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Theta/Beta Ratio Neurofeedback Effects on Resting and Task-Related Theta Activity in Children with ADHD

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Abstract

The EEG theta band displays distinct roles in resting and task states. Low resting theta and transient increases in frontal-midline (fm) theta power during tasks are associated with better cognitive control, such as error monitoring. ADHD can disrupt this balance, resulting in high resting theta linked to drowsiness and low fm-theta activity associated with reduced cognitive abilities. Theta/beta ratio (TBR) neurofeedback aims to normalize resting state activity by downregulating theta, which could potentially unfavorably affect task-related fm-theta. This study examines the TBR neurofeedback's impact on both resting and fm-theta activity, hypothesizing that remission depends on these effects. We analyzed data from a multi-center, double-blind randomized controlled trial with 142 children with ADHD and high TBR (ICAN study). Participants were randomized into experimental or sham NF groups. EEG measurements were taken at rest and during an Oddball task before and after neurofeedback, assessing global electrodes for resting theta and fm electrodes during error dynamics. Post-intervention changes were calculated as differences, and ANOVAs were conducted on GROUP, REMISSION, and CONDITION variables. Final analysis included fewer participants for all analyses. Resting state analysis showed no significant effects on global or fm-theta after TBR neurofeedback. Error dynamics analysis was inconclusive for global and fm-theta in both remitters and non-remitters. Results suggest that the current TBR neurofeedback protocol did not reduce aberrant resting state theta, and emphasize the need for refined protocols targeting specific theta-band networks to reduce resting-state theta without affecting fm-theta related to cognitive control.

Keywords Children with ADHD · Theta–beta ratio neurofeedback · Fm-theta · Task-related and resting state theta · Error-related dynamics · ICAN study

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a childhood-onset disorder with a worldwide prevalence rate of 5% (Polanczyk et al., 2015) and adult persistence rates

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Stefanie Enriquez-Geppert and Jaroslav Krc have contributed equally to this paper.

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from 4 to 76% (Caye et al., 2016; Sibley et al., 2017; Van Meter et al., 2024). ADHD is characterized by symptoms of inattention, hyperactivity, and impulsivity that interfere with functioning or development. The disorder is also associated with alterations in cognitive and brain functions, affecting higher-level executive functions (including deficient error monitoring). This might lead to reduced learning, as well as basic self-regulatory and reward processes, impacting individuals across the lifespan (Franke et al., 2018; Mohamed et al., 2019). Notably, some ADHD-related impairments decline and change over time (Cortese et al., 2012; Kaiser et al., 2020). A general interest of the research is objective measurement of atypical cognitive and brain function in ADHD, to better understand the disorder's etiology, and identify biomarkers and treatment targets for precision medicine (Bzdok & Meyer-Lindenberg, 2018).

A prevalent neurophysiological finding in children with ADHD is an increased theta activity and decreased beta activity at rest, often reflected in a high theta/beta ratio (TBR) (Barry et al., 2003) with a more diffuse topography (Ahmadi et al., 2020). Increased resting theta activity is associated with suboptimal levels of hypoarousal (Sergeant et al., 2003) indicating fatigue and drowsiness (Loo & Arns, 2015) and is related to lower cognitive abilities including executive functions and attention in children and adolescence (Cai et al., 2021; Maguire & Schneider, 2019; Perone et al., 2018). Although not topographically specific (e.g., Heinrich et al., 2014), TBR, typically calculated at central midline (CZ), has been suggested and endorsed by the Food and Drug Administration (FDA) as a complementary diagnostic biomarker for childhood and adolescent ADHD (Snyder et al., 2015; FDA, 2013). Despite this endorsement, meta-analyses have shown declining effect sizes for TBR and low differentiation between children with and without ADHD (Arns et al., 2013). Increased resting-state theta activity appears in only a one-third of children with ADHD (Bussalb et al., 2019). Consequently, TBR is now considered more a prognostic biomarker, providing insights into treatment outcomes for interventions like pharmacology, physical activity and neurofeedback (Arns et al., 2008, 2012; Janssen et al., 2016).

TBR is for instance used for treatment stratification in neurofeedback (Krepel et al., 2020). Children with ADHD and elevated TBR respond better to the TBR neurofeedback protocol (reflected by behavioral assessment), which could lead to more effective treatment when participants are assigned to specific NF training based on their EEG profile (Gevensleben et al., 2009). TBR protocol aims to downregulate theta at midline sites (e.g., Fz, FCz or Cz) to normalize high resting theta activity and reduce ADHD symptoms.

Alongside overlapping midline EEG scalp topography, frontal-midline (fm) theta is also particularly relevant to ADHD. Generally, fm-theta is associated with executive functions and signals the need for cognitive control and has been linked to medial–frontal brain regions, including the midcingulate cortex also known as anterior cingulate cortex (Cavanagh & Frank, 2014; Cohen, 2014). In contrast to resting state theta activity, fm-theta has a specific topography, with a fronto-central maximum at Fz (Ishihara et al., 1981; Mitchell et al., 2008).

Unlike resting theta activity, fm-theta is transiently increased during high cognitive control and strategic behavioral adjustments in healthy participants. The specific pattern of high power and low frequency activity is particularly effective for coordinating cognitive processes across distant brain areas (Buzsáki & Draguhn, 2004; Cavanagh & Frank, 2014; Cohen, 2014). Increased fm-theta occurs, for example, after errors (Cavanagh & Shackman, 2015; Cooper et al., 2019) and during post-error slowing (PES), which functions to inhibit premature post-error responses and reallocates attention to improve performance (Danielmeier & Ullsperger, 2011). Fm-theta activity is also related to event-related potentials such as the error-related negativity (ERN), the N2, and the feedback-related negativity (FRN) (McLoughlin et al., 2022). Using machine-learning approaches, response inhibition performance has been predicted with about 72% accuracy and best by theta activity in contrast to other brain features like ERPs (Vahid et al., 2018). Enhancing fm-theta through neurofeedback at fm electrodes has shown specific effects for the experimental group compared to sham feedback, enhancing proactive cognitive control in adults (Enriquez-Geppert et al., 2014; Eschmann & Mecklinger, 2022; Marcos-Martínez et al., 2023), including those in (sub)clinical groups reporting executive function complaints, both with and without a psychiatric disorder (Smit et al., 2023).

