledge concerning neurophysiological impairments in ADHD, an orientation on physiological and neuro-

physiological models led to a new approach to alternative treatment modules. One of these neurophysiological oriented treatments is neurofeedback targeting the underlying neurophysiological variations in ADHD. Neurofeedback has been shown to be an effective treatment in children with ADHD. The impaired self-regulation abilities in ADHD suggest a beneficial effect of training the SCPs. So far, SCP feedback in children with ADHD led to symptom improvements as well as to related neurophysiological changes of the CNV. In regards to the need of treatment options for adult ADHD, these promising results led to the idea of investigating SCP feedback in adults with ADHD as a new treatment.

Hypotheses:

ADHD patients differ from healthy controls

1. It is hypothesised that, in comparison with healthy controls, adults with ADHD:

    a) show increased scores not only on ADHD related scales, but also on comorbid disorders like depression, anxiety, and borderline

    b) show a decreased performance in attention related processes such as an inferior outcome in measures of attention, slower reaction times, higher reaction time variability and increased omission and commission errors

    c) show a decreased CNV amplitude.

Treatment effects

2. It is hypothesised that, adults with ADHD will benefit from SCP feedback. And after thirty sessions of SCP feedback will show:

    a) decreased self-rated and third-party rated symptoms of ADHD

    b) reduced scores of secondary symptoms of depression and anxiety

    c) increased scores in intelligence and attention related tests, reduced reaction time, reduced reaction time variability, and omission as well as commission errors

    d) an increased CNV amplitude.

Self-regulation

3. It is hypothesised that, over four measurement points in the feedback, as well as the in the transfer condition

    a) the ability to shift the SCPs into negativation and positivation improves

    b) the differentiation between negativation and positivation increases and

    c) the duration of cued negativation and positivation during a trial prolongs.

Control for unspecific effects

4. It is hypothesised that, over five assessments with the FERT questionnaire the patients treatment expectations, the willingness of the patient to engage, and the judgement of professional competence of the therapist do not change significantly.

Correlations

5. Correlations are hypothesised between self-rated and third-party rated symptom reduction and CNV amplitude reduction with

    a) each other

    b) other outcome variables (comorbid symptoms and neuropsychological measures)

    c) training performance

    d) in regards to the influence of unspecific effects it is hypothesised that the patients treatment expectations, the willingness of the patient to engage, and the judgement of professional competence of the therapist do not correlate positively with behavioural and neurophysiological changes.

Methods

2

The study presented in this thesis was conducted at the Institute of Medical Psychology & Behavioural Neurobiology at the University of Tübingen. It was approved by the ethics committee of the University of Tübingen, and all participants signed informed consent. The ADHD group, as well as the group of healthy controls, were recruited through the University of Tübingen via announcements in the local newspaper and on notice boards in Tübingen.

2.1 Procedure

The general procedure will be described first. All detailed explanations about abbreviated questionnaires and methods follow in section 2.2.

ADHD group

The first step in the recruitment of the ADHD group was a short phone interview in which demographics and exclusion criteria like psychiatric or neurological disorders or ongoing psychotherapy where assessed (see appendix 1). After successful completion of the phone questionnaire a package was sent to the potential participant which included information about the study (see appendix 2), the letter of informed consen, and the questionnaires: ADHS-SB, WURS-K, BDI, STAI, EHI, and BSL. The package also included a pre-paid envelope to send the signed informed consent and the completed questionnaires back for review. When the participants fulfilled all inclusion criteria they where invited for the diagnostic interviews SCID and WRI and the concentration test d2-R. In case of a confirmed adult ADHD diagnosis the participant

received two third-party questionnaires (FEA and FEA-FFB) and moved on to the neurophysiological assessments.

The participants first took part in the NIRS assessment (explained in section 2.3) where the CFT-20-R was also conducted. The EEG assessment was conducted in a separate appointment. After completion of all pre-assessments (T1) the neurofeedback training began. As depicted in figure 2.1 after 15 sessions of SCP feedback, participants underwent the NIRS and the EEG assessments and filled in several questionnaires (ADHD-SB, BDI, STAI, BSL, FEA) as a halfway “T2" assessment. After a three week break in which the participants were asked to practice the neurofeedback techniques with a transfer-DVD and transfer cards at home, they came back for the last 15 sessions of neurofeedback.

In every fifth neurofeedback session a checklist about lifestyle changes and the FERT questionnaire were filled in. After completion of all 30 sessions of neurofeedback the NIRS and EEG assessments were repeated as well as the questionnaires (ADHD-SB, BDI, STAI, BSL, FEA), the WRI interview, the CFT-20-R and the d2-R attention test (post assessment = T3).

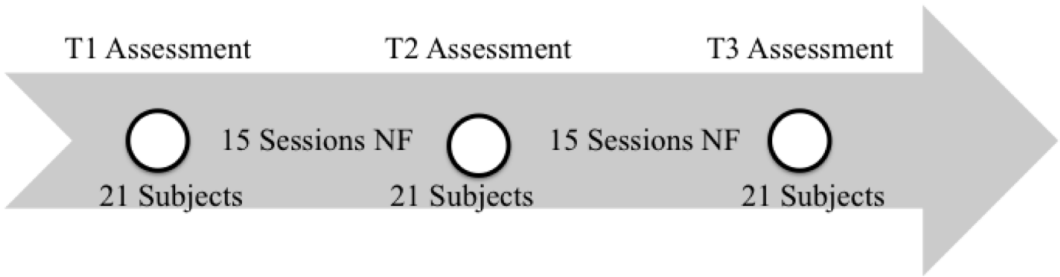

Figure 2.1: Study flow over all three measurement points (T1 = pre assessment (Time point 1), T2 = halfway assessment and T3 = post assessment), number of sessions and number of patients

Controls

The controls underwent only part of the diagnostic procedure, including the ADHD-SB, BDI, STAI, EHI, BSL, d2, CFT-20-R, demographic and medical history questionnaire, and the EEG and NIRS assessment. The controls were assessed at two time points but did not receive any treatment in between. The first measurement was performed

whenever they were recruited. The time between the first and the second measurement was dependent on the amount of time it took the matched patient to complete treatment (+/- two months).

2.2 Screening and diagnostics

Phone screening

The phone screening served as a first point of contact with the potential participants. Demographic information such as name, sex, age, handedness, years of education, and occupation was collected. The patients medical history was assessed for previous episodes of head injury with loss of consciousness, current medication and dosage history, other substances currently being taken, current conditions such as high blood pressure, epilepsy, head injury, psychiatric disorders, and other neurodegenerative disorders. The screening also excluded for pregnancy, current psychotherapy, and former participation in a neurofeedback training. A package with information material and questionnaires was send out to the participants if none of the exclusion criteria were met (the complete phone screening is attached in appendix 1).

Home questionnaires

The package of home questionnaires contained a letter, information material describing the complete study, informed consent, and eight questionnaires checking for ADHD symptoms as well as for the main comorbidities associated with ADHD.

Current ADHD

The "ADHS-Selbstbeurteilungsskala" (ADHD-SB) is a 22-item sub-scale self-rated questionnaire of the "Homburger ADHS-Skalen für Erwachsene" (HASE; (Rösler et al., 2008)). The self-report questionnaire assesses the participant's current symptoms, according to the 18 diagnostic criteria for ADHD listed in the DSM-IV and ICD-10-R, on a 0-3 Likert scale. A minimum of 18 points have to be met to fulfil ADHD criteria. Four additional questions ask about psychological strain, severity of problems, and duration of the problems. Retest-reliability was found between 0.78 and 0.89 and internal constancy between 0.70 and 0.90.

Childhood ADHD

The "Wender Utah Rating Scale - Kurzform" (WURS-K) is a 25-item sub-scale question-

naire of the HASE (Rösler et al., 2008). The questionnaire establishes a retrospective diagnosis of childhood ADHD symptoms for adult ADHD evaluation using a 0-4 Likert scale. A minimum score of 30 must be met to fulfil criteria for childhood ADHD. The total score excluded four of the items which check for reliability and must not add up to above 10.

Depression

The Becks-Depression-Inventory (BDI) is a self-rated questionnaire assessing symptoms of depression during the last two weeks (Hautzinger, Keller, & Kühner, 2006). The inventory consists of 21 items, each including four statements related to depression that are to be rated on a 0-3 Likert scale according to severity of each symptom. The items are simply added for scoring and the total score can range from 0 to 63. A score above 28 points (reflecting a severe depression) resulted in exclusion of the participant.

Borderline

The "Borderline Symptom List - Kurzform" (BSL) is a 23 item self-rated questionnaire used to assess the presence of Borderline Personality Disorder symptoms on a 0-4 Likert scale (Bohus et al., 2009). Participants with a score above 47 points were excluded from the study.

Anxiety

The State-Trait Anxiety Questionnaire (STAI) is a self-rated questionnaire with 20 items about temporary "state anxiety" (STAI-S) and 20 items about long-term "trait anxiety" (STAI-T) rated on a 0-4 Likert scale (Spielberger, Gorsuch, & Lushene, 1970). Each scale results in a total score that can range from 0 to 80. According to the manual, females with a score above 57 and males with a score above 54 on either scale were excluded from further participation.

Handedness

The Edinburgh Handedness Inventory (EHI) is a self-rated questionnaire that assesses right or left hand dominance for 10 activities (Oldfield, 1971). Handedness was not an exclusion criteria.

If none of the exclusion criteria (see table 2.1) had been met the participants were invited for the diagnostic interviews.

Table 2.1: Exclusion criteria

Instrument	Cut off value
ADHD-SB	> 18
WURS-K	> 30
BDI	< 28
BSL	< 47
STAI	> 57
IQ	> 80
Psychotherapy	not currently
Psychiatric disorder	none

Diagnostics and questionnaires

The interviews were conducted by an experienced psychologist in a pleasant setting. The session started with a short introduction and room for questions. Then the d2 Test of Attention was conducted, followed by two interviews.

d2 Test of Attention

The "Aufmerksamkeits-Belastungstest" (d2-R) is a 10-minute assessment in which participants cross out the target letter from a series of similar letters. It measures concentration, commission, and omission errors (Brickenkamp, Schmidt-Atzert, & Liepmann, 2010). The total number of items processed, minus errors, indicates combined speed and accuracy scores for attentional and inhibitory control (d2-KL value).

SCID-Interview

The Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) is a semi-structured interview for the assessment of major DSM-IV-TR Axis I diagnoses (Wittchen, Zaudig, & Fydrich, 1997). It was used to exclude for any major comorbidities like current depression, mania, bipolar disorder, psychosis, schizophrenia, substance abuse, anxiety or obsessive-compulsive disorder. Additionally, the borderline section from the SCID-II for DSM-IV-TR Axis II Disorders (Wittchen et al., 1997) was used to exclude patients with a borderline personality disorder.

ADHD-Interview

The "Wender-Reimherr Interview" (WRI) is a structured interview as a scale of the HASE (Rösler et al., 2008). The interview investigates 28 psychopathological characteristics associated with adult ADHD. Responses are rated by the interviewer on a

0-2 Likert scale for each question as well as on a 0-4 Likert scale for severity of each symptom. Seven symptoms were assessed with five to ten questions per symptom. Criteria for the core symptoms of inattention and hyperactivity have to be fulfilled as well as at least two other symptoms out of hot temper, affective lability, emotional reactivity, disorganisation, and impulsivity.

Third-Party ADHD questionnaire

The “Fragebogen zur Erfassung von ADHS im Erwachsenenalter, frühere Probleme - Fremdbeurteilung” (FEA-FFB) is a third-party questionnaire designed to evaluate childhood ADHD related problems and symptoms for adult patients, completed by a parent or family member (Döpfner, Lehmkuhl, & Steinhausen, 2006).

The “Fragebogen zur Erfassung von ADHS im Erwachsenenalter, aktuelle Probleme - Fremdbeurteilung" (FEA) is a third-party questionnaire designed to evaluate current ADHD related problems and symptoms for adult patients, completed by a spouse, family member, employer or a close friend (Döpfner et al., 2006).

Both third-party questionnaires included 20 items about 18 symptom criteria and five additional items about clinical relevance of the symptoms, all items were rated on a 0-3 Likert scale. Investigations of reliability and validity for both questionnaires are still under testing. Official norms and cut-off scores are not yet available. For interpretation, a specific value can be calculated by dividing the sum of all 20 items by 20. A value from 0.5 - 1.0 indicates a small symptom severity, a value from 1.0 - 1.5 medium symptom severity and a value above 1.5 severe symptoms. These two third-party questionnaires were handed to the participant after the interviews with the instruction to get them filled in by a family member or a close friend.

Questionnaire about unspecific effects

The “Fragebogen zur Erfassung relevanter Therapiebedingungen” (FERT) is a 31-item self-rated questionnaire to assess relevant treatment conditions, patient expectations, and patient-therapist interactions (Vollmann et al., 2009) (see attachment 3) . The FERT assesses six factors of unspecific effects on a 7-point Likert scale. The factors are: patients treatment expectations, goodness of fit between patient and therapist, therapeutic relationship, professional competence of the therapist, persuasiveness of the therapist, and willingness of the patient to engage in the therapy. Not all of the

factors were suitable for neurofeedback treatment. Thus, only the factors patients treatment expectations, professional competence of the therapist, and willingness of the patient to engage in the therapy were used for analysis. The patients filled in the FERT every fifth neurofeedback session i.e. in session 5, 10, 15, 20, 25, and 30.

Intelligence test

The Culture Fair Test-20 Revised (CFT-20-R) is a nonverbal intelligence test in which logical problems (continuation of a matrix, classification, similarities, and topological reasoning) need to be solved (Weiss, 2008). An IQ below 80 resulted in exclusion from the study. The test was conducted after the NIRS measurement for the ADHD group and at the start of the psychometric testing for the control group as it was a matching criterion.[1]

2.3 Neurophysiological measurements

EEG Recording

EEG data was recorded using 22 EEG channels positioned according to the international 10-20 system with the NeXus-32 (Mind Media B.V. with Biotrace$^+$ Software). The NeXus-32 is a DC amplifier, in which EEG is sampled at 500 Hz with a range of 263 μV and a bandwidth of DC to 70 Hz. EEG activity was recorded using the NeXus EEG electrode cap with sintered electrodes referenced to common average at electrode sites Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, Oz, O2 (International 10/20-System; Jasper (1958)). Eye movements were recorded with two horizontal pre-gelled Ag/AgCl electrodes attached to the outer canthus of the right and left eye and two vertical electrodes attached above and below the middle of the left eye. Impedance levels for all electrodes were below 5 kΩ. Data were stored for offline analysis.

Participants were seated in a reclined chair during the measurement. The EEG measurement included the following tasks in that order: alternating eyes open/eyes closed for 1 min each for a total of 8 min, eyes closed (15 min), eyes open (5 min) resting state,

[1] One patient in this study was 66 years old. As the CFT-20-R is only normed for the age group up to 60 years this patient and his matched control were rated by the norms for the oldest age group.

active auditory P300 oddball, P300 auditory oddball, and active auditory CNV. The instructions for each task were played back to the participant via two loud speakers at 90 dB. The sound pressure level of all tones in all paradigms was also 90 dB and the speakers stood in a distance of 1 m from the participant and with a 0.5 m horizontal distance from each other.

Additionally, physiological measures for heart rate, skin conductance, temperature, and breathing were also recorded during the EEG assessment. The resting state and physiological data are reported in Wyckoff (in preparation), and the P300 data in Mayer (in preparation). The ERP-tasks were presented in the order they are described with a short break between each task.

Auditory Contingent Negative Variation (CNV)

The CNV task was an active, auditory, eyes-closed task. A warning stimulus S1 (500 Hz, 50 ms) was followed by a stimulus S2, which was either a No-Go low tone (1000 Hz, 50 ms, N = 150) or a Go high tone (2000 Hz, 50 ms, N = 50). The subjects where instructed press the space bar as quick as possible after the Go-tone with their dominate hand. The time between S1 and S2 was 1850 ms and the time between S2 and S1 varied randomly between 2000 and 2400 ms. The task lasted for 13 min (see figure 2.2).

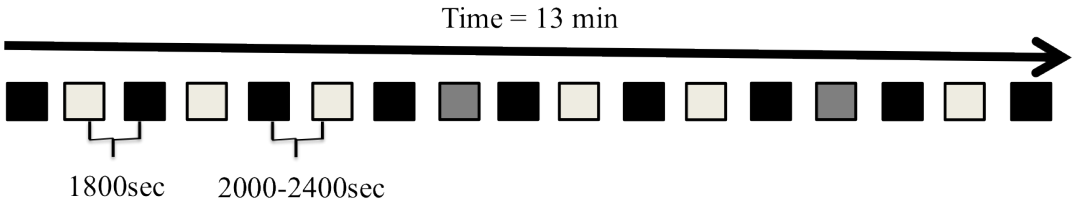

Figure 2.2: CNV experimental design. Black squares represent the warning stimulus, the white the No-Go stimulus and the gray the Go stimulus

NIRS

The data used for this thesis are part of a larger project which also included a NIRS assessment of all participants. During this assessment a 10 min working memory task (n-back task) and an 8 min response inhibition task (Go-NoGo task) was conducted. After the NIRS assessment the CFT-20-R was conducted.

2.4 SCP-Feedback Sessions

SCP feedback was conducted with the THERAPRAX® (neuroConn GmbH, Germany). The training protocol was developed by researchers in the laboritory at the Institute of Medical Psychology & Behavioural Neurobiology Tübingen and has been used for many years in a variety of studies (e.g. Kotchoubey, Strehl, Holzapfel, Schneider, et al., 1999; Strehl, 2009).

SCPs were recorded at Cz, referenced against the right mastoid A1 with a ground electrode on the left mastoid A2. Eye movements were recorded with two horizontal electrodes attached to the outer canthus of the left and right eye and two vertical electrodes attached above and below the middle of the left eye. Ag/AgCl ring electrodes were used on all sites (see figure 2.3 for the electrode set-up).

The system performed an online artefact correction for eye movements during the training. Before each training session the system performed a calibration of eye movements which was used to recalculate the EEG signal. This way the contamination of the EEG signal from eye movement artefacts was minimised.

Additionally, an online artefact detection was performed by the system. It detected all signal changes above 200 μV due to movements of the patient or the cables. In case of an artefact the trial was aborted and repeated. Participants were trained one

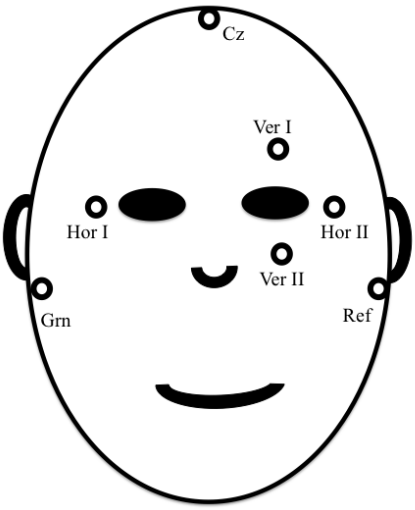

Figure 2.3: Neurofeedback electrode setup. Grn = Ground, Hor = horizontal, Ref = reference, Ver = vertical

to five times per week for a total of 30 sessions. Each session lasted approximately one hour, including preparation time. Each SCP feedback session consisted of four blocks of 40 trials. Each trial lasted for twelve seconds and consisted of three phases: a baseline phase (seconds 0-2), an active phase (seconds 2-10) and a reinforcement phase (seconds 10-12) (see figure 2.4. The two seconds baseline data were set to zero before each active phase. At the end of the baseline phase, participants were cued by a triangle directed to the top of the screen to “activate” their brain (regulate a negative SCP-shift) or by a triangle directed to the bottom of the screen to “deactivate” their brain (regulate a positive SCP-shift).

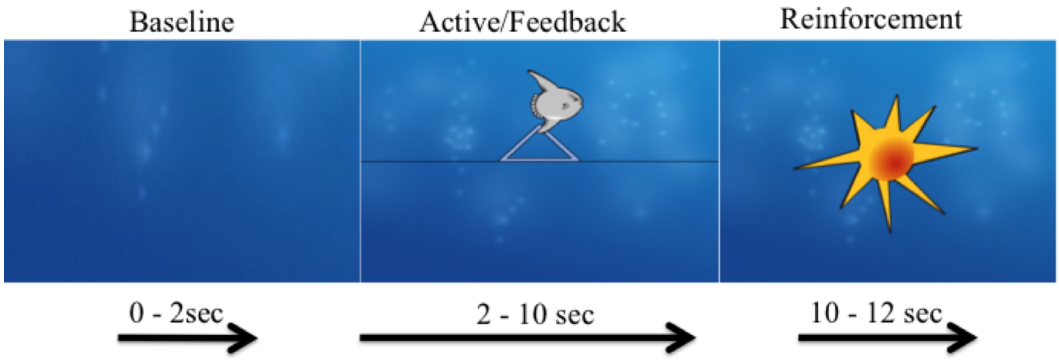

Figure 2.4: SCP feedback phases

Trials, which required activation and deactivation, were randomly distributed with a 50/50 rate. In the active phase an object moved from left to right across the screen and provided the patient with feedback of their brain activity by moving up or down (up indicating activation and down indicating deactivation). In the reward phase participants received a visual reward if they directed their brain activity in the cued direction for at least two seconds during the second half of the trial. If they could not perform in the cued direction the screen remained empty. Forty trials constituted a “block" and a session contained four blocks. Thirty sessions were hold, usually 2-3 per week. See figure 2.5 for an overview of trial, block and session.

To generalise newly acquired regulation skills to everyday life situations, the third block served as “transfer block” in which no visual feedback was presented during the active training phase. The level of success was indicated with a visual reward only.

