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Theta/beta neurofeedback in children with ADHD: Feasibility of a short-term setting and plasticity effects

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ABSTRACT

Neurofeedback (NF) is increasingly used as a therapy for attention-deficit/hyperactivity disorder (ADHD), however behavioral improvements require 20 plus training sessions. More economic evaluation strategies are needed to test methodological optimizations and mechanisms of action. In healthy adults, neuroplastic effects have been demonstrated directly after a single session of NF training. The aim of our study was to test the feasibility of short-term theta/beta NF in children with ADHD and to learn more about the mechanisms underlying this protocol.
Children with ADHD conducted two theta/beta NF sessions. In the first half of the sessions, three NF trials (puzzles as feedback animations) were run with pre- and post-reading and picture search tasks. A significant decrease of the theta/beta ratio (TBR), driven by a decrease of theta activity, was found in the NF trials of the second session demonstrating rapid and successful neuroregulation by children with ADHD.
For pre-post comparisons, children were split into good vs. poor regulator groups based on the slope of their TBR over the NF trials. For the reading task, significant EEG changes were seen for the theta band from pre- to post-NF depending on individual neuroregulation ability. This neuroplastic effect was not restricted to the feedback electrode Cz, but appeared as a generalized pattern, maximal over midline and right-hemisphere electrodes.
Our findings indicate that short-term NF may be a valuable and economical tool to study the neuroplastic mechanisms of targeted NF protocols in clinical disorders, such as theta/beta training in children with ADHD.

1. Introduction

Neurofeedback (NF) involves a brain-computer interface which enables participants to learn to gain self-control over specific aspects of their neural activity. Neuroregulation skills are acquired through a series of repeated sessions and behavioral, cognitive and/or emotional effects can be induced based on the NF protocol applied. NF can be conducted alone or in conjunction as a neuro-behavioral training, which addresses the successful application of these skills in daily life, i.e., how and when to apply the cognitive strategies, while linking their use to cues (comparable to the use of verbal self-instructions; Gevensleben et al., 2014b). There are many forms of NF, but one specific protocol that is often used is EEG-based theta/beta NF which aims at reducing theta and enhancing beta activity - thus addressing tonic aspects of cortical activation (Ros et al., 2014). This NF protocol has been developed as an effective treatment for children with attention-deficit/hyperactivity disorder (ADHD) with evidence from randomized trials demonstrating that core symptoms of ADHD (i.e., inattention, motor hyperactivity and impulsivity; American Psychiatric Association, 2013) decreased to a larger extent compared to active control conditions like EMG biofeedback (medium effect sizes) (Arns et al., 2014).

As a rationale for applying theta/beta training in ADHD, authors typically referred to findings from earlier resting-state EEG studies comparing children with ADHD to typically developing controls (see e.g. Heinrich et al., 2007). These studies reported that children with ADHD have elevated levels of slow-wave theta activity and reduced faster-wave alpha/beta activity (corresponding to exaggerated theta/beta and theta/alpha ratios; for review see Barry et al., 2003). However, recent findings argue against considering the theta/beta ratio (TBR) in the resting EEG as a reliable EEG biomarker for ADHD, suggesting that, at best, only a subgroup of children with ADHD exhibit an excessive TBR at rest (see meta-analysis of Arns et al., 2013). During an attentive state, Heinrich et al. (2014) found an increased TBR only for children

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with the predominantly inattentive subtype of ADHD while children with the combined subtype showed deviations in the upper-theta/lower-alpha (5.5–10.5 Hz) range, thus not supporting a generally increased TBR in ADHD during task processing. Due to these contrasting EEG findings concerning children with ADHD, it remains open whether theta/beta training is mainly suited for a subgroup of children with ADHD and should thereby be viewed as 'correcting' abnormal oscillatory activity. On the other hand, theta/beta NF can alternatively be seen as a method for augmenting general brain activation or plasticity, resulting in enhanced cognitive or attentional states, consistent with the way it is practiced in so-called peak-performance applications (Gruzelier, 2014), i.e., not contingent on abnormal brain oscillations.

In previous NF studies, evidence was found for oscillation-specific effects of theta/beta training in children with ADHD by assessing pre- vs. post-training EEG recordings. Higher baseline theta activity in the resting EEG (recorded in an eyes open condition) over centro-parietal regions predicted greater reductions of ADHD symptom severity after theta/beta training (Gevensleben et al., 2009). Additionally, the decreases of theta activity inter-individually correlated with clinical improvements pre- to post-NF training. These findings were replicated by Janssen et al. (2016) in regard to the resting EEG. However their active condition (Stop Signal Task) produced a non-significant finding, which may be an issue of statistical power. Gevensleben et al. (2009) also observed a decrease in theta activity (no change of beta activity) in the resting EEG after NF, but this effect was also observed for a NF training of slow cortical potentials. Monastra et al. (2002) reported a decrease of the TBR and clinical symptoms after theta/beta training in children with ADHD characterized by a high baseline TBR. However, among other differences, pre- and post-training EEG assessments encompassed several conditions (resting and task conditions) and could therefore also represent enhanced online regulation-skills, reflective of task-specific 'EEG states', rather than spontaneous 'EEG traits'.

