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Neurofeedback of slow cortical potentials as a treatment for adults with Attention Deficit-/Hyperactivity Disorder

Kerstin Mayer [a,*], Friederike Blume [b], Sarah Nicole Wyckoff [a,c], Luisa Leonie Brokmeier [a], Ute Strehl [a]

[a] Institute for Medical Psychology and Behavioural Neurobiology, University of Tübingen, Silcherstrasse 5, 72076 Tübingen, Germany
[b] LEAD Graduate School, University of Tübingen, Gartenstraße 29, 72074 Tübingen, Germany
[c] SenseLabs, 1918 N. Higley Rd., Mesa, AZ 85205, USA

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- Neurofeedback leads to symptom improvements in adults with ADHD.
- Neurofeedback leads to neurophysiological changes in adults with ADHD.
- Acquisition of self-regulation skill leads to long-term clinical improvements.

ABSTRACT

Objective: Attention Deficit-/Hyperactivity Disorder (ADHD) has been treated successfully in children with neurofeedback (NF). In this study, for the first time NF is investigated in adults with ADHD. To answer the question of specificity the relationship between treatment outcome and self-regulation ability is assessed.
Methods: Twenty-four participants underwent 30 sessions of slow cortical potential NF. Measurements of ADHD and comorbid symptoms, as well as neurophysiological data (reaction time (RT) and RT variability (RTV) and contingent negative variation (CNV)) were performed before and after treatment, and again six months after sessions were completed. Participants were categorized into self-regulation learners and non-learners.
Results: Significant improvements on all symptom scales were observed with medium to large effect sizes after treatment and six months post treatment. RT and RTV decreased significantly and there was a trend for an increased CNV. Half of the participants successfully learned to regulate their brain activity. In the long-term, symptoms in the group of learners improved more than in non-learners with large effect sizes.
Conclusion: NF is effective in treating adult ADHD long-term. The impact of self-regulation ability and possible unspecific effects still require further investigation.
Significance: This study is the first to investigate the effects of NF in adults with ADHD, relating clinical outcome to self-regulation performance.

1. Introduction

Attention Deficit-/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder; 30–65% of children with ADHD keep their symptoms in adulthood (Faraone et al., 2006). This leads to a prevalence rate of 4–5% in the adult population (Goodman and Thase, 2009). Behavioral symptoms of ADHD are associated with three presentations: predominantly inattentive, predominantly hyperactive-impulsive and combined type (American Psychiatric Association, 2013). Symptomatology in adult ADHD is similar to that described in its pediatric form, but hyperactivity is instead perceived as inner restlessness in adults. Deficits experienced during childhood continue to impact the life of adults with ADHD and lead to social, educational, and occupational problems. These problems can include short and unstable relationships, high school and higher education drop outs, frequent job loss, increased

* Corresponding author.
E-mail addresses: kerstin.mayer@uni-tuebingen.de (K. Mayer), friederike.blume@uni-tuebingen.de (F. Blume), wyckoffsarah@gmail.com (S.N. Wyckoff), luisa.brokmeier@student.uni-tuebingen.de (L.L. Brokmeier), ute.strehl@uni-tuebingen.de (U. Strehl).

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delinquency and substance abuse (Sobanski, 2006), and increased mortality rates (Dalsgaard et al., 2015). Additionally, the comorbidity with other psychiatric disorders such as depression, anxiety and substance abuse is as high as 65–89% (Sobanski, 2006). Further, the supply of treatment options for adult ADHD is still sparse (Ginsberg et al., 2014; Kessler et al., 2006; Kooij et al., 2010). Pharmaceuticals are effective in reducing ADHD symptoms (Banaschewski et al., 2006), though long-term effectiveness is unclear (van de Loo-Neus et al., 2011) and patients may refuse to take medications at all. Psychotherapy approaches (Groß et al., 2015) are available, however, new and well evaluated treatment options are needed.

In children and adults with ADHD, core symptoms and associated self-regulation abilities are related to less cortical excitability, which is reflected in slowing of the EEG, i.e. an increased theta activity (Barry et al., 2004; Clarke et al., 2008), and reduced amplitudes of event related potentials (ERP), such as the contingent negative variation (CNV) (Weate et al., 1993; van Leeuwen et al., 1998; Hennighausen et al., 2000; Sartory et al., 2002; Banaschewski et al., 2003, 2004; Dhar et al., 2010; Mayer et al., 2012, 2015b). The CNV belongs to the family of slow cortical potentials that can be observed in participants performing a Go/NoGo task, for instance; a negative potential shift occurs during the expectation of an imperative stimulus to provide necessary cortical and motor resources that allow a fast and correct response (Walter, 1964). Reduced CNV amplitude in patients with ADHD indicates difficulties in the provision of resources for attention processes and the regulation of excitability thresholds. The lack of attention can also be observed in slow reaction times (RT) and high reaction time variability (RTV) (Nigg et al., 2005; Dhar et al., 2010; Tamm et al., 2012). This and other pathological problems associated with ADHD (for a review: Albrecht et al., 2015) indicate a treatment with neurofeedback (NF), which targets the underlying neurophysiological deviances in ADHD.

For more than a decade, NF has been investigated as a possible alternative treatment for ADHD in children (Arns et al., 2014). By enabling the patient to acquire skills to self-regulate certain brain activity patterns, NF is thought to reduce behavioral problems associated with the core symptoms, such as poor attention, impulsivity, and hyperactivity. In a meta-analysis, large effect sizes for impulsivity and inattention, and a medium effect size for hyperactivity were reported for theta/beta, sensorimotor rhythm and slow cortical potentials (SCP) protocols in ADHD (Arns et al., 2009). This study focuses on SCP-NF, as there may be a slight advantage of SCP-NF over theta/beta and sensorimotor rhythm protocols (Mayer et al., 2013). Moreover, recent evidence no longer supports the presumption that increased theta and beta reductions are reliable ADHD markers (Doehnert et al., 2013; Holtmann et al., 2014).

SCP-NF focuses on the regulation of cortical excitation and inhibition and aims to improve activation and deactivation of the brain (Strehl, 2009). The protocol is largely standardized (Mayer et al., 2013) and used independently of ADHD subtype. SCPs are characterized as very slow (<1 Hz) electrical shifts in the brain activity that last up to several seconds after stimulus onset and can be measured as electrical negativation and positivation on the scalp (Birbaumer et al., 1990). They reflect the threshold regulation mechanisms of cortical activation (negative shift) and cortical deactivation/inhibition (positive shift), which is related to attention processes (Birbaumer et al., 1990). The SCP-NF protocol was originally developed for the treatment of epilepsy, a condition characterized by difficulties in regulating cortical excitation thresholds which lead to epileptic seizures (Rockstroh et al., 1993). During SCP-NF, patients successfully learn to control and regulate these thresholds to prevent seizures (Rockstroh et al., 1993; Kotchoubey et al., 2001). Also in patients with ADHD, SCP-NF leads to changes in EEG parameters. Most interestingly, the CNV amplitude, which is closely related to SCP negativation, increases after SCP-NF (Heinrich et al., 2004; Wangler et al., 2011). A large CNV amplitude is associated with increased attention, anticipation and/or preparation of cognitive or motor responses (Walter, 1964). With a larger CNV amplitude, the amount of cognitive energy is rising and leads to faster reaction times, better stimulus selection, short-term memory and attention (Birbaumer et al., 1990).

After SCP-NF for children with ADHD, third-party rated symptom improvements of more than 25% are reported (Heinrich et al., 2004; Strehl et al., 2006; Drechsler et al., 2007; Gevensleben et al., 2009b). Furthermore, changes in neuropsychological measures, such as increased reaction time (RT) and decreased error rates, were observed (Heinrich et al., 2004; Strehl et al., 2006; Drechsler et al., 2007). Long-term effects regarding the stability of self-regulation skills, as well as further attention and behavior improvements, have been observed six months (Strehl et al., 2006) to two years post treatment (Gani et al., 2008).