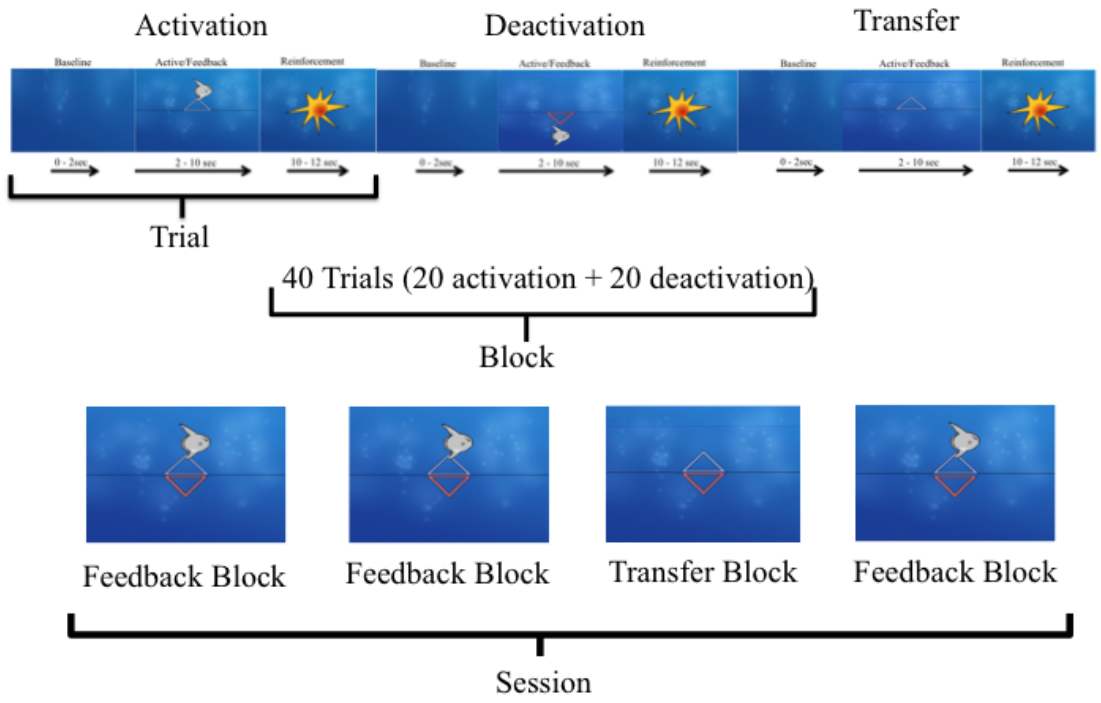

Figure 2.5: Overview of trial, block and session

Participants were also instructed to use their self-regulation in everyday life situations (e.g. to activate before a meeting or reading a text or to deactivate when they wanted to relax). After the first 15 SCP feedback sessions the T2 measurements were conducted. The participants then had a three week break from training. This was done to give the participant a break from the training and also to allow time for the training to come to effect. Participants were asked to practice the feedback techniques two-three times per week for 8 min. To aid practice they received a DVD with a replay of the transfer task without the visual reward during the reinforcement phase. They also received a training card with a picture of the active phase in a transfer task. Participants were instructed to use the card as an aid to “activate” or “deactivate" whenever they felt the need. The patients returned after the three weeks break,for the remaining 15 sessions of neurofeedback and the following T3 assessment.

2.5 Control group

The control group was used to investigate in neuropsychological and physiological differences between adults with ADHD and healthy controls. Also, the control group was measured twice to control for repetition or time effects on all outcome variables.

Matching

The healthy controls were matched in age, gender, and IQ to the ADHD group. The matching for age was +/- 1 year for the 18-35 year old participants and +/- 3 years for the 36-66 year old participants. This decision was based on the assumption that the brain of an adult does not go through major changes in late adulthood. The controls were matched for IQ minus one standard deviation and plus 1.5 standard deviations from the score of the matching ADHD participant. This decision was based on the fact that the ADHD participants did the CFT-20-R after the one hour NIRS assessment and the controls did the CFT-20-R as their first measurement. Therefore, the controls were expected to be less tired and have more concentration.

Procedure

After reading the information material (see attachment 4) and signing the informed consent, the controls underwent only part of the diagnostic procedure. The CFT-20-R had to be the first test for the controls as it determined if the control participant would be a match for the ADHD participant. While the experimenter analysed the CFT-20-R the participant filled in the ADHD-SB and BDI.

If the IQ was not a match the participant was excluded from any further measurements. If the IQ was a match and the ADHD-SB and BDI fulfilled criteria (score below 18 and 28 points respectively) the participant underwent the d2-R and filled in the STAI, EHI, and BSL. Some of the participants continued with the EEG-assessment on the same day and underwent the NIRS assessment on a separate day, while others scheduled a separate appointment for the EEG and the NIRS assessments. All controls came back for their second assessment depending on the time the matched ADHD patient needed to compete the therapy +/- 2 months. The second assessment was an exact replicate of the first one.

The controls got compensated for their participation. They received 5 Euro after the IQ test if they were not a match. The included controls received 20 Euro after all

T1 measurements and an additional 45 Euro after they completed all measurements for the second assessment. One control did not return for the second assessment.

2.6 Analysis

2.6.1 Outcome variables

2.6.1.1 Behavioural

The behavioural outcome variables were the questionnaire data: ADHD-SB, BDI, STAI, BSL, and FEA-AFB (the last only for the ADHD group) as well as the paper-pencil tests d2-R and CFT-20-R. For further analysis, and to make the ADHD-SB and the FEA more comparable, the outcome value was calculated by dividing the sum of all items by 18 for the ADHD-SB. The d2-R attention test, RT, RTV, omission, and commission errors from the CNV task served as behavioural neuropsychological outcome variables.

2.6.1.2 Electrophysiological

EEG data was analysed with the software program Brain Vision Analyzer (Brain Products, Munich, Germany). The data was down sampled to 256 Hz, re-referenced to the mastoids and and a 24 dB/octave Butterworth filter was applied from 0.05 Hz to 30 Hz and 50 Hz notch filter was also applied. The EEG data was segmented for the Go-trials 700 ms prior S1 until 3000 ms after S1. The baseline correction was performed 700 ms prior to S1. The criteria for the artefact rejection for single segments were: maximum allowed voltage step 50 μV, maximum allowed absolute difference of two values in the segment were 300 μV, maximum and minimum allowed amplitude was between (-100) and 100 μV, the lowest allowed activity (Max - Min) was 0.5 μV, and the interval length was 100 ms. The CNV mean amplitude was calculated 1000 - 1800 ms post S1. All ERPs were analysed for the electrode sites F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4.

2.6.1.3 Training data

The training data were analysed at four time points: beginning, half-way, after three week break, and final. The average of sessions 2 and 3 served as a beginning assessment without training experience. The average of sessions 13 and 14 served as a

half-way measurement, the average of sessions 16 and 17 as a measurement after the three week break, and the average of sessions 28 and 29 served as the final assessment of training performance. In the case of noted technical artefacts in the patient log, like sweat artefact, calibration problems or equipment based artefacts the next closest session was selected, but never session 1 or 30 due to habituation and possible increased expectational effects. When certain block averages were contaminated with drifts, the block was exchanged by the same block from the next closest session. Two independent raters went through this procedure and picked the blocks that were included in analysis.

Each time point was calculated by the mean positivation and mean negativation of block 1, 2 and 4 from sessions 2+3, 13+14, 16+17, and 28+29 (or equivalent) for the feedback condition, as well as block 3 from each session for the transfer condition. The “Eldith Analyzer" software built in the THERAPRAX® analysed the time interval from second 5 to second 10 during each trial. A value above 200 μV was excluded as an artefact and a low-pass filter of 5 Hz was applied. The remaining trails were averaged for each block by the software.

The final nine outcome variables constituted: of mean amplitude of negativation (neg) and positivation (pos), differentiation score between mean amplitude of negativation, and positivation (pos minus neg) (diff). Further, the time the cued negativation was less positive than the cued positivation was calculated (dur). All variables, except the transfer coefficient, were calculated separately for the feedback (FB) and transfer (TR) condition.

The transfer coefficient score (Coeff) was calculated by the ratio of TRdiff to FBdiff which constitutes a measure of how well the SCP differentiation achieved during the feedback trials was generalised to the transfer condition. To account for reverse differentiation (pos < neg) expressed in negative values, the constant of 100 was added to the individual differentiation values. A value above 1 indicates a bigger differentiation for TR than FB. See figure 2.6 for an overview of the nine resulting training outcome variables and their abbreviations.

Variable	Feedback	Transfer
Amplitude:		
Positivation	FBpos	TRpos
Negativation	FBneg	TRneg
Differentiation	FBdiff	TRdiff
Duration	FBdur	TRdur
Coefficient	Coeff	

Figure 2.6: Overview of the abbreviations of the analysed training variables

2.6.1.4 Change scores

Change scores were calculated for most of the described variables. The used formula depended on the expected direction of change to receive a positive value indicating the hypothesised change. For all questionnaires, reaction times, errors, and CNV amplitude a reduction in the score was expected from T1 to T3. Therefore, the change score was calculated by subtracting the T1 measurement value from the T3 measurement value. For IQ, d2, and all training variables an increase score was expected and therefore T1 was subtracted from T3 to obtain the change score.

2.6.1.5 Missing data

For different reasons not all data were collected completely. Some of the missing values were analysed with the “Missing value analysis" of IBM SPSS 20. The EM method estimates the means, the covariance matrix, and the correlation of quantitative variables with missing values (Wirtz, 2004). The missing values were only imputed if the Little MCRA Chi-square test was not significant and therefore it can be assumed that data are “missing completely at random - MCAR". The data was not imputed if the test was significant. Following data were missing:

Patient group

The T1 EEG data for one patient that were saved in a corrupted file. Data for one patient that did not hand in the T1 FEA questionnaire, as well as data to eight other patients who did not hand in the T2 or T3 FEA questionnaire. For one patient some T2 questionnaires went missing (BDI, BSL and STAI). The T3 CFT-R-20 went missing for

one patient. Only the questionnaire and the CFT-20-R data were imputed.

Control group

One control did not come back for the second measurement. His data was only used for the baseline analysis.

2.6.2 Statistical Analysis

Statistical analysis was performed with the software IBM SPSS statistics version 20. All data was tested for normal distribution. If not stated otherwise the data was normally distributed.

The effect size was calculated depending on the analysis used. Cohens *d* was calculated for significant results as well as trends for *t* tests with (M1-M2)/((SD1+SD2)/2). A small effect was interpreted for a Cohens *d* value around 0.2, a medium effect size around 0.5 and a large effect size around 0.8.

For the *ANOVA* partial eta square is reported ($\eta 2$). Partial eta^2 its classified by $\eta 2 > .001$ as a small effect, $\eta 2 > .06$ a medium effect and $\eta 2 > .14$ a large effect. For the non-parametic test Mann-Whitney *U* test for independent samples *r* was computed by $r = Z/\sqrt[2]{n}$ and with similar effect strength ranges as Cohens *d*.

Finally, for the non parametric Friedman *ANOVA* Kendall's coefficient of concordance (Kendall's *W*) was used. Kendall's *W* ranges from 0 to 1 whereas higher values indicate a stronger relationship. For the results of all *ANOVA*s the Greenhouse Geisser corrected values are used.

2.6.2.1 Behavioural data

For baseline comparison independent *t* tests were calculated for ADHD total score, BDI, STAI trait and state, and BSL. To rule out measurement repetition effects a repeated measures ANOVA was performed with the within-subject factor TIME (pre vs.post) and between-subject factor GROUP (ADHD vs. control) for the variables ADHD total score BDI, STAI trait and state, and BSL.

Separate repeated measures *ANOVA*s were performed with the within-subject factor TIME (pre, midway, post) for the patient data for the variables ADHD score (total, attention, hyperactivity and inattention), FEA (total, attention, hyperactivity, and inat-

tention), BDI, STAI trait and state, and BSL. Post-hoc dependent *t* tests were calculated for all significant results and trends to compare each of the three measurement points.

For all symptom scales of the WRI interview a repeated measures ANOVA was performed with the within-subject factor TIME (pre, post).

2.6.2.2 Neuropsychological data

For baseline comparison independent *t* tests were calculated for RT, RTV, omission and commission errors, and d2-R attention test. A repeated measures *ANOVA*was performed with the within-subject factor TIME (pre vs post) and between-subject factor GROUP (ADHD vs. control) for the variables, RT, RTV, omission and commission errors, d2-R attention test, and CFT-R-20. A repeated measures *ANOVA* was performed with the within-subject factor TIME (pre, midway, post) for the patient group for the same variables.

Post-hoc dependent *t* tests were calculated for all significant results and trends to compare each of the three measurement points.

2.6.2.3 Neurophysiological data

The ERP amplitude data was not normally distributed therefore the non parametric Mann-Whitney *U* test was performed for baseline comparison for the CNV mean amplitude at F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 and electrode groups frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), right (F4, C4, P4), midline (Fz, Cz, Pz), and left (F3, C3, P3).

The data was not normally distributed for all electrode positions. However, there is no non-parametric test to compare two groups over two time points and therefore a repeated measure *ANOVA* with the within-subject factor TIME (pre vs post) and between-subject factor GROUP (control vs. patient) was calculated for the CNV mean amplitude at F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 and electrode groups frontal, central, parietal, right, midline, and left.

A repeated measures *ANOVA* was performed with the within-subject factor TIME (pre, midway, post) for the patient group for the same variables. Post-hoc dependent *t*

tests were calculated for all significant results and trends to compare each of the three measurement points.

2.6.2.4 Training data

The data was not normally distributed therefore the non parametric Friedman's *ANOVA* was performed for the ADHD group for the variables FBpos, FBneg, FBdiff, FBdur, TRpos, TRneg, TRdiff, TRdur, FBcoeff, and TRcoeff (see figure 2.6). For post hoc testing the Wilcoxon signed-rank test was used to explore differences between all four time points. This was done even if the Friedman's ANOVA was not significant because changes between all training phase were of interest.

2.6.2.5 FERT

A repeated measures *ANOVA* was performed with the within-subject factor TIME (6 steps) for the patient data for the variables patients treatment expectations, professional competence of the therapist, and willingness of the patient to engage in the therapy. Post-hoc dependent t tests were calculated for all significant results and trends to compare each of the six measurement points.

2.6.2.6 Correlation and regression

Correlations were calculated with the outcome variables self-rated ADHD symptom change, third-party rated ADHD symptom change and mean CNV amplitude change and all treatment variables and their change scores as well as the change scores of IQ, d2-R, RT, omission and commission errors, and the FERT variables (mean score over all six measurement points and change score). For normally distributed data the pearson correlation (r) was performed and for not normally distributed data the spearman correlation (r_s). All tests were 2-tailed. All predictors with correlations higher than r or $r_s = .3$ were entered into a stepwise regression analysis (Strehl, Kotchoubey, Trevorrow, & Birbaumer, 2005).

Results 3

3.1 Descriptive data

Participants

The demographic data from all participants are presented in table 3.1. The sample included four unemployed people, ten students, one young mother, and six people in various jobs. In terms of highest education, a 10-year school degree was attained by two participants, six had their “Abitur", eight a master or diploma, one a PhD, and four a finished training-ship. As described in the methods, the controls were matched in age, gender, and IQ (see table 3.1). The average time between measurements was 26.67 weeks (*SD* = 7.45, *Min/Max* = 16-43). One of the control participants did not return for the second measurement for personal reasons.

Table 3.1: Descriptive data patients

	ADHD group		**Control group**	
	Mean	Min-Max	Mean	Min-Max
Sample size	21 (8 female)		21 (8 female)	
Age	35.61 (12.19)	22-66	36 (12.21)	22-65
Handedness	62.50 (51.28)	-64.71-100	61.79 (60.97)	-100-100
IQ	109.76 (13.43)	80-127	112.86 (8.53)	95-130

Note: Standard deviation in brackets

Diagnostic criteria

None of the participants were diagnosed with any current disorder assessed with the

SCID-I. An overview of baseline diagnostics is displayed in table 3.3. According to the HASE interview, six participants were categorised as primarily inattentive, 15 as combined type, and none as primarily hyperactive. Eight patients had a previous ADHD diagnose and five of those received medication. Two participants reported

Table 3.2: ADHD diagnostics

Table 3.3: Descriptive data patients

	Method	**Cut-off**	**M**	**SD**	**Min**	**Max**
Childhood symptoms	WURS-K	≥30	34.43	10.32	21	65
	FEA FFB	n.a.	25. 47	10.34	3	37
Current symptoms	WRI all	≥21	37.86	6.52	27	52
	ADHD-SB	≥18	29.10	5.96	18	43
	FEA	n.a.	1.34	0.49	0.5	2.3

Note: WURS-K = Wender Utah Rating Scale - Kurzform (Self-rated symptoms during childhood), FEA FFB = Fragebogen zur Erfassung von ADHS im Erwachsenenalter, früḧere Probleme - Fremdbeurteilung (Third party questionnaire about symptoms during childhood), WRI all = Wender-Reimherr Interview (ADHD symptom interview), ADHD-SB = ADHS-Selbstbeurteilungsskala (ADHD self-assessment scale), FEA = Fragebogen zur Erfassung von ADHS im Erwachsenenalter, aktuelle Probleme - Fremdbeurteilung (Third party questionnaire about current symptoms). Cut-off: Inclusion criteria. n.a.: no defined cut-off scores available yet.

drinking alcohol regularly, but no addiction could be diagnosed. Further, two patients reported using cannabis on a regular basis. They were asked not to consume any cannabis twelve hours before each session.

All 21 participants completed the entire study. There were no dropouts. Some participants took longer breaks within the training due to personal reasons (long university related breaks, moving houses, or heavy work load).

3.2 Baseline comparison

Behavioural questionnaire data

The independent t test for behavioural questionnaire data revealed significant group difference for ADHD symptoms ($t(40) = 14.271, p < .001, d = 2.78$), Symptoms of depression ($t(40) = 5.312, p < .001; d = 1.04$), state anxiety ($t(40) = 5.715, p < .001, d = 1.17$), trait anxiety ($t(40) = 7.221, p < .001, d = 1.76$) and borderline symptoms ($t(40) =$

$5.283, p < .001, d = 1.12$). Mean, standard deviation and maximum/minimum are depicted in table 3.6.

Table 3.4: Descriptive data

	ADHD group ($N = 21$)		**Control group** ($N = 21$)	
	Mean	Min-Max	Mean	Min-Max
ADHD-SB	29.09 (5.97)	18-43	4.33 (5.27)	0-18
BDI	12.33 (7.24)	0-27	3 (3.51)	0-13
STAI-S	44.95 (8.66)	28-66	32.33 (5.28)	26-45
STAI-T	48.67 (4.48)	33-63	32.86 (6.69)	23-49
BSL	19.38 (12.72)	3-50	3.61 (4.99)	0-23

Note: Standard deviation in brackets. ADHD SB = ADHS-Selbstbeurteilungsskala (ADHD self-assessment scale), BDI = Becks Depression Inventory, STAI-S = State Trait Anxiety Inventory-State, STAI-T = State Trait Anxiety Inventory-Trait, BSL = Borderline Symptom List

Behavioural neuropsychological data

The independent *t* test for behavioural neuropsychological data revealed significant group difference for slower RT in the ADHD group ($M = 491.62$, $SD = 189.33$) compared to the control group ($M = 356.64$, $SD = 91.78$; $t(39) = 2.927, p < .000, d = 0.65$). Further, the RTV expressed though the individual SD of each participant was significantly higher for the ADHD group ($M = 157.52$, $SD = 99.53$) compared to the control group ($M = 97.41$, $SD = 64.19$; $t(39) = 2.31, p < .05, d = 0.52$). The amount of omission and commission errors did not differ significantly, but showed a trend towards an increased error rate in the ADHD group (See table 3.5).

Contrary to the hypothesis there was no difference in attention measured with the d2-R (ADHD: $M = 103.95$, $SD = 2.55$; Controls: $M = 104.57$, $SD = 1.831$; $t(40) = 0.845, n.s., d = -0.12$).

Baseline differences in ERPs

The data was not normally distributed for all electrode positions. Therefore the nonparametric test Mann-Whitney U test for independent samples was performed. With the exception of two electrode positions, the CNV amplitude was reduced for

Table 3.5: Omission and commission errors for the patient and control group

	ADHD *n = 20*	**Controls** *N = 21*	*df*	*t*	*p*	d
Omission	1.4 (1.9)	1.1 (1.5)	39	0.67	*n.s.*	0.06
Commission	1.4 (1.8)	1.0 (1.5)	39	0.77	*n.s.*	0.08

Note: Standard deviation in brackets, n.s. = not significant

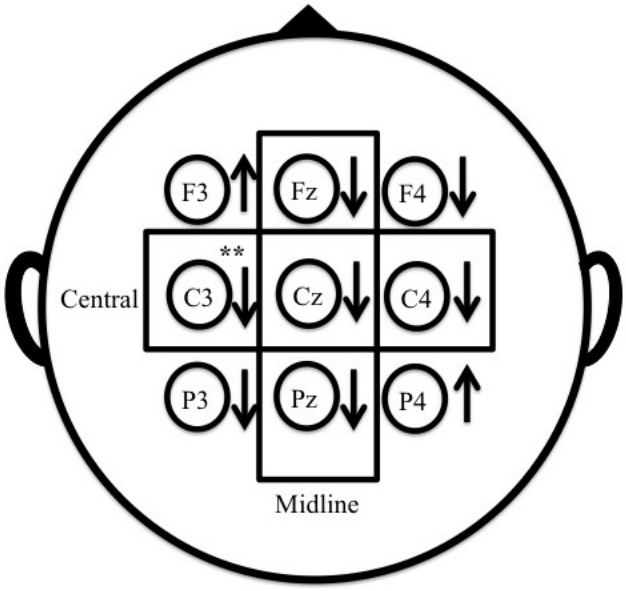

Figure 3.1: Overview of CNV reductions for each electrode and electrode group. An arrow pointing down indicates a reduced CNV amplitude in the ADHD group compared to the control group. An arrow pointing up an increased CNV amplitude in the ADHD group compared to the control group.

the ADHD group. As presented in figure 3.1, the Mann-Whitney U test for independent samples revealed smaller CNV amplitudes for the electrode position C3 for the ADHD group (M= 0.58, SD= 4.21) compared to the control group (M= -1.59, SD= 2.48; $U = 107, Z = -2.686, p < .01, r = -.42$) and a trend for Fz for the ADHD group (M= -0.59, SD= 3.21) compared to the control group (M= -2.23, SD= 2.83; $U = 141, Z = -1.80, p = .072, r = -.28$), the central electrode group ($U = 139, Z = -1,85, p = .064, r = -.29$), and the midline electrode group ($U = 141, Z = -1.80, p = .072, r = -.28$). Figure 3.2 depicts the CNV for both groups on electrode position C3.