Taken together, more clarification is needed concerning the mechanisms of action of theta/beta training in ADHD. Further efforts are required to learn more about the underlying mechanisms as well as to test potential optimizations. However, due to the length of typical NF trials for ADHD treatment (30–40 sessions), more economical evaluation strategies would be helpful to study these aspects. In this respect, short-term assessments may provide an elegant alternative. Using a single-session design in several studies (Ros et al., 2010; Ros et al., 2013; Kluetsch et al., 2014), Ros and colleagues focused on a desynchronizing form of NF, which involved inducing cortical 'activation' by reducing EEG spectral power, particularly of sensory 'alpha' (8–12 Hz) rhythms. They found that this NF protocol can be quickly learned by healthy adult participants, while demonstrating its neuroplastic effects in the direct aftermath of NF, i.e., up to 30 min after termination of training. In the Ros et al. (2010) study, post-NF resting-state changes directly correlated with the degree of EEG entrainment during NF, consistent with mechanisms of Hebbian plasticity (see Ros et al. (2014) for a review). Subsequently, Ros et al. (2013) reported a positive correlation between post-NF changes in resting-state alpha rhythm and self-reported 'on task' mind-wandering. Lastly, Kluetsch et al. (2014) proceeded to apply this single-session protocol to a clinical population with post-traumatic stress disorder, uncovering an association between individual alpha rhythm increase (or 'rebound') and improvement in subjective wellbeing. These studies provide mechanistic insights as well as clear evidence that plastic changes may occur after exposure to only one session of NF training.

In the present study, we applied a comparable short-term design for theta/beta NF training in children with ADHD. We intended to test the feasibility of this approach and to learn more about the mechanisms underlying this protocol which is frequently applied in ADHD therapy. Instead of conducting a controlled study, we chose to differentiate between good regulators (GR) and poor regulators (PR) based on the acquisition of neuroregulation ability. We hypothesized that: 1. Children with ADHD would be able to significantly decrease their TBR within two training sessions. 2. In cognitive tasks conducted directly after the training sessions, larger decreases of the TBR accompanied by improved performance would be observed in good regulators compared to poor regulators, indicating neuroplasticity.

2. Methods

2.1. Participants

Thirty-one children with a diagnosis of ADHD (according to DSM-IV criteria), aged ten to fifteen years old, participated in this study. Participants were recruited from a waiting list of families who had contacted the outpatient department of our clinic, expressing interest in receiving neurofeedback therapy. All children had normal or corrected to normal vision. Of those children, three failed to complete all three appointments and six had too many artefacts in the EEG, resulting in twenty-two complete data sets for analysis. ADHD diagnosis was based on a semi-structured clinical interview and confirmed using German ADHD rating scale for parents (FBB-HKS; Breuer et al., 2009): DSM-IV combined subtype ($n = 11$), inattentive subtype ($n = 11$). Comorbid diagnoses were allowed, while neurological impairments and learning disability ($IQ < 80$) were exclusion criteria. Medication for the treatment of ADHD was continued unchanged during study participation, other medications were not allowed. Characteristics of the sample are summarized in Table 1.

Written informed consent was obtained from each child and parent. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Erlangen. For their participation, each child received 20 Euros.

2.2. Design and procedure

The study consisted of three appointments: one acquaintance session and two theta/beta NF sessions with pre- and post-NF behavioral and EEG assessments. The acquaintance session was used to introduce NF and the tasks to the participants and to clarify about how to avoid artefacts in the EEG. This session lasted ca. 1 h and was administered with a 5 electrode montage and an abbreviated version of the NF sessions. The theta/beta NF sessions were used for analysis and recorded using a 15 electrode EEG montage. These sessions took place at the same time of day and lasted for 2 to 2.5 h.

Each session consisted of two NF phases: 1. A NF driven puzzle task, with reading and picture search tasks being conducted before and after

Table 1
Sample characteristics.

Sample characteristics	
Age (years)	13.4 ± 1.3
IQ	110.3 ± 10.9
Sex (m/f)	21/1
Medication (yes/no)	6/16
Methylphenidate, extended release	4
Lisdexamfetamine dimesylate	1
Atomoxetine	1
Sample comorbidities	
Dyslexia	5
Conduct disorder	2
Tourette syndrome/tic disorder	3
Emotional disorder	3
Obsessive-compulsive disorder	1
Asperger syndrome	1
German ADHD rating scale (FBB-HKS)	
Total score	1.6 ± 0.6
Inattention	1.5 ± 0.8
Hyperactivity/impulsivity	1.2 ± 0.8

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the NF trials; 2. An attention task with concurrent NF in which the pre- and post-assessment were trials of the attention task without NF (transfer trials). Due to the long format, the attention task was deemed to be too taxing for the children and will be excluded from the rest of the manuscript (see Fig. 1).

2.2.1. EEG and NF

2.2.1.1. Recording and preprocessing. During rest, reading and picture search tasks, EEG was recorded using a 32 channel BrainAmp amplifier (Brain Products, Gilching, Germany) and Brain Vision Recorder. Sintered Ag/AgCl electrodes were used. Prior to electrode application, the skin was cleaned using medical alcohol and gently abraded using abrasive EEG paste. For the acquaintance session, five electrodes were applied separately above and below the left eye, forehead (ground), earlobe (reference) and at Cz. For the NF sessions, 15 electrodes were applied: 2 EOG electrodes (below each eye), ear clip reference electrode, and a standard electrode cap (Easycap, Herrsching, Germany) with 12 electrodes (FP1, FPz (ground), FP2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). After electrode placement, impedances were brought to below 20 kΩ, with the reference and ground electrode below 10 kΩ. Children were instructed to minimize body and facial movements and blinks as much as possible during the recording times. EEG was recorded with a sampling rate of 500 Hz.

2.2.1.2. NF. For NF, the program Self-Regulation and Attention Management (SAM; developed by our group) was used. NF was provided based on the signal at Cz (referenced to the left earlobe). Sampling frequency was 500 Hz and EEG signals were high-pass filtered at 1 Hz and low pass filtered at 30 Hz. Gratton & Coles (Gratton et al., 1983) blink correction was used. Amplitudes of above ±100 μV were interpreted as artefacts, as well as higher frequency activity (25–35 Hz) of >10 μV. Butterworth filters (48 dB/octave) were used to calculate the theta and beta feedback activity, which was recalculated 10 times per second using a moving 2 s window. Feedback was based on the TBR. For each trial, baseline values and mean EEG deviations from baseline (effective values) were exported from the SAM program at a 20% artefact threshold.