Despite this, NF is not a generally accepted treatment. Its effectiveness has been observed in many studies (for an overview: Arns et al., 2009, 2014), however, the specificity of the method, i.e. the extent to which the improvement in ADHD symptomatology is specifically related to the NF itself, is still questioned. This is mainly due to the lack of blinded placebo control groups, which are difficult to design in the NF setting (Arns et al., 2014). As double blind, placebo-controlled studies – the gold standard of pharmacological methods – cannot be achieved in psychotherapy, and therefore neither in NF, this study seeks to control specificity with a different approach: assessing EEG learning in NF (Zuberer et al., 2015). NF aims to change brain activity, and thereby aims to improve clinical symptoms associated with ADHD (Gevensleben et al., 2014b). Consequently, if participants do not learn to regulate and change their brain activity, behavioral changes either cannot be expected, or simply reflect non-specific effects of the treatment. "If you do not learn to change what is being trained, you do not change the neocortical dynamics; if you do, then you do change the neocortical dynamics and the thalamocortical dynamics as well" and this "show[s] that EEG neurofeedback is not some kind of nonspecific or placebo phenomenon but is linked directly to changes in cortical functioning" (Lubar, 1997, p. 123). Aiming to assess the specificity of NF, it has to be determined whether individuals effectively learn to regulate their brain activity or not. Therefore, assessment and analysis of the training data and its correlation with the training outcome should be examined.

To date, only a few studies followed this attempt, though with different methods and outcomes (Zuberer et al., 2015). Some studies used the training data to categorize participants into learners and non-learners (Strehl et al., 2006; Studer et al., 2014), based on the ability to create negativity in the feedback and/or transfer condition, or via median split according to the differentiation between negative and positive shifts of brain potentials (Drechsler et al., 2007; Doehnert et al., 2008). Other studies used mean training performance to calculate correlations with the clinical outcome (Drechsler et al., 2007). The performance during sessions was shown to correlate with symptom reduction, and the ability to produce negativation in the transfer trials predicted clinical outcome (Strehl et al., 2006; Drechsler et al., 2007). Thus, it seems that the skill to create negativity and/or a differentiation between both states might be a good indicator of learned regulation. However, this requires further investigation and this study serves as a next step along this approach.

This leads us to the several aims of this study: (1) to assess efficacy: Do adults with ADHD benefit from SCP-NF by reducing self-rated ADHD symptoms, third-party rated ADHD symptoms, or comorbid symptoms of depression and anxiety (state and trait)? Do they benefit from improved CNV, reaction time (RT) and RT

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variability (RTV)? (2) To assess acquisition of self-regulation skill: are adults with ADHD able to learn to regulate their SCP? (3) To assess specificity: do regulation abilities influence the outcome measures?

2. Methods

This study is part of a larger project conducted at the Institute of Medical Psychology and Behavioral Neurobiology, and the University Department of Psychiatry and Psychotherapy at the University of Tübingen, in which three biofeedback protocols, including a semi-active control group, for adult ADHD are being compared (Mayer et al., 2015a). The project planning started in June 2010 and the last data for this part of the project was collected in November 2014; the other components of the project are still ongoing. The project was approved by the local ethics committee in Tübingen, and written informed consent was given by all participants.

2.1. Participants

The participants were recruited through the University of Tübingen via email, newspaper advertisement, and bulletins. All participants were between 18 and 60 years old and had an IQ above 80. Participants with any serious physical illness or chronic diseases, any neurological disorders, or current psychiatric disorders other than ADHD were excluded.

Participants had to fulfill DSM-IV criteria for ADHD inattentive, hyperactive, or combined type assessed by a trained psychologist as described below. ADHD medication was allowed during the training sessions, but participants were instructed not to take the medication 24 h before EEG assessments. They were furthermore asked to keep a stable dose throughout the treatment phase. Participants received 30 sessions NF free of charge.

2.2. Assessments

2.2.1. Questionnaires and IQ-test

Participants underwent several assessments to confirm the ADHD diagnosis, including the German version of the Wender Utah Adult ADHD structured interview, and the childhood (WURS-K) and current ADHD (ADHD-SB) questionnaires of the German Adult ADHD test battery (HASE; Rösler et al., 2008). To test for comorbid disorders, the German version of the Structured Clinical Interview (SCID-I; Wittchen et al., 1997) and other questionnaires assessing depression (BDI; Hautzinger et al., 2006) and anxiety (STAI; Spielberger et al., 1970) were used. The IQ of participants was assessed with the Culture Fair Intelligence Test (CFT-20-R; Weiss, 2008). Scores higher than 80 were required to participate in the study.

The main tool to assess ADHD symptom severity (ADHD-SB) was a self-rating, 22-item sub-scale questionnaire of the HASE (Rösler et al., 2008) German Adult ADHD test battery (ADHD cut-off = 18). Further, a third-party ADHD symptom questionnaire (FEA) was used, in which a significant other rated the participants' symptom severity for 20 items on a 0–3 Likert scale (Döpfner et al., 2006). A third measure of ADHD was the German version of the adult ADHD Wender–Reimherr Interview (WRI; Rösler et al., 2008). A trained psychologist administered all oral assessments.

In every fifth NF session, participants completed a questionnaire to assess expectancy effects with regards to the treatment (FERT; Vollmann, 2009).

2.2.2. EEG recordings

EEG data was recorded using 22 EEG channels positioned according to the international 10–20 system (Jasper, 1958) with the NeXus-32 DC amplifier (Mind Media B.V. with Biotrace$^+$ Software). The EEG was recorded with a sampling rate of 512 samples per second 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, and O2, with additional electrodes placed on the right and left mastoid for offline re-referencing. 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. Instead of impedance testing, the Nexus-32 utilizes DC offset checking to assess connection and signal quality. DC offset was monitored and kept below ±25,000 μV peak-to-peak.

2.2.3. Go/NoGo task

The Go/NoGo task was part of a 60 min EEG recording including resting EEG (15 min eyes closed, 5 min eyes open) and two other active tasks. The instructions for the task were played back to the participant via two speakers at 90 dB. The sound pressure level of all tones in all paradigms was also 90 dB. The speakers were placed at a distance of 1 m from the participant with a 0.5 m horizontal distance from each other. Participants were seated in a reclined chair during the measurement. The Go/NoGo task was an active, auditory, eyes-closed task designed to elicit the CNV component. A warning stimulus, S1 (500 Hz, 50 msec, $N = 200$), was followed by a stimulus, S2, which was either a NoGo low-pitched tone (1000 Hz, 50 msec, $N = 150$) or a Go high-pitched tone (2000 Hz, 50 msec, $N = 50$). The subjects were instructed to press the space bar of a standard computer keyboard with their dominant hand as quickly as possible after the Go-tone was sounded. The time between S1 and S2 was 1.8 sec, and the time between S2 and S1 varied randomly between 2.0 and 2.4 sec. All tones lasted for 50 msec. The duration of the task was 13 min (see Fig. 1). Median of reaction time (RT), average reaction time variability (RTV), and response errors to the Go-stimulus were measures of task performance.

2.2.4. Neurofeedback

SCP-NF was conducted with the THERA PRAX® (neuroConn GmbH, Ilmenau, Germany). The training protocol was developed by researchers in the laboratory at the Institute for Medical Psychology and Behavioral Neurobiology, Tübingen and has been used for many years in a variety of studies (Kotchoubey et al., 1999; Strehl, 2009). SCPs were recorded at the vertex (Cz), referenced against the right mastoid A1 with a ground electrode on the left mastoid A2. Data were recorded with a sampling rate of 128 samples per second. Eye movements were recorded with two horizontal and two vertical electrodes. Ag/AgCl ring electrodes were used on all sites. The system performed an online artifact correction for eye movements during the training by using an eye movement calibration file, which was created before each session. In addition, the system detected all signal changes above 200 μV due to movements of the participant or the cables online. In case of an artifact, the trial was aborted and repeated. Participants were trained up to five times per week for a total of 30 sessions. The average duration of training was 24.48 weeks ($SD = 8.18$ Min/Max = 15–49) including a three weeks break after the first 15 sessions. Each session lasted approximately one hour, including preparation time, and consisted of four blocks of 40 trials each. One trial lasted 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). The two seconds baseline data was set to zero before each active phase. At the end of the baseline phase, participants were cued to "activate" their brain (regulate a negative SCP-shift) by a triangle directed to the top of