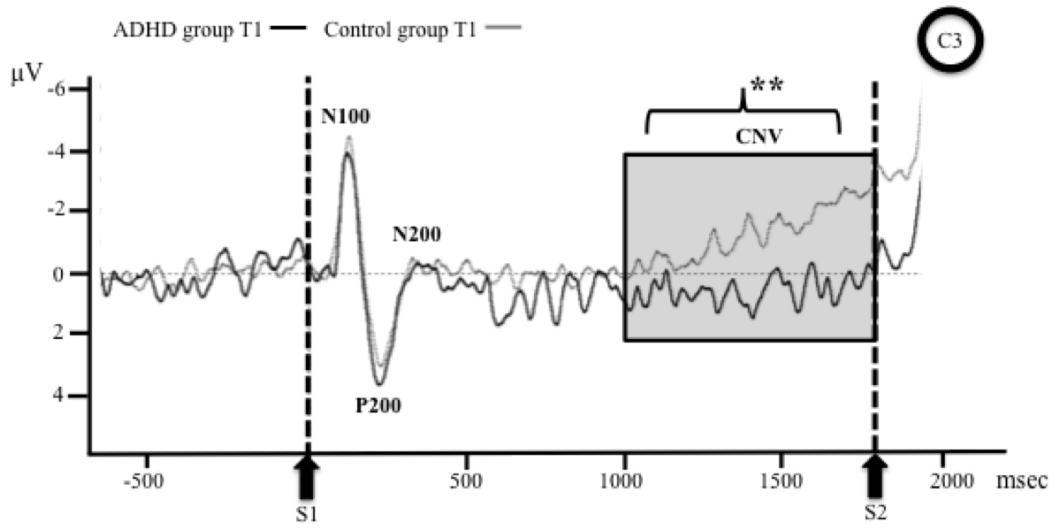

Figure 3.2: Baseline comparison of brain wave reaction to the warning stimulus at C3 for ADHD and control group. Early components and CNV are labeled. S1 = warning stimulus, S2 = Go stimulus. ** indicates a significant difference on the $p < .01$ level.

3.3 Training effects

3.3.1 Behaviour

A repeated measures between-subjects ANOVA over two measurement points with the factor TIME showed significant decreases for all symptoms. Further, to rule out any time effects, the factor GROUP x TIME showed significant reductions of all symptoms in the ADHD group only (see table 3.6).

Table 3.6: Behavioural changes for the patient and control group

	ADHD group ($N = 21$)		Control group ($n = 20$)		ANOVA	
	Pre	Post	Pre	Post	F	η2
ADHD-SB	29.10 (5.96)	21.48 (7.01)	4.55 (5.31)	3.90 (4.98)	11.98**	.24
BDI	12.33 (7.25)	6.10 (4.99)	2.80 (3.47)	2.85 (3.48)	18.23***	.32
STAI-T	48.67 (7.48)	41.00 (8.51)	32.20 (6.13)	32.00 (7.33)	5.14*	.12
STAI-S	44.95 (8.66)	39.05 (9.04)	32.00 (5.13)	32.10 (6.43)	14.39**	.27
BSL	19.38 (12.73)	7.67 (4.89)	2.65 (2.35)	2.55 (3.65)	15.58***	.29

*Note: Repeated measures ANOVA with the factor TIME x Group. One drop-out in the control group. * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$*

ADHD scores

ADHD symptoms of five patients remitted. The repeated measures within-subjects ANOVA over three measurement points showed a significant decrease of symptoms in the ADHD-SB overall score for the factor TIME ($F(1.7, 34.31) = 12.17, p < .000, \eta 2 = .38$). Also, a significant decrease was observed for all individual symptom scales of inattention ($F(1.8, 36.8) = 8.97, p < .001, \eta 2 = .31$), hyperactivity ($F(1.9, 38.2) = 6.12, p < .01, \eta 2 = .23$), and impulsivity ($F(1.9, 38.5) = 8.68, p < .001, \eta 2 = .30$). See figure 3.3 for individual values. Further, a significant decrease for the third-party assessment FEA overall score ($F(1.4, 28.5) = 5.28, p < .05, \eta 2 = .21$), as well as all individual symptom scales of inattention ($F(1.8, 37.2) = 9.482, p < .001, \eta 2 = .32$), hyperactivity ($F(1.7, 33.9) = 8.69, p < .005, \eta 2 = .30$) and impulsivity ($F(1.9, 38.5) = 3.95, p < .05, \eta 2 = .17$) was observed. See figures 3.3 and 3.4 for individual values. The scale assessing suffering from the symptoms decreased significantly from the FEA T1 ($M = 6.28$, $SD = 3.19$) to T2 ($M = 6.22$, $SD = 3.34$) and T3 ($M = 4.91$, $SD = 2.93$; $F(1.9, 38.5) = 4.03, p < .05, \eta 2 = .11$) but not the ADHD-SB T1 ($M = 4.24$, $SD = 1.58$) to T2 ($M = 3.29$, $SD = 1.42$) and T3 ($M = 3.52$, $SD = 2.11$; $F(1.7, 34.2) = 2.34, p = .059, \eta 2 = .17$).

Additionally, significant decreases were obtained for comorbid symptoms of depression ($F(1.8, 38.5) = 14.169, p < .001, \eta 2 = .42$), state anxiety ($F(1.8, 38.5) = 4.639, p < .05, \eta 2 = .19$), trait anxiety ($F(1.7, 38.5) = 14.77, p < .001, \eta 2 = .43$) and borderline ($F(1.5, 38.5) = 14.56, p < .001, \eta 2 = .42$). See figure 3.5 for individual values.

Post-hoc dependent t tests revealed significant differences at different time points. Paired comparison of T1 with T3 yielded significantly decreased scores for all ADHD-SB self-assessed symptoms overall ($t(20) = 4.38, p < .001, d = 1.18$), for inattention ($t(20) = 3.72, p < .001, d = 0.83$), hyperactivity ($t(20) = 3.41, p < .001, d = .95$), and impulsivity ($t(20) = 3.94, p < .001, d = 0.79$), for FEA inattention ($t(20) = 3.94, p < .001, d = 0.55$) and comorbid symptoms of borderline ($t(20) = 4.22, p < .000, d = 1.33$), trait anxiety ($t(20) = 4.77, p < .001, d = 0.96$) and depression ($t(20) = 4.83, p < .001, d = 0.67$). Paired comparison of T1 with T2 showed significant reductions for FEA hyperactivity ($t(20) = 4.28, p < .001, d = 0.75$), ADHD-SB overall ($t(20) = 3.34, p < .001, d = 0.72$), as well as borderline ($t(20) = 4.04, p < .001, d = 0.77$), trait anxiety ($t(20) = 3.19, p <$

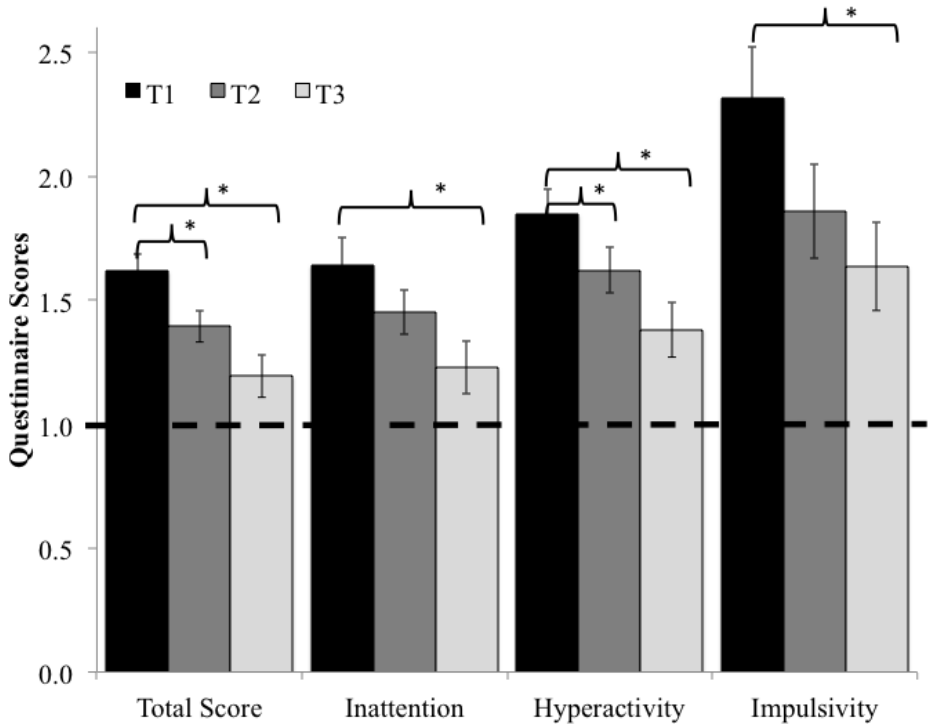

Figure 3.3: Self-rated ADHD symptoms (ADHD-SB), The dashed line represents the cut off of 18 (converted for better comparison (sum of all 18 items divided by 18) * indicates significant *t* tests $p < .000$

$.001, d = 0.62$), and depression ($t(20) = 3.44, p < .001, d = 1.02$). Only the FEA overall rating significantly decreased from T2 to T3 ($t(20) = 3.66, p < .002, d = .32$).

Only the results that were significant after Bonferroni correction of p-values ($p < .05/14$) are presented. Before Bonferroni correction of p-values all but the T2 to T3 comparisons reached significance for most values. See full table of t- and p-values in attachment 5.

ADHD scores interview

In a repeated measures within-subjects ANOVA over two time points the overall score of the WRI interview decreased in TIME (pre, post) on the symptom rating scale ($F(1,20) = 17.730, p < .001$) and the global assessment of severity of symptoms ($F(1,20) = 14.116, p < .001$). The decrease for individual symptoms is shown in table 3.7.

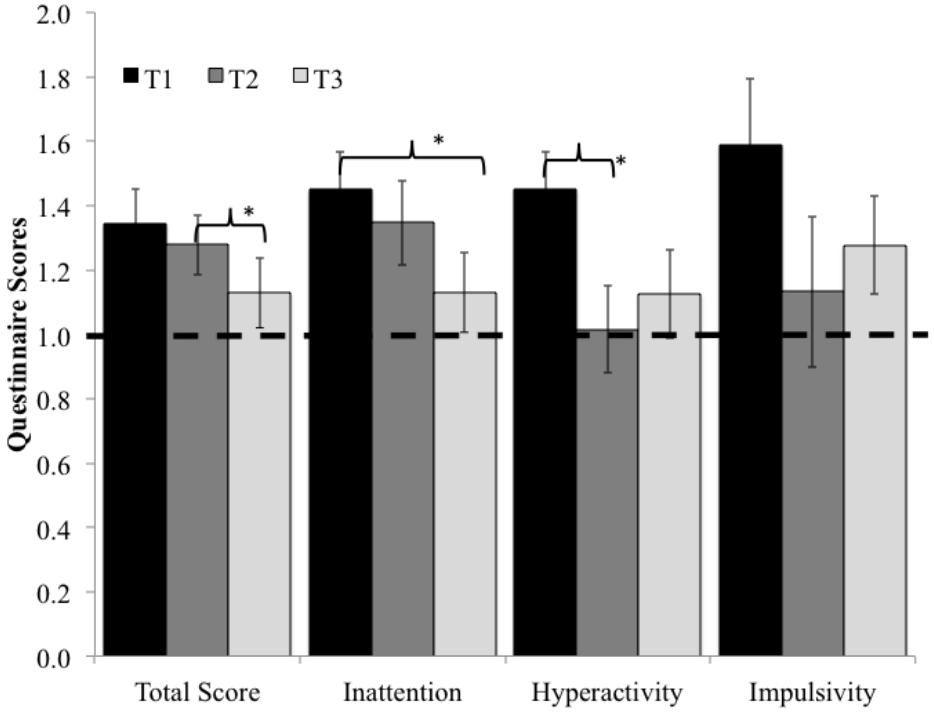

Figure 3.4: Third party rated ADHD symptoms (FEA), The dashed line represents the cut off from mild to medium symptom severity. * indicates significant *t* tests $p < .000$

Table 3.7: Wender Reimherr Interview of adult ADHD outcome $N = 21$

$N = 21$	**Pre**	**Post**	*df*	**F**	**p**	η2
Overall	37.86 (6.52)	30.71 (7.89)	1	17.73	.000	.47
Global	12.19 (3.69)	9.31 (2.34)	1	14.12	.000	.41
Inattention	8.43 (1.47)	6.95 (1.83)	1	13.61	.001	.41
Global	2.36 (0.59)	1.71 (0.56)	1	26.41	.000	.57
Hyperactivity	4.67 (1.20)	3.62 (1.40)	1	9.42	.006	.32
Global	1.83 (0.68)	1.50 (0.64)	1	4.84	.020	.20
Hot temper	3.33 (1.80)	3.10 (2.26)	1	0.31	.581	.02
Global	1.24 (0.93)	1.17 (0.86)	1	0.18	.679	.01
Affective lability	4.90 (2.00)	3.71 (2.05)	1	2.21	.153	.10
Global	1.52 (1.04)	1.12 (0.71)	1	2.44	.134	.11
Emotional reactivity	2.10 (1.87)	1.48 (1.66)	1	8.60	.008*	.30
Global	0.88 (0.95)	0.55 (0.71)	1	3.864	.06	.16
Disorganisation	7.38 (2.44)	6.14 (2.48)	1	7.87	.011	.28
Global	2.24 (1.07)	1.57 (0.66)	1	10.57	.004	.35
Impulsivity	7.05 (2.40)	5.71 (2.37)	1	12.31	.002	.38
Global	2.12 (0.89)	1.67 (0.68)	1	8.64	.008	.30

Note: Mean scores and standard deviations in brackets of the WRI interview as well as TIME degrees of freedom (df), the F value and p-values of the repeated measures ANOVA are shown before and after SCP feedback.

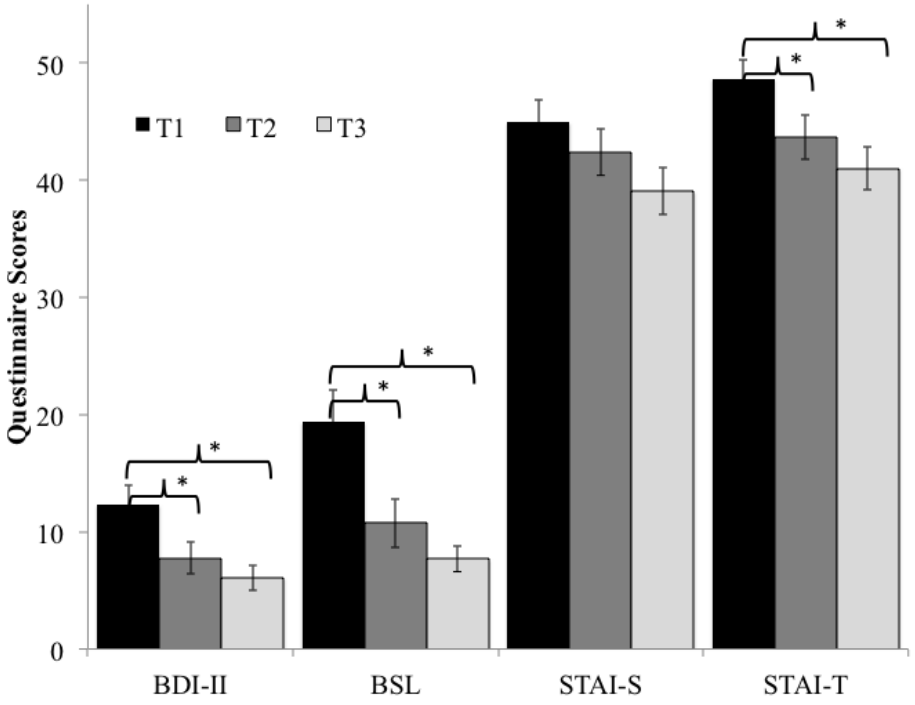

Figure 3.5: Decreases of comorbid symptoms depression (BDI-II), trait anxiety (STAI-T), state anxiety (STAI-S) and borderline (BSL). * indicates significant *t* tests $p < .000$

Neuropsychological measures

A repeated measures between-subjects ANOVA over two measurement points with the factor TIME showed significantly increased scores in the CFT-20-R and d2-R attention test. The GROUP x TIME effect was not significant for the CFT-20-R and d2-R attention test (see table 3.8).

Table 3.8: Changes in attention and IQ scores

	ADHD group ($N = 21$)		Control group ($n = 20$)		ANOVA	
	Pre	Post	Pre	Post	*F*	*p*
d2-R	103.95 (11.69)	109.38 (12.28)	104.10 (8.32)	108.05 (10.97)	0.77	.386
IQ	109.76 (13.44)	119.55 (16.23)	112.80 (8.75)	120.30 (15.98)	0.37	.549

Note: Repeated measures ANOVA with the factor TIME x Group. One drop-out in the control group.

For the RT analysis, one participant from the ADHD group was excluded as an extreme outlier of the normal distribution. The repeated measures between-

subjects ANOVA for two time points revealed a significant decrease in RT from T1 to T3 over TIME in mean average ($F(1,37) = 19.12, p < .001, \eta 2 = .34$) and median ($F(1,37) = 17.90, p < .001, \eta 2 = .33$). There was a trend towards decreased RTV ($F(1,37) = 3.09, p = .087, \eta 2 = .078$). The factor TIME x Group yielded a trend towards a larger decrease of mean RT for the ADHD group (Pre: $M = 480.31$, $SD = 98.60$; Post: $M = 370.89$, $SD = 154.59$) compared to the control group (Pre: $M = 362.29$, $SD = 89.79$; Post: $M = 320.85$, $SD = 121.34$; $F(1,37) = 3.88, p = .056, \eta 2 = .10$; See figure 3.6). Differences in median RT ($F(1,37) = 2.69, n.s., \eta 2 = .07$) and the RTV ($F(1,37) = 1.04, n.s., \eta 2 = .03$) did not reach significance.

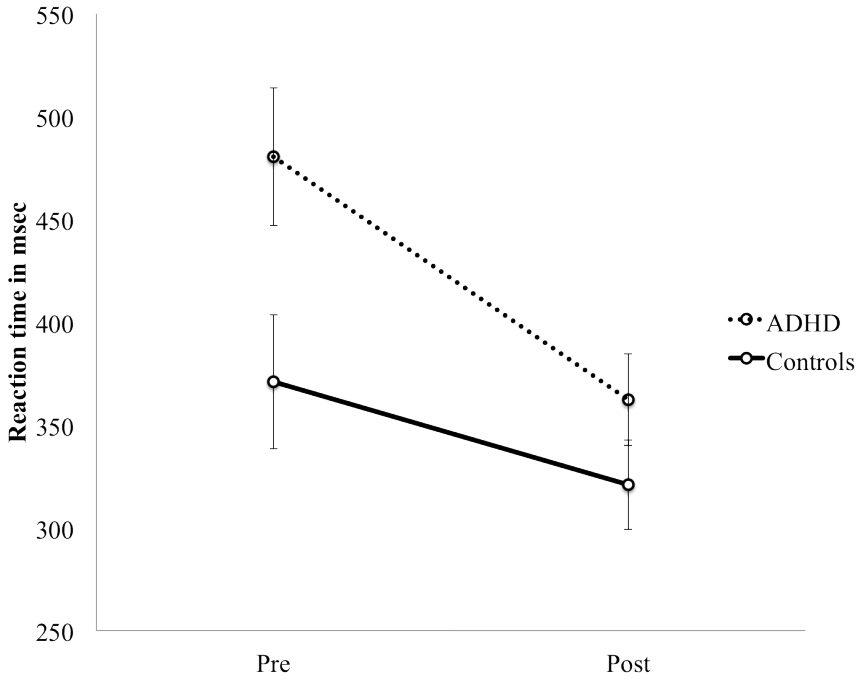

Figure 3.6: Reaction times pre post for the ADHD (dashed line) and control group (solid line)

Post-hoc dependent t-tests for the ADHD group revealed significant reductions of the mean RT between all time point comparisons, T1 to T2 ($t(18) = 2.23, p < .05, d = .33$), T1 to T3 ($t(18) = 3.51, p < .005, d = .74$) and T2 to T3 ($t(19) = 2.23, p < .05, d = .65$; See figure 3.7). The repeated measures between-subjects ANOVA over two time points showed that omission errors reduced significantly over TIME ($F(1,38) = 17.61, p < .001, \eta 2 = .317$) but not Time x Group ($F(1,38) = 0.20, n.s., \eta 2 = .005$). There was no significant difference in TIME ($F(1,38) = 2.03, n.s., \eta 2 = .051$) or TIME x GROUP

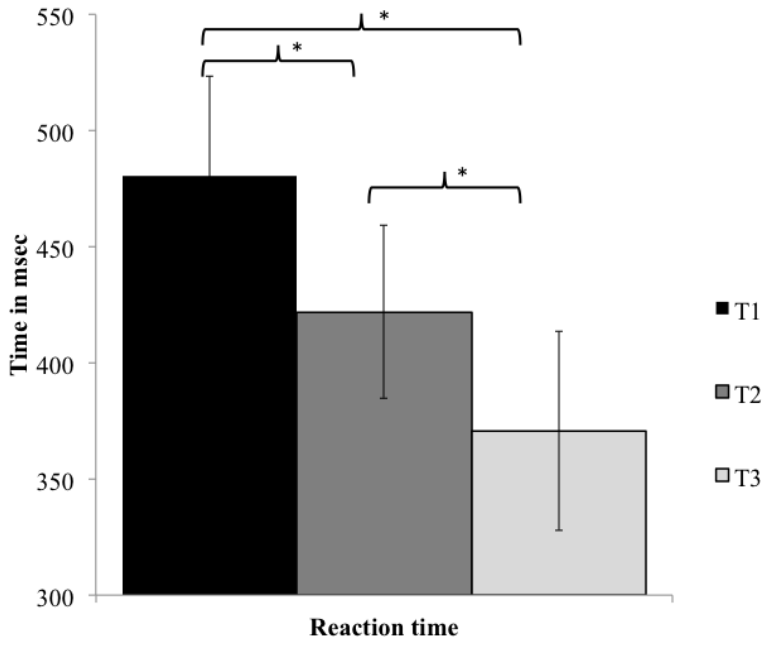

Figure 3.7: Reaction time decease over all three time points for the ADHD group. $n = 19$ due to one extreme and one missing data set.