2.2.2. NF training

2.2.2.1. NF baseline and thresholds. Baselines were assessed prior to each NF phase. For each theta/beta baseline measurement, children looked at a standard incomplete puzzle (see description below), with five pieces uncovered and which did not change, for 2 min. After each NF puzzle,

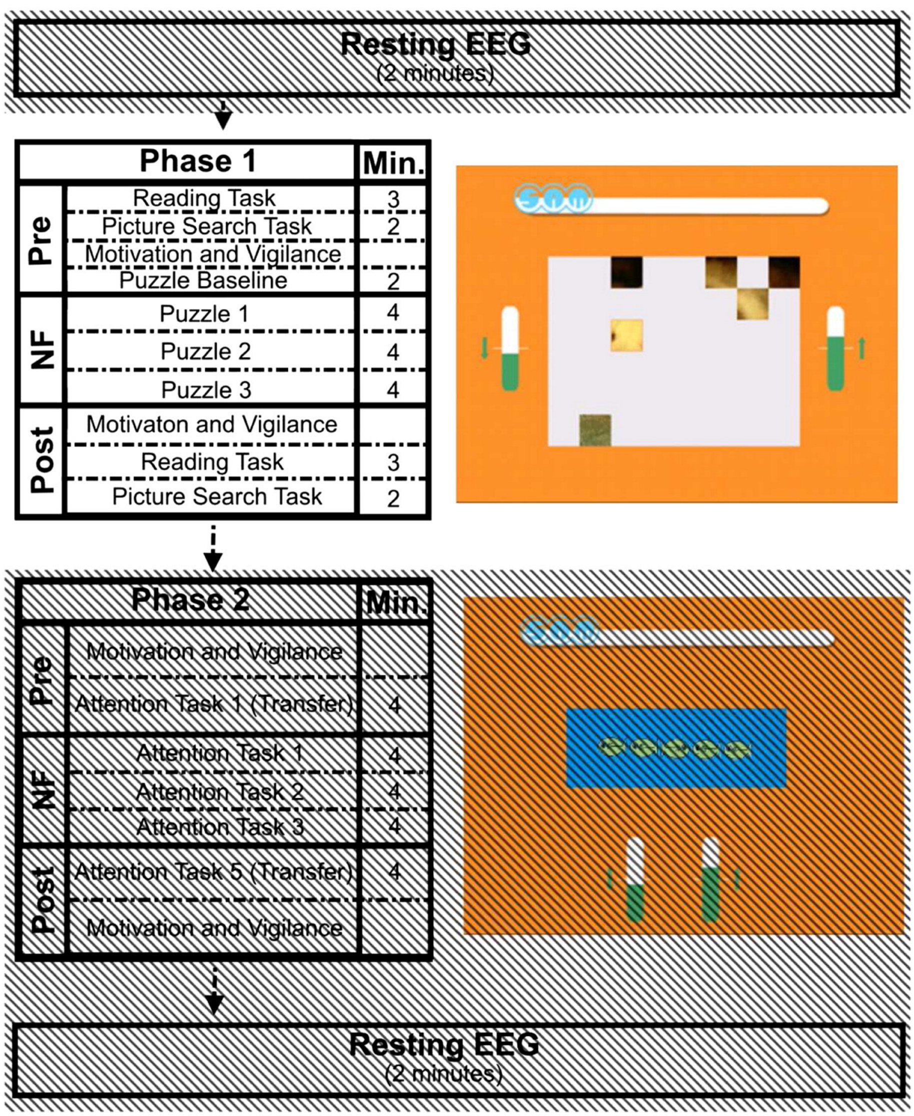

Fig. 1. NF session sequence and example of NF tasks. Grey areas reflect data that are not reported in this paper.

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the baseline was adjusted if too little positive feedback (<50%) was received.

2.2.2.2. Puzzle task animation. The puzzle task was presented on a 19 inch computer screen that was located approximately 64 cm from the child. Children were instructed to take a comfortable and relaxed seated position. Three puzzles (240 s each) were presented in each session, with six puzzles randomized across the two NF sessions. Puzzles were pictures of altered normal objects (ex. A duck with airplane wings), measuring 21 by 17 cm, with 48 puzzle pieces. At the beginning of the task 5 pieces were presented uncovered and 15 were required to be solved in order to see the complete picture at the end of a trial as a positive reward. A puzzle piece was 'solved' (stayed in place and a new puzzle piece was revealed) when the child regulated their TBR in the correct direction for a cumulative 5 s.

Regulation activity was presented on the left (theta) and right (beta) side of the puzzle in a moving bar image (bars 7.5 cm by 1.5 cm) (see Fig. 1). Each bar had a line in the center to indicate baseline value and an arrow indicating the desired direction of the activity (theta down/beta up). The average activity was presented by a green line, updated every 30 s, which was supposed to be below or above the middle line (respectively). Artefacts were monitored and children were asked to minimize movements and blink normally during the EEG and NF portions of the experiment, and were reminded of this when artefacts were excessively present.

Children were instructed to discover what was depicted on a picture by uncovering puzzle pieces that would be revealed when they moved the bars on either side of the puzzle in the correct direction, the theta 'sleepy wave' down and the beta 'hello-awake-wave' up, by being focused and calm. A puzzle piece appeared on the screen that was outlined in orange, and when they regulated in the desired direction, the puzzle piece would be set and the next puzzle piece could be solved. NF trainer and child reflected briefly about the regulation performance and artefact minimization after each trial.