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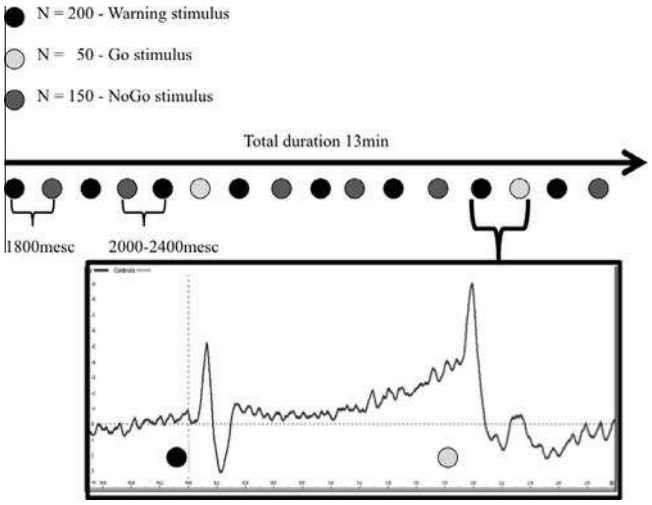

Fig. 1. CNV experimental design of the Go/NoGo task. Black circles represent the warning stimulus (S1), white circles the Go stimulus (S2Go) and gray circles the NoGo stimulus (S2NoGo). Between S1 and S2Go the CNV amplitude is depicted.

the screen or to "deactivate" their brain (regulate a positive SCP-shift) by a triangle directed to the bottom of the screen with a 50/50 rate for each direction. In the active phase, an object moved from left to right across the screen and by moving up (indicating activation) or down (indicating deactivation) provided the participant with feedback of his/her brain activity. 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 move the feedback object in the cued direction, no positive reinforcement was provided and the screen remained empty. Additionally, the therapist gave feedback and reinforcement according to the participant's performance. To generalize newly acquired regulation skills to everyday life situations, the third block served as "transfer block" in which no visual feedback was provided during the active training phase. The level of success was indicated with a visual reward and the therapist's feedback. See Fig. 2 for the NF design. 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 mentally relax). After the first 15 SCP-NF sessions, participants had a three week break. During this time, they had to practice their regulation skills with the aid of a training card depicting the training screen and a DVD showing an 8 min transfer session as seen during the sessions but without the rewarding sun. Participants were told to document their actual practice frequency, which was on average twice a week or less. After the break, participants returned for the remaining 15 sessions of NF and the following post assessment. In every fifth session, participants completed a questionnaire about relevant therapy conditions (FERT) to assess their treatment expectation on a 7-point Likert scale (Vollmann, 2009). The mean expectation over all five measurements was entered into the analysis.

2.2.5. Study flow

The first screening consisted of a short first-contact telephone questionnaire in which major inclusion and exclusion criteria were assessed. We then mailed a package with ADHD-SD, WURS-K, BDI and STAI questionnaires as well as information material and the informed consent form to participants if they fulfilled all criteria. In cases when criteria were confirmed, participants were invited to a diagnostic interview including SCID-I and WRI. On a separate day, the CFT-20R (Weiss, 2008) and the EEG was performed. After successful inclusion, 30 sessions of SCP-NF were conducted. In every fifth session participants filled in the FERT. After 15 sessions participants had a mid-treatment assessment (including questionnaires and EEG recordings) and took a three week break from training. After all 30 sessions, the EEG and questionnaire assessment was performed again. A follow-up (FU) assessment was conducted after 6 months including three further NF sessions. See Fig. 3 for an overview of the study flow.

2.3. Data analysis

2.3.1. Electrophysiological analysis

EEG data was analyzed with the Brain Vision Analyzer (Brain Products, Munich, Germany) for the Go/NoGo task. The data was down sampled to 256 Hz and re-referenced to the mastoids. Furthermore, a 24 dB/octave Butterworth filter was applied from 0.05 Hz to 30 Hz; a 50 Hz notch filter was also applied. The EEG data was segmented for the Go-trials 700 msec prior to S1 until 3 sec after S1. The baseline correction was performed 700 msec prior to S1. The criteria for artifact rejection for single segments were as follows: maximum allowed voltage step was 50 μV, maximum allowed absolute difference of two values in the segment was 300 μV, maximum and minimum allowed amplitude was between −100 and 100 μV, lowest allowed activity (Max–Min) was 0.5 μV, and interval length was 100 msec. The CNV mean amplitude was calculated 1–1.8 sec post S1. The CNV amplitude was analyzed for the average of electrode sites C3, Cz, and C4. Participant data was only included if at least 15 segments remained after artifact rejection.

2.3.2. Training data analysis

The training data were exported into Brain Vision Analyzer (Brain Products, Munich, Germany). A low cutoff filter of 0.01 Hz and a 50 Hz notch filter were applied. The data was segmented for the negativation and positivation 200 msec before and 10 sec after the start of each trial and baseline correction was performed 100 msec prior to the start of a trial. The criteria for the semi-automatic artifact rejection for single segments were as follows: maximum allowed voltage step was 50 μV, maximum allowed absolute difference of two values in the segment was 150 μV, maximum and minimum allowed amplitude was between −150 and 150 μV, and the interval length was 200 msec. A trained researcher went through all data to exclude drifts and missed artifacts. The mean amplitude was calculated for the time interval 3–8 sec after the start of each trial.

Differentiation was calculated by subtracting the mean positivation amplitude from the mean negativation amplitude. Therefore, six measures for all sessions were obtained: negativation, positivation, and differentiation for the feedback as well as the transfer condition.

The values for each participant were looked at individually for sessions 2–29 (session 1 was excluded to allow habituation to the training setting and session 30 for possibly altered motivation facing the very last session).

2.3.3. Learners versus non-learners

We defined our categorization according to earlier approaches (Strehl et al., 2006; Drechsler et al., 2007; Doehnert et al., 2008; Studer et al., 2014) described above, and the assumption that creating a high differentiation between positivation and negativation during the transfer condition is the highest level of self-regulation skill that can be reached. In contrast to other studies that compared increase of regulation ability over the course of the training, we decided that it is most important to show this ability at the end of training. This is based on the observation that some participants did very well in the first few sessions more by chance. During the course of training they often deteriorated and needed time to develop deliberate control over the signal. In a pre-post

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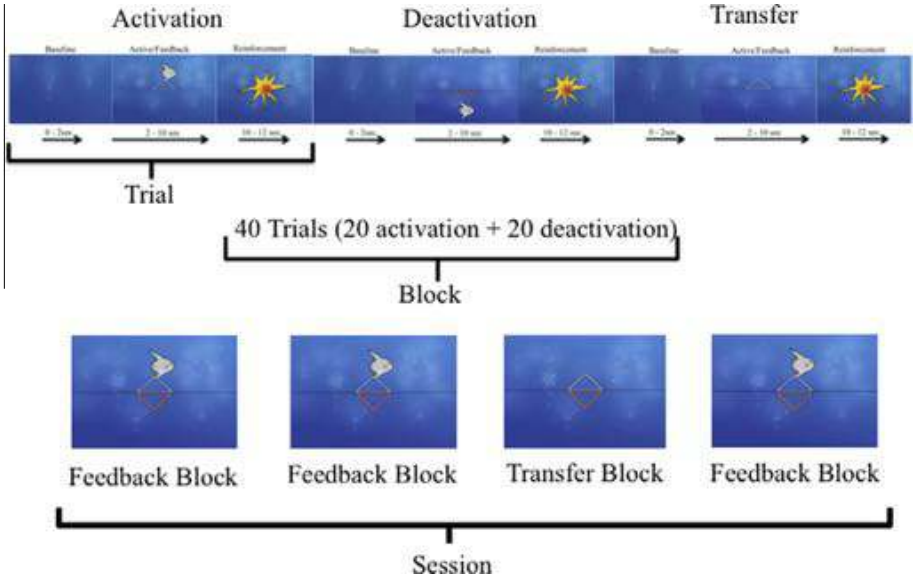

Fig. 2. Overview of the NF session design. (With friendly permission from neuroConn GmbH, Ilmenau, Germany.)

comparison the data might look like participants did not increase their regulation ability. To ensure that artifacts or single good or bad sessions did not corrupt the data, we decided to use the mean of three sessions (27, 28, and 29).