($F(1,38) = 1.53, n.s., \eta 2 = .039$) in commission errors, but generally only a few commission and omission errors were made within each group. See figure 3.8 for individual values.

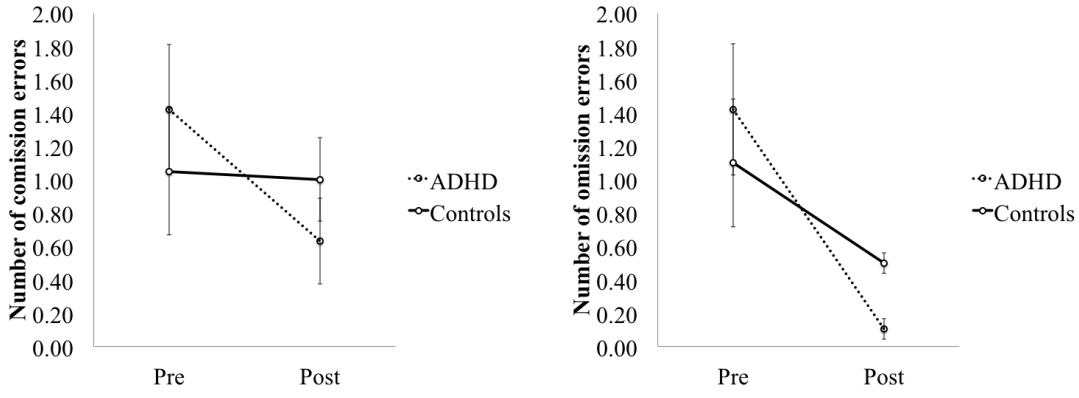

Figure 3.8: Right: number of commission errors, Left: number of omission errors pre post for patient ($n = 20$) and control group ($n = 20$). Dashed line ADHD group, solid line control group

3.3.2 Event Related Potentials

CNV

The repeated measures between-subjects ANOVA over two time points revealed significant increases of the CNV amplitude over TIME but only trends over TIME x GROUP. The results are presented in table 3.9. The increasing amplitude in comparison to the T1 control measurement is depicted in figure 3.9.

The repeated measures within-subject ANOVA over three time points for the ADHD group revealed a significant increase of the CNV amplitude for the parietal electrode group ($F(1.44, 27.35) = 4.41, p < .05, \eta 2 = .19$) and right side electrode group ($F(1.63, 30.91) = 3.82, p < .05, \eta 2 = .17$). There was a trend towards an increase in CNV amplitude for the central electrode group ($F(1.42, 20.22) = 3.58, p = .056, \eta 2 = .16$) and the left side electrode group ($F(1.62, 30.69) = 3.02, p = .073, \eta 2 = .14$). See figure 3.9 for an example of the CNV increase over three time points at C3. Post hoc t tests revealed only significant increases from T1 to T3 or T2 to T3 (see table 3.10).

Table 3.9: Changes in CNV amplitude

		ADHD group (n = 20)				Control group (n = 20)				ANOVA		
		Pre		Post		Pre		Post		F	p	η2
		M	*SD*	*M*	*SD*	*M*	*SD*	M	*SD*			
Frontal												
	TIME	-0.98	2.60	-2.03	1.96	-1.63	2.80	-1.98	3.10	1.95	.171	.049
	TIME x Group									0.50	.496	.012
Central												
	TIME	0.09	3.49	-2.09	1.77	-1.63	2.38	-2.23	2.38	6.09	.018*	.138
	TIME x Group									1.99	.167	.050
Parietal												
	TIME	0.23	2.75	-1.64	1.29	-0.61	2.05	0.90	1.63	5.98	.019*	.136
	TIME x Group									3.16	.083	.077
Left												
	TIME	0.06	2.70	-1.59	1.74	-1.05	2.05	-1.82	1.88	6.90	.012*	.154
	TIME x Group									0.91	.347	.023
Midline												
	TIME	-0.15	4.00	-2.19	1.61	-1.91	2.45	1.90	2.02	2.97	.093	.072
	TIME x Group									3.02	.090	.074
Right												
	TIME	-0.57	2.24	-1.98	1.85	-0.90	2.39	-1.39	2.28	4.49	.04*	.11
	TIME x Group									1.08	.306	.028
C3												
	TIME	0.58	4.21	-1.61	2.11	-1.71	2.48	-2.46	2.37	4.81	.035*	.112
	TIME x Group									1.16	.289	.030
Cz												
	TIME	0.09	5.26	-2.41	1.96	-2.24	2.88	-2.24	2.38	2.67	.111	.066
	TIME x Group									2.65	.112	.065
All												
	TIME	-0.39	4.34	-3.26	2.60	-2.10	3.71	-2.89	3.32	5.91	.020*	.135
	TIME x Group									1.89	.178	.047

Note: Repeated measures ANOVA with the factor TIME and TIME x Group. df = 1

* $p < 0.05$ *M = Mean, SD = Standard deviation*

Table 3.10: Paired-sample t-test for CNV amplitude

		Pre		Post		*df*	*t*	*p*	*d*
	Time	*M*	*SD*	*M*	*SD*				
C4									
	T1-T3	-0.39	2.37	-2.26	2.20	19	2.78	.012	0.82
	T2-T3	-1.23	2.28	-2.26	1.97	20	2.10	.049	0.48
P3									
	T1-T3	1.22	4.46	-1.77	1.73	19	2.79	.012	0.97
	T2-T3	-0.35	2.45	-1.76	1.68	20	2.14	.045	0.68
Fz									
	T1-T3	-0.59	3.21	-2.60	2.18	19	2.13	.047	0.75
Right									
	T1-T3	-0.57	2.24	-1.98	1.85	19	2.40	.027	0.68
Left									
	T1-T3	0.64	2.71	-1.59	1.75	19	2.22	.039	1
Parietal									
	T1-T3	0.23	2.75	-1.64	1.29	19	2.81	.011	0.93
	T2-T3	-0.58	1.76	-1.58	1.28	20	2.27	.035	0.66
Central									
	T1-T3	0.09	3.49	-2.09	1.77	19	2.29	.034	0.83

Note: M = Mean, SD = Standard deviation

3.4 Self-regulation

The average duration of training was 24.48 weeks (*SD* = 8.18 *Min/Max* = 15-49) including a three week break after the first 15 sessions. Figure 3.11 depicts a typical increase of self-regulation ability from session 2+3 to session 28+29 for feedback and transfer condition.

The Friedman's ANOVA revealed significant increases over the four measurement points for FBpos ($\chi^2(3, N = 21) = 16.71, p < .001$, Kendall's $W = .27$), FBdur ($\chi^2(3, N = 21) = 16.27, p < .001$, Kendall's $W = .26$) and FBdiff ($\chi^2(3, N = 21) = 18.83, p < .000$, Kendall's $W = .30$). See figure 3.14. There was a trend for a decreasing transfer coefficient ($\chi^2(3, N = 21) = 6.31, p = .097$, Kendall's $W = .10$). Over all four time points there were no significant differences or trends for negativation, or any of the transfer variables.

Bonferroni corrected ($p = .05/4 = .0125$) Wilcoxon signed-rank test revealed significant changes over the feedback sessions from 2+3 to 13+14 for FBdiff increase ($Z = -2.80, p < .005$) and a trend towards FBdur increase ($Z = -1.76, p = .079$); from 2+3 to

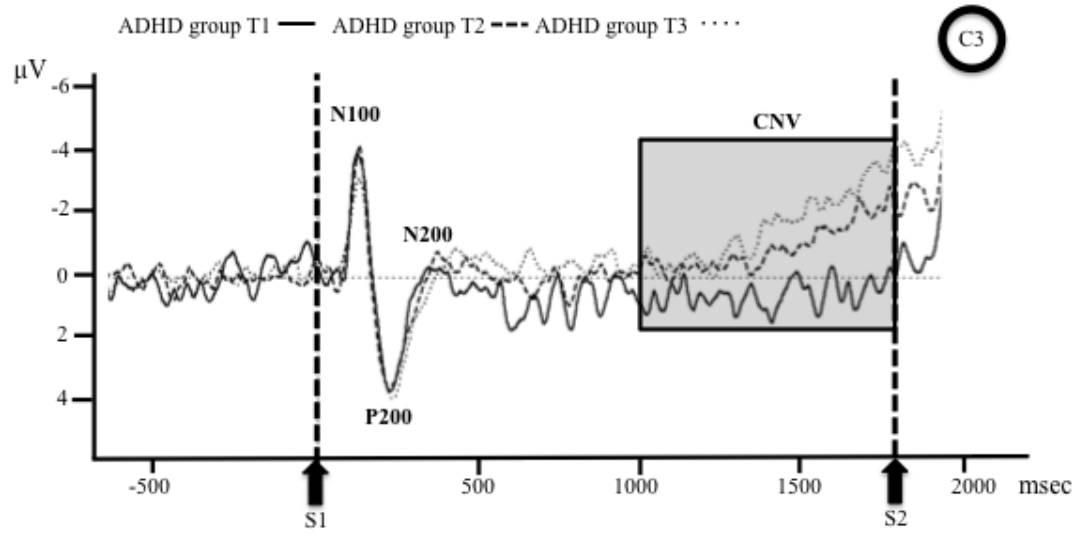

Figure 3.9: CNV amplitude changes over three time points for the ADHD group at electrode position C3. S1 = warning stimulus, S2 = Go stimulus.

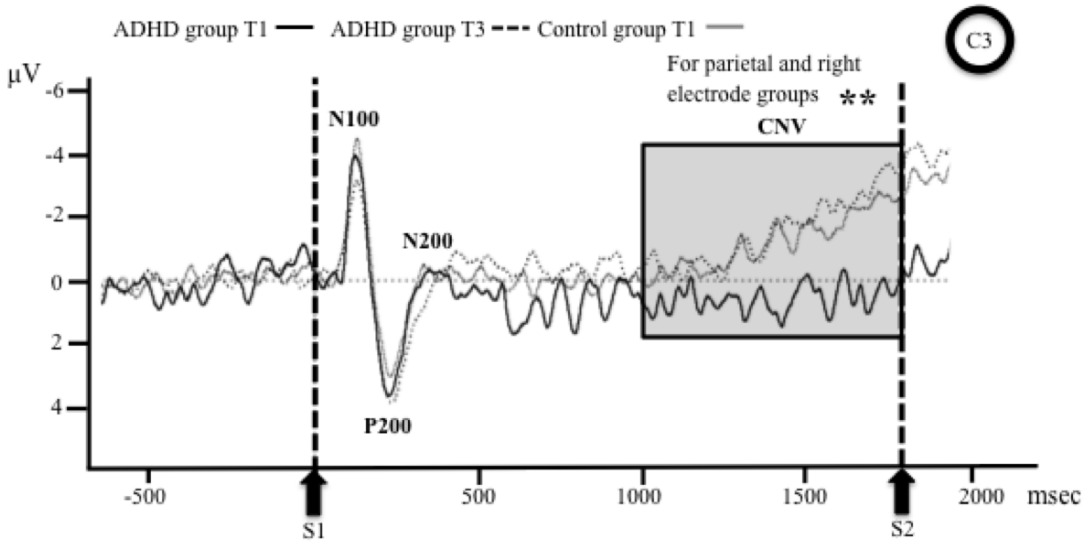

Figure 3.10: CNV amplitude for T1 and T3 for the ADHD group and T1 for the control group at electrode position C3. S1 = warning stimulus, S2 = Go stimulus. ** = significance level $p < .05$ for parietal and right electrodes in the repeated measures within-subject ANOVA over three time points for the ADHD group.

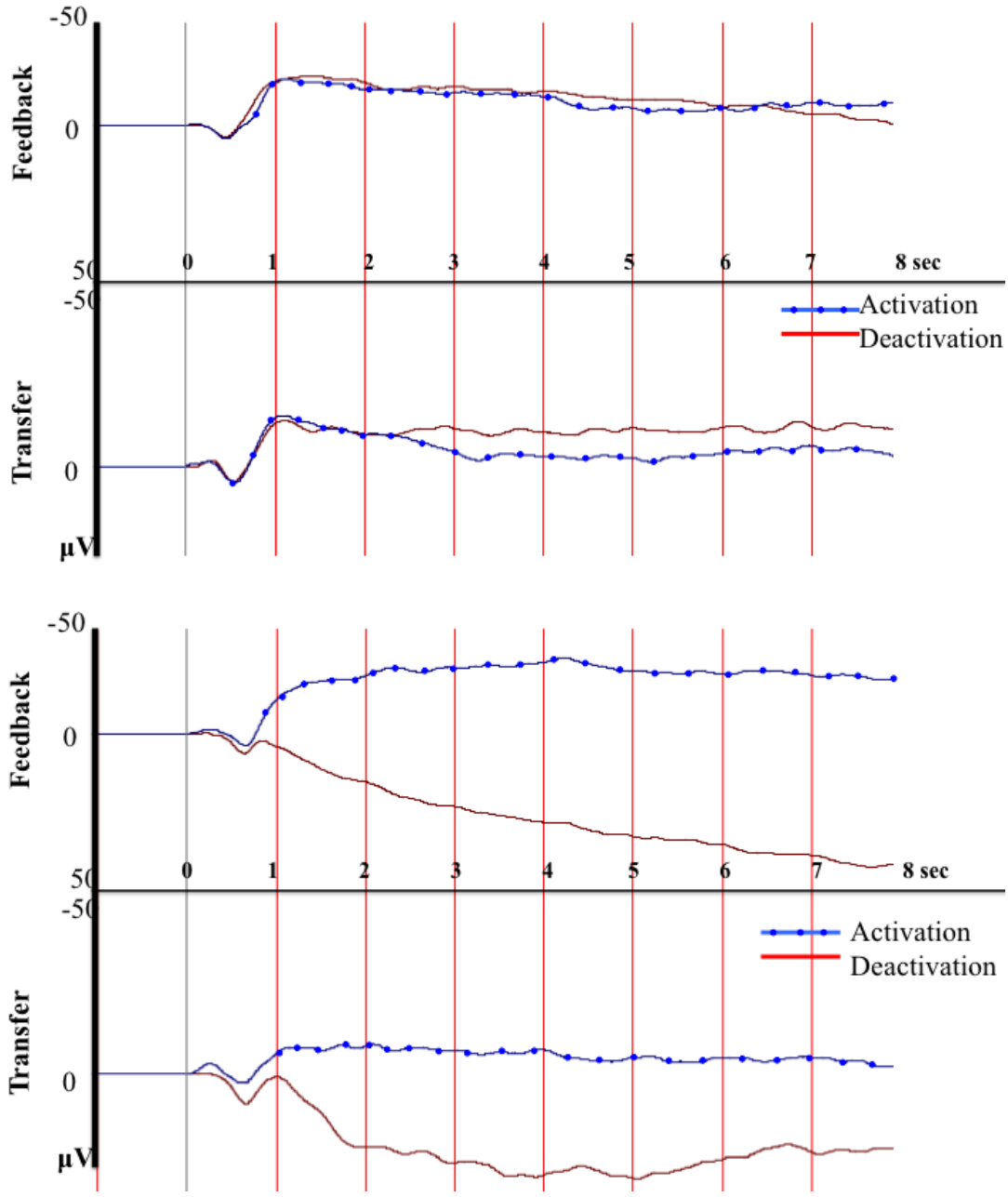

Figure 3.11: Learned self regulation ability for one subject for session 2+3 (top) to session 28+29 (bottom) for feedback (top of each figure) and transfer condition (bottom of each figure). The red line represents the averaged activation (negativation) trials and the blue line represents the averaged deactivation (positivation) trials.

16+17 for FBpos increase ($Z = -3.18, p < .001$) and FBdiff increase ($Z = -2.87, p < .005$) and a trend towards FBdur increase ($Z = -2.28, p = .023$); from 2+3 to 28+29 for FBpos increase ($Z = -3.46, p < .001$), FBdur increase ($Z = -3.24, p < .001$), FBdiff increase ($Z = -3.46, p < .001$), and transfer coefficient decrease ($Z = -2.73, p < .01$); from 13+14 to 16+17 a trend for FBpos increase ($Z = -2.31, p = .021$), TRpos increase ($Z = -1.65, p = .099$), and FBneg decrease ($Z = -2.03, p = .042$); from 13+14 to 28+29 for FBpos increase ($Z = -2.69, p < .01$), FBdur increase ($Z = -2.72, p < .01$) and a trend towards TRpos increase ($Z = -1.80, p = .073$) and FBdiff increase ($Z = -2.14, p = .033$); and finally from 16+17 to 28+29 a trend towards FBdiff increase ($Z = -1.89, p = .058$), transfer coefficient decrease ($Z = -2.31, p = .021$), FBdur increase ($Z = -2.05, p = .041$), and TRdiff decrease ($Z = -1.69, p = .092$). The training lapse for each variable is depicted in figures 3.12 - 3.15.

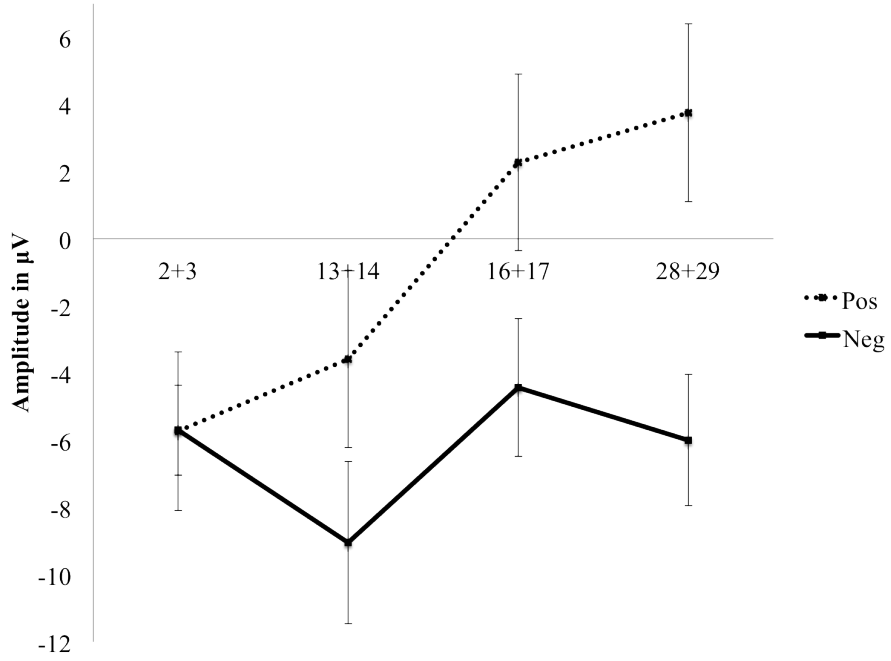

Figure 3.12: Amplitude changes for the feedback condition over four measurement points. Pos = Positivation, Neg = Negativation

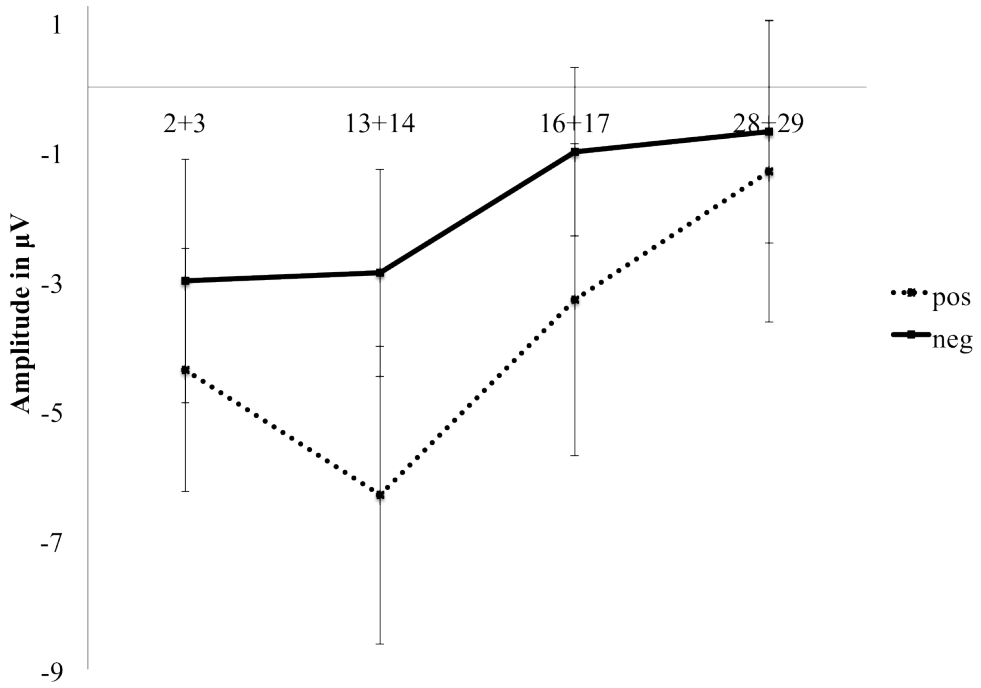

Figure 3.13: Amplitude changes for the transfer condition over four measurement points. Pos = Positivation, Neg = Negativation

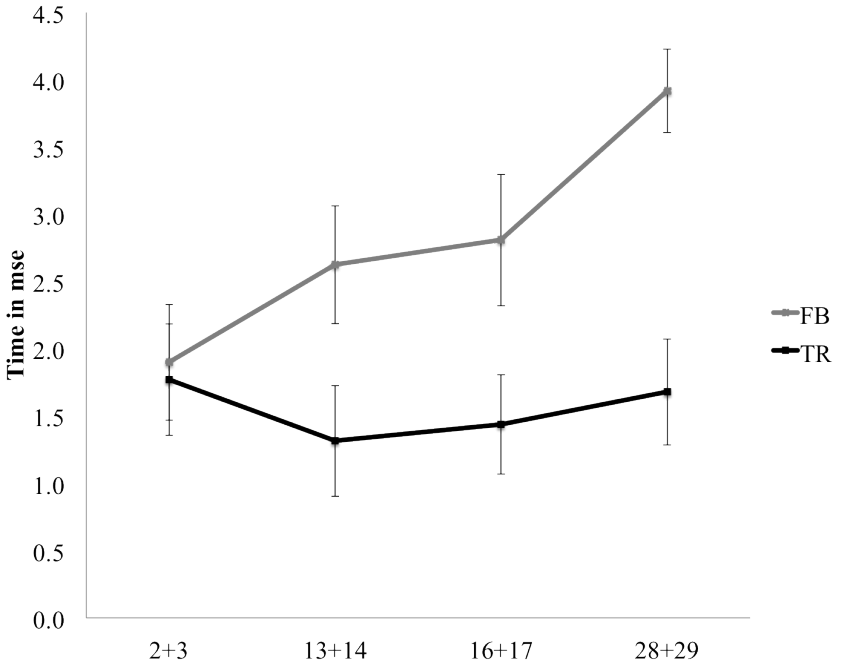

Figure 3.14: Change of the duration a participant was abel to differentiate in the correct direction over four measurement points. FB = Feedback condition, TR = Transfer condition

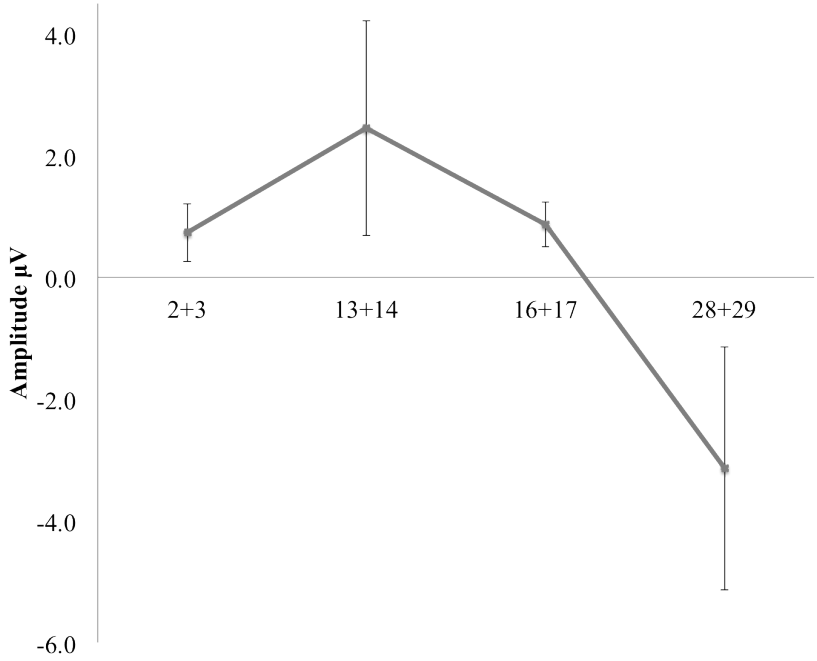

Figure 3.15: Amplitude changes for the transfer coefficient over four measurement points

3.5 Control of unspecific effects

The Friedman's ANOVA revealed significant increases over the six measurement points for the rating for professional competence of the therapist ($\chi^2(5, N = 21) = 14.10, p = .015$, Kendall's $W = .13$) and a trend towards decreasing willingness of the patient to engage in the therapy ($\chi^2(5, N = 21) = 9.43, p = .093$, Kendall's $W = .09$). There were no changes over time for patients treatment expectations ($\chi^2(5, N = 21) = 4.27, n.s.$, Kendall's $W = .04$). See figure 3.16 for the development over all assessment points.