2.2.3. Cognitive performance tasks (pre-post)

Reading and picture search tasks were presented in a randomized and counterbalanced order. Both tasks were clipped to a vertical board ca. 20 cm from the child.

2.2.3.1. Reading task. Silent reading was chosen as a cognitive task based on the procedure from Monastra et al. (2002). Reading passages were selected from grade appropriate reading comprehension tests: Elementary level material (grades 1–4) from the education server of Rheinland Pfalz (Bildungsserver Rheinland Pfalz – Materialen zur Lesekompetenz, 2016); upper level class material (grades 5–8) from the end of year exams for the state of Bavaria (Jahrgangsstufentests Deutsch Bayern, 2016). For each grade, there were four reading passages and their presentation was randomized between the trials. Texts were presented for 3 min on an A4 sheet of paper. After reading the passage, three reading comprehension questions were presented both visually and verbally. Questions were used to encourage motivation, but not as a dependent outcome variable.

2.2.3.2. Picture search task. The picture search task was chosen as a paper equivalent to the puzzle neurofeedback task. The task was taken from the Snijders-Oomen Nonverbal Intelligence Tests (SON) (Snijders and Snijders-Oomen, 1970; Tellegen and Laros, 1993) and presented on an A3 sheet of paper with three images, one search item and two images in which the item was hidden. Children were given 2 min to circle as many of the hidden images as possible. The score on the task was calculated as the number of items found minus the number of errors and used as a dependent outcome variable.

2.2.4. Additional assessments

Children were asked to rate their motivation and vigilance on a 10 point Likert scale four times throughout each session, accompanied by a rating from the tester. Motivation: completely unmotivated (1), completely motivated (10); Vigilance: completely tired (1), completely awake (10). This was asked before and after each NF phase.

2.3. Analysis

EEG signals for each phase of testing were analyzed with separate protocols according to the method of acquisition: NF (SAM Program); cognitive tasks (Brain Vision Recorder).

2.3.1. Neuroregulation

Neuroregulation was assessed using the mean effective value of the theta and beta activity for each NF trial. The effective values for the first and third puzzle were used to assess whether neuroregulation occurred. The effective values over all three puzzles were used to create the TBR, which was then used to create groups based on regulation ability. This resulted in different participants in each group for each session, but the number of participants in each group remained equal (11 Good Regulators: 11 Poor Regulators).

Groups were formed by assessing the regression coefficient for each participant over the three NF puzzles, separately for each NF session. The median split of the coefficients across participants was used to create two groups: those who fell below the median split (more TBR reduction from baseline) were defined as having better learned to neuroregulate (Good Regulators, GR); those who fell above the median split (less TBR reduction from baseline) were defined as not having learned to regulate as well (Poor Regulators, PR).

2.3.2. EEG at pre- and post-testing

EEG signal during the reading and picture search conditions were analyzed using Brain Vision Analyzer version 2.0 (Brain Products, Gilching, Germany). EEG signal was resampled to 256 Hz and filtered (low cutoff: 0.1 Hz, 12 dB/Oct.; high cutoff: 30 Hz, 12 dB/oct; notch: 50 Hz). Gratton & Coles ocular correction (Gratton et al., 1983) was applied with blink detection by algorithm. Raw data automatic inspection was then applied to 9 channels (C3, Cz, C4, F3, Fz, F4, P3, Pz, P4) with a maximal allowed amplitude difference during intervals of 100 μV and an interval length of 200 ms. Artefacts were marked as bad 300 ms before and 700 ms after an event. For participants with naturally higher theta and/or beta amplitudes, not attributable to artefacts, the maximal allowed difference was adjusted accordingly. The clean EEG was divided into 2 s segments and transformed to the frequency spectrum using the Fast Fourier Transform (FFT) using a 10% Hanning window and a resolution of 0.5 Hz. Data was then averaged across segments and the mean areas of the theta (4–7.5 Hz), alpha (8–12.5 Hz) and beta (13–20 Hz) bands were exported for statistical analysis. For the eyes closed condition, analysis was conducted similarly but with additional minimal and maximal allowed amplitude of −150 to 150 μV. The TBR was calculated by dividing the theta band average by the beta band average for each time (pre-, post-NF) and task (reading, picture search task) respectively.

2.3.3. Statistics

Statistical analysis was performed using SPSS version 21.0 (IBM Corp, Armonk, NY). There were three categories of dependent variables: 1. Neuroregulation during NF trials, 2. Cognitive performance and 3. EEG signal assessed during cognitive tasks. Neuroregulation was assessed for the deviation from baseline of theta, beta, and the TBR in the first and third puzzle. The cognitive performance measure consisted of the score on the picture search task pre- and post-NF. EEG signal for the reading and picture search task was assessed pre- and post-NF for each of the frequency bands (theta, alpha, beta) and TBR separately for Cz and globally, defined by the factor Region (frontal [F3, Fz, F4],

Table 2
Puzzle NF task regulation effective values in μV (mean ± standard deviation) for each session (1 and 2). Statistics provided for TIME (T) and TIME × GROUP interactions (T × G). No T × G is provided for the TBR values due to the grouping based on TBR.