Both behavioral and brain measures of executive functions are associated with a variety of psychiatric disorders (Abramovitch et al., 2021; McLoughlin et al., 2022). In ADHD, error-related fm-theta appears reduced compared to healthy controls (Keute et al., 2019), indicating functional and structural impairments that contribute to deficits in PES, as observed in ADHD (Balogh & Czobor, 2016). These deficits can explain reduced learning, replication of errors, and impaired everyday activities (Mohamed et al., 2019). Changes in fm-theta amplitude also predicted reaction time variability (Guo et al., 2020; Keute et al., 2019), which supports the hypothesis that theta dysregulation may underlie the inability to implement and optimize task-relevant responses in ADHD (McLoughlin et al., 2014).

Several studies have explored the relationship between resting theta and task-related theta activity in optimal behavior. Klimesch (1999) summarized evidence from both animal and human research, indicating that low resting-state theta and high task-related theta are most optimal for cognitive and memory performance. A recent review indicates that elevated theta EEG power during resting state is associated with diminished cognitive functions, such as executive functioning and attentional abilities, whereas increased theta activity during cognitive tasks correlates with enhanced performance (Tan et al., 2024), which seems to be more consistent in children and adolescents than in adults (Lithfous et al., 2015; Vlahou et al., 2014). Developmentally, frequency bands with similar functional and topographical features seem slower in younger age compared to older (e.g., Isler et al., 2023). To account for this, the boundaries of frequency bands are often set lower for younger children, for instance theta ranges are from 3 to 5 Hz for infants and 4–8 HZ for adults (Orekhova et al., 1999), or individual peak frequencies are suggested (Doppelmayr et al., 1998). Both types of theta activity are influenced differently, resting theta decreased across brain regions with age, suggesting improved neural efficiency (Liu et al., 2014). Concurrently, task-related theta activity in the anterior cingulate cortex increased, correlating with better performance in a response inhibition task among children aged 8–18 years. The shift in EEG power from lower to higher frequency bands as children age has led to the hypothesis that elevated power in lower-frequency bands (such as delta and theta) during rest in children may indicate a delay in brain maturation (Matsuura et al., 1993). This delay can be triggered by factors such as early environmental adversities, as demonstrated by longitudinal studies comparing children who experienced severe psychosocial deprivation with typically developing children in the theta band (e.g., Debnath et al., 2020; Vanderwert et al., 2016).

Recent studies further emphasize the importance of the interplay between resting and task-related theta in cognitive control in adults (Pscherer et al., 2019, 2020, 2022). For instance, Pscherer et al. (2019) investigated theta in a conflict-modulated Go/Nogo task, and found the strength of resting theta activity modulated the increases of task-related theta during conflicts in response inhibition. Low resting theta activity reduced response inhibition performance and was associated with increases of task-related theta activity in the parietal cortex during inhibition. Pscherer et al. (2020) demonstrated that high resting theta activity was associated with higher peaks of theta-related N2 amplitudes during conflict conditions of a conflict task. Additionally, higher resting theta activity correlated with the fm-theta related N2 peak in an inhibition task (Pscherer et al., 2022), suggesting that resting-state theta could form a foundation and facilitate control-related theta activity. In summary, resting theta and task-related fm-theta reflect distinct rhythmic neural processes within the 4–8 Hz theta band in the human EEG, each associated with different functional networks and differentially affected in ADHD.

The current research question examines the effects of downregulating theta at middle frontal electrodes (either Cz or FCz) using a TBR neurofeedback protocol in children with ADHD. Because this approach closely resembles fm-theta upregulation protocols in adults, the aim is to understand how TBR neurofeedback impacts excessive resting theta without affecting the necessary transient increases of fm-theta during cognitive control. Answering this question could elucidate the mechanisms of action of the TBR neurofeedback protocol, identify reasons for non-remission, and ultimately help optimize neuromodulatory treatments. In the current study, we assess available data from the International Collaborative ADHD Neurofeedback study (ICAN) (Arnold et al., 2021). In this study it was found that both neurofeedback (NF) and control groups demonstrated significant improvements in parent/teacher-rated inattention from baseline to the end of treatment and at the 13-month follow-up. However, there was no significant difference between the NF and control groups in terms of improvement in inattention at either the end of treatment or the 13-month follow-up. Here we are focusing on measures of resting state activity and Oddball task processing before and after participants undergo a TBR neurofeedback protocol. Our hypotheses that remission (defined in two ways: as a CGI-severity rating of 1 or 2, and an ADHD symptom rating item mean < 1.00 (see Arnold et al., 2021) depends on differential effects on resting theta and fm-theta activity after TBR neurofeedback are:

- Hypothesis 1. Remitters in the experimental group will show a decrease in globally measured resting theta activity compared to the remaining individuals (of the sham NF group).
- Hypothesis 2. Remitters in the experimental group will show greater fm-theta activity increase than the remaining individuals (of the neurofeedback group) during and/or after error conditions compared to the correct trials.
- Hypothesis 3. Non-remitters in the experimental group will show no changes in resting theta activity compared to the remaining individuals (of the neurofeedback group).
- Hypothesis 4. Non-remitters in the experimental group will show only reduced fm-theta activity increase during and/or after errors, compared to remitters (of the sham NF group) during and/or after error conditions compared to the correct trials.

An exploratory analysis was performed for the Oddball targets and distractors, in which specifically fm-theta was assessed for targets and distractors, considering a possible contribution of response inhibition along with attention allocation.

Methods

Inclusion and Exclusion Criteria of the ICAN Study

Existing data were analyzed from the ICAN study (Arnold et al., 2021), a double-blind randomized controlled trial (RCT) involving 142 children aged 7–10 years rigorously diagnosed with ADHD. Children were screened using the Child Interview for Psychiatric Syndromes (*ChIPS) for both child and parent (P-ChIPS) and had to meet the DSM-5 criteria for either inattentive or combined presentation of ADHD. They additionally had to have a *T* score > 64 on inattentive symptoms on the Conners3 by both the parent and teacher.

To be eligible for inclusion in the ICAN, participants required an IQ greater than 80 and could not be taking any psychoactive medications other than those prescribed for ADHD. Exclusion criteria included convergence insufficiency, sleep apnea, restless legs syndrome, plan to move or change school, concomitant psychosocial treatment. Only children with a TBR ≥ 4.5 at Fz or Cz (10–20 system), measured by the Lubar-Monastra Assessment Suite (Thought Technology, Toronto, ON, Canada) were included. Prior to each major assessment, children were required to discontinue their ADHD medication for 5 days. The study was conducted at two centers: Ohio State University and University of North Carolina at Asheville, with data collected between August 2014 and February 2018.