Bonferroni corrected ($p = .05/6 = .008$) Wilcoxon signed-rank test revealed trends towards increased willingness from session 5 to 20 ($Z = -2.36, p = .018$) and from session 10 to 20 ($Z = -1.92, p = .055$) and session 10 to 25 ($Z = -1.86, p = .062$), There was also a trend for increased competency rating from session 5 to 15 ($Z = -1.74, p = .083$), from session 5 to 20 ($Z = -1.76, p = .078$), from session 5 to 25 ($Z = -1.87, p = .062$), from session 5 to 30 ($Z = -2.28, p = .023$), from session 10 to 15 ($Z = -1.90, p = .058$), from session 10 to 25 ($Z = -1.76, p = .077$) and from session 10 to 30 ($Z = -2.10, p = .036$).

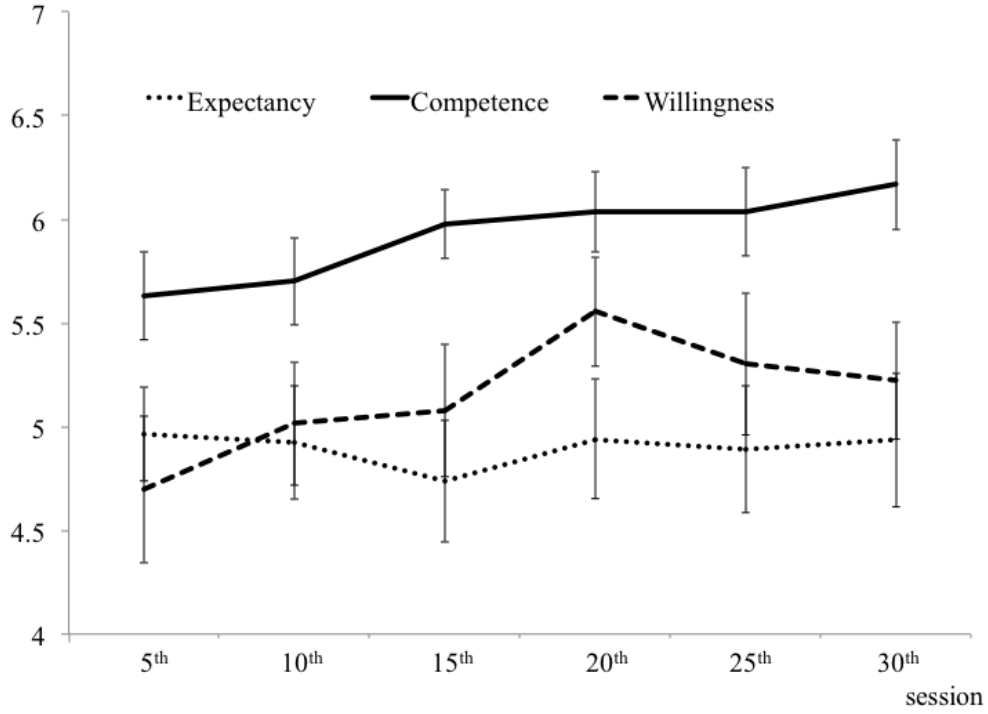

Figure 3.16: Development of FERT variables over the course of training

3.6 Correlation and regression

Three main outcome variables self-rated ADHD symptom change (ADHS-SB), third-party rated ADHD symptom change (FEA), and mean CNV amplitude change, did not correlate significantly with each other. There was a slight trend towards a correlation between ADHD-SB change and CNV ($r_s = .312,\ p_{two-tailed} = .18$). See figure 3.17.

The ADHD-SB change significantly correlated with the change in the BDI depression scale ($r = .458, p_{two-tailed} > .05$) and the change in the STAI-T trait anxiety ($r = .518, p_{two-tailed} > .05$) and trended towards a significant correlation for the change in the STAI-S state anxiety ($r = .391, p_{two-tailed} = .079$) and the change in the BSL borderline symptoms ($r = .391, p_{two-tailed} = .079$). There were no correlations in the change score of the ADHD-SB with the FEA or WRI interview. The changes in FEA did not correlate with any of the other comorbid self-rated symptom reductions. The WRI interview total score correlated with the STAI-T change score ($r = .459, p_{two-tailed} > .05$).

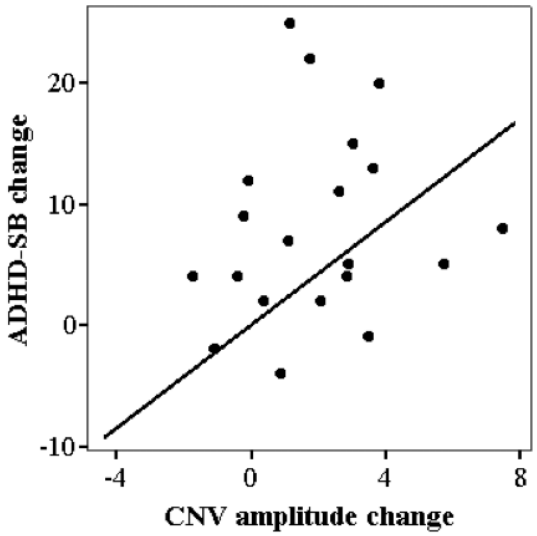

Figure 3.17: Correlation of ADHD-SB change and CNV change

All correlations for the outcome variables (i.e. ADHS-SB, FEA, and mean CNV amplitude) with the treatment data and the behavioural outcome with $r_s > .3$ are displayed in table 3.11.

For ADHD-SB change a stepwise regression was calculated with the predictors TRdiffpost, TRneg pre, FBneg pre, FBneg post, EXP_MW, WILL_chan and COM_MW. The prediction model contained two of the seven predictors and was reached in two steps with no variables removed. The model was statistically significant ($F(2, 18) = 10.92$, $p < .001$) and accounted for approximately 55% of the variance of ADHD symptom change ($R^2 = .548, AdjustedR^2 = .498$). Self-rated ADHD symptom change was predicted by increased WILL_chan and EXP_MW (see figures 3.18 - 3.19) . See table 3.12 for the raw and standardised regression coefficient as well as the beta values.

For the FEA ADHD change, a stepwise regression was calculated with the predictors FBpo_chan, FBpos pre, RT_chan, Will_MW, and Com_chan. No statistically significant prediction model was found.

For CNV mean amplitude change, a stepwise regression was calculated with the predictors TRpos post, TRneg pre, TRneg post, FBpos post, FBneg pre, FBneg post, IQ_chan, and WILL_MW. No statistically significant prediction model was found. A

Table 3.11: Correlations

	ADHD-SB	FEA	CNV
Training			
TRdiff post	.344		
FBpos_chan		.406	
FBneg_chan		.328	
TRpos post			-.380
TRneg pre	-.333		-.319
TRneg post			-.463*
FBpos pre		-.346	
FBpos post			-.349
FBneg pre	-.344		-.408
FBneg post	-.392		-.418
CNV			
CNV_pre			.651**
CNV_post			-.674**
Behaviour			
IQ_chan			.392
RT_chan		-.320	
FERT			
Exp_MW	.546*		
Will_MW		-.302	.412
Will_chan	.634**		
Com_MW	.590**		
Com_chan		.420	

Note: * $p_{two-tailed} < 0.05$ ** $p_{two-tailed} < 0.01$. *ADHD-SB = self-rated ADHD symptom change, FEA = third-party rated ADHD symptom change, CNV = Mean change of all electrodes for the CNV amplitude, TR = Transfer, FB = Feedback, chan = Change score, pos = positivation, neg = negativation, diff = differentiation, FERT = questionnaire concerning unspecific effects, Exp = Expectations, Will = Willingness, Com = Competency, MW = mean over all assessment points.*

Table 3.12: Regression analysis for ADHD-SB change

	B	SE B	β
Step 1			
Constant	0.49	0.08	
Will_chan	0.14	0.05	.59**
Step 2			
Constant	-0.35	0.31	
Will_chan	0.12	0.04	.48**
Exp_MW	0.17	0.06	.46*

Note: $R^2 = .34$ *for step 1;* $\Delta R^2 = .20$ *for step 2 (*$ps > .01$*).* * $p < 0.05$ ** $p < 0.01$. ΔR^2 *= change in* R^2 *from model 1 to 2. Will_chan = Change score for willingness, Exp_MW = mean expectancy over all assessment points*

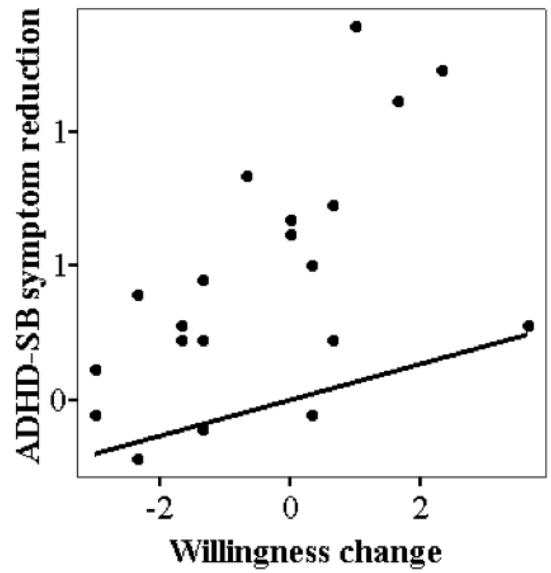

Figure 3.18: Correlation of ADHD-SB change and willingness change score

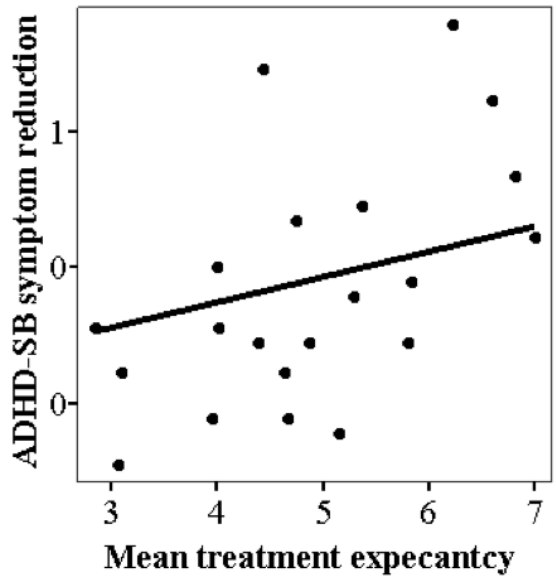

Figure 3.19: Correlation of ADHD-SB change and mean expectation

stepwise regression for CNV mean amplitude change and the predictors CNV_pre and CNV_post resulted in a prediction model that contained two of the two predictors and was reached in two steps with no variables removed. The model was statistically significant ($F(2,17) = 79.01, p < .001$) and accounted for approximately 89% of the variance of CNV mean amplitude change ($R^2 = .90$, *Adjusted* $R^2 = .89$). CNV mean amplitude change was predict by decreased CNV amplitude at baseline and increased CNV amplitude by the end of training (see figure 3.20) See table 3.13 for the raw and standardized regression coefficient as well as the beta values.

Table 3.13: Regression analysis for CNV amplitude change

	B	SE B	β
Step 1			
Constant	2.11	0.35	
CNV_MW pre	0.39	0.08	.74***
Step 2			
Constant	.394	0.28	
CNV_MW pre	0.353	0.04	.74***
CNV_MW post	-.89	0.11	-.60***

Note: $R^2 = .55$ *for step 1;* $\Delta R^2 = .35$ *for step 2 (ps* $> .000$*).* *** $p < 0.001$.ΔR^2 *=change in* R^2 *from model 1 to 2. CNV_MW = mean of CNV amplitude over all electrodes*

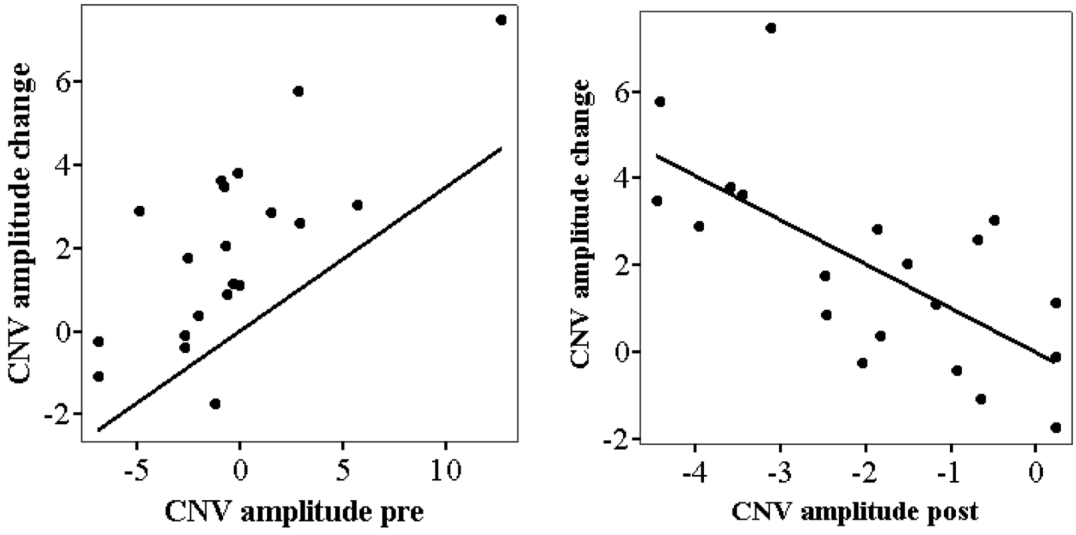

Figure 3.20: Correlation of CNV change and CNV before training (top) as well as CNV after treatment (bottom)

4 Discussion

The present study had two major aims. The first aim was to assess if adults with attention deficit-/hyperactivity disorder (ADHD) differed from healthy controls in their neuropsychological as well as neurophysiological measurements. The second and main aim was to assess if adults with ADHD are able to learn self-regulation through slow cortical potential (SCP) feedback and if that ability led to changes in symptom severity, neuropsychological and neurophysiological measurements. Thirty one-hour sessions of SCP feedback trained the self-regulation of negative and positive SCP shifts which are associated with activation or deactivation of the brain. Self-rated and third-party rated symptom questionnaires, tests of attention, and the Contingent Negative Variation (CNV) amplitude were assessed as outcome variables pre, midway, and post treatment (T1, T2, and T3).

Up to now, no study has investigated in the effect of SCP feedback on adult ADHD. Only recently the interest and research in adult ADHD started to grow and treatment options were developed. More research has been done in children with ADHD and SCP feedback has been shown to be effective in their treatment.

This study confirms certain differences between adults with ADHD and healthy controls. Furthermore, it reveals SCP feedback as an effective and efficacious treatment for symptoms of adult ADHD. Thus, this study contributes to a future acknowledgement of SCP feedback as a treatment for adult ADHD.

4.1 ADHD patients differ from healthy controls

It was hypothesised that adults with ADHD show increased scores on ADHD scales as well as on comorbid disorders (i.e. depression, anxiety and borderline) compared to healthy controls. This hypothesis was confirmed as the ADHD group differed significantly from the control group not only on all symptom scales of ADHD but also on symptom scales of the other psychiatric disorders. Although participants with current depression, anxiety, and borderline were excluded the bias towards higher prevalence on these scales is evident and highlights the extended comorbidity in ADHD patients.

The second hypothesis concerned a decrease performance in attention related processes in the ADHD group (i.e.test of attention, slower reaction times (RT), higher RT variability (RTV), and increased error rates). The attention deficit in ADHD was not detectable on all scales. Contrary to the expectations, there was no difference between the ADHD and control group in short-term attention assessed with d2-R Test of Attention. However, this confirms the theory that patients with ADHD often manage to concentrate and focus for a short period of time (Lauth & Schlottke, 2002). The attention deficit becomes more obvious in monotonous tasks in which concentration is required over a long period. To capture the attention deficit, Lauth and Schlottke (2002) recommend prolonged testing times or tests that were designed for long-term attention for at least 20 min. The d2-R Test, as a 5 min test of short-term concentration, was selected in an attempt to compass the extensive TAP but this was an erring retrenchment.

The attention deficit did become obvious in the 12 min CNV task during a 90 min EEG measurement. As expected, the ADHD group showed slower RT, as well as elevated RTV which differed from the control group with a medium effect size. These differences can be regarded as inefficient information processing and have been reported in other studies as well (Dhar et al., 2010; McLoughlin et al., 2010). A slower reaction time is related to slower information processing. There are several theories about the meaning of the increased RTV in ADHD. In general, an increased RTV in ADHD is interpreted as occasional interruptions of sustained attention (Tamm et al., 2012).

Furthermore, the attention deficit, as well as impulsivity, was assessed with the amount of omission and commission errors. The expected elevation of these errors in the ADHD group was not found to be significant, but there was a slight trend towards more errors in the ADHD group. The task caused very few errors in both groups and for all measurement points. It can be assumed that the task was too simple and may not have been long enough to evoke a large amount of mistakes and to make the attention deficits observable in the error rates. However, as mentioned above, the attention deficit is visible in the RT and RTV. Future studies should aim to use the standardised TAP or any test with a high discriminability between ADHD and healthy controls to capture the inattention, as well as the impulsivity, in the error rates. However, more research is needed to develop a test with high discriminative power, as the most reliable differences are often only observable in ERPs and not in performance data (Nonnenmacher, 2013).

The hypothesised reduced CNV amplitude for adult ADHD was confirmed in this study, however, not as consistent as expected. Significant differences were observed for only one electrode site (C3) and a trend with medium effect size was observed on several electrodes and electrode groups.

To understand why the significantly pronounced difference was observed on C3 the underlying processes need to be explained. The activity recorded at C3 arises from the left precentral gyrus or also called Brodman area 4 (Tyner, Knott, & Mayer, 1989). More precisely, C3 is located over the shoulder to wrist area of the left precentral gyrus (also called primary motor cortex) and is involved in the planning and executing of movements of the right hand (Homan, Herman, & Purdy, 1987). The precentral gyrus is also activated during pure imagination (Roth et al., 1996). An increased activation of this area is evident as the participants were asked to react with their dominant right hand to the Go-stimulus.[1] As mentioned in section 1.1.3.4 the CNV is also related to motor preparation and attention. A reduced CNV in the ADHD group indicates that after the warning stimulus fewer resources for attention to the task and poor motor preparation for the right hand were available. Therefore a most pronounced difference between the ADHD and the control group at electrode position C3 is plausible. The

[1] Only two left handed people were included in each group who reacted with their dominant left hand.

poor motor preparation observed in the CNV is also indicated by the slower RT and RTV.

A big goal in applied neuroscience is to find a stable pattern in neurobiological or neurophysiological differences in ADHD and other disorders to use these for diagnostic testing. The observed differences in the CNV amplitude are a first step towards a neurophysiological marker of adult ADHD. Several disorders are characterised by alterations in the P300 amplitude and latency. However, these disorders reach from schizophrenia to dyslexia to ADHD (Jucla, Nenert, Chaix, & Demonet, 2009; Singh & Basu, 2009; Szuromi et al., 2010). Observing consistent alterations in the CNV could provide an additional and maybe more specific marker for ADHD. Using EEG and ERP measurements as a diagnostic tool is also more cost effective compared to other genetic (Krause et al., 2006) or MRI approaches. However, more research needs to be done to investigate and validate using the CNV amplitude for diagnostic testing.