	Full sample		Good regulators		Poor regulators		Statistics (repeated-measure ANOVAs)
	1	3	1	3	1	3	
Theta (4–7.5 Hz)							
1	6.09	6.08	5.98	5.78	6.20	6.37	T: $F(1,20) = 0.03$, p = n.s., part. $\eta^2 = 0.00$
	± 0.97	± 0.98	± 1.13	± 1.05	± 0.83	± 0.86	T × G: $F(1,20) = 17.45$, $p < 0.001$, part. $\eta^2 = 0.47$
2	6.31	6.20	6.44	6.18	6.19	6.22	T: $F(1,20) = 5.32$, $p = 0.031$, part. $\eta^2 = 0.20$
	± 1.12	± 1.09	± 1.06	± 1.03	± 1.21	± 1.20	T × G: $F(1,20) = 15.41$, $p = 0.001$, part. $\eta^2 = 0.44$
Beta (13–20 Hz)							
1	2.80	2.82	2.70	2.75	2.89	2.89	T: $F(1,20) = 1.05$, p = n.s., part. $\eta^2 = 0.05$
	± 0.50	± 0.53	± 0.47	± 0.53	± 0.53	± 0.55	T × G: $F(1,20) = 0.99$, p = n.s., part. $\eta^2 = 0.05$
2	2.82	2.85	2.74	2.77	2.90	2.90	
	± 0.52	± 0.53	± 0.33	± 0.39	± 0.65	± 0.65	T: $F(1,20) = 2.06$, p = n.s., part. $\eta^2 = 0.09$
							T × G: $F(1,20) = 0.41$, p = n.s., part. $\eta^2 = 0.02$
TBR							
1	2.21	2.20	2.25	2.15	2.18	2.25	T: $F(1,20) = 0.33$, p = n.s., part. $\eta^2 = 0.20$
	± 0.40	± 0.43	± 0.48	± 0.49	± 0.33	± 0.38	
2	2.29	2.23	2.37	2.26	2.20	2.20	T: $F(1,20) = 9.99$, $p = 0.005$, part. $\eta^2 = 0.32$
	± 0.49	± 0.50	± 0.44	± 0.45	± 0.54	± 0.56	

central [C3, Cz, C4], parietal [P3, Pz, P4]) and Laterality (left [F3, C3, P3], midline [Fz, Cz, Pz], and right [F4, C4, P4]).

In the first step of the analysis, one-way repeated measures ANOVAs containing the within subject factor TIME were computed for the dependent variables: 1. Neuroregulation (theta, beta, and TBR) for the first and third puzzle; 2. Cognitive performance (score) for the picture search task for pre- and post-NF; 3. EEG signal during cognitive tasks at Cz and globally (alpha, theta, beta, TBR) for pre- and post-NF. In the second step of the analysis, two-way repeated measures ANOVAs were conducted using the same dependent variables and within subject factor (TIME) as above, with the additional between-subject variable GROUP (GR vs. PR). For the GROUP analysis TBR was not considered, since it was used for group assignment.

Two additional two-way repeated measures ANOVAs were performed with the between-subject factor GROUP (GR vs. PR) and within-subject factor TIME (pre- vs. post-NF) for the dependent variables motivation and vigilance. Age and baseline group differences were assessed using univariate ANOVAs. A possible effect of the DSM-IV subtype and dyslexia comorbidity were tested using chi-squared tests. Correlation analysis was additionally conducted to assess the relationship between neuroregulation (regression coefficient) and signal changes during the cognitive tasks from pre- to post-NF, when the corresponding ANOVAs were found to be significant. Correlations were only conducted with the whole group results due to the small sample size and Bonferroni-Holm correction was used.

3. Results

3.1. Neuroregulation measures

A main effect of TIME was found in the second NF session for both theta and TBR in which both theta and TBR decreased from the first to third puzzle. An interaction between TIME and GROUP was found for theta in both sessions, characterized by a decrease in theta for the GR and an increase for the PR (see Table 2). No significant effect of TIME or interaction of TIME × GROUP was found for beta. Looking at the course of the activity in the target bands over the trials (see Fig. 4), the theta signal changed over time for the second NF session clearly for the whole group and when separated by regulation ability. In all cases the theta was suppressed from the first to third trial more so in the beginning (120 s) than in the end of the trial with no change in beta. The effect is more pronounced for the GR than the PR. Comparing baseline EEG values of GR and PR, no significant differences between GR and PR were obtained for theta activity or beta activity for either test session, all $p > 0.05$.

3.2. Performance measures: pre- vs. post-testing

In the second NF session, there was a tendency toward significance for TIME regarding the score on the picture task, $F(1,21) = 3.12$, $p < 0.10$, partial $\eta^2 = 0.13$, in which the score increased from pre to post test: pre (9.95 ± 2.40), post (10.82 ± 2.24). No effects or trends were seen in the first session and division by group did not reveal any other significant or near significant effects.

3.3. Spectral measures during non-NF tasks: pre vs post testing

3.3.1. Picture search task

No significant TIME or interaction effects were found for the picture search task for either session at Cz (all $p > 0.05$). When looking at the 9 electrode analysis, a significant TIME × Laterality interaction was seen for the first session theta band, $F(1,21) = 5.01$, $p < 0.05$, partial $\eta^2 = 0.19$, in which theta was highest at midline (pre: 4.87 μV; post: 4.96 μV)[1] and right (pre: 4.62 μV; post:4.66 μV) electrodes and tended to increase, while at left (pre: 4.27 μV; post: 4.26 μV) electrodes it was low and slightly decreased. Additionally there was a TIME × Laterality × Region interaction, $F(1,21) = 3.21$, $p < 0.05$, partial $\eta^2 = 0.13$, with the largest theta decrease seen at F3 (0.07 μV decrease). No other effects or interactions of TIME or GROUP were found for the second session or the other bands.

3.3.2. Reading task

Regarding spectral EEG parameters at Cz for the reading task, no significant effect was found in either session for the factor TIME. In the second session, a significant TIME × GROUP interaction was found for the theta band, $F(1,20) = 5.74$, $p < 0.05$, partial $\eta^2 = 0.22$, in which the theta activity at Cz for the GR decreased (pre: 5.32 ± 0.60 μV; post: 5.08 ± 0.60 μV) while activity for the PR increased (pre: 5.03 ± 0.74 μV; post: 5.17 ± 0.87 μV) from pre to post test. No other bands or the TBR were significant for the reading task.