ICAN Treatment Description

The ICAN study included an experimental (active NF) and sham NF (control) group. The neurofeedback protocol aimed to downtrain theta (4–8 Hz) and upregulate beta (13–21 Hz) at Cz or Fz, depending on which electrode site had the higher TBR at screening. Overall, they went through 38 treatment (active or sham NF) sessions in a 14-week period, with 6-, 13-, and 25-month FU (dated from baseline). Additionally, the protocol focused on reducing muscle movements (EMG, 45–60 Hz). Children received additional reinforcement through a points system. They were randomized in a 3:2 ratio into either the actual TBR neurofeedback ($n = 84$) or control group ($n = 58$) with pre-recorded EEG of another child as the basis for NF, a sham NF condition. The assignment process was performed double-blinded. EEGer neurofeedback software (EEG Software LLC, Northridge, CA) was used with a ProComp Infiniti (Thought Technology, Toronto, ON, Canada) or Atlantis (BrainMaster, Bedford, OH) amplifier. Amplifiers were randomly assigned, balanced between treatment conditions.

The ICAN study included a multimodal treatment approach. Regardless of group assignments, both groups received coaching, lifestyle recommendations on sleep and diet, and time management strategies. All children could also earn gift cards or cash through the points system. If children had better score in TBR after 5 periods in a session they could get a point, 20 points could be cashed for 15 dollars. Points could be also banked to accumulate to 20 points.

Outcome Measures

Parent- and teacher-rated inattention was assessed as primary clinical outcome using DSM inattentive symptoms on the Conners 3rd Edition: Long Version (C3P and C3T). For a full overview of outcomes see (Arnold et al., 2021), Neurofeedback Collaborative Group 2022. Remission (loss of diagnostic severity) was measured in two ways: by a Clinical Global Impression severity rating of 1 or 2, and by an average ADHD symptom rating below 1). The whole treatment was stopped at mid-point if the child did not show a 10% improvement in the average of parent and teacher inattentive ratings, but all assessment measures were still collected. Lower units of children dropped before the end of the treatment, for whom midpoint assessment was carried forward in Intention-to-Treat analysis.

EEG Measures: Resting State and Oddball Tasks

Main EEG measures included resting state and an auditory Oddball task, which were performed at baseline, mid-treatment, treatment end, and at 6, and 13 months follow up. EEG signal were recorded from the following 26 electrode channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, P7, P3, Pz, P4, P8, O1, Oz, O2 with the sampling frequency 500 Hz.

EEG data during resting state was measured with eyes closed and eyes open, with a duration of 2 min each.

The Oddball task is designed to measure aspects of attention, novelty detection, and response inhibition to distractor stimuli. In this study, the task involved auditory targets presented 17% of the time with a frequency of 1000 Hz. Participants were required to respond to these targets with both the left and right hand, while standard tones at a frequency of 500 Hz, serving as distractors, had to be ignored. Inter-Stimulus-Interval between two consecutive stimuli onsets differed between sessions and participants and was on average between 1000 and 1050 ms (ranging ± 10 ms within session). The duration of the Oddball task was around 6 min.

EEG Processing and Time–Frequency Decomposition

EEG data were automatically preprocessed using Python (code available at: https://github.com/brainclinics/TDBRAIN). In short, EOG artifacts were corrected using a regression-based technique (Gratton et al., 1983). Following artifacts were identified and excluded: electromyography, sharp channel-jumps (up and down), pulse and baseline shift, crosstalk, high kurtosis, residual eye blink, extreme voltage swing, electrode bridging, and extreme correlation. Data was then downsampled to 250 Hz and segmented into 2000 ms epochs that in Oddball task contained the event (stimulus or response) onset marker at 1000 ms. Data was also high pass (0.3 HZ), low pass (100 Hz) and notch filtered (60 Hz) with bidirectional IIR filter in a zero-phase manner, ensuring no phase shift occurs in the filtered data. For full details on preprocessing, see van Dijk et al. (2022) with the code freely available at https://brainclinics.com/resources/ since our data were preprocessed in the same way.

For further preprocessing we used MATLAB software (version R2017b, Natick, Massachusetts: The MathWorks Inc.) and its EEGLAB toolbox (Delorme & Makeig, 2004). Time–frequency decomposition followed and included sinusoidal wavelet transforms, using an increasing number of cycles with increasing frequency: range: 2–30 Hz; starting with 1 cycle at 2 Hz and increasing by 0.5 Hz per frequency; using 70 frequency steps. Power values in the time–frequency representation were normalized to the average baseline power for each frequency band. Decibel transform was used for normalization [dB $\text{power} = 10 * \log_{10}(\text{power/baseline})$]. The baseline power was computed as the average power from 0 to 900 ms. Mean event related spectral perturbations (ERSP) values were calculated as the average power spectrum over a sliding latency window (small steps ~ 5.53 ms intervals) across trials.

Data Extraction

For EEG analysis, inclusion criteria required that participants have EEG datasets from both measures before neurofeedback training (pre) and after or at 6-months follow up (both referred to as post treatment hereafter). A minimum number of five trials for errors in the Oddball task, fifteen for correct distractor and target trials of the Oddball task each, and thirty trials for resting state activity were required (see Boudewyn et al., 2018). For each participant, trials in each condition were randomized, and the number of trials per condition was equalized to ensure that all participants had the same number of trials per condition.

In this study, the Oddball task was primarily used to assess error dynamics, and secondarily to evaluate potential response inhibition functions. Five possible response conditions can be dissociated. Participants could:

- Respond correctly with two button presses to the target
- Correctly ignore the distractor (no response)
- Omit the response to target stimuli (omission error)
- Respond during the distractor presentation (commission error)
- Press only one button or press three times instead of correctly using two button presses (other errors)

To increase the number of trials for analyses, we included all three error types—omission errors, commission errors and other errors. These will be collectively referred to as "errors" throughout the analyses and in the rest of the text.

Maximum power of the averaged theta (4–8 Hz) was determined across selected electrodes in sensors of interest (SOI). Resting theta activity was measured at electrodes T3, T4, and Pz in resting state (global theta) as it is less specific than fm-theta and found also at temporal and parietal electrode sites (Ahmadi et al., 2020). Fm-theta was based on the electrodes Fz, FCz, and Cz in the Oddball task as these electrodes represent the specific maximal peak topography (Ishihara et al., 1981; Mitchell et al., 2008). Maximum theta power was identified (peak picking) within specific time windows, based on our expectations of the main theta activity associated with different tasks and events, i.e. parts with the most prevalent task/event effect on particular theta activity. For 2000 ms epochs we utilized segments from 1000 to 1720 ms to search for global theta maximum in resting state. Likewise, we analyzed segments from 950 to 1400 ms to identify theta maximum related to responses (starting at 1000 ms) to Oddball stimuli (fm-theta). Additionally, the segment from 1100 to 1400 ms was used to detect the theta maximum associated with the processing of the Oddball stimulus (fm-theta). Choices for time windows are aligned with the existing literature (e.g. Cohen, 2011; Luu et al., 2003), that reported theta power peak approximately 200–400 ms after the stimulus presentation as well as post-response. Time window for resting state theta activity was placed in the second half of the epoch to mimic the other time windows used in the study. Mean theta power was calculated by averaging the power within ± 1 Hz of the typical theta range of 5–7 Hz around the identified theta maximum. This averaging was performed within a ± 50 ms time interval (resulting in a 100 ms time window) over the frequency range of 4–8 Hz.