4.2 Treatment effects

4.2.1 Behaviour

The investigation of the effects of SCP feedback on adult ADHD constitutes the main aim of this study. The hypothesised improvements for ADHD as well as comorbid symptom scales were confirmed. The ADHD group improved significantly on primary self-rated and third-party rated ADHD symptoms. Ten patients had a symptom reduction of over 25% and symptoms of five patients remitted, i.e. they did not meet criteria for an ADHD diagnosis anymore. However, two patients had a slight increase in self-rated ADHD symptoms and three an increase in third-party rated ADHD symptoms.

The data suggest that self-rated symptoms decreased earlier, i.e. at T2, than the third-party rated symptoms. However, only thirteen participants returned the T2 third-party questionnaires. Although the missing data were statistically imputed for calculation, this effect should not be interpreted in depth as the true data is missing.

A significant decrease of all primary symptoms (i.e. inattention, hyperactivity, and impulsivity) was observed in the ADHD interview, as well as a significant decreases in disorganisation and emotional reactivity. Generally, all symptoms decreased. However,

this could partly be due to the Rosenthal effect (Rosenthal & Jacobson, 1966) in which expectancy of the investigator influences the outcome. The interviews were conducted by the same unblinded investigator for pre and post treatment. The same investigator also conducted the neurofeedback sessions. Therefore it is possible that expectations of the interviewer partly contributed to the rated symptom decrease.

As hypothesised, all comorbid symptoms of depression, anxiety, and borderline deceased significantly. This suggests that SCP feedback does not only effect symptoms of ADHD, but also related comorbidities. Respectively improvement of the ADHD symptoms led to improvements of related symptoms. This suggests a possible application of SCP feedback for other disorders like depression and anxiety.

Reductions in symptoms of ADHD ($d = 1.18$), as well as comorbid symptoms ($d = 0.67$-1.33) were related to medium to high effect sizes in this study. These findings are comparable with effects of behavioural and pharmacological therapies. Unfortunately, not all studies reported effect sizes, so only a few comparisons can be made. In a study of short cognitive behavioural therapy in adult ADHD large effect sizes (partial $\eta 2 = 0.68$) were observed for improvements in the attention score (Virta et al., 2010). For CBT and medication combined therapy, large effect sizes were reported for ADHD symptom reduction ($d = 1.2$, additionally $d = 0.4$ for comorbid symptoms Safren et al., 2005), and ($d = 0.91$ Rostain & Ramsay, 2006). In a review by Fredriksen et al. (2012) of pharmacological treatment in adult ADHD, effect sizes from $d = 0.3$ to 2.17 were reported. This comparison suggests that SCP feedback treatment can compete with the effects of behavioural therapy, as well as pharmacological therapy.

A follow-up assessment would yield more valuable information about long-term efficacy and possible superior effects of SCP feedback over medical treatment , as long-term effects have been observed in children with ADHD (Gani et al., 2008; Gevensleben, Holl, et al., 2010; Strehl et al., 2006). Overall, the results of this study confirm symptom improvements of SCP feedback studies conducted with children (for an overview: Mayer, Wyckoff, & Strehl, 2012). This supports SCP feedback as a promising treatment for adult ADHD.

At the end of the interview each patient was openly asked to evaluate the treatment and the outcome. Altogether, the evaluations were positive and the reported

improvements in the questionnaires were confirmed. Often, the patients reported that they gained more consciousness about their symptoms and themselves. On the one hand, they described it on the level of being more receptive to information about ADHD. On the other hand, they reported an increased awareness about what state they were in during a particular moment. They reported that they were able to use this awareness to judge if it was worth trying to concentrate in that state and also indicated they were able to actively change the state using the learned self-regulation abilities.

A frequent criticism of the treatment was the high time costs. In total the participants had to attend 37 appointments. Some participants travelled over an hour to attend the treatment. However, once patients started the treatment no one dropped out. Some took longer breaks due to their studies or personal matters, but everyone finished the treatment and completed the study.

To what extend the treatment success might be influenced through unspecific effects will be discussed later in section 4.4.

4.2.2 Neuropsychological changes

The hypothesised neuropsychological changes (i.e. IQ, test of attention, reduced RT, reduced RTV, and reduced error rates) after SCP feedback were partly confirmed. After thirty sessions of SCP feedback the IQ score and the d2-R attention test score increased significantly over time. Furthermore, the error rate decreased significantly over time. However, this was also true for the control group. Therefore these improvements must be attributed to the task repetition and practice effects rather than treatment.

However, as hypothesised, the RT in the CNV Go-No/Go task became faster in the ADHD group. This was not attributed to a task repetition effect, as the control group showed only a slight decrease in RT. Therefore, it can be assumed that SCP feedback led to an increased information processing speed in adults with ADHD.

Similar effects were observed after one-time administration of stimulants to adults with ADHD (Oberlin, Alford, & Marrocco, 2005). Also, a single dose of atomoxetine in adults with ADHD decreased RT and reduced commission errors (Chamberlain et al., 2007). Furthermore, a small increase in RT was observed after CBT and cognitive

training (Virta et al., 2010). This highlights not only similar effects in behavioural improvements due to SCP feedback, but also similar neuropsychological improvements.

The trend towards decreased RTV and error rate over time were observed in the ADHD and the control group and cannot solely be attributed to treatment. These improvements are most likely influenced by task repetition and practice effects. In a SCP feedback study of children with ADHD only small but not significant RTV increases were observed (Drechsler et al., 2007). However, other kinds of treatment have shown significant improvements in RTV. Decreased RTV, as well as shorter RTs, were reported following treatment with stimulant medication in children with ADHD (Epstein et al., 2011; Kratz et al., 2012). Also, a one-time administration of methylphenidate led to reduced RTV in healthy men (Nandam et al., 2011). Furthermore, a three months meditation program for health adults led to decreased RTV but not to faster RTs (Lutz et al., 2009).

To summarise, the observed improved RT improvement might represent generally improved sustained attention after SCP feedback which is comparable to pharmacological treatment and somewhat superior to behavioural therapy. However, the lack of group specific improvements in RTV may show that the occasional drop-outs of attention are still present in the ADHD group after treatment.

4.2.3 Neurophysiological changes

The hypothesised increase of CNV amplitude was observed over time. However this increase showed only trends rather than significant results for group specificity. These trends were most pronounced over parietal electrodes and midline electrodes in the group comparison. In the analysis over all three measurement points for the ADHD group, significant changes were visible only after all 30 sessions of SCP feedback for C4, P3, parietal, and right side electrode groups, as well as a trend for P4, Fz, central, and left side electrode groups. However, reduced CNV amplitudes at baseline in the ADHD group were found mainly over central and midline electrode groups. The CNV amplitude is related to negative SCP shifts and the negative, as well as the positive, shifts were trained during the SCP feedback. As the training was conducted over Cz, the strongest CNV increase was expected at this site (Heinrich et al., 2004). This

was not confirmed in this study. However, the CNV amplitude at Cz had the highest standard deviations of all electrode sites especially at T1 and T2, which might have contributed to the lack of significant changes.

The increase at parietal sides are also surprising as the parietal cortex (i.e. electrode site P3 and P4) is related to visual motor coordination and spatial memory (Tyner et al., 1989), but the task used was an auditory eyes-closed Go/NoGo task. The activation increase at parietal areas might be interpreted as an increased involvement of additional brain areas for an increased task performance reflected in faster RT and reduced errors.

Pharmacological treatment with methylphenidate in children with ADHD also led to increased CNV amplitude at Cz (Kratz et al., 2012) and a correlation of RTV decrease and CNV increase was observed. This could not be confirmed in the present study. Only a small positive correlation between the improved IQ score and the CNV increase was observed, but no correlation between RT, RTV or error rate.

Moderate correlations between the baseline and the post treatment CNV amplitude were observed. The smaller the baseline CNV amplitude the more increase was observed after training. And as one could expect, the patients with the largest CNV amplitude at the end of training underwent the largest increase in CNV amplitude. The regression analysis revealed that the baseline CNV accounted for 55% of the CNV change and together with the post CNV amplitude 90% of the variance were explained. Hence, a small CNV amplitude in patients with ADHD predicted a large potential for CNV change after SCP feedback.

Together with the moderate correlation of symptom reduction and CNV change, discussed later in section 4.2.4, this could be interpreted in a way that patients with a small CNV might benefit from SCP feedback more than patients with rather normal CNV amplitude. A bigger CNV amplitude is related to good preparatory and attentional processes. Therefore, patients with a small CNV have more room for improvement on the neurophysiological as well as the behavioural level.

Wangler et al. (2011) observed a direct relationship between a high baseline CNV and high symptom reductions. They attributed the high baseline CNV to the ability to initially recruit more resources. With aid of the training, children with a high baseline

CNV learned to apply and transfer these resources into daily life. The children with a small CNV had to build up the resources first before transferring it to their daily lives. In the present study a correlation of symptom reduction and CNV change was observed, but not between symptom reduction and baseline CNV. Here, it seems like a large physiological change is related to a large symptom reduction. This partly contradicts Wangler et al. (2011) conclusions and indicates the need for more research towards a possible use of baseline CNV as a predictor of success or as an indicator for number of sessions.

Generally, changes were observed over all parietal, central, and midline electrode sites. This suggests that SCP feedback produced a global increase of CNV amplitude which is related to an increased allocation of resources and therefore attention to the relevant stimulus. This increased attention is reflected in the improved information processing speed.

A slight increase of the CNV amplitude was already observed after 15 sessions of SCP feedback. However, significant changes were only found after 30 sessions. This suggests that more than 15 and possibly more than 30 sessions of SCP feedback are needed to affect the neurophysiology, although improvements in symptoms were reported after only 15 sessions.

4.2.4 Correlation of outcome variables

It was hypothesised that changes in self-rated ADHD symptoms, third-party rated ADHD symptoms, as well as the change in CNV over all nine analysed electrode sites, would correlate with each other and with other outcome variables (i.e. comorbid symptoms and neuropsychological measures).

Only the self-rated ADHD symptom reduction and the CNV increase showed a moderate correlation. The larger the symptom reduction the larger the CNV amplitude increase. This result suggests that the behavioural improvement is correlated to the neurophysiological changes, which supports the theory that neurophysiological abnormalities underlie the symptoms of ADHD. Thus, treating the relevant brain activities can lead to symptom improvements.

The self-rated ADHD symptom changes also correlate with self-rated changes in depression, state and trait anxiety, as well as borderline symptoms. No correlations were observed between any self-rated questionnaires and the third-party rated questionnaire or expert interview. For comparison, only one study assessed self-rated and third-party rated symptom scales with the Conners Adult ADHD Rating Scales (CAARS) (Solanto et al., 2010). They found reductions in both scales: however, they did not calculate correlations. The validation of the CAARS showed high correlations between the self-report and the observer-report ratings, especially for the clinical expert ratings (Christiansen et al., 2011). The same was expected for the rating scales used in this study. However, the questionnaires were taken from different manuals and were therefore not as comparable and validated as the CAARS. This could be a methodological limitation of the present study. Additionally, this could also be due to large unspecific effects that influenced the self-ratings and not the third-party ratings. This possibility is discussed further in section 4.4.

4.3 Self-regulation

It was hypothesised that the ability to self-regulate SCPs would be reflected in increases of activation and deactivation amplitude, their differentiation and the duration of cued negativation and positivation during a trial. All of the variables were assumed to increase over all four measurement points in the feedback and transfer condition. Overall, adults with ADHD learned to self-regulate their SCPs after thirty sessions of SCP feedback. However, the outcome was not as consistent as expected and observed in other studies. So far, the analysis of SCP progress treatment data has only be done in a few studies for healthy adults (Kotchoubey, Haisst, Daum, Schugens, & Birbaumer, 2000), adults with epilepsy (Kotchoubey et al., 1996; Kotchoubey, Strehl, Holzapfel, Schneider, et al., 1999; Rockstroh et al., 1993) and more recently for children with ADHD (Blume, 2011; Drechsler et al., 2007; Strehl et al., 2006). These studies only investigated in pre, post and follow-up time points and no gold standard exist for this type of analysis. The analysis of the present study was modelled after the most recent studies investigating children with ADHD.

Several variables were used to assess the ability to self-regulate SCPs over four measurement points (average of session 2+3, 13+14, 16+17 and 28+29). One variable was the amplitude change for cued negativation, representing the ability to shift into an active state (further referred to as activation), and the amplitude change for cued positivation, representing the ability to shift into cortical inhibition (further referred to as deactivation Birbaumer et al., 1990). During the SCP feedback the participants trained to shift into both of these states equally under feedback and transfer conditions. Resulting from these two amplitudes, a differentiation variable was calculated to indicate the ability to differentiate between the two states. The third outcome variable was the time the activation and the deactivation differed in the demanded direction. This is a measure of how long the differentiation was produced during the last 5 sec of each trial. As all the variables are interrelated they will be discussed together but for the feedback and the transfer condition separately.

Feedback condition

As expected, under the feedback condition, on average the participants were not able to create a difference between activation and deactivation during the first few SCP feedback sessions (2+3). The differentiation and the duration of correct differentiation were minimal.

After the first half of SCP feedback (13+14) the differentiation and duration significantly increased due to an increase in the ability to activate and to deactivate. Both amplitudes were located in the negative range but with a clear differentiation. After the three week break (16+17) the amplitude for deactivation increased into the positive range and the amplitude for activation decreased (i.e. became less negative), respectively shifting towards the amplitude level at the start of treatment. However, the differentiation and duration increased further. At the end of training (28+29) the differentiation and duration increased even further due to increasing deactivation and a small amount of activation amplitudes into their expected direction.

This is the first time that the improved training performance and reduced ADHD symptoms are mainly due to an increase in the ability to shift into deactivation. This has not been observed before and is somewhat unexpected. ADHD is associated with a general lower excitability level and hypoarousal (see section 1.1.3.4). This

would be related to low negative SCP shifts (i.e. low activation) in patients with ADHD. However, the negative SCP shifts were only investigated in relation to the CNV amplitude (Heinrich et al., 2004; Mayer, Wyckoff, Schulz, & Strehl, 2012) but not in a comparison (healthy vs. ADHD) of spontaneously fluctuating SCP shifts. Nevertheless, it was expected that the patients with ADHD would benefit from an increased ability to create activation, just as observed in children with ADHD (Blume, 2011; Drechsler et al., 2007; Strehl et al., 2006). The question remains why the adults showed mainly an increase in deactivation shifts but also reduced symptoms.

An answer to this question may lie in SCP feedback studies with adults and a new attempt to understand the training components and their changes. In a SCP feedback study with epileptic adults, Rockstroh et al. (1993) observed age to be an important mediating variable in learning self-regulation. Participants older than 35 years did not show successful regulation. Also, in a group of young healthy adults only a trend towards increased differentiation was observed after ten sessions of SCP feedback (Studer, 2011). However, the comparison of healthy younger and older adults did not support these findings (Kotchoubey et al., 2000). Over four sessions of SCP feedback the younger adult groups (20-30 years) and the older adult group (50-65 years) showed the ability to regulate into activation and deactivation. However, the activation and deactivation amplitudes both proceeded in the negative range whereby this was even more pronounced in the older group. This difficulty to create deactivation was referred to age-related processes. The authors related that to decreased cortical inhibitory processes with age, as well as neurophysiological theory of attention. The neurophysiological theory of attention describes three types of attentional processes, arousal, activation and effort (Pribram & McGuinness, 1975). It is assumed that older people have a decreased arousal and activation and therefore e.g. stimulus evoked ERPs, like the CNV, are reduced (Siniatchkin et al., 2010; Zanto et al., 2011). However, older people are able to invest more effort into a task which would be related to more voluntary activation and the ability to shift into negativation during SCP feedback (Kotchoubey et al., 2000).

To understand this theory in relation to the present training data it is important to look at the different SCP feedback phases (see 2.4). During SCP feedback the

participant learned to produce three rather than two different brain states: activation, deactivation, and a “neutral" state during the baseline phase. The activity level during the “neutral" or resting state influenced how well the participant was able to shift into activation or deactivation during the feedback phase. If the “neutral" state was already very active/negative it was difficult to shift into an even more active/negative state and vice versa. At the beginning of training, the amplitudes for activation and the deactivation states both lay in the negative range. Therefore the “neutral" state of the participants must have been in a rather deactivated, positive brain state which would support the described decreased activation in ADHD (Clarke et al., 2008; Satterfield & Dawson, 1971; Sergeant, 2000, 2004) and in healthy, older adults (Kotchoubey et al., 2000). An already deactive “neutral" state makes it hard to create the deactivation in a positive range, but with voluntary effort the participants were able to produce activation.

It can be assumed that through the course of training the “neutral" state was changed into a more active/negative state. From there it was easier to shift into both states in the right polarity which led to the observed decreased activation amplitude but increased differentiation. This points to a general shift towards a more active brain following SCP feedback. To test this assumption the data from the baseline phase need to be analysed pre and post treatment. Future research should include this analysis.

The answer to the question why this was not observed in children lies in the enhanced deactive “neutral" state as a result of ADHD as well as age. In children, the enhanced deactivation was only due to ADHD and therefore maybe less obvious in the training data. The deactivation became more enhanced in adults as a result of ADHD and age. That made the deficit more obvious and the potential to increase SCP positivity during training was higher than the one observed in children. To test this assumption healthy children and adults, as well as children and adults with ADHD, need to be trained with SCP feedback. Then, the training data can be compared and results should disentangle the amount of deactivation enhancement due to ADHD or age.

Age-related differences were not hypothesised for training data or any other outcome variable, and were therefore not analysed in the present study. However, retro-

spectively, an age-related analysis of all data would have been of great interest as the age range lay between 21 and 66 and other studies suggest that a training difference in different age groups can be observed (Kotchoubey et al., 2000). Future research or analysis should take this variable into account.

As derived from the data, the general shift of the activation level suggests an improved excitation threshold after SCP feedback. As already mentioned, to prove the assumption of a general increased brain activation the baseline training data need to be analysed. However, the assumptions were already supported by the increase in CNV amplitude and improved RT observed in the ERP task. SCP negativation is essential for the mobilisation of resources (Birbaumer et al., 1990). Therefore, a general shift into activation/negativation facilitates the attention processes reflected in increased CNV amplitude and improved RT.

Furthermore, the data support the importance of the break in between treatment. The differentiation and amplitude distribution increased and changed after the break. This suggests that the brain needs time to adjust and process the newly learned regulation ability.

Transfer condition

The results of the transfer condition somewhat support the assumptions drawn from the feedback condition, but also show an unexpected development. The data from the feedback condition suggested a generally more deactivated brain state that shifted towards a more activated brain state over the course of training. This can also be observed in the transfer condition. At the start of training (2+3) activation and deactivation show a small differentiation in the negative range. This points toward a rather deactive general brain state in the “neutral" state which made it easy to shift in an active state. Over the course of treatment both amplitudes shifted towards the midline which indicates a shift of the “neutral", general brain state towards more activation.

However, the course of the activation and deactivation amplitude developed unexpectedly. Over all four assessment points the deactivation was more negative than the activation resulting in a reversed differentiation. This reverse differentiation peaked after the first half of treatment (13+14) and almost reaches zero at the end of treatment

(28+29). The activation amplitude decreased continuously over all four measurement points.

This is unexpected in view of the fact that past studies have found that the ability to activate in the transfer condition was correlated with symptom reduction and a predictor for clinical outcome (Drechsler et al., 2007; Strehl et al., 2006). In the present study, symptom reductions were observed for 17 of the participants but only 13 were able to successfully activate during the transfer condition and only eight improved this ability over the course of training.

The deactivation amplitude decreased after the first half of treatment and results in a big reverse differentiation at that point. After the three week break it increases constantly until the end of treatment but never reaches positivity. The duration of correct differentiation fluctuated only in a small range around 1.5 sec. This underlines the poor self-regulation ability during the transfer condition. Drechsler et al. (Drechsler et al., 2007) found similar results, reporting that during the transfer condition the differentiation did not increase and the deactivation amplitude slightly decreased. However, they found a significant increase in the activation amplitude. Strehl et al. (2006) also found significant increases in the activation amplitude in the feedback and the transfer condition. In the study by Blume (2011) 80% of the participants achieved an increase in activation amplitude but the results were rather mixed for the deactivation amplitude. Also, most adults with epilepsy learned the self-regulation, reflected in an increased differentiation (Kotchoubey et al., 2001; Rockstroh et al., 1993; Strehl et al., 2005). In the study with healthy adults, the older group performed better during the transfer condition which was related to the age effect of effort (Kotchoubey et al., 2000).

A last variable to assess training success was the transfer coefficient. The transfer coefficient combines the feedback and the transfer condition and indicates how well a good differentiation in the feedback condition is transmitted to the transfer condition. The transfer coefficient decreased continuously over the course of treatment indicating a worse differentiation in the transfer condition than in the feedback condition. This trend is also obvious in the differentiation data, in which a large differentiation

was observed in the feedback condition but a small differentiation in the transfer condition.

It can only be speculated why the self-regulation ability was not achieved during the transfer condition. The data from feedback condition, the CNV amplitude increase, and the RT improvement suggest that the excitation threshold was changed and improved by the SCP feedback. Therefore the self-regulation ability learned in the feedback condition must have been generalised at some level. Why this generalisation is not reflected in a good performance during the transfer condition is unclear. Possible explanations lie in the comparison of the study design of SCP feedback studies with children, adults with epilepsy, and healthy adults.

A possible explanation is a lack of motivation. In studies with children token systems were applied (Blume, 2011; Drechsler et al., 2007; Strehl et al., 2006), healthy adults received 10 Euro per session whenever they reached a certain threshold (Kotchoubey et al., 2000), and epilepsy patients received behavioural treatment to learn the application of SCP regulation in real-life situations (Kotchoubey et al., 2001). None of these additional motivations were applied in the present study. In the light of motivational deficits and a strong need of positive feedback and praise (R. A. Barkley, 2006) this might have led to the performance deficit. Maybe it was especially hard to stay self-motivated in the difficult and challenging transfer condition which led to much frustration. It can only be assumed that with more training the transfer performance would improve.

Also, it looks like after the first half of training the patients were able to regulate into two different stages although the direction was reversed. This suggests an automatisation of regulation, however reversed. When an SCP shift was produced in the reverse direction, the reward was held off and the participant got frustrated. This either resulted in low motivation and effort, or in high effort to direct the activation in the right direction. The high effort might have disrupted the automatised shift, but could not lead to a desired differentiation. At present, this is only speculation and needs more investigation to be replicated and explained.