Examination of the global EEG effects found a significant TIME x Region x GROUP interaction in the first session beta band, $F(1,20) = 4.47$, $p < 0.05$, partial $\eta^2 = 0.18$; the PR decreased their beta activity in the

[1] Due to different processing strategies in the NF program and Brain Vision Analyzer, amplitude values cannot be compared directly.

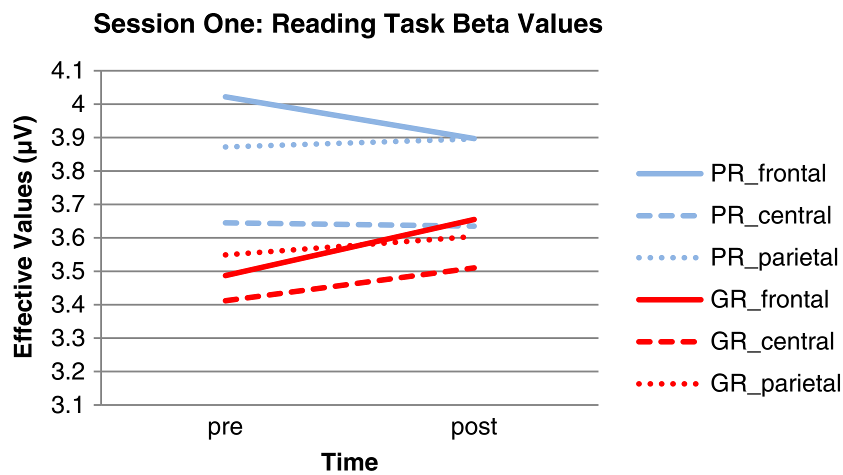

Fig. 2. First session beta values during reading task from pre-puzzle NF to post-puzzle NF. Time (pre, post) × Region (frontal [F3, Fz, F4], central [C3, Cz, C4], parietal [P3, Pz, P4]) × Group (Poor Regulators [PR]; Good Regulators [GR]).

frontal area with little change seen in the central and parietal areas, while for the GR all areas had a marginally increased beta, with the largest difference in the frontal area (see Fig. 2). For the second session, there was a global TIME x GROUP effect for the theta band, $F(1,20) = 4.37$, $p = 0.05$, partial $\eta^2 = 0.18$, where the GR decreased their theta activity (pre: 4.77 μV; post: 4.62 μV) while the PR increased (pre: 4.44 μV; post: 4.54 μV). For theta there was a significant TIME x Laterality x GROUP interaction, $F(1,20) = 7.60$, $p < 0.01$, partial $\eta^2 = 0.28$, in which the increase of the PR and decrease of the GR was more pronounced in the midline and right electrode groups than in the left electrode group. (see Fig. 3). No statistical difference was found for the second session spectral EEG activity in the alpha band, beta band or the TBR.

3.4. Additional assessments

Motivation ratings were not found to be statistically different between groups for either of the self-ratings or tester-ratings, $p > 0.05$. Vigilance ratings were found to be statistically different between groups in the first puzzle for both the self-ratings, $F(1,19) = 7.37$, $p < 0.05$, partial $\eta^2 = 0.28$, and tester-ratings, $F(1,19) = 7.37$, $p < 0.05$, partial $\eta^2 = 0.28$. For the self-rating the PR decreased in vigilance while the GR increased from pre to post (PR: pre = 7.70, post = 6.60; GR: pre = 6.27, post = 7.18); the tester-rating assessed the PR to have had a larger drop in vigilance than the GR (PR: pre = 8.40, post = 7.20; GR: pre = 6.91, post = 6.82). There was no pre-post difference between the vigilance ratings for either self- or tester-ratings for the second puzzle. Participant age, ADHD subtype, and number of participants with dyslexia did not differ between groups for either session, $p > 0.10$.

Correlation assessment of the significant finding from the picture search task revealed a significant correlation between the neurofeedback regression coefficient and the change in signal from pre to post for the first session theta value at C4, $r = 0.42$, $p < 0.05$. For the reading task, a significant correlation was found for the second session theta for F4, $r = 0.48$, $p < 0.05$, and C4, $r = 0.44$, $p < 0.05$. However these results did not remain significant after Holm-Bonferroni correction.

4. Discussion

Here, based on a traditionally applied NF protocol for ADHD, we investigated the feasibility of short-term theta/beta NF (i.e., two training sessions) for children with ADHD in order to more directly elucidate its mechanism(s). We could demonstrate that children with ADHD achieved a significant decrease of their TBR during neuroregulation trials within two sessions, which was mainly driven by decreases of theta activity. Moreover, we found an association between neuroregulation ability and decreases of theta activity in a reading task, but no performance improvements or EEG changes depending on neuroregulation ability in the picture search task.

4.1. Neuroregulation ability

During the puzzle task, for the group as a whole, we found significant decreases of the TBR and the theta band for the second, but not the first session. When the group was divided by regulation ability, visual assessment of the regulation curves indicated clear time effects within the third trial in the second session, but these effects were not more pronounced in poor regulators (PR) compared to good regulators (GR). This suggests that better neuroregulation was not simply due to greater regulation stability over the trial. However, significant effects between GR and PR were obtained for the theta band but not the beta band, indicating that TBR neuroregulation was mainly driven by a reduction of theta activity. This finding is consistent with EEG studies which have observed higher theta activity as more indicative of ADHD than decreased beta activity (Barry et al., 2003; Heinrich et al., 2014).