Statistical Analysis

For statistical analysis, difference scores were calculated. Regarding the extracted theta power, differences were obtained by subtracting the mean power measured in resting state and in the Oddball task after neurofeedback from the power measured before. Therefore, positive values indicate a reduction in power following neurofeedback.

This subtraction procedure (pre-post) was applied similarly to the behavioral data: reaction times (RTs) and accuracies after neurofeedback were subtracted from the values before neurofeedback. Positive values of RTs reflect faster responses after neurofeedback training, while positive values in accuracy reflect a decline in performance after neurofeedback training.

For these exploratory analyses, an alpha significance level of 0.05 was used. Effect sizes are reported for $\eta^2 p$ and interpreted according to Cohen (1988) as follows: a small effect is indicated by $\eta^2 p = 0.01$, a medium effect by $\eta^2 p = 0.06$, and a large effect by $\eta^2 p = 0.14$ or higher. Data were statistically processed within the statistical software R (version 4.1.0) and jamovi (The jamovi project (2020), version 2.2.5, https://www.jamovi.org).

Resting State Analysis (Hypothesis 1,3)

The resting state analysis tests whether the TBR neurofeedback led to downregulating aberrant theta activity during rest. Out of the initial 142 children, 68 (experimental group: $n = 44$, sham NF group: $n = 24$) (remitters: $n = 19$, non-remitter: $n = 49$) were included for further analysis due to having complete datasets for resting state measure before and after the treatment (i.e. at treatment end or the 6 months follow up).

Global and frontal-midline theta changes were tested with two two-way ANOVAs during resting state with each of the two between-subjects variables: GROUP (experimental vs sham NF group), and REMISSION (remitters vs non-remitters). Homogeneity of variance and normality of residuals were assessed. Based on our hypothesis we expect a significant interaction GROUP x REMISSION.

Error-Processing in the Oddball-Task (Hypothesis 2, 4)

The resting state analysis tests whether the TBR neurofeedback affected cognitive control networks and associated fm-theta activity during error processing. Out of the initial 142 children, 30 (experimental group: $n = 17$, sham NF group: $n = 13$) (remitters: $n = 8$, non-remitter: $n = 22$) were included for further analysis due to having complete datasets for errors during the Oddball task measures before and after the treatment. Differences in global and frontal-midline theta between error and correct trials were compared. Specifically, correct target responses were analyzed one and two trials before the errors, as well as the error trials themselves. Behavioral analysis was not performed since errors contained also omission errors.

Global and frontal-midline theta changes were tested with two repeated measures ANOVAs with each of the two between-subjects variables: GROUP (experimental vs sham NF group), and REMISSION (remitters vs non-remitters), and one within-subject variable: CONDITION (errors vs correct responses). Homogeneity of variance and normality of residuals were assessed.

Based on our hypotheses we expect significant interactions of GROUP x REMISSION x CONDITION or REMISSION x CONDITION. If significance is found, planned comparisons will be conducted to assess differences between remitters and non-remitters in the experimental and the sham NF group.

Post-Error Processing in the Oddball-Task (Hypothesis 2, 4)

Post-error processing assessed, if TBR neurofeedback affected cognitive control networks and associated fm-theta activity after errors. Out of the initial 142 children, 30 (experimental group: $n = 17$, sham NF group: $n = 13$) (remitters: $n = 8$, non-remitter: $n = 22$) were included for further analysis due to having complete datasets for post-error analysis during the Oddball task measures before and after the treatment.

Differences in global and frontal-midline theta activity were assessed for correct trials before and after an error. Specifically, we analyzed correct responses to targets and distractors at one or two trials before an error, as well as correct responses to targets and distractors one trial after an error. Behavioral analysis for accuracies and RTs was not performed since correct responses included targets with responses and distractors that had to be ignored.

Global and frontal-midline theta changes were tested with two repeated measures ANOVAs during resting state with each the two between-subjects variables: GROUP (experimental vs sham NF group), and REMISSION (remitters vs non-remitters), and one within-subject variable: CONDITION (pre error vs post errors). Homogeneity of variance and normality of residuals were assessed.

Based on our hypotheses we expect also for this analysis significant interactions of GROUP x REMISSION x CONDITION and/or REMISSION x CONDITION. If significance is found, planned comparisons will be conducted to assess differences between remitters and non-remitters in the experimental and the sham NF group.

Oddball Task (Exploratory Analysis)

The resting state analysis tests whether the TBR neurofeedback affected cognitive control networks and associated fm-theta activity during possible response inhibition aspects during distractor processing. Out of the initial 142 children, 51 (experimental group: $n = 32$, sham NF group: $n = 19$) (remitters: $n = 17$, non-remitter: $n = 34$) had complete datasets for the Oddball task measures before and after the treatment.

Global and frontal-midline theta changes were tested with two two-way ANOVAs during resting state with each the two between-subjects variables: GROUP (experimental vs sham NF group), and REMISSION (remitters vs non-remitters), and one within-subject variable: CONDITION (target vs distractors). Homogeneity of variance and normality of residuals were assessed.

Behavioral analyses were tested with repeated measures ANOVA for changes following the intervention regarding accuracy and two-way ANOVA for RTs. In accuracy we used within and between-subject variables as follows: the two between-subjects variables were GROUP (experimental vs sham NF group), and REMISSION (remitters vs non-remitters), the one within-subject variable was CONDITION (target vs distractors). In reaction time only the two between-subjects variables were used. Homogeneity of variance and normality of residuals were assessed.

Results

An overview of all analyses and results (including *p*-values of nonsignificant effects) can be found in Table 1.

Resting State Analysis (Hypothesis 1,3)

In general, global theta showed a minimal mean change of − 0.013 (SD = 0.619) and fm-theta of − 0.012 (SD = 0.789) (see theta power for all conditions in Fig. 1), revealing no significant changes in either global theta or fm-theta after the intervention. The following sections show the results in detail.