Another major difference to other SCP feedback studies is the modification of the activation and deactivation ratio during the course of training. In most studies

the ratio was shifted from 50/50 to e.g. 75/25 half-way through treatment (Blume, 2011; Kotchoubey et al., 2001; Leins et al., 2007; Strehl et al., 2006). However, some studies used the 50/50 ratio for all training sessions as well, but observed good training performance (Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Heinrich et al., 2004; Rockstroh et al., 1993).

The presented data arises from the group average. Individual course of treatment looked rather different from the observed group average. For example, six participants achieved an increased differentiation during the transfer condition and seventeen an increased differentiation during the feedback condition. Also, the individual amplitude change was quite variable. In a single trial for one patient it could range from just above zero to over 120 μV and in individual block averages from 0.3 μV to 40 μV. All this information got lost in the group average.

Finally, the correct data analysis procedure may not have been used. The present study geared the analysis to the most recent analysis technique used in SCP feedback studies with children (Blume, 2011). However, the individual z-standardised t-value approach used in early epilepsy studies, might have yielded more consistent results (Rockstroh et al., 1993). Future research and analysis should investigate a gold standard of training data analysis. This would also benefit the comparison of different studies.

4.3.1 Predictors of outcome

It was hypothesised that the three outcome variables, self-rated ADHD symptom reduction, third-party related symptom reduction, and CNV amplitude change, were correlated with the training performance (i.e. all training variables and their change scores). The outcome is described for all moderate and significant correlations.

There was only one significant negative correlation between CNV amplitude and the negativation amplitude during the transfer condition (TRneg) at the end of training. The larger the CNV amplitude became the more negativity was produced during the transfer trials at the end of training. This is somewhat surprising regarding the inconsistent average training data. However, this highlights that some patients were able to produce negativity in the transfer condition and this was related to high im-

provements in the CNV amplitude. A regression model could not identify a significant predictor, but the correlation between CNV amplitude increase and ADHD symptom reduction, as well as CNV amplitude increase and TRneg post performance, indicates a relationship between the variables. The relationship is not statistically significant but somewhat confirms results from the children studies which found that a predictor for clinical outcome was the ability to produce a negativation in the transfer condition (Drechsler et al., 2007; Strehl et al., 2006).

Further, a moderate negative correlation between CNV amplitude change and the negativation amplitude during the feedback condition (FBneg) at the end of training was observed which also indicates a benefitting relationship between the CNV amplitude change and the ability to produce negativity. A moderate negative correlation between the CNV amplitude change and FBneg pre and post indicates a relationship between the ability to produce negativity during SCP feedback and the change in the experimentally evoked CNV amplitude. Further, there was a moderate negative correlation between the CNV amplitude change and the deactivation amplitude in the feedback (FBpos) and transfer condition (TRpos) at the end of training. The better the ability to create positivity at the end of training, the less the CNV amplitude changed over the course of training. This correlation confirms the expected outcome drawn from studies with children. It was expected that the ability to negativate is associated with a larger CNV change (Heinrich et al., 2004) and the ability to deactivate would rather be associated with a CNV inhibition. Further, this correlation partly contradicts the assumption drawn earlier that the increased positivity is related to a generally increased activation during the baseline phase. However, the CNV change is only correlated with the deactivation amplitude at the end of training, but not to the amplitude change. Therefore no further conclusions should be drawn without analysing the baseline data.

FBneg amplitude at the start and end of treatment also showed a moderate negative correlation with self-rated symptom reduction which means that the ability to produce negativity at the start and end of training correlated with large symptom reductions. Further the differentiation in the transfer condition at the end of treatment showed a moderate positive correlation with self-rated symptom reduction. This highlights

the relationship between good self-regulation ability and high self-rated symptom reductions.

This relation between training success and symptom reduction can also be observed in the positive moderate correlation between the change scores of activation and deactivation during the transfer trials and the third-party rated symptom reductions. And finally, the higher the FBpos amplitude at the start of treatment the smaller the third-party rated symptom reductions. Nevertheless, none of the correlations was significant and the regression analysis for the third-party rated symptom reductions did not reveal any predictors from the training performance.

Kotchoubey et al. (1999) had the similar problem in explaining why good self-regulation ability did not significantly correlate with significant clinical improvements. An analysis of the individual data might yield valuable information. Further, groups of good and bad performers as well as an age-related analysis, might have a better predictive value.

4.4 Control for unspecific effects

Unspecific effects or placebo effects are part of every treatment and it is important to know the amount of specificity of the treatment effect to declare it as an effective treatment. As mentioned in the introduction 1.2.3, the needed double blind or sham condition designs are a challenge for neurofeedback treatment. Therefore, the unspecific effects were measured with the FERT questionnaire (Vollmann et al., 2009) which yields valuable information about the influence of possible unspecific effects. The relevant analysed factors constituted patients treatment expectations, evaluation of the professional competence of the therapist, and willingness of the patient to engage in the therapy. It was hypothesised that none of these unspecific factors change significantly over the course of training. This hypothesis was only confirmed for the patient treatment expectations.

The treatment expectations did not change over time. They stayed stable around the value of five on the 1-7 Likert scale which reflects a “rather agree". Similar results were found in a study with adult epilepsy patients (Kotchoubey, Strehl, Holzapfel, Schneider, et al., 1999). This suggests that the expectations were not only due to the

novelty of the treatment but that the patients also believed in the treatment effect over the course of treatment.

The willingness of the patient to engage in the therapy increased until the 20th session from “undecided" towards “agree" and decreased from there to “rather agree". The items were related to how open the patients were to express negative emotions. However, the patients often had trouble to answer the related questions as they did not feel the need to express negative emotions. They became rather annoyed about the questionnaire, respectively the questions that did not relate to neurofeedback treatment. This might explain the decrease in the factor willingness to engage in the treatment or respectively, to fill in the questionnaire.

The rating of professional competence of the therapist increased constantly over all sessions from “rather agree" to “agree". This might reflect the increasing self-assurance of the therapist over the weeks and months of the study that the patient felt as well.

The change of these factors does not reveal an influence of unspecific factors in the treatment. However, the following correlation and regression analyses yield this information. It was hypothesised that none of the assessed factors correlate positively with behavioural and neurophysiological changes. This was not true for all factors.

As the treatment expectations did not change over time, the mean expectation was correlated with the self-rated symptom reduction and revealed significant positive correlation; the higher the symptom reduction the higher the treatment expectations. Therefore, unspecific effects are present in the treatment outcome.

This is also shown in the positive correlation of the mean rating of professional competence and self-rated symptom reduction, whereby a high symptom reduction is related to high ratings of the professional competence of the therapist. The better the patients felt professionally and well cared for the more their symptoms reduced. Kotchoubey et al. (1999) also found high ratings in competency of the therapist, however only for the indefinite responder group (as compared to a responder and a non-responder group).

Finally, the change in willingness to engage in the therapy correlated positively with symptom reduction; the willingness decreased as the symptom reduction increased.

For an unspecific effect the opposite would be expected. The willingness of the patient to engage in the therapy was assessed through questions about daring to report embarrassing or negative feelings. Maybe the patients answered that question more in terms of not having any of these negative emotions instead of not daring to report them. This would be supported by the improvements on the depression scale.

In the regression analysis, the change in willingness accounted for 34% of the variation in self-rated ADHD symptom reduction. The complete model included the mean expectancy as well and accounted for 55% of the variation. The regression analysis did not identify the rating of the professional competence of the therapist as a predictor for symptom reduction. If the willingness did actually reflect reduced depression or negative feelings then this is a good explanation for the high predictive value. However, this would not support unspecific effects, but rather the reduced comorbid symptoms through SCP feedback.

Expectancy as an unspecific effect is revealed in the regression analysis with a predictive power of approximately 20% i.e. approximately 20% of the symptom reduction can be explained by the unspecific or placebo effect of expectation. However, a correlation with expectancy was somewhat anticipated and wanted. “Neurofeedback practitioners should embrace placebo effects and learn to systematically encourage and maximise placebo components that contribute to positive treatment response" (Hammond, 2011).

Correlations with two other outcome variables were observed, but did not reach significance. There was a small negative correlation with mean willingness and the third-party rated symptom reduction; the smaller the willingness of the patient to engage in the therapy the higher the third-party rated symptom reduction. This argues against an unspecific effect, respectively for the hypothesis that this factor reflects the experience of negative emotions rather than the failure of reporting them. Therefore, low patient rated negative emotions are correlated with a perceived symptom reduction of relatives or friends.

Further, a positive correlation with the increased rating of competency of the therapist and the third-party rated symptom reduction was observed. The more the patients perceived the therapist as professional and presumably communicated this

perception at home, the higher the relatives or friends perceived and rated the patients symptom reduction.

Last but not least, a positive correlation of the mean willingness with the mean CNV change score was observed; the more the patients were willing to engage in the therapy, the more the CNV amplitude increased. Keeping the assumption that this factor might reflect negative emotions, this means that the more negative emotions the patient experienced the more the CNV amplitude increased. This might be related to the general symptom severity, which would lead to the assumption that high symptom severity is related to more potential to change the neurophysiology. However, this is just a gedankenexperiment.

The second approach to control for unspecific effects is the correlation between neurofeedback training performance and behavioural, as well as neurophysiological changes (Leins, 2004; Lubar, 1997). Moderate correlations can be observed between the self-rated ADHD symptom reduction and the CNV amplitude change and both of these outcome variables with the training variable FBneg. This highlights a relationship that can only be due to specific effects of SCP feedback.

A final comment about the control of unspecific effects is a neurobiological consideration. In patients with impaired dopaminergic related frontal functions (e.g. Parkinson's disease and Alzheimer dementia) the observation of less placebo effect was explained with the impaired reward system (Benedetti et al., 2010). ADHD is also known to be a frontal disorder with changes in the dopaminergic reward system. Therefore the question arises if worrying about a large amount of unspecific effects accounting for symptom reductions is actually indicated.

4.5 Limitations

The present study could not confirm all hypotheses, and led to a number of unexpected results. This was a pilot study and therefore several methodological weaknesses might be responsible for this.

First of all a bigger sample size would have been favourable to obtain more statistical power. This way, observed trends e.g. CNV increase and RT and RTV decrease pre-post treatment might become statistically significant.

The hypothesised differences between the ADHD group and the control group were not confirmed for all variables (i.e. test of attention, error rate, and CNV amplitude at all sites). There are a number of possible explanations for this. Firstly, it is possible that the sample ADHD population was not representative. This could be due to the difficulties in diagnosing ADHD (Bell, 2011) and the fairly large diversity of symptoms. Further, the patient sample consisted out of many highly functional adults with ADHD (i.e. students, doctoral students, and well positioned employees). It was difficult to find patients with severe ADHD, and respectively obtain them to participate in the study. This was also due to the exclusion criteria (e.g. current depression, anxiety, and ongoing psychotherapy). Therefore, the patient sample might not be representative for ADHD (i.e. did not include the wide range of ADHD subtypes and severity) and expected differences might have not been observed for that reason.

Another reason for the lack of differences between the ADHD and the control group might be the CNV protocol and measurement. The protocol did elicit only a small amount of errors which made it hard to find differences between the two groups and measurement points. This might be explained by a ceiling effect. Also, there was a relatively high variation within the CNV amplitude which resulted in non normally distributed data. Some participants showed high alpha activity which could not be filtered out and led to large standard variations. This might have been due to the eyes-closed condition of the CNV task. But also, patients who normally had been on medication were asked to not take any 24h before the EEG measurement. Some of these patients showed particularly high alpha probably due to tiredness without their stimulants. This might also contribute to the lack of a significant group specific increase of the CNV amplitude pre-post treatment.

Another methodological weakness of this study is revealed in the correlation of self-rated and third-party rated symptom reduction. It was hypothesised that they would correlate with each other; however this was not the case. This might be due to the selection of questionnaires. The self-rated and third-party rated questionnaires were taken from different manuals because the standardised and validated HASE instrument did not include a third-party rated questionnaire. However, symptom scales might be more comparable and consistent taken from the same manual if

the questions were the same, except written in “I" or “he/she" form. Anyway, a standardised German third-party questionnaire was not available at the time of the study.

Finally, the training data did not confirm the hypothesised pattern of increasing negativation amplitude. This could be due to the method of analysis. As mentioned earlier there is no validated method available. Here, the field is still open for alternative procedures that might yield more consistent results. The analysis should include the baseline phase as well as the processing and statistical analysis approach used in earlier epilepsy studies (Rockstroh et al., 1993).

4.6 Conclusion

This is the first study investigating in slow cortical potential (SCP) feedback in adults with ADHD. This is also one of the first studies investigating in an ADHD population with participants older than 50 years (age range: 21-66). The results confirm that differences between adults with ADHD and healthy adults (e.g. slower reaction time and smaller contingent negative variation (CNV) amplitude) persist into mid adulthood. These findings suggest that decreased CNV amplitude could be used as a neurophysiological marker for ADHD. The observed persistent neurophysiological deficits endorse the application of neurofeedback as a neurophysiological treatment option for adult ADHD which has been effective in children with ADHD already (Drechsler et al., 2007; Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Heinrich et al., 2004; Leins et al., 2007; Strehl et al., 2006; Wangler et al., 2011).

The results of this study indicate that SCP feedback is an effective treatment for adult ADHD. We observed a reduction in ADHD symptoms, as well as a reduction in comorbid symptoms measured using self- and third-party rated questionnaires. Improvements of neuropsychological as well as neurophysiological variables of CNV amplitude were achieved. Observed differences between adults with ADHD and healthy controls diminished following SCP feedback.

Adults with ADHD were able to learn self-regulation of SCPs. The average training data showed an unexpected and inconsistent pattern of variable change over the course of treatment. Instead of the expected main increase in negativation amplitude,

a main increase in positivation amplitude was observed. However, individual data and somewhat the averaged data show that self-regulation was achieved. However, future analysis and research should investigate in better analysis techniques and age-related and age-mediated differences in learning SCP regulation.

A number of unspecific effects were identified as part of SCP feedback outcome, as observed in all kinds of treatments. However, these unspecific effects cannot account for all treatment effects. Correlations between the symptom reduction, training performance, and CNV amplitude change suggest that SCP feedback is an effective and efficacious treatment. However, the latter needs more controlled testing.

SCP feedback is already an effective (Mayer, Wyckoff, & Strehl, 2012) and long-term (Gani et al., 2008) treatment for children with ADHD. The present study constitutes the first step towards an acknowledged and recognised treatment option for adult ADHD, too. Future research should aim to strengthen this acknowledgment and advance this new, effective, and long-term treatment option for adults with ADHD.

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Appendix

This appendix includes forms and tables referred to in the main document:

1. Phone questionnaire
2. Information material for the ADHD group
3. FERT questionnaire
4. Information material for the control group
5. t-values ADHD score

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Demographischer Fragebogen

Patientencode:_____

Geburtstag: _____

Geschlecht: Männlich ☐ Weiblich ☐

Händigkeit: Rechts ☐ Links ☐ Beidhändig ☐

Höchster Bildungsabschluss: _____

Wie viele Jahre haben Sie in Bildungsanstalten verbracht (Schule, Universität, Berufsschule, etc.)? _____

Was ist Ihr Beruf? _____

Wurde bei Ihnen eine ADHS diagnostiziert? Ja ☐ Nein ☐

Haben Sie schon mal an einer Neurofeedbackstudie teilgenommen? Ja ☐ Nein ☐

Befinden Sie sich zurzeit in Psychotherapeutischer Behandlung? Ja ☐ Nein ☐

Vorerkrankungen und Medikamenten:

Hatten Sie schon mal eine Kopfverletzung mit Bewusstlosigkeit? Ja ☐ Nein ☐

Wenn ja, bitte beschreiben Sie wo und wie lange Sie bewusstlos waren: _____

_____

Haben Sie neurologische Vorerkrankungen, wie z.B. Epilepsie? Ja ☐ Nein ☐

Wenn ja, bitte beschreiben Sie. _____

_____

Nehmen Sie im Moment regelmäßig Medikamente? Ja ☐ Nein ☐

Wenn ja welche und für wie lange? _____

_____

Wenn weiblich, nehmen Sie die Pille? Ja ☐ Nein ☐

Wenn weiblich, sind Sie schwanger? Ja ☐ Nein ☐

Haben Sie schon mal über einen längeren Zeitraum regelmäßig Medikamente eingenommen? Ja ☐ Nein ☐

Wenn ja beschreiben Sie bitte Art, Dauer und Zeitpunkt: _____

_____

Leiden Sie an einer der folgenden Krankheiten:

	Lungenkrankheit	Ja ☐	Nein ☐
	Herzkrankheiten	Ja ☐	Nein ☐
	Diabetes	Ja ☐	Nein ☐
	Bluthochdruck	Ja ☐	Nein ☐
	Rheuma	Ja ☐	Nein ☐
Andere Erkrankungen, wie:			
	Parkinson	Ja ☐	Nein ☐
	Schlaganfall	Ja ☐	Nein ☐
	Multiple Sklerose	Ja ☐	Nein ☐
	Epilepsie	Ja ☐	Nein ☐
	Bipolare Störung	Ja ☐	Nein ☐
	Psychosen	Ja ☐	Nein ☐
	Zwangshandlungen	Ja ☐	Nein ☐
	Chronische Tics	Ja ☐	Nein ☐
	Tourettesyndrom	Ja ☐	Nein ☐

Haben Sie einen Herzschrittmacher? Ja ☐ Nein ☐

Besteht bei Ihnen eine Rot-Grün-Blindheit? Ja ☐ Nein ☐

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Neurofeedback für Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) bei Erwachsenen: Ein Vergleich von Training der langsamen kortikalen Potentiale und Nah-Infrarotspektroskopietraining

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Informationsblatt für Studienteilnehmer

Sehr geehrte Dame, sehr geehrter Herr,

Wir bedanken uns für Ihr Interesse an der oben genannten Studie. In dieser Studie werden die Wirkmechanismen einer neuen Art von Psychotherapie zur Behandlung einer Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) bei Erwachsenen erforscht. Deswegen fördern Sie durch Ihre freiwillige Teilnahme nicht nur die psychologische Grundlagenforschung, sondern auch die Entwicklung klinisch-psychologischer Verfahren, die hoffentlich zu einem besseren Verständnis und einer erfolgreicheren Behandlung von ADHS im Erwachsenenalter beitragen werden.

Im Folgenden werden Hintergrund, Ziele und Methoden sowie der erwartete Nutzen und mögliche Risiken dieser Studie dargestellt. Sollten Sie beim Verständnis irgendwelche Schwierigkeiten haben, können Sie sich jederzeit an die Studienleiter wenden.

Hintergrund und Ziele

An unserem Institut wir bereits seit vielen Jahren Forschung zu ADHD betreiben. Lange Zeit ging man davon aus, dass die Störung ausschließlich im Kindesalter besteht und sich mit dem Erwachsenenalter auswächst. Mittlerweile konnte anhand wissenschaftlicher Studien gezeigt werden, dass diese Krankheit bei bis zu 80% der Betroffenen auch im Erwachsenenalter bestehen bleibt. Noch ist unser Wissen über diese Erkrankung vergleichsweise gering und daher auch die Therapieverfahren noch wenig entwickelt. Daher sind wir auf wissenschaftliche Studien angewiesen, um mehr über diese Störung und ihre Behandlungsmöglichkeiten zu erfahren. In dieser Studie wollen wir vor allem Informationen über die Unterschiedliche Arbeitsweise von Gehirnen von ADHS-Patienten gewinnen und mit der Neurofeedbacktherapie vorliegende Fehlfunktionen umtrainieren. EEG-Neurofeedback (siehe unten) ist bei Kindern schon ein bewährtes Verfahren und soll nun auch im Erwachsenenbereich getestet werden. NIRS-Neurofeedback (siehe unten) ist ein sehr neues

aber auch sehr vielversprechendes Verfahren, welches hier getestet und mit dem EEG-Neurofeedback verglichen werden soll.

Teilnahmebedingungen und Ablauf

Wenn Sie an unserer Studie teilnehmen möchten, ist es notwendig zunächst an einer diagnostischen Untersuchung teilzunehmen, damit wir prüfen können, ob die Teilnahmekriterien bei Ihnen erfüllt sind. Die umfassende Diagnostik wird etwa 4 bis 5 Stunden dauern und beinhaltet ein Interview, verschiedene computergestützte Verfahren zur Messung von Konzentrationsvermögen und Aufmerksamkeitsleistungen sowie eine Elektroenzephalogramm (EEG)- und eine funktionelle Nah-Infrarotspektroskopie (fNIRS)-Untersuchung (siehe unten).

Zudem bitten wir Sie darum, zuhause verschiedene Fragebögen auszufüllen. Wenn Sie die Teilnahmekriterien erfüllen, werden Sie an einem Neurofeedbacktraining (siehe unten) mit insgesamt 30 Sitzungen (Dauer: ca. 1 Stunde) teilnehmen. Dieses Training umfasst 2 Sitzungen pro Woche über 15 Wochen. Direkt im Anschluss an die 15. und an die letzte Sitzung müssen wieder Fragebögen ausgefüllt werden, und computerbasierte Messungen sowie eine fNIRS-Untersuchung und eine EEG-Ableitungen stattfinden. Der dritte und letzte Messtermin wird sechs Monate im Anschluss daran stattfinden.
Ihre persönlichen Daten – Name, Adresse, Krankheitsgeschichte, usw. – unterliegen der Schweigepflicht und werden in der Gesamtheit nur dem Versuchsleiter bekannt. Computerdateien werden ohne Namen nach einer internen Codierung benannt (psyeudonymisiert), so dass es für Dritte (die eventuell an der Auswertung beteiligt werden) unmöglich ist, eine Verbindung zu Ihrer Person herzustellen. Alle gesammelten Daten werden auf den jeweiligen Computern und zusätzlich auf externen Festplatten verschlüsselt gespeichert. Alle Daten werden in digitalem und Papierformat für 10 Jahre aufbewahrt und nach diesen 10 Jahren vernichtet.