The GR group was not characterized by a higher baseline TBR, a higher theta band or a lower beta band activity. In previous NF studies, higher baseline theta activity was reported as a predictor for clinical treatment outcome of theta/beta NF in ADHD (Gevensleben et al., 2009). Our findings suggest that baseline theta activity and acquisition of NF regulation capability (as a moderator of outcome) may not be inherently related to each other, at least in the short term setting. However, this does not exclude the possibility that neuroregulation ability, as assessed in a rather early training phase, may serve as a further predictor for the success of theta/beta NF or number of training sessions required – comparable to findings obtained for NF training of slow cortical potentials in ADHD (Gevensleben et al., 2014a).

When looking at our specific NF testing protocol, children received explicit instructions to discover what was depicted on the picture of the puzzle and that they had to be focused and calm. Since learning was demonstrated on the group level for the second session, the use of explicit instructions may be appropriate for theta/beta training, while for other NF protocols (like sensorimotor rhythm NF), an absence of a mental strategy was reported to result in better neuroregulation (Kober et al., 2013). Additionally, the decrease of regulation performance at the end of each puzzle (after about 120 s., when the picture

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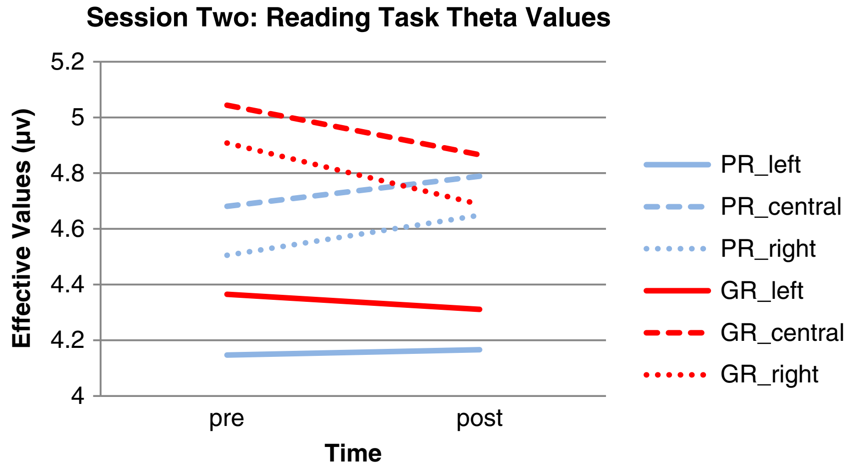

Fig. 3. Second session theta values during reading task from pre-puzzle NF to post-puzzle NF. Time (pre, post) × Laterality: left [F3, C3, P3], midline [Fz, Cz, Pz], and right [F4, C4, P4]) × Group (Poor Regulators [PR]; Good Regulators [GR]).

is recognized) sheds light on the importance of such controlled cognitive effort invested by the participants.

Based on practical experiences, we adapted the threshold after a trial if the amount of positive feedback in a trial was below 50% to keep the children motivated and to achieve better learning. Indeed, applying this algorithm, a higher number of children were able to achieve improvements in theta/beta neuroregulation over the course of the second session. However, it has to be noted that the optimal choice of thresholds, which may be different for different NF protocol, has not been studied systematically by now. In any case, information about the setting of thresholds should be provided in study reports.