In sum, we categorized the participants into learners and non-learners based on their ability to create differentiation between negativation and positivation in the transfer condition of the last three sessions. The differentiation value had to be above zero so that the average amplitude during negativation trials would be more negative than during positivation trials.

2.3.4. Change scores

Change scores were calculated so that positive values were obtained for changes in the expected direction. Consequently, for all questionnaires, the RT and RTV pre-measurement value was subtracted from the post-measurement value, the pre-measurement value from the FU measurement value and the post-measurement value from the FU. The CNV was calculated the other way round (post – pre; FU – pre, FU – post).

2.4. Statistical analysis

The statistical analysis included three steps. First, paired *t*-tests were performed for pre-post measurement of all participants for all questionnaires, RT, RTV and CNV amplitude. Second, an ANOVA was performed for pre-, post- and FU testing for all participants. Third, independent *t*-tests were calculated for change scores (pre-post) of all variables with the grouping variable learner/non-learner as well as for the FU change score (pre-FU). The effect size, Cohens' *d*, was calculated. A small effect is observed for $d \leqslant 0.2$, a medium effect for $d \leqslant 0.5$, and a large effect for $d \geqslant 0.8$.

Correlations were calculated with Pearson's *r* for change scores of ADHD, CNV, RT, and RTV, training data, and FERT.

3. Results

3.1. Symptoms

In total, 24 participants were included in the analysis; nine female and 15 male. Nine participants were of the inattentive subtype (two female) and 15 of the mixed subtype. Five participants (one female) took stimulant medication with different dosages. The median duration of 30 sessions of training (including the three week break) was 24.97 weeks. No one dropped out during this time. Three participants could not return for FU as they moved away and two participants were not in their FU time frame at time of analysis. Two participants returned for the FU assessment but could not manage to finish the three sessions of NF. Descriptive data see Table 1.

3.2. Missing data

The data from the FBB is not complete for all participants, as we did not receive the third-party questionnaire back for all measurement points. FU data is available for questionnaires for 18 participants, RT and RTV for 17, and CNV for 16 participants due to data set errors.

The paired *t*-test of pre and post data for all participants revealed significant reductions in self-rated ADHD symptoms (Pre: $M = 30.88$, $SD = 6.49$; Post $M = 21.88$, $SD = 6.22$; $t(23) = 5.85$, $p \leqslant .000$, $d = 1.40$), third-party rated ADHD symptoms (Pre: $M = 24.94$, $SD = 10.53$; Post $M = 18.56$, $SD = 12.03$; $t(17) = 3.87$, $p \leqslant .001$, $d = 0.57$), and ADHD symptoms rated in the WRI (Pre: $M = 37.58$, $SD = 6.28$; Post $M = 33.92$, $SD = 8.94$; $t(23) = 2.47$, $p \leqslant .05$, $d = 0.47$). On a descriptive level, self-rated symptoms reduced over 25% in 14 patients. Six of those patients did not meet the criteria for ADHD diagnosis anymore. Three patients showed a slight increase of self-rated symptoms, however this was not clinically significant.

Further, comorbid symptoms decreased over time for depression (Pre: $M = 11.92$, $SD = 7.29$; Post $M = 6.13$, $SD = 4.96$; $t(23) = 4.81$, $p \leqslant .000$, $d = 0.93$), state anxiety (Pre: $M = 45.17$, $SD = 9.82$; Post $M = 40.42$, $SD = 8.81$; $t(23) = 2.192$, $p \leqslant .05$, $d = 0.51$), and trait anxiety (Pre: $M = 49.08$, $SD = 7.85$; Post $M = 42.13$, $SD = 8.16$; $t(23) = 4.25$, $p \leqslant .000$, $d = 0.87$).

3.3. Neurophysiology

The paired *t*-test of pre and post data for the Go/NoGo task revealed significant improvements in RT ($t(22) = 3.477$, $p \leqslant .05$, $d = 0.65$) and RTV ($t(23) = 2.28$, $p \leqslant .05$, $d = 0.45$) over time (see Fig. 4). The CNV showed a trend of increase over time ($t(23) = 2.02$, $p = .055$, $d = 0.46$) (see Fig. 5).

Due to different sample sizes in individual measurements, the ANOVAs had to be calculated separately for ADHD-SB, BDI, and STAI ($n = 21$), FBB ($n = 8$), WRI ($n = 17$), CNV ($n = 16$), and RT and

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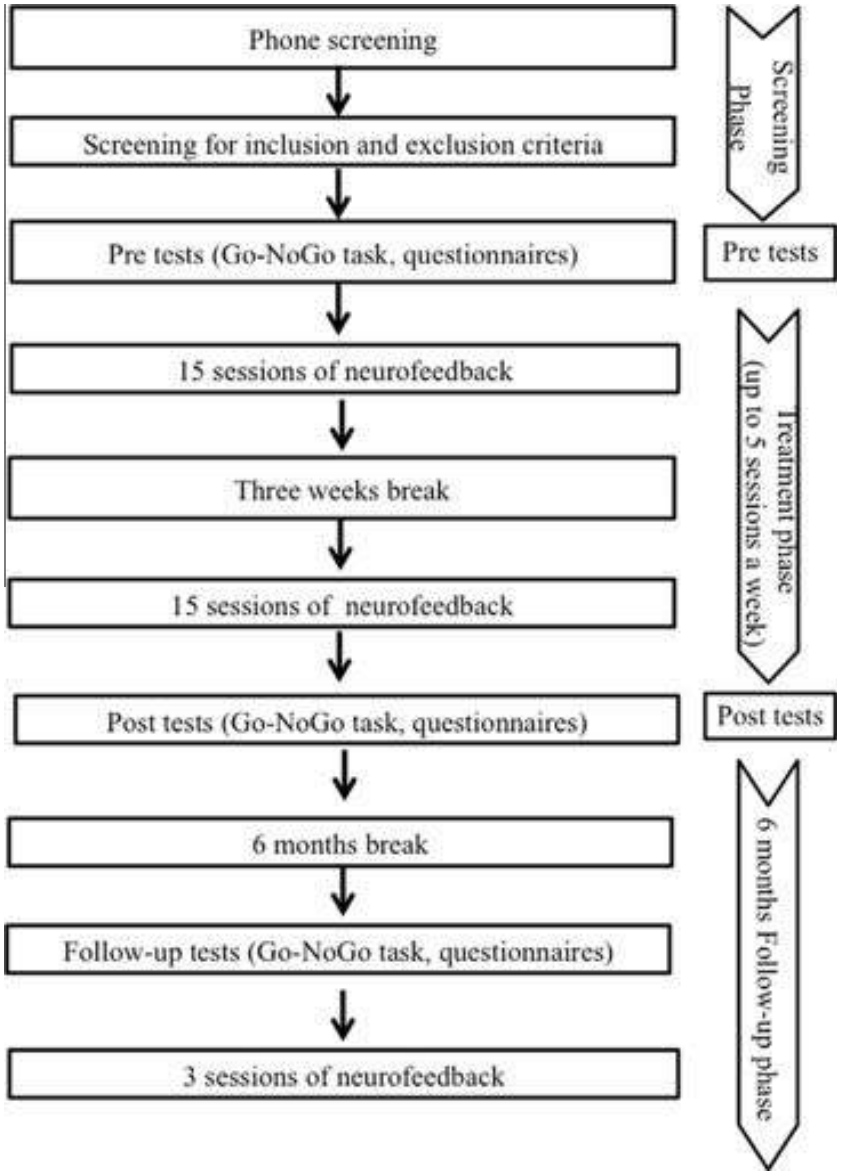

Fig. 3. Overview of the study flow.

Table 1
Descriptive data (WURS-K = self-rated childhood ADHD symptoms, ADHD-SB = self-rated current ADHD symptoms, FERT = mean expectation).