Global theta: Contrary to expectations, there was no significant interaction effect or main effects of GROUP or REMISSION. Fm-theta: Similarly, there were no significant interaction effects or main effects of GROUP or REMISSION.

Error-Processing in the Oddball-Task (Hypothesis 2, 4)

In general, global theta showed a mean change of 0.108 (SD = 1.024) and fm-theta of 0.160 (SD = 1.385) (see Fig. 2 for theta power in all conditions).

Global-theta: There was a significant main effect of REMISSION (F(1,26) = 5.336, $p < 0.05$, $\eta^2 p = 0.170$; large effect size). Temitters showed an increase of global theta after the intervention with a mean change of 0.475 (SD = 1.16) while non-remitters showed a decrease in global theta with a mean change of − 0.32 (SD 0.905). There was a trend towards statistical significance for the CONDITION X REMISSION interaction (F(1,26) = 3.330, $p = 0.08$, $\eta^2 p = 0.114$; with medium effect size), and for the three-way interaction of CONDITION X GROUP X REMISSION (F(1,26) = 3.590, $p = 0.069$, $\eta^2 p = 0.121$; medium effect size), with effect sizes suggesting an underpowered sample. There were no significant main effects of GROUP or CONDITION, nor significant interactions for GROUP X REMISSION or CONDITION X GROUP.

Fm-theta: There was a significant three-way interaction of CONDITION X GROUP X REMISSION (F(1,26) = 6.097, $p < 0.05$, $\eta^2_p = 0.190$; large effect size). However, due to substantial differences in the number of remitters and non-remitters within both the experimental and sham NF groups, planned comparisons are not reported. Additionally, there was a trend towards statistical significance for the CONDITION X REMISSION interaction (F(1,26) = 3.859, $p = 0.06$, $\eta^2 p = 0.129$; medium effect size). There were no significant main effects for GROUP, REMISSION, or CONDITION, and no significant interactions of GROUP X REMISSION, and CONDITION X GROUP.

Post-Error Processing in the Oddball-Task (Hypothesis 2, 4)

In general, global theta showed minimal mean changes of − 0.066 (SD = 0.880) and fm-theta of − 0.328 (SD = 1.033), accordingly the statistical analysis regarding global theta and fm-theta changes showed no effects (see Fig. 3 for theta power in all conditions of post-error processing). For details see the next sections.

Global theta and Fm-theta: There was a trend to statistical significance for the CONDITION X REMISSION interaction (F(1,26) = 3.781, $p = 0.063$, $\eta^2_p = 0.127$; medium effect size) in fm-theta. There were no significant main effects nor interactions for the other variables.

Target and Distractor Processing in the Oddball Task (Exploratory Analysis)

Theta Activities During Target and Distractor Processing

In general, changes in theta had a mean of 0.003 (SD = 0.590) for global theta, and a mean of − 0.093 (SD = 0.875) for fm-theta (see Fig. 4 for theta power in all conditions of the Oddball task).

Global theta: The main effect of REMISSION was significant (F(1,47) = 4.357, $p < 0.05$, $\eta^2 p = 0.085$; medium effect size). Remitters showed a substantial reduction in global theta (M = − 0.253, SD = 0.47), while non-remitters showed a slight increase (M = 0.122, SD = 0.61). There were no significant main effects for GROUP or CONDITION. Additionally, there were no significant two-way interactions for GROUP X REMISSION, CONDITION X GROUP, or CONDITION X

Table 1 Overview of the conducted analyses and all results

Analysis	Sub analysis	GROUP (Exp vs. Sham NF)	REMISSION (Remitters vs. Non-remitters)	CONDITION (different per analysis)	2-Way Interactions	3-Way Interactions
Analysis 1: Resting state Exp ($n=44$), Sham NF ($n=24$) X Non-remitter ($n=49$), Remitter ($n=19$)	Global theta	GROUP F(1,64) = 0.102, $p=0.750$, η^2p = 0.002	REMISSION F(1,64) = 0.001, $p=0.979$, η^2p < 0.001	NA	GROUP x REMISSION F(1,64) = 0.132, $p=0.717$, η^2 p = 0.002	NA
	Frontal-midline theta	GROUP F(1,64) = 1.855, $p=0.178$, η^2p = 0.028	REMISSION F(1,64) = 0.959, $p=0.331$, η^2p = 0.014	NA	GROUP x REMISSION F(1,64) = 0.102, $p=0.750$, η^2p = 0.002	NA
	Behavioral	NA	NA	NA	NA	NA
Analysis 2: Errors processing Exp ($n=17$), Sham NF ($n=13$) X Non-remitter ($n=22$), Remitter ($n=8$)	Global theta	GROUP F(1,26) = 0.255, $p=0.618$, η^2p = 0.010	REMISSION F(1,26) = 5.336, $p<0.05^*$, η^2p = 0.170	CONDITION F(1,26) = 2.44, p = 0.130, η^2p = 0.086	CONDITION x REMISSION F(1,26) = 3.330, $p=0.08^{\cdot}$, η^2p = 0.114 GROUP X REMISSION F(1,26) = 2.476, $p=0.128$, η^2p = 0.087 CONDITION X GROUP (F(1,26) = 1.220, $p=0.280$, η^2p = 0.045	CONDITION x GROUP x REMISSION F(1,26) = 3.590, $p=0.069^{\cdot}$, η2p = 0.121
	Frontal-midline theta	GROUP F(1,26) = 0.232, $p=0.634$, η^2p = 0.009	REMISSION F(1,26) = 1.530, $p=0.227$, η^2p = 0.056	CONDITION F(1,26) = 0.003, p = 0.959, η^2p < 0.001	CONDITION x REMISSION F(1,26) = 3.859, $p=0.06^{\cdot}$, η^2p = 0.129 GROUP X REMISSION F(1,26) = 2.555, $p=0.122$, η^2p = 0.089 CONDITION X GROUP F(1,26) = 0.497, $p=0.487$, η^2p = 0.019	CONDITION x GROUP x REMISSION F(1,26) = 6.097, $p<0.05^*$, η2p = 0.190
	Behavioral	NA	NA	NA	NA	NA

Table 1 (continued)