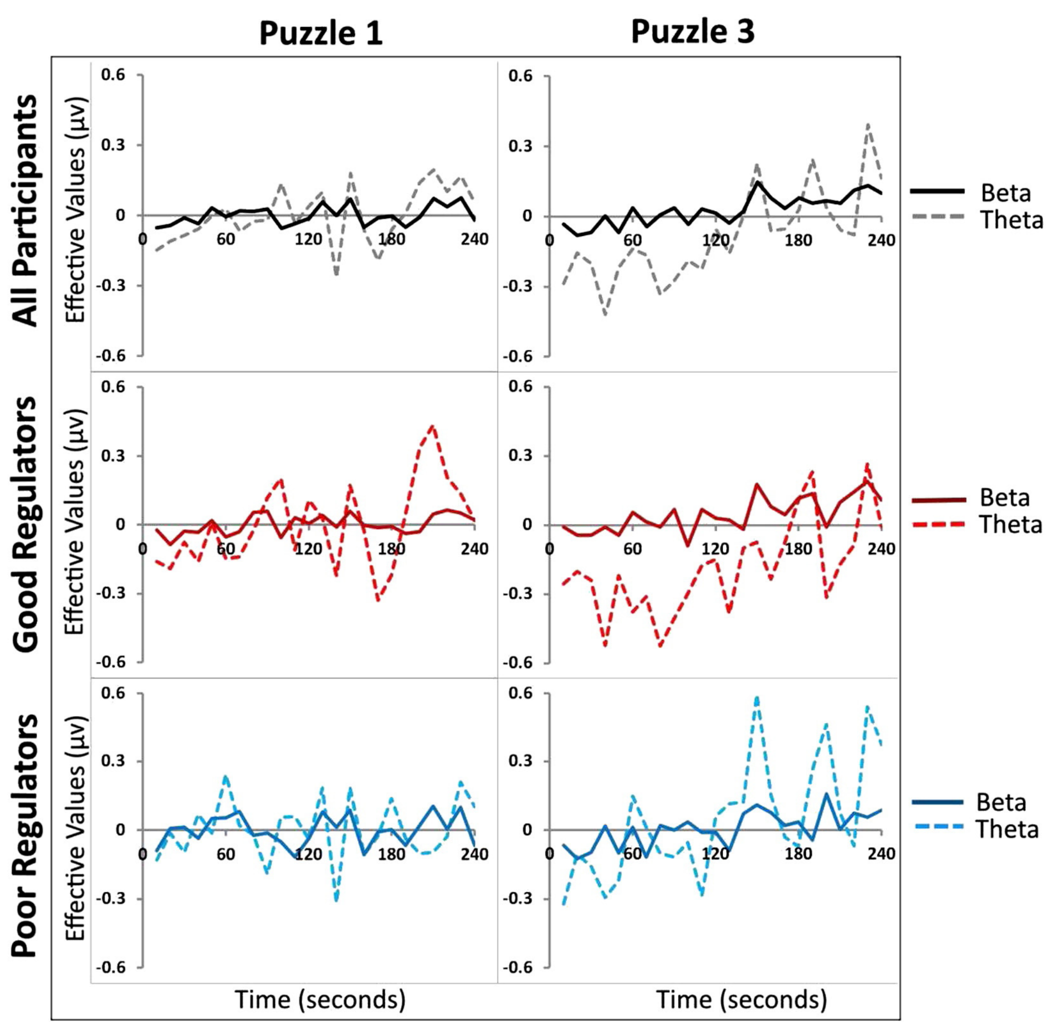

Fig. 4. Effective values over time for the second session puzzle NF.

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4.2. Neuroplasticity effects

Theta band reduction from pre- to post-session were found during reading for the GR in the second session. GR did not differ significantly from PR regarding motivation and vigilance in this session, suggesting that these factors do not seem to account for the differential effects between GR and PR. Since theta/beta NF has a temporally-direct influence on the reading task TBR, this partly supports recent proposals of a potential Hebbian mechanism behind NF effects (Ros et al., 2014). In short, this can be understood by the fact that neuronal connectivities that usually synchronize to give rise to the theta rhythm are functionally "extinguished" during the desynchronization phase of the NF (which coincides with reduced theta power). Moreover, it is the first such proof-of-principle demonstration in a clinical population, given that the findings by Kluetsch et al., 2014 revealed a homeostatic (i.e., anti-Hebbian) mechanism. Finding a significant difference in the EEG-pattern of the second session reading task, but not the first session, between GR and PR may indicate that successful learning might be required for successful neuroregulation. The separation of GR and PR for the first session probably did not accurately reflect neuroregulation ability, but may simply be by or due to vigilance. However, it may also be indicative that successful neuroregulation is required for task specific changes in cognitive processing.

The finding of changes after NF in the theta band but not necessarily the beta band or regarding the TBR is something that has also been reported in other studies for the resting EEG (for example Gevensleben et al., 2009). In contrast, Monastra et al. (2002) found a decrease in the TBR both at rest and during a reading task after theta/beta training. Since we did not operationalize reading performance as a dependent outcome measure, it cannot be assessed whether reduced theta during reading is of functional relevance. A reading task with operationalized performance evaluation should be integrated into future studies. Additionally, this theta effect was not restricted to the feedback electrode (Cz) but showed up as a more generalized pattern (though more pronounced over midline and right-hemispheric electrodes). Methodological optimizations should be implemented in subsequent studies to test whether learning of neuroregulation can be facilitated by incorporating additional electrodes for feedback calculation (providing a more specific feedback signal).

We could not find corresponding effects for the picture search task. In principle, both reading task and picture search task are thought to require visual attention. In the picture search task, working memory processes (associated with increases in frontal midline theta; Hsieh and Ranganath, 2014) may have interfered with or counteracted the more generalized theta pattern addressed by theta/beta NF thus accounting for the null finding for this task.

4.3. Conceptual aspects

The finding in the reading task, which we interpreted as a plasticity effect, was revealed by comparing PR and GR groups. This finding suggests that, in addition to the classic controlled design, there may be more options to critically assess regulation performance. Associations between regulation ability and pre- to post-changes can also provide evidence for the specificity of effects probably reflecting causal (i.e., Hebbian) relations. However, a non-controlled setting still does not provide evidence to assess whether pre- post-effects, ex. score increase from pre- to post-measurement in the picture search task, are related to NF or simply reflect practice effects. Based on this, the decision of whether or not to use a controlled design should depend on a study's main objectives.

Training sessions in our study were rather long and consisted of two parts. As previously mentioned, the second part was deemed to be too taxing for the children and excluded from the analysis. Due to this conceptual shortcoming, we could not investigate whether plasticity effects are also reflected in the resting EEG, which was recorded at the beginning and at the end of the sessions, or whether they can only be seen during task processing.

Of course, short-term designs do not allow conclusions to be drawn about the clinical effectiveness of the intervention in the long-term. However, they may be considered as an economical and elegant way to more directly study the neural mechanisms of NF protocols (Ros et al., 2013) and, as demonstrated here, are feasible for theta/beta NF in children with ADHD. Particularly in the field of ADHD, we see potential advantages for this short term approach; children with ADHD often show fluctuating motivation during the course of a long (30 + sessions) NF training which may influence the assessment of the associations between neuroregulation ability and outcome at different time points throughout the training (Zuberer et al., 2015). Additionally, when interpreting NF as a behavioral treatment, training outcome does not only depend on improved neuroregulation, but other factors (transfer into daily life, self-efficacy) also contribute (Gevensleben et al., 2014c) and should be accounted for. In short-term settings, these factors can be better controlled and/or do not play a significant role.

4.4. Conclusions and outlook

In our two-session theta/beta NF study, children with ADHD learned to decrease their TBR, accompanied by a reduction of theta activity in a reading task for good regulators directly after the NF trials. Thus, our findings document the feasibility of a short-term approach to study mechanisms of NF-associated plasticity in children with ADHD.

It remains to be investigated whether effects are restricted to an active task-driven state or if they also occur at rest. Moreover, the reading performance should be operationalized in further studies to learn more about the functional relevance of the theta band-related effect. Additionally, this theta band effect was seen globally, which calls into question whether Cz is the optimal site for the feedback electrode. Future studies could use this short term approach for fine tuning different methodological criteria, such as whether feedback calculated from multiple electrodes and/or source-space allows faster and more durable acquisition of control of the TBR.

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