	Mean (SD)	Min–Max
Age	34.29 (10.38)	22–53
IQ	110.33 (13.48)	80–134
WURS-K	36.04 (10.86)	21–65
ADHD-SB	30.88 (6.49)	18–44
FERT	4.04 (0.97)	2.4–5.8

RTV ($n = 18$). The ANOVA over all three assessments revealed the following results. ADHD symptoms decrease significantly over time on all scales for ADHD-SB ($F(1.7, 34.9) = 20.41$, $p \leqslant .000$, $\eta_2 = .51$), FBB ($F(1.6, 9.5) = 5.93$, $p \leqslant .05$, $\eta_2 = .50$), and WRI ($F(1.9, 30) = 6.33$, $p \leqslant .01$, $\eta_2 = .28$). Comorbid symptoms decreased significantly for depression ($F(1.5, 29.9) = 10.07$, $p \leqslant .001$, $\eta_2 = .34$), state ($F(1.8, 36) = 5.9$, $p \leqslant .01$, $\eta_2 = .23$), and trait anxiety ($F(1.5, 30.1) = 11.49$, $p \leqslant .001$, $\eta_2 = .37$). RT ($F(1.21, 20.6) = 23.39$, $p \leqslant .000$, $\eta_2 = .58$) and RTV ($F(1.2, 18) = 4.64$, $p \leqslant .05$, $\eta_2 = .24$) decreased significantly over time (see Table 2). The ANOVA did not reveal significant differences for CNV over all three assessments ($M_{pre} = -0.76$ μV, $SD = 1.74$; $M_{post} = -1.61$ μV, $SD = 1.84$; $M_{FU} = -1.28$ μV, $SD = 2.66$) $F(1.6, 24) = 0.84$, $p = .42$, $\eta_2 = .05$).

Post hoc t-tests revealed a significant decrease from pre to post for ADHD-SB ($t(19) = 4.87$, $p \leqslant .000$, $d = 1.37$), and from pre to FU ($t(19) = 4.71$, $p \leqslant .000$, $d = 1.35$), but not from post to FU testing ($t(19) = -.30$, $p = .76$, $d = -0.06$). The WRI ADHD score decreased significantly from pre to FU ($t(16) = 4.12$, $p \leqslant .001$, $d = 0.92$), but not pre to post ($t(16) = 1.60$, $p = .13$, $d = 0.38$), or post to FU ($t(16) = 1.75$, $p = .10$, $d = 0.40$). The FBB ADHD score decreased significantly from pre to post ($t(7) = 2.92$, $p \leqslant .05$, $d = 0.61$), and pre to FU ($t(7) = 3.19$, $p \leqslant .05$, $d = 0.79$), but not from post to FU ($t(6) = 0.92$, $p = .39$, $d = 0.16$) (see Fig. 6).

For comorbid symptoms, depression decreased significantly from pre to post ($t(23) = 4.81$, $p \leqslant .000$, $d = 0.93$), and pre to FU ($t(20) = 2.82$, $p \leqslant .05$, $d = 0.73$), but not post to FU. Similar results were found for state ($t(23) = 2.19$, $p \leqslant .05$, $d = 0.51$) and trait anxiety ($t(23) = 4.25$, $p \leqslant .000$, $d = 0.87$) pre to post, and pre to FU (State: $t(20) = 2.99$, $p \leqslant .01$, $d = 0.81$; Trait: $t(20) = 3.05$, $p \leqslant .01$, $d = 0.72$), but not Post to FU (see Table 3).

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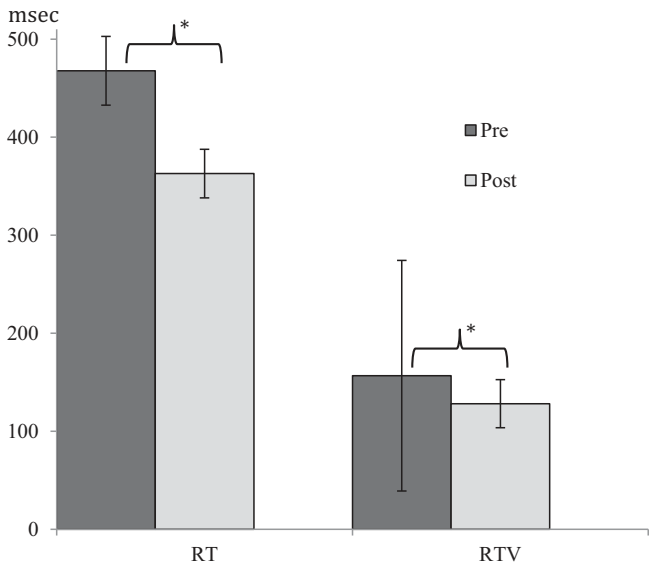

Fig. 4. Reaction time (RT) and reaction time variability (RTV) in msec pre and post treatment $N = 24$. $^{*}p > .05$.

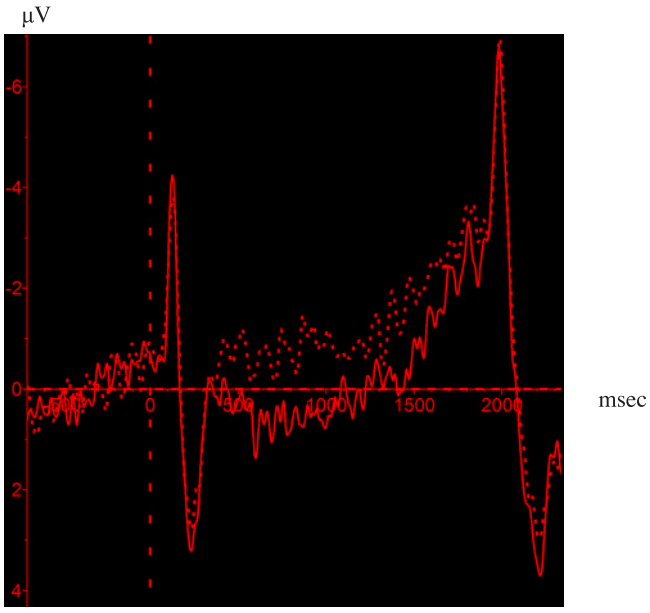

Fig. 5. CNV pre (solid line) and post (dashed line) treatment exemplified on C4.

Table 2
Reaction time (RT) and RT variability (RTV) in msec.

	M_1 (*SD*)	M_2 (*SD*)	df	*t*	*p*	*d*
RT pre-post	467.76 (168.25)	362.06 (118.79)	23	3.48	.002	0.73
RT pre-FU	498.09 (177.67)	327.30 (101.34)	16	5.70	.000	1.18
RT post-FU	365.98 (120.62)	327.30 (101.34)	16	3.32	.004	0.36
RTV pre-post	151.77 (117.49)	111.27 (51.56)	23	2.28	.032	0.31
RTV pre-FU	173.62 (130.67)	105.91 (27.51)	16	2.30	.036	0.72
RTV post-FU	121.08 (54.94)	105.91 (27.51)	16	1.35	.195	0.35

Post-hoc *t*-test for RT and RTV showed significant decreases for all time points except for RTV post to follow-up (see Table 2).

3.4. Learner vs. non-learner

The categorization resulted in 13 non-learners and 11 learners according to the mean differentiation in sessions 27, 28, and 29. This value was used to categorize the participants into learners and non-learners (see Table 4 for mean differentiation and categorization). Fig. 7 shows a learning curve of one participant in the first two sessions of training and in the last two sessions of training.

The independent *t*-test comparing the groups before treatment showed a trend for larger RTV ($t(15.34) = -2.14$, $p = .049$, $d = -1.09$) in the group of non-learners. All other variables did not differ from each other in the comparison of both groups (see Fig. 8).

The independent *t*-test comparing the groups of learners and non-learners in their change scores pre-post treatment revealed significant differences of RTV ($t(13.08) = -2.45$, $p < .05$, $d = -1.35$). There is a small trend for a larger improvement in self-rated ADHD symptoms in the group of learners. Third-party rated ADHD symptoms with WRI and FBB, RT and CNV did not show significant differences between the groups. See Table 5 for all values.