Analysis	Sub analysis	GROUP (Exp vs. Sham NF)	REMISSION (Remitters vs. Non-remitters)	CONDITION (different per analysis)	2-Way Interactions	3-Way Interactions
Analysis 3: PES Exp ($n=17$), Sham NF ($n=13$) X Non-remitter ($n=22$), Remitter ($n=8$)	Global theta	GROUP F(1,26) = 0.699, $p=0.411$, $\eta^2p=0.026$	REMISSION F(1,26) = 0.059, $p=0.811$, $\eta^2p=0.002$	CONDITION F(1,26) = 0.065, $p=0.801$, $\eta^2p=0.002$	GROUP X REMISSION F(1,26) = 1.154, $p=0.293$, $\eta^2p=0.042$ CONDITION X GROUP F(1,26) = 0.018, $p=0.895$, $\eta^2p=0.001$ CONDITION X REMISSION F(1,26) = 1.036, $p=0.318$, $\eta^2p=0.038$	CONDITION X GROUP X REMISSION F(1,26) = 0.356, $p=0.556$, η2p = 0.014
	Frontal-midline theta	GROUP F(1,26) = 2.120, $p=0.157$, $\eta^2p=0.075$	REMISSION F(1,26) = 0.015, $p=0.903$, $\eta^2p=0.001$	CONDITION F(1,26) = 0.140, $p=0.712$, $\eta^2p=0.005$	CONDITION x REMISSION F(1,26) = 3.781, $p=0.063$·, $\eta^2p=0.127$ GROUP X REMISSION F(1,26) = 0.804, $p=0.378$, $\eta^2p=0.030$ CONDITION X GROUP F(1,26) = 0.360, $p=0.554$, $\eta^2p=0.014$	CONDITION X GROUP X REMISSION F(1,26) = 0.253, $p=0.619$, η2p = 0.010
	Behavioral	NA	NA	NA	NA	NA

Table 1 (continued)

Analysis	Sub analysis	GROUP (Exp vs. Sham NF)	REMISSION (Remitters vs. Non-remitters)	CONDITION (different per analysis)	2-Way Interactions	3-Way Interactions
Analysis 4: Oddball Exp ($n=32$), Sham NF ($n=19$) X Non-remitter ($n=34$), Remitter ($n=17$)	Global theta	GROUP $F(1,47)=2.236$, $p=0.142$, $\eta^2p=0.045$	REMISSION $F(1,47)=4.357$, $p<0.05$*, $\eta^2p=0.085$	CONDITION $F(1,47)=1.135$, $p=0.292$, $\eta^2p=0.024$	GROUP X REMISSION $F(1,47)=0.526$, $p=0.472$, $\eta^2p=0.011$ CONDITION X GROUP $F(1,47)=0.062$, $p=0.805$, $\eta^2p=0.001$ CONDITION X REMISSION $F(1,47)=0.431$, $p=0.515$, $\eta^2p=0.009$	CONDITION X GROUP X REMISSION $F(1,47)=0.475$, $p=0.494$, $\eta 2p=0.010$
	Frontal-midline theta	GROUP $F(1,47)=1.116$, $p=0.296$, $\eta^2p=0.023$	REMISSION $F(1,47)=0.544$, $p=0.465$, $\eta^2p=0.011$	CONDITION $F(1,47)=2.06$, $p=0.158$, $\eta^2p=0.042$	CONDITION x REMISSION $F(1,47)=4.478$, $p<0.05$*, $\eta^2p=0.087$ GROUP X REMISSION $F(1,47)=0.023$, $p=0.880$, $\eta^2p<0.001$ CONDITION X GROUP $F(1,47)=1.38$, $p=0.246$, $\eta^2p=0.029$	CONDITION X GROUP X REMISSION $F(1,47)=2.69$, $p=0.108$, $\eta 2p=0.054$
	Behavioral	ACC: GROUP $F(1,47)=0.535$, $p=0.468$, $\eta^2p=0.011$ RT: GROUP $F(1,47)=0.283$, $p=0.597$, $\eta^2p=0.006$	ACC: REMISSION $F(1,47)=0.132$, $p=0.718$, $\eta^2p=0.003$ RT: REMISSION $F(1,47)=0.156$, $p=0.695$, $\eta^2p=0.003$	ACC: CONDITION $F(1,47)=0.04$, $p=0.842$, $\eta^2p=0.001$	ACC: GROUP X REMISSION $F(1,47)=0.645$, $p=0.426$, $\eta^2p=0.014$ ACC: CONDITION X GROUP $F(1,47)=1.629$, $p=0.208$, $\eta^2p=0.033$ ACC: CONDITION X REMISSION $F(1,47)=0.172$, $p=0.680$, $\eta^2p=0.004$ RT: GROUP X REMISSION $F(1,47)=0.018$, $p=0.894$, $\eta^2p<0.001$	ACC: CONDITION X GROUP X REMISSION $F(1,47)=0.677$, $p=0.415$, $\eta 2p=0.014$

Table note: Overview of the between and within subject designs of the four analyses. Significant results and trends are also listed in the cells and highlighted by italics

Exp experimental, *n.s.* not significant, *NA* not applicable

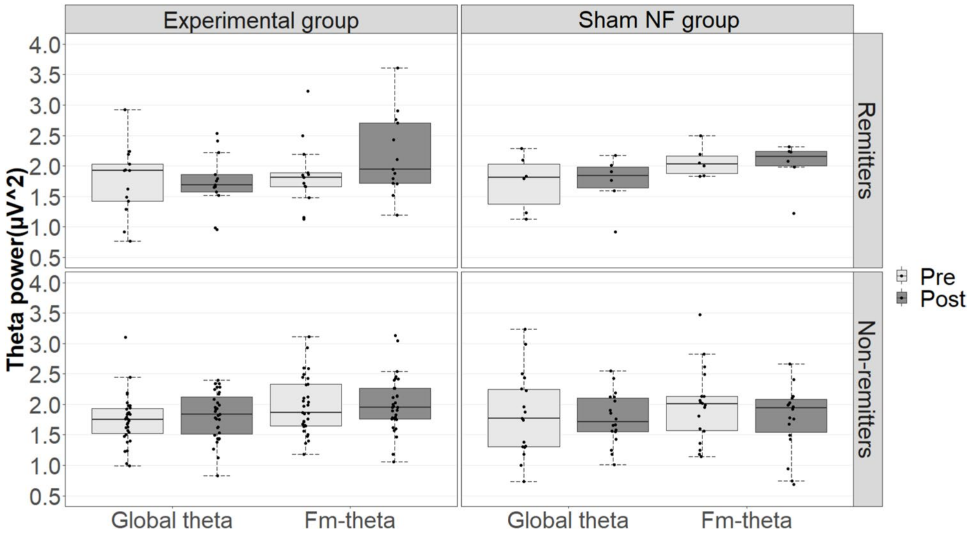


Fig. 1 Box plots of mean global and fm-theta theta power during resting state. Note: Theta activity is presented in both the experimental (left) and sham NF group (right), and within this for global (left) and fm−theta (right). The figure is further divided into remitters (top row) and non−remitters (bottom row). Data are shown before (pre-treatment in light gray) and after (post-treatment in dark gray) TBR neurofeedback training

REMISSION, and the three-way interaction of CONDITION X GROUP X REMISSION was also non-significant.