Das Elektroenzephalogramm (EEG)

In der EEG-Untersuchung wird Ihr Elektroenzephalogramm (EEG) erfasst. D.h. es wird Ihnen kein elektrischer Strom verabreicht, sondern es werden Ihre eigenen Hirnströme gemessen. Zu diesem Zweck werden auf Ihrer Kopfhaut und auf Ihrem Gesicht insgesamt 36 Elektrodenangebracht. Auf die Stellen wo die Elektroden liegen, wird hautverträgliches Elektrolytgel aufgetragen, um eine gute Leitfähigkeit zu gewährleisten. Die Stellen im Gesicht werden zusätzlich mit Alkohol gereinigt.

Während der EEG-Untersuchung werden Ihnen über Lautsprecher Geräusche dargeboten. Ihre Lautstärke ist so angepasst, dass sie gut hörbar und gleichzeitig nicht unangenehm laut sind. Von den Reaktionen Ihres Gehirns auf diese einfachen Reize können wir auf bestimmte mit der Aufmerksamkeit verbundene Grundfunktionen des Gehirns schließen.

Kommen Sie bitte zu den EEG-Untersuchungen mit frisch gewaschenen Haaren, die auch nicht mit Haarlack, Stylinggel oder sonstigen Präparaten nachbehandelt wurden, damit die nötige Leitfähigkeit schnell und unproblematisch erreicht wird. Das Elektrolytgel ist leicht auswaschbar und wenn Sie möchten, können Sie Ihre Haare gleich nach dem Experiment bei uns im Institut waschen und trocknen.

Es sind keine Risiken oder Nebenwirkungen der EEG-Ableitung bekannt. Es besteht jedoch die Möglichkeit von vorübergehenden Hautreizungen, hervorgerufen durch das Reinigen der Kopfhaut mit abrasivem Reinigungsgel und dem anschließenden Auftragen von Elektrodengel zur Verbesserung der elektrischen Leitfähigkeit zwischen Haut und Elektrode.

Die funktionelle Nah-Infrarotspektroskopie (fNIRS)

Die Nah-Infrarotspektroskopie ist ein Untersuchungsverfahren, mit dem die Durchblutung des Gehirns gemessen werden kann, ohne dass in das Gehirn selbst eingegriffen werden muss. Dazu werden kleine „Messknöpfchen“ (Optoden) in einer Gummiplatte an die

Kopfhaut gelegt und mit einem Band befestigt. Mit diesem Messinstrument wird nun unschädliches Licht genau festgelegter Wellenlänge ausgesendet und die Menge an reflektiertem Licht gemessen. An Hand dieses Messergebnisses können dann Durchblutungsänderungen des Gehirns errechnet werden, die einen Hinweis auf die Hirnaktivität geben.

Während der fNIRS-Untersuchung sollen Sie drei Aufgaben bearbeiten, die Ihnen auf einem Computerbildschirm präsentiert werden. Mit Hilfe dieser Aufgaben können wir Prozesse untersuchen, die mit Aufmerksamkeit, Wortflüssigkeit und Arbeitsgedächtnis zusammenhängen. Alle Aufgaben werden Ihnen jeweils zu Beginn ausführlich erklärt. Computerkenntnisse sind nicht erforderlich, um die Aufgaben zu lösen.

Kommen Sie bitte auch zu den fNIRS-Untersuchungen mit frisch gewaschenen Haaren, die auch nicht mit Haarlack, Stylinggel oder sonstigen Präparaten nachbehandelt wurden, damit die „Messknöpfchen“ (Optoden) schnell und unproblematisch angebracht werden können.

Es sind keine Risiken oder Nebenwirkungen der fNIRS-Untersuchung bekannt.

Das Neurofeedbacktraining

Nachdem alle Voruntersuchungen abgeschlossen sind, beginnt das Neurofeedbacktraining. In unsere Studie werden zwei verschiedene Neurofeedbacktrainingsarten verwendet. Bei insgesamt 40 Studienteilnehmern werden jeweils 20 zufällig auf das ein oder andere Training aufgeteilt. Diese Aufteilung erfolgt nach Abschluss der Voruntersuchungen.

Das EEG - Neurofeedback-Training

Während des Neurofeedback-Trainings sitzen Sie vor einem Computerbildschirm. Ihre Gehirnströme werden über eine aufgeklebte Messelektrode abgeleitet und steuern ein Computerprogramm. Je nach Konzentrationsgrad können Sie mit Ihrer Gedankenkraft verschieden Objekt nach oben oder unten bewegen. Mit diesem computergestützten Verfahren können Sie somit selber Strategien erarbeiten, um sich besser zu konzentrieren und Ihr Verhalten zu steuern.
Da insgesamt nur 7 Elektroden für das Neurofeedback-Training geklebt werden müssen, ist es nicht nötig dass Sie zu den Sitzungen mit frisch gewaschenen Haaren kommen.

Sollte entgegen der vorliegenden Erfahrungen und entgegen der Erwartung irgendein Teil der Untersuchung oder des Trainings zu anstrengend für Sie sein, wird diese(s) abgebrochen. Darüber hinaus dürfen Sie die Untersuchung bzw. das Training auch aus anderen Gründen, die Sie niemandem erklären müssen, jederzeit beenden. Dadurch entstehen für Sie keine Nachteile.

Das NIRS - Neurofeedback-Training

Während des Neurofeedback-Trainings sitzen Sie vor einem Computerbildschirm. Die Durchblutung Ihres Gehirns wird von den „Messknöpfchen“ (Optoden) aufgezeichnet und steuert ein Computerprogramm. Dabei hören Sie verschiedene Töne, die Ihnen anzeigen, ob Sie sich stark konzentrieren oder entspannen sollen. Auf dem Computerbildschirm können Sie sehen, wie gut Ihnen dies jeweils gelingt. Mit diesem computergestützten Verfahren können Sie somit selber Strategien erarbeiten, um sich besser zu konzentrieren und Ihr Verhalten zu steuern.
Die „Messknöpfchen“ (Optoden) brauchen einen sehr guten Kontakt zur Kopfhaut, um Ihre Hirndurchblutung aufzeichnen zu können. Deshalb ist es nötig dass Sie auch vor den Trainings-Sitzungen keinen Haarlack, Stylinggel o.ä. benutzen.

Da es sich beim Neurofeedbacktraining um eine Therapie handelt, wird für die Teilnahme ein Betrag von 150€ berechnet. Nach erfolgreicher Teilnahme an der gesamten Studie (also nach der letzten Messung sechs Monate nach Trainingsende) bekommen Sie diesen Betrag als Belohnung für Ihren Aufwand wieder ausgezahlt. Falls Sie diesen Betrag nicht

finanzieren können, werden wir über eine individuelle Lösung sprechen. Ihre Teilnahme ist vollkommen freiwillig und sie können jederzeit ohne Angabe von Gründen und jeglicher Nachteile die Studie abbrechen.

Falls Sie weitere Fragen haben, steht die Versuchsleiterin Ihnen gerne zur Verfügung.

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Datum: ..... Code-Nr.: .....

FERT

Auf der folgenden Seite finden Sie eine Reihe von Aussagen, die sich auf die Therapie beziehen. Im *ersten Abschnitt* geht es um Einschätzungen der letzten, d.h. der am kürzesten zurückliegenden Therapiesitzung. Die Aussagen im *zweiten Abschnitt* beziehen sich auf die Woche vor der letzten Therapiesitzung.

Wählen Sie für jede Aussage diejenige Antwort, die für Sie am besten zutrifft. Bitte versuchen Sie, möglichst spontan und aufrichtig zu antworten. Es gibt keine richtigen oder falschen Antworten. Uns interessiert Ihre persönliche Meinung.

Lesen Sie bitte alle Sätze durch und lassen Sie keine Antwort aus. Wenn Sie sich unsicher sind, wählen Sie die am ehesten zutreffende Antwort.

Aus Gründen der Vereinfachung wird im Fragebogen nur die männliche Form „der Therapeut" verwendet, anstatt immer beide Formen „der Therapeut/die Therapeutin" aufzuführen.

Diese Untersuchung dient allein wissenschaftlichen Forschungszwecken und wird anonym durchgeführt und ausgewertet.

Geben Sie bitte Ihren Namen nicht an, sondern machen Sie lediglich folgende
Angaben zu Ihrer Person:

Alter: ..... **Geschlecht:** O m. O w.

Schulabschluss:
kein Schulabschluss ..... O
Hauptschule..... O
Realschule/mittlere Reife..... O
Abitur..... O
Abgeschlossenes Studium (Universität; FH)..... O

Partnerschaft:
verheiratet o. feste Partnerschaft..... O
keine feste Partnerschaft ..... O

Wie lange leiden Sie unter der Problematik, derentwegen sie die Therapie begonnen haben (Angabe in Monaten/Jahren)?

.....

Wie stark fühlen Sie sich zurzeit dadurch belastet?

sehr stark..... O
stark..... O
mittelmäßig..... O
wenig..... O
gar nicht..... O

Datum: ..... Code-Nr.: .....

FERT

Die Zahlen bedeuten folgendes:

① = „stimmt überhaupt nicht" ② = „stimmt nicht" ③ = „stimmt eher nicht" ④ = „stimmt teils-teils"

⑤ = „stimmt eher" ⑥ = „stimmt " ⑦ = „stimmt voll und ganz"

1. Abschnitt

In der letzten Therapiesitzung...

1.	wirkte das Auftreten meines Therapeuten professionell.	① ② ③ ④ ⑤ ⑥ ⑦
2.	hat mein Therapeut schwierige Zusammenhänge verständlich erklärt.	① ② ③ ④ ⑤ ⑥ ⑦
3.	hat mich das Verhalten meines Therapeuten irritiert.	① ② ③ ④ ⑤ ⑥ ⑦
4.	habe ich mich getraut, Dinge zu sagen, die mir peinlich sind.	① ② ③ ④ ⑤ ⑥ ⑦
5.	ging mein Therapeut planvoll und zielorientiert vor.	① ② ③ ④ ⑤ ⑥ ⑦
6.	wirkte mein Therapeut überzeugt von seinem Vorgehen.	① ② ③ ④ ⑤ ⑥ ⑦
7.	habe ich mich sicher gefühlt.	① ② ③ ④ ⑤ ⑥ ⑦
8.	habe ich gemerkt, dass mein Therapeut viel Erfahrung hat.	① ② ③ ④ ⑤ ⑥ ⑦
9.	habe ich mich gut mit meinem Therapeuten verstanden.	① ② ③ ④ ⑤ ⑥ ⑦
10.	hatte ich den Eindruck, dass mein Therapeut ein Spezialist für meine Beschwerden ist.	① ② ③ ④ ⑤ ⑥ ⑦
11.	habe ich gespürt, dass mein Therapeut mich schätzt.	① ② ③ ④ ⑤ ⑥ ⑦
12.	hatte ich das Gefühl, dass mein Therapeut mir seine ehrliche Meinung sagt.	① ② ③ ④ ⑤ ⑥ ⑦
13.	habe ich gemerkt, dass mein Therapeut viel über psychische Probleme weiß.	① ② ③ ④ ⑤ ⑥ ⑦
14.	fühlte ich mich von meinem Therapeuten als Mensch akzeptiert.	① ② ③ ④ ⑤ ⑥ ⑦
15.	habe ich gespürt, dass ich meinem Therapeuten vertrauen kann.	① ② ③ ④ ⑤ ⑥ ⑦
16.	haben wir gut zusammengearbeitet.	① ② ③ ④ ⑤ ⑥ ⑦
17.	bin ich das Risiko eingegangen, auch unangenehme Gefühle zu erleben.	① ② ③ ④ ⑤ ⑥ ⑦
18.	habe ich gemerkt, dass meinem Therapeut positive Veränderungen genauso wichtig sind wie mir.	① ② ③ ④ ⑤ ⑥ ⑦
19.	habe ich mich unwohl gefühlt.	① ② ③ ④ ⑤ ⑥ ⑦
20.	hatte ich das Gefühl, dass ich mich verteidigen muss.	① ② ③ ④ ⑤ ⑥ ⑦
21.	konnte ich über meinen Schatten springen.	① ② ③ ④ ⑤ ⑥ ⑦
22.	hat sich mein Therapeut sehr einfühlsam verhalten.	① ② ③ ④ ⑤ ⑥ ⑦
23.	habe ich gemerkt, dass mein Therapeut gut ausgebildet ist.	① ② ③ ④ ⑤ ⑥ ⑦

Datum: ..... Code-Nr.: .....

FERT

Die Zahlen bedeuten folgendes:

① = „stimmt überhaupt nicht" ② = „stimmt nicht" ③ = „stimmt eher nicht" ④ = „stimmt teils-teils"
⑤ = „stimmt eher" ⑥ = „stimmt " ⑦ = „stimmt voll und ganz"

2. Abschnitt

In der Woche vor der letzten Therapiesitzung....

24.	habe ich in der Therapie einen Weg gesehen, um mit meinen Schwierigkeiten fertig zu werden.	① ② ③ ④ ⑤ ⑥ ⑦
25.	war ich überzeugt, dass es mir am Ende der Therapie deutlich besser gehen wird.	① ② ③ ④ ⑤ ⑥ ⑦
26.	habe ich mir gedacht, dass ich am Ende der Therapie mit meinem Alltag besser zurecht kommen werde.	① ② ③ ④ ⑤ ⑥ ⑦
27.	war ich überzeugt, dass sich durch die Therapie bald Verbesserungen einstellen werden.	① ② ③ ④ ⑤ ⑥ ⑦
28.	hatte ich das Gefühl, dass die Therapie mir helfen wird.	① ② ③ ④ ⑤ ⑥ ⑦
29.	habe ich geglaubt, dass die Therapie zu einer Verbesserung der Symptome führen wird.	① ② ③ ④ ⑤ ⑥ ⑦
30.	habe ich gedacht, dass ich mich am Ende der Therapie viel wohler fühlen werde.	① ② ③ ④ ⑤ ⑥ ⑦
31.	war ich überzeugt, dass sich mein Leben durch die Therapie nachhaltig verändern wird.	① ② ③ ④ ⑤ ⑥ ⑦

Vielen Dank!

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Neurofeedback für Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) bei Erwachsenen:
Ein Vergleich von Training der langsamen kortikalen Potentiale und Nah-Infrarotspektroskopietraining

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Informationsblatt für Studienteilnehmer

Sehr geehrte Dame, sehr geehrter Herr,

Wir bedanken uns für Ihr Interesse an der oben genannten Studie. In dieser Studie werden physiologische Unterschiede zwischen gesunden Kontrollprobanden und Patienten mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) erforscht. Deswegen fördern Sie durch Ihre freiwillige Teilnahme nicht nur die psychologische Grundlagenforschung, sondern auch die Entwicklung klinisch-psychologischer Verfahren, die hoffentlich zu einem besseren Verständnis und einer erfolgreicheren Behandlung von ADHS im Erwachsenenalter beitragen werden.

Im Folgenden werden Hintergrund, Ziele und Methoden sowie der erwartete Nutzen und mögliche Risiken dieser Studie dargestellt. Sollten Sie beim Verständnis irgendwelche Schwierigkeiten haben, können Sie sich jederzeit an die Studienleiter wenden.

Hintergrund und Ziele

An unserem Institut wir bereits seit vielen Jahren Forschung zu ADHD betreiben. Lange Zeit ging man davon aus, dass die Störung ausschließlich im Kindesalter besteht und sich mit dem Erwachsenenalter auswächst. Mittlerweile konnte anhand wissenschaftlicher Studien gezeigt werden, dass diese Krankheit bei bis zu 80% der Betroffenen auch im Erwachsenenalter bestehen bleibt. Noch ist unser Wissen über diese Erkrankung vergleichsweise gering und daher auch die Therapieverfahren noch wenig entwickelt. Daher sind wir auf wissenschaftliche Studien angewiesen, um mehr über diese Störung und ihre Behandlungsmöglichkeiten zu erfahren. In dieser Studie wollen wir vor allem Informationen über die Unterschiedliche Arbeitsweise von Gehirnen von ADHS-Patienten gewinnen.

Teilnahmebedingungen und Ablauf

Sie nehmen im Rahmen einer gesunden Kontrollgruppe an der Studie teil. Die Kontrollpersonen müssen in einigen Kriterien mit einem weiteren Studienteilnehmer aus der Therapiegruppe übereinstimmen. Dafür wird ein Vorabscreening durchgeführt. Wenn Sie als Kontrollperson aufgenommen werden können, bitten wir Sie verschiedene Fragebögen auszufüllen. Danach werden Sie an zwei Terminen an einer Elektroenzephalogramm (EEG)- und eine funktionelle Nah-Infrarotspektroskopie (fNIRS)-Untersuchung (siehe unten) teilnehmen. Das Ausfüllen der Fragebogen, die EEG- und NIRS-Untersuchungen werden ungefähr 4 Stunden dauern. Drei bis vier Monate nach der ersten Messung folgt eine Folgemessung mit dem gleichen Ablauf. Der gesamte zeitliche Aufwand für die Studie beträgt also 8 Stunden.

Ihre persönlichen Daten unterliegen der Schweigepflicht und werden in der Gesamtheit nur dem Versuchsleiter bekannt. Computerdateien werden ohne Namen nach einer internen Codierung benannt (pseudonymisiert), so dass es für Dritte (die eventuell an der Auswertung beteiligt werden) unmöglich ist, eine Verbindung zu Ihrer Person herzustellen. Alle gesammelten Daten werden auf den jeweiligen Computern und zusätzlich auf externen Festplatten verschlüsselt gespeichert. Alle Daten werden in digitalem und Papierformat für 10 Jahre aufbewahrt und nach diesen 10 Jahren vernichtet.

Das Elektroenzephalogramm (EEG)

In der EEG-Untersuchung wird Ihr Elektroenzephalogramm (EEG) erfasst. D.h. es wird Ihnen kein elektrischer Strom verabreicht, sondern es werden Ihre eigenen Hirnströme gemessen. Zu diesem Zweck werden auf Ihrer Kopfhaut und auf Ihrem Gesicht insgesamt 36 Elektroden angebracht. Auf die Stellen wo die Elektroden liegen, wird hautverträgliches Elektrolytgel aufgetragen, um eine gute Leitfähigkeit zu gewährleisten. Die Stellen im Gesicht werden zusätzlich mit Alkohol gereinigt.

Während der EEG-Untersuchung werden Ihnen über Lautsprecher Geräusche dargeboten. Ihre Lautstärke ist so angepasst, dass sie gut hörbar und gleichzeitig nicht unangenehm laut sind. Von den Reaktionen Ihres Gehirns auf diese einfachen Reize können wir auf bestimmte mit der Aufmerksamkeit verbundene Grundfunktionen des Gehirns schließen.

Kommen Sie bitte zu den EEG-Untersuchungen mit frisch gewaschenen Haaren, die auch nicht mit Haarlack, Stylinggel oder sonstigen Präparaten nachbehandelt wurden, damit die nötige Leitfähigkeit schnell und unproblematisch erreicht wird. Das Elektrolytgel ist leicht auswaschbar und wenn Sie möchten, können Sie Ihre Haare gleich nach dem Experiment bei uns im Institut waschen und trocknen.

Es sind keine Risiken oder Nebenwirkungen der EEG-Ableitung bekannt. Es besteht jedoch die Möglichkeit von vorübergehenden Hautreizungen, hervorgerufen durch das Reinigen der Kopfhaut mit abrasivem Reinigungsgel und dem anschließenden Auftragen von Elektrodengel zur Verbesserung der elektrischen Leitfähigkeit zwischen Haut und Elektrode.

Die funktionelle Nah-Infrarotspektroskopie (fNIRS)

Die Nah-Infrarotspektroskopie ist ein Untersuchungsverfahren, mit dem die Durchblutung des Gehirns gemessen werden kann, ohne dass in das Gehirn selbst eingegriffen werden muss. Dazu werden kleine „Messknöpfchen“ (Optoden) in einer Gummiplatte an die Kopfhaut gelegt und mit einem Band befestigt. Mit diesem Messinstrument wird nun unschädliches Licht genau festgelegter Wellenlänge ausgesendet und die Menge an reflektiertem Licht gemessen. An Hand dieses Messergebnisses können dann Durchblutungsänderungen des Gehirns errechnet werden, die einen Hinweis auf die Hirnaktivität geben.

Während der fNIRS-Untersuchung sollen Sie zwei Aufgaben bearbeiten, die Ihnen auf einem Computerbildschirm präsentiert werden. Mit Hilfe dieser Aufgaben können wir Prozesse

untersuchen, die mit Aufmerksamkeit und Arbeitsgedächtnis zusammenhängen. Beide Aufgaben werden Ihnen jeweils zu Beginn ausführlich erklärt. Computerkenntnisse sind nicht erforderlich, um die Aufgaben zu lösen.

Kommen Sie bitte auch zu den fNIRS-Untersuchungen mit frisch gewaschenen Haaren, die auch nicht mit Haarlack, Stylinggel oder sonstigen Präparaten nachbehandelt wurden, damit die „Messknöpfchen“ (Optoden) schnell und unproblematisch angebracht werden können.

Es sind keine Risiken oder Nebenwirkungen der fNIRS-Untersuchung bekannt.

Vergütung

Ihre Teilnahme wird mit 8 Euro pro Stunde vergütet. Sie erhalten 20 Euro nach dem Abschluss der ersten und die verbleibenden 44 Euro nach Abschluss aller Untersuchungen. Die Teilnahme am Vorabscreening ohne weitere Untersuchungen kann mit 5 Euro vergütet werden.

Falls Sie weitere Fragen haben, steht die Versuchsleiterin Ihnen gerne zur Verfügung.

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	T1:T2		T1:T3		T2:T3	
	t	p	t	p	t	p
ADHD-SB	3.34	.001**	4.38	.000***	2.20	.020*
Attention	2.15	.022*	3.72	.000***	2.42	.012*
Hyperactivity	1.91	.035*	3.41	.001**	1.67	.055
Impulsivity	3.01	.003**	3.95	.000***	1.25	.112
Suffer	2.68	.005**	1.48	.078	-0.46	.326
FEA	0.83	.208	2.76	.005**	3.66	.001**
Attention	1.61	.056*	3.94	.000***	2.77	.005**
Hyperactivity	4.28	.000***	2.52	.010**	-1.19	.124
Impulsivity	2.51	.010*	1.96	.032*	-0.92	.184
Suffer	0.12	.452	2.33	.016*	2.64	.008**
BDI	3.44	.002**	4.83	.000***	1.68	.054*
STAIS	1.47	.079	2.68	.007**	1.80	.044*
STAIT	3.19	.002**	4.77	.000***	2.52	.010**
BSL	4.04	.000***	4.22	.000***	1.81	.042*