The comparison of (FU minus pre) change scores revealed a significantly higher improvement in self-rated ADHD symptoms for the group of learners ($n = 9$) compared to the non-learners ($n = 12$) ($t(19) = 2.37$, $p < .05$, $d = 1.09$) (see Fig. 8). There was also a trend in the same direction for WRI ($t(15) = 1.81$, $p = .09$, $d = 0.94$). Further, from post to FU assessment the group of non-learners differed significantly from the learners in their change score of state anxiety ($t(18) = -1.81$, $p = .09$, $d = -0.85$) and FBB ($t(6) = 1.97$, $p = .10$, $d = 1.61$).

3.5. Correlations

Correlations for change scores of ADHD, CNV, RT, RTV, and FERT revealed few significant correlations for the overall group (see Table 6). Changes in ADHD symptoms correlated significantly with the FERT score ($r = .44$, $p_{\text{two-tailed}} < .05$) and the subcategory hyperactivity correlated with RT ($r = -.42$, $p_{\text{two-tailed}} < .05$). The learner group showed a correlation of FERT and the subcategory inattention ($r = .63$, $p_{\text{two-tailed}} = .04$). There were no significant correlations in the group of non-learners.

4. Discussion

In this study, we investigated the effect of 30 sessions of SCP-NF on 24 adults with ADHD. The goals of this study were to investigate whether adults with ADHD benefit from a treatment with SCP-NF and whether SCP-NF leads to changes in brain activity. We also aimed to examine whether adults with ADHD were able to learn to regulate their SCP, and whether the acquired regulation ability influences the outcome.

Overall, this study is the first to show that SCP-NF leads to significant symptom reduction in adults with ADHD. Self-rated as well as third-party rated symptoms of ADHD decreased on all scales after 30 sessions of SCP-NF with medium to high effect sizes. Fourteen participants experienced a symptom reduction of over 25% and symptoms of six participants remitted, i.e. they did not meet criteria for an ADHD diagnosis anymore. Similar results were reported from SCP-NF studies for children with ADHD (Heinrich et al., 2004; Strehl et al., 2006; Drechsler et al., 2007; Gevensleben et al., 2009a). Further, the symptom reduction was stable six months after the training which suggests long-term effects of SCP-NF similar to those found in children with ADHD (Strehl et al., 2006; Gevensleben et al., 2010). On an individual

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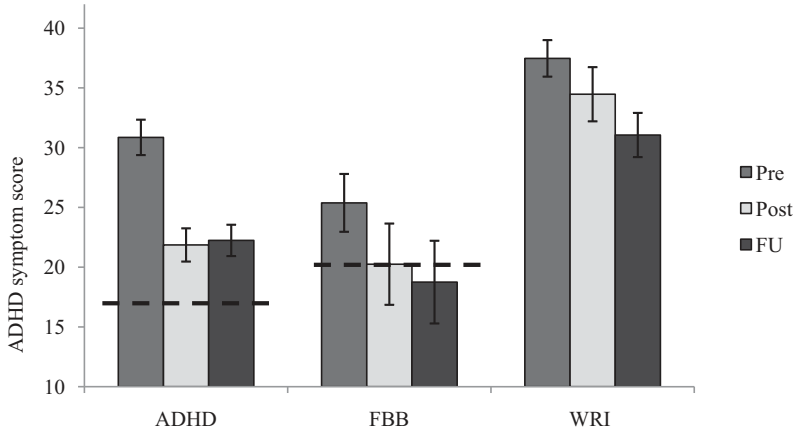

Fig. 6. Mean values and standard error for the three ADHD symptom assessments ADHD = self-rated ADHD symptoms, FBB = third-party rated symptoms, WRI = Wender Reimherr Interview. The dotted line represents the ADHD cut-off value for the questionnaires.

Table 3
Mean values (standard deviation) for comorbid symptoms of depression (BDI), state (STAI-S) and trait anxiety (STAI-T).

	M_{pre} (*SD*)	M_{post} (*SD*)	M_{FU} (*SD*)
BDI	11.92 (7.29)	6.13 (4.96)	7.10 (5.92)
STAI-S	45.17 (9.82)	40.42 (8.81)	37.48 (9.20)
STAI-T	49.08 (7.85)	42.13 (8.16)	43.24 (8.41)

Table 4
Overview of mean differentiation values of session 27, 28, and 29 (mean diff) for each participant and the resulting group assignment.

Participant	Mean diff in μV	Category
1	12.78	Learner
2	−6.75	Non-learner
3	−4.59	Non-learner
4	−8.36	Non-learner
5	−7.15	Non-learner
6	9.11	Learner
7	1.27	Learner
8	−2.24	Non-learner
9	6.19	Learner
10	−13.65	Non-learner
11	−3.51	Non-learner
12	−11.65	Non-learner
13	8.91	Learner
14	1.60	Learner
15	9.08	Learner
16	−4.70	Non-learner
17	23.79	Learner
18	−8.74	Non-learner
19	−15.98	Non-learner
20	1.25	Learner
21	−23.35	Non-learner
22	38.65	Learner
23	6.18	Learner
24	5.46	Learner

level, six months after the end of treatment, symptoms decreased further in ten participants, remained stable in two and increased slightly in nine participants.

Moreover, symptoms rated on comorbid scales (depression and anxiety) improved with medium to high effect sizes after SCP-NF and were stable after six months. This suggests either that SCP-NF does not only affect symptoms of ADHD, but also related comorbidities, or that improvement of ADHD symptoms led to improvements of related symptoms. The direction of this relationship is unknown and needs further investigation. Six months after treatment, the improvements in depression and anxiety also remained stable, while cases of state anxiety decreased even further. This suggests a possible application of SCP-NF in other disorders such as depression and anxiety. Additionally, the improvements in ADHD and comorbid symptoms with medium to high effect sizes are comparable to other studies investigating behavioral (Safren et al., 2005; Rostain and Ramsay, 2006) and pharmacological treatments (for a review: Fredriksen et al., 2013).

Not only symptoms, but also ADHD related impairments improved after treatment. RT and RTV decreased significantly with large effect sizes after 30 sessions of SCP-NF and were stable at the six-month follow-up. This indicates an increased information processing speed and less occasional lapses of attention after SCP-NF, as is also observed after administration of ADHD medication, like stimulants (Oberlin et al., 2005) or atomoxetine (Chamberlain et al., 2007) in adults with ADHD. A decreased RTV was also reported following treatment with stimulant medication in children (Epstein et al., 2011; Kratz et al., 2012) and adults (Lutz et al., 2009) with ADHD. The relation of these neurophysiological measurements and ADHD symptoms becomes apparent in our data with the correlation of decreased symptoms of hyperactivity and faster RT.

The CNV over central electrode sites (C3, Cz and C4) increased after 30 sessions close to significance with a medium effect size. After six months the amplitude slightly decreased, but not below the initial level. This indicates that cortical excitability increased due to SCP-NF, as reported in studies with children with ADHD (Heinrich et al., 2004; Wangler et al., 2011), though our data did not reach significance. In an 11-year FU study assessing ERPs of children with ADHD, Doehnert et al. (2013) found that the CNV might be a stable maker for ADHD. Therefore, our expectation to increase the CNV with SCP-NF in adults might not be easily realized. It is possible that it might be easier for children with ADHD to produce this change, as Heinrich et al. (2004) reported in their study. However, other studies with children with ADHD were not able to replicate these results (Doehnert et al., 2008). An additional factor might be a lack of motivation at the end of the long and repetitive testing time, as suggested by Doehnert et al. (2008). Further, age does not seem to be the only factor affecting the ability to change the CNV through SCP-NF. In an investigation of NF effects in healthy adults, Studer et al. (2014) found a significant increase of CNV after SCP-NF which was related to a good ability to create negativity during the NF.

To our knowledge, there are no studies that tested long-term development of CNV in any population or after any kind of treatment. Hence, we cannot make any conclusions about the CNV decline in the six-month FU at this point.