Fm-theta: There was statistically significant two-way interaction of CONDITION x REMISSION (F(1,47) = 4.48, $p < 0.05$, $\eta^2_p = 0.087$; medium effect size). In remitters, fm-theta increased for target processing with a mean change of 0.580 (SD = 1.10) while for distractor processing fm-theta decreased with a mean difference of − 0.078 (SD = 1.32), (t(1,47) = 2.123, $p = 0.39$). There were no significant main effects of GROUP, REMISSION, or CONDITION. There were no significant two-way interactions of GROUP X REMISSION, or CONDITION X GROUP. The three-way interaction of CONDITION X GROUP X REMISSION was not significant.

Accuracies and Reaction Times During Target and Distractor Processing

In general, accuracies were around 89.03% (SD = 8.66) before the neurofeedback and 88.30% (SD = 8.07) after the neurofeedback and reaction times were 0.486 s (SD = 0.07) before the neurofeedback and 0.468 s (SD = 0.07) after the neurofeedback (see Figs. 5 and 6 for a behavioral overview of the Oddball task in all conditions). Changes in accuracy scores had a mean of 0.738 (SD = 9.358) and RTs a mean of 0.018 (SD = 0.059). The behavioral data statistical tests were all non-significant. For the details see the following part.

Accuracy: There were no significant main effects nor interactions. RT for target stimuli: There was no significant main effect of GROUP or REMISSION or their interaction.

Discussion

The study aimed to investigate the effects of TBR neurofeedback on theta activity in children with ADHD both at rest and during the error-dynamics of an Oddball task, while considering clinical improvement in remitters and non-remitters. Using data from the ICAN multi-center, double-blind RCT, EEG measures were analyzed before and after neurofeedback treatment. Surprisingly, the results indicated no significant effects on global or fm-theta activity during resting state. However, error dynamics (during error processing and after errors) revealed effects on both global and fm-theta. Exploratory analysis of target and distractor processing, which reflect attention and possible inhibitory processes, indicated decreased general theta during task processing. The following sections discuss the results, limitations and the implications in more detail.

Theta Activity in Rest and During Task

Resting State Theta Effects

TBR neurofeedback, administered over 40 sessions, was expected to reduce resting state theta activity observed outside the training session after treatment. However, the results did not support this hypothesis, as no changes in general theta nor fm-theta were observed. Several potential

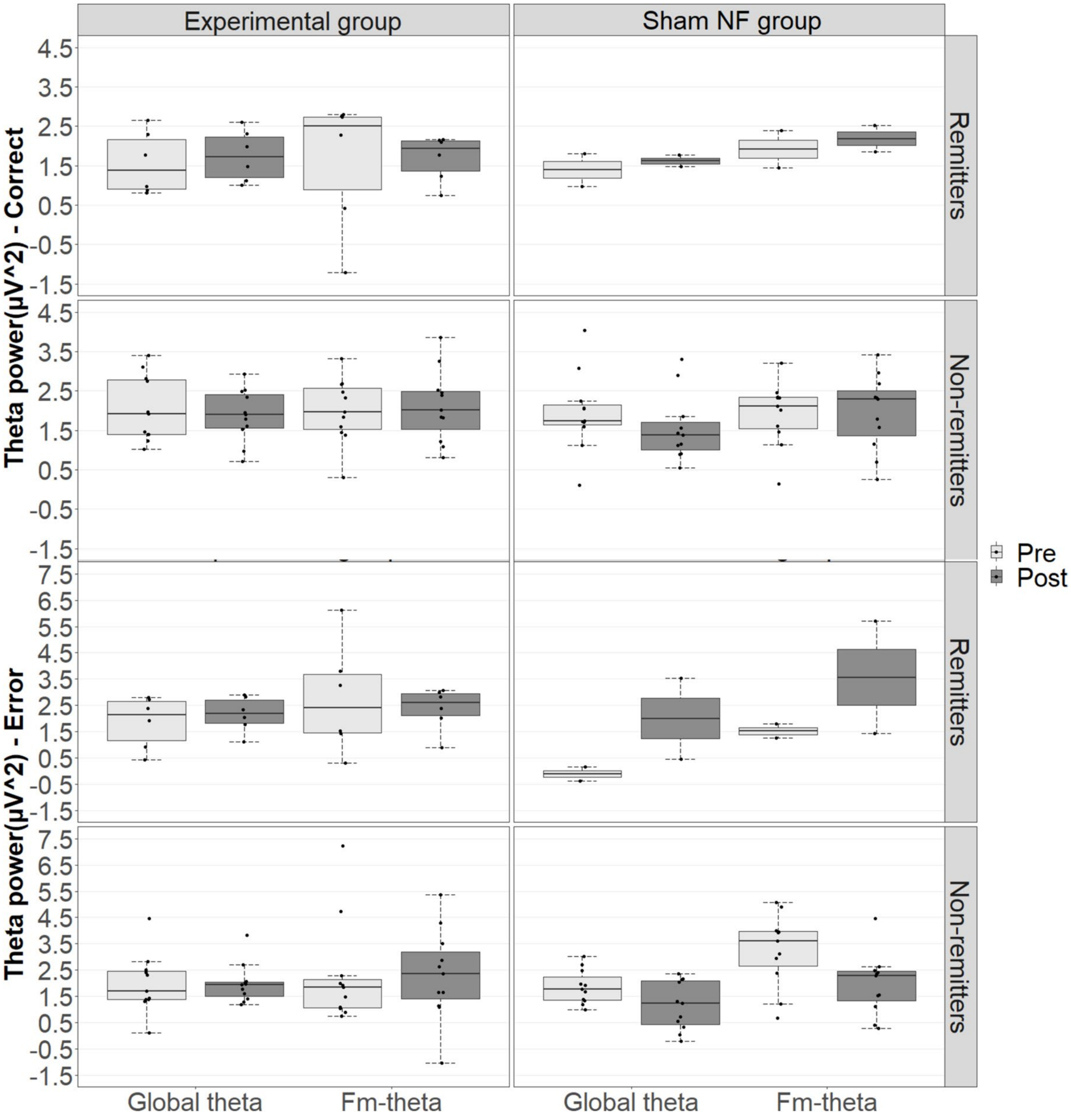


Fig. 2 Box plots of mean global and fm-theta theta power during error processing. Note: Theta activity is presented in both the experimental (left) and sham NF group (right), and within this for global (left) and fm−theta (right). The upper half of the figure reflects theta during correct stimuli responding, the lower half error processing. The figure is further divided into remitters (top row) and non-remitters (bottom row). Data are shown before (pre-treatment in light gray) and after (post-treatment in dark gray) TBR neurofeedback training