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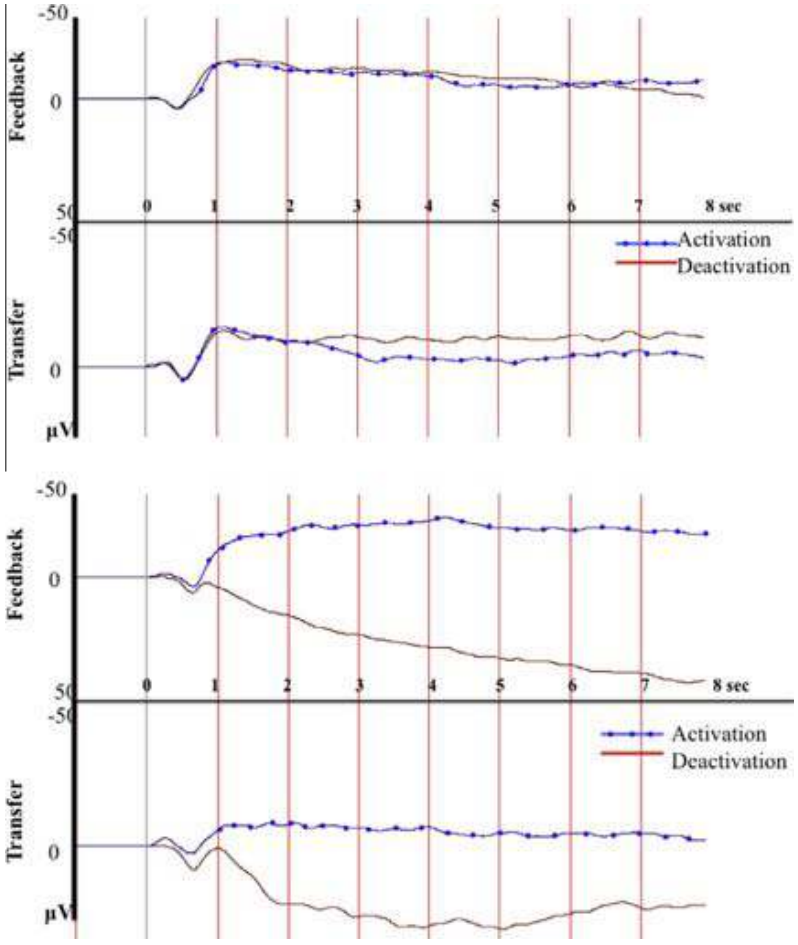

Fig. 7. Learned self-regulation ability for one subject sessions 2 + 3 (top) and sessions 28 + 29 (bottom) for feedback and transfer condition. The solid line represents the averaged positivation (deactivation), the dotted line the averaged negativation (activation) trials.

In 30 sessions of SCP-NF, 11 of the 24 participants learned to successfully self-regulate their brain activity. Learner and non-learner did not differ in any demographic data like age, sex, ADHD score, comorbid symptoms, or expectancy about treatment outcome. CNV amplitudes and RT did not show significant differences among the groups, but there was a trend for larger RTV in the group of non-learners. After 30 sessions of SCP-NF, we observed significant differences between the groups of learners and non-learners. Directly after treatment, there was a statistical trend with medium effect size for a larger improvement in ADHD symptoms in learners. This trend developed into a significant difference between the groups after six months. Additionally, we found a similar trend for third-party rated symptoms. This indicates that participants who learned to self-regulate their brain activity benefited more and in the long run from the treatment compared to those who did not learn this skill. The findings also indicate specific effects of SCP-NF, as unspecific effects were not observed to sustain permanently (Benedetti et al., 2005). Additionally, the significant correlation of hyperactivity reduction and RT improvement in the group of learners indicates that self-rated symptom reduction is reflected in objective measures of RT. We did not find any significant group difference for comorbid symptoms, which decreased in both groups and stayed almost at the same level after six months. This may indicate unspecific effects of SCP-NF on comorbid symptoms.

An unexpected group difference was observed for RTV. Both groups improved in RTV, but the group of non-learners improved significantly more compared to the group of learners. However, the group of non-learners started with higher RTV and never reached the level of the group of learners. A similar pattern was observed for the CNV on a descriptive level. Non-learners showed a slightly lower CNV before treatment compared to learners. Over the course of treatment, non-learners increased their CNV more than learners. These results cast the impression that the group of non-learners profited more from the treatment on a neurophysiological level. However, this might be due to the fact that they also experienced a greater potential for this improvement, as their baseline level was lower compared to the group of learners. As regards to the symptoms these results are similar to the effects found in children with ADHD (Wangler et al., 2011). In this study, children with a higher baseline CNV improved more from SCP training according to their parents' ratings of clinical symptoms.

In general we would have expected better training performance in terms of both the amount of learners and individual performance. Therefore, another question would be why participants were not as good as expected in learning how to self-regulate positive and negative potential shifts. This could be due to several reasons. One reason might be that we did not include a rewarding token system like most of the studies with children did (Strehl et al., 2006; Holtmann et al., 2014). This fact might have altered the training motivation of participants. Another factor might be the standardized and therefore rigid training protocol. Participants often asked the therapist to change some parameters like the amount of transfer trials, the length of the trials or the possibility to just train in one direction in each block. In a clinical practice, it is reasonable to individually adjust the training protocol and

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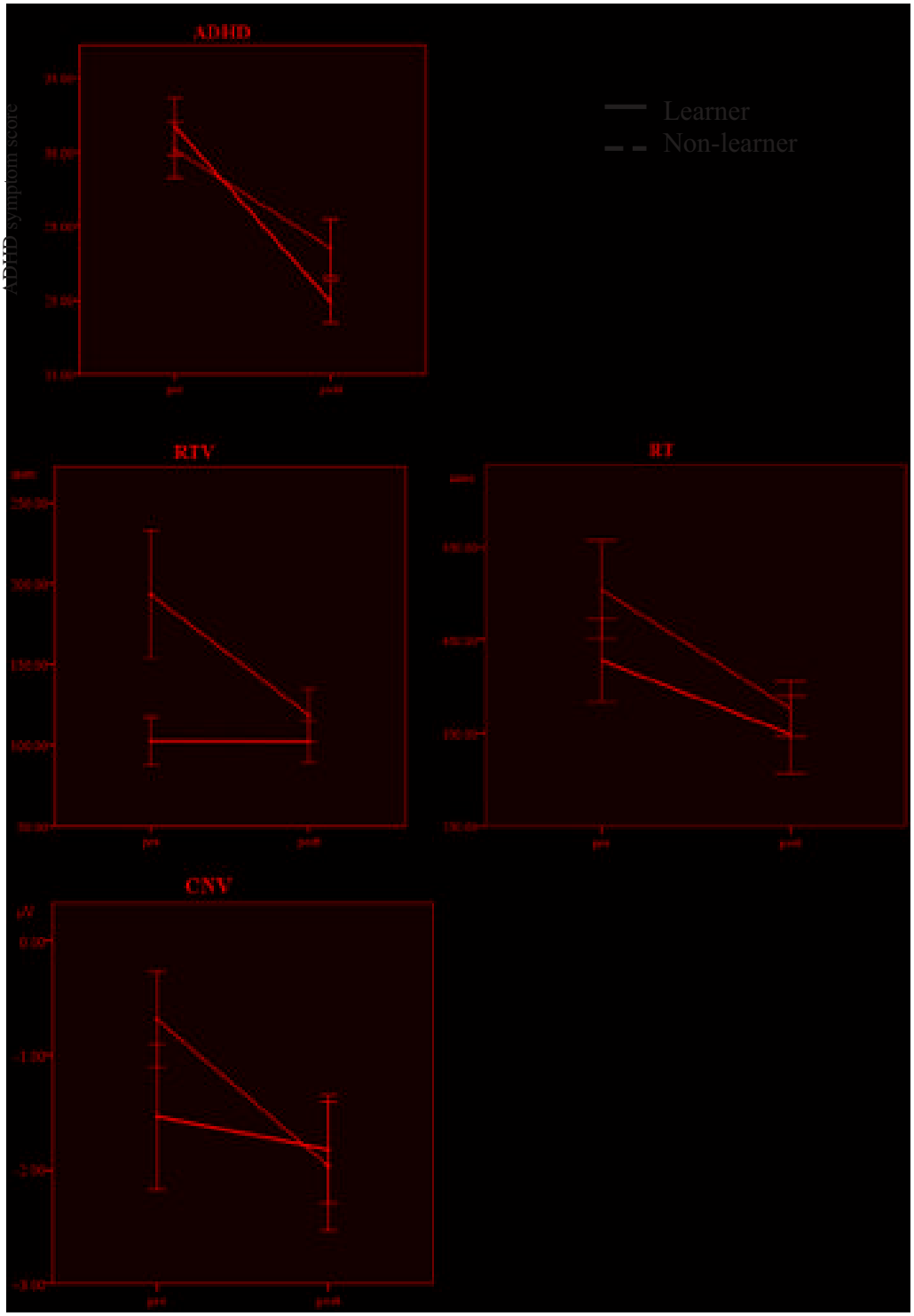

Fig. 8. Mean values for pre and post training separate lines for learners and non-learners for RT, RTV, ADHD and CNV.

therefore yield better learning and treatment outcome. In the standardized study protocol, however, individual needs could not be addressed. Future studies might wish to include more individualized SCP-NF protocols to create a more realistic clinical setting and therefore use the full potential of NF being a method of cognitive-behavioral therapy.