explanations exist for these findings. Children may not have learned to regulate their resting state theta during neurofeedback, they may have learned but failed to show a transfer effect, or they might have down-regulated a different theta network. This could be due to the TBR neurofeedback protocol's insufficient targeting of specific theta networks, hindering the translation of the training effects to general resting states. Without performing source analyses for neurofeedback training effects, these explanations remain speculative. Critiques about the lack of specificity in neurofeedback protocols are not new and have led to further developments in the field (Taschereau-Dumouchel et al., 2021).

The results align with the findings from the original ICAN study, where significant remission benefits were attributed to nonspecific effects rather than specific TBR-related neurofeedback effects (Neurofeedback Collaborative Group, 2023). Additionally, motivational factors, such as the value of reinforcement, could play a role. For instance, Pérez-Elvira et al. (2021) showed

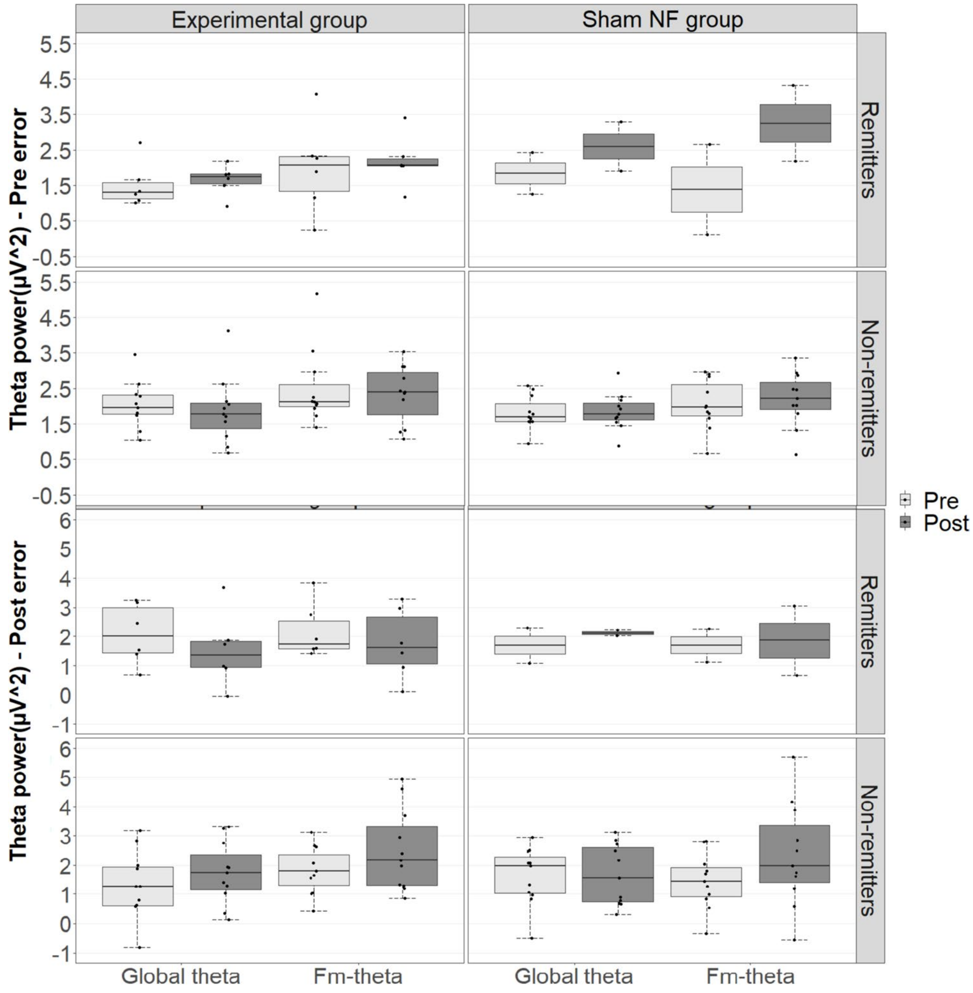


Fig. 3 Box plots of mean global and fm-theta theta power during post error processing. Note: Theta activity is presented in both the experimental (left) and sham NF group (right), and within this for global (left) and fm−theta (right. The upper part reflects that during correct stimuli responding, the lower part error processing. The figure is further divided into remitters (top row) and non-remitters (bottom row). Data are shown before (pre−treatment in light gray) and after (post-treatment in dark gray) TBR neurofeedback training

that participants who selected their reinforcers increased their sensorimotor rhythm more than those using imposed reinforcers during neurofeedback.

Error Dynamics and Theta Effects

We observed changes in theta activity during error dynamics. Specifically, during error processing, there was a general reduction in global theta activity in remitters compared to non-remitters. This might suggest that TBR neurofeedback did not specifically affect global theta but rather that reductions in theta during the Oddball task occurred for other reasons. An interaction was noted hinting at differences involving remission and treatment condition during errors or correct responses for fm-theta, but planned comparisons were underpowered. Post-error dynamics did not show significant effects in general, nor were there changes in fm-theta or behavioral performance.

Target and Distractor Processing

The pattern observed during correct responding to targets and distractors mirrored the results seen in the results in error processing discussed above: remitters exhibited a general decrease in global theta compared to non-remitters after the intervention. Analysis of fm-theta revealed a more complex pattern, with increases observed during target processing and decreases during distractor processing in remitters, regardless of group assignment. These neural changes were not accompanied by changes in behavioral performance. Consistent with previous study results, these findings suggest that TBR neurofeedback may not have specific effects on theta activity or behavioral outcomes. The possibility that maturation effects drive these changes remains speculative rather than evidence-based.

Fig. 4 Box plots of mean global and fm-theta theta power during target and distractor processing of the Oddball task. Note: Theta activity is presented in both the experimental (left) and sham NF group (right), and within this for global (left) and fm−theta (right). The upper half of the figure reflects that during target processing, the lower half during distractor processing. The figure is further divided into remitters (top row) and non-remitters (bottom row). Data are shown before (pre-treatment in light gray) and after (post−treatment in dark gray) TBR neurofeedback training