Another important aspect from the perspective of behavioral therapy is the transfer of self-regulation to daily life. In our protocol, we only suggested methods for how to realize the transfer, but we did not actively practice them in contrast to investigations with children in which active transfer was realized, e.g. doing homework immediately after the NF session (Strehl et al., 2006; Drechsler et al., 2007; Holtmann et al., 2014).

Furthermore, participants might need more sessions to achieve better training performance as well as a stable change in the CNV, though this might not be true in every case. Learning the self-regulation skill must not necessarily be conceived as linear, with learners showing a constant increase in self-regulation

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Table 5
Mean change scores (standard deviation) of learner and non-learner for all main outcome variables.

	$M_{learner}$ (*SD*)	$M_{non\text{-}learner}$ (*SD*)	df	*t*	*p*	*d*
ADHD	11.82 (5.79)	6.62 (8.22)	22	1.76	.09	0.75
CNV	0.29 (2.30)	1.28 (1.68)	22	−1.23	.23	−0.52
RT	79.37(146.21)	128.26 (145.47)	21	−0.80	.43	−0.35
RTV	0.37 (20.97)	74.46 (106.88)	13.1	−2.45	.03*	−1.35
WRI	5.64 (5.75)	2.00 (8.20)	22	1.24	.23	0.53
FBB	7.11 (7.32)	2.86 (4.91)	14	1.32	.17	0.71

ADHD = Self-rated attention deficit hyperactivity symptoms; CNV = Contingent negative variation; RT = reaction time; RTV = reaction time variability; WRI = Wender Reimherr interview; FFB = third-party rated ADHD symptoms.
* $p < 0.05$.

Table 6
Correlations of all main outcome variables.

	ADHD	WRI	FBB	CNV	RT	RTV	Train	FERT
ADHD	1							
WRI	.313	1						
FBB	.332	−.197	1					
CNV	−.297	−.011	−.415	1				
RT	.033	−.109	.030	−.057	1			
RTV	−.018	.147	.348	.089	−.557**	1		
Train	.291	.152	.021	−.137	.124	.184	1	
FERT	.444*	.160	−.027	−.339	.248	−.109	.335	1

ADHD = Self-rated Attention Deficit-/Hyperactivity Disorder symptoms; CNV = Contingent negative variation; RT = reaction time; RTV = reaction time variability; WRI = Wender Reimherr interview; FFB = third-party rated ADHD symptoms; Train = trainings data; FERT = treatment expectation questionnaire.
* $p < .05$.
** $p < .01$.

competences of SCP, for instance, which is in turn reflected by a constant increase of amplitudes reached in negativation and positivation trials. However, such a constant increase might not always be observed (e.g. Blume, 2011; Gevensleben et al., 2014a). Decreasing performance under constant and intense NF training might be related to overtraining in patients specifically sensitive to high training load (Kreider et al., 1998; Mathews, 2008). A decrease in performance does not necessarily mean that participants unlearned to self-regulate the parameters trained, but rather cannot perform up to their competences. After a decrease in training load or break in the NF training, regeneration processes allow for a performance up to the patient's competences (Blume, 2011). Consequently, we need to be cautious of categorizing participants into groups of learners or non-learners prematurely, as training performance does not necessarily reflect the competences participants acquired in the course of the training. This might question our categorization of learner and non-learner or would challenge this approach even in principle.

Additionally, for the matter of article length we left out the midway assessment, which was conducted after the first 15 sessions. The midway assessment may have delivered valuable information, such as in the paper of Gevensleben et al. (2014a). They found an increase in CNV pre to midway but a decrease in midway to post treatment. They also discussed this in context of over-training.

Lastly, according to Ros et al. (2014), we should take into account that plastic changes cannot necessarily be expected to follow a linear path when the underlying topology of structural and functional reorganization in networks is strongly non-linear. Therefore, learning might not be evident in the training session data and maybe changes in oscillation or structural data from functional magnetic resonance tomography would deliver more insight. Gevensleben et al. (2014b) raised several interesting questions in their theory paper on NF models and their application. They discussed different mechanisms of action like acquisition of regulation capability and generalization to daily life behavior to the point of "personalized medicine" NF. This cannot be discussed in detail, but should definitely be considered for future research and application.

Contrary to our assumption, we did not find any correlation of training performance with the outcome variables observed. One would, for instance, expect that the acquired ability to create negativity, or a large differentiation between positivity and negativity during the SCP-NF, would influence the CNV increase or ADHD symptom decrease. However, none of these correlations were observed. This leads to the idea that the CNV should not only be seen as a dependent variable but also as an independent one. Like in Wangler et al. (2011), differences in the CNV might not only be an outcome but also a precondition of efficient NF treatment.

In theory, we expected a higher benefit of SCP-NF for the group of learners compared to the group of non-learners, as only those who master the SCP regulation should have the full benefit of the treatment (Lubar, 1997). This benefit was obvious in higher symptom improvements in learners, however the neurophysiological measures do not fit into the picture. Finally, we have to discuss the impact of unspecific variables. To control for some of these unspecific effects, we continuously measured the participants' expectations regarding the outcome of treatment (Vollmann, 2009) in every fifth session of SCP-NF. The mean expectation scored an "I agree partly" (4) in response to the question "I feel like the therapy will lead to an improvement of my symptoms" ranking from "I do not agree" (2) to "I fully agree" (7) on a seven point scale. This score correlated significantly with self-rated ADHD symptom improvements. The treatment expectancy is regarded as an unspecific effect. This correlation was apparent in the overall group and in the group of learners. This suggests that higher expectations might influence the motivation to learn the regulation skill and thereby produce greater symptom improvement. The success in learning and more positive reinforcement might reflect cause and effect in treatment expectations. To access the full amount of unspecific effects contributing to the effects of SCP-NF, we must wait for the comparison with the control group after the complete study is finished (Mayer et al., 2015a).

4.1. Limitations

In addition to the already mentioned challenges of NF studies and the discussed intervening effects in the study, there are some general limitations to this investigation. With a total sample size of 24 and a group size of eleven and 13, the power is low in this study, especially in the FU measurement. We tested many variables which might lead to false negative, but also false positive, results. However, in general we observed medium to large effect sizes, which indicate robust results.

One might suspect that the ADHD subtype might influence the treatment outcome. However no meaningful changes were found in a post hoc analysis including the subtype as a variable. An elaborated investigation in different subtypes with a larger sample might be worthwhile. As mentioned above, this data is part of a bigger project, which is currently in progress (Mayer et al., 2015a). Therefore, this is not a randomized controlled trial, but rather serves as a first impression of the effect of SCP-NF and its specificity on adults with ADHD.

5. Conclusion

The combination of neurophysiological changes and unspecific expectation effects resulted in a significant reduction of ADHD and comorbid symptoms as well as neurophysiological parameters

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that persist over time. So far, our data do not reveal the underlying factors of learned self-regulation of SCP. More research and further analysis of the current dataset including the active and semi-active control condition is needed to disentangle these relationships.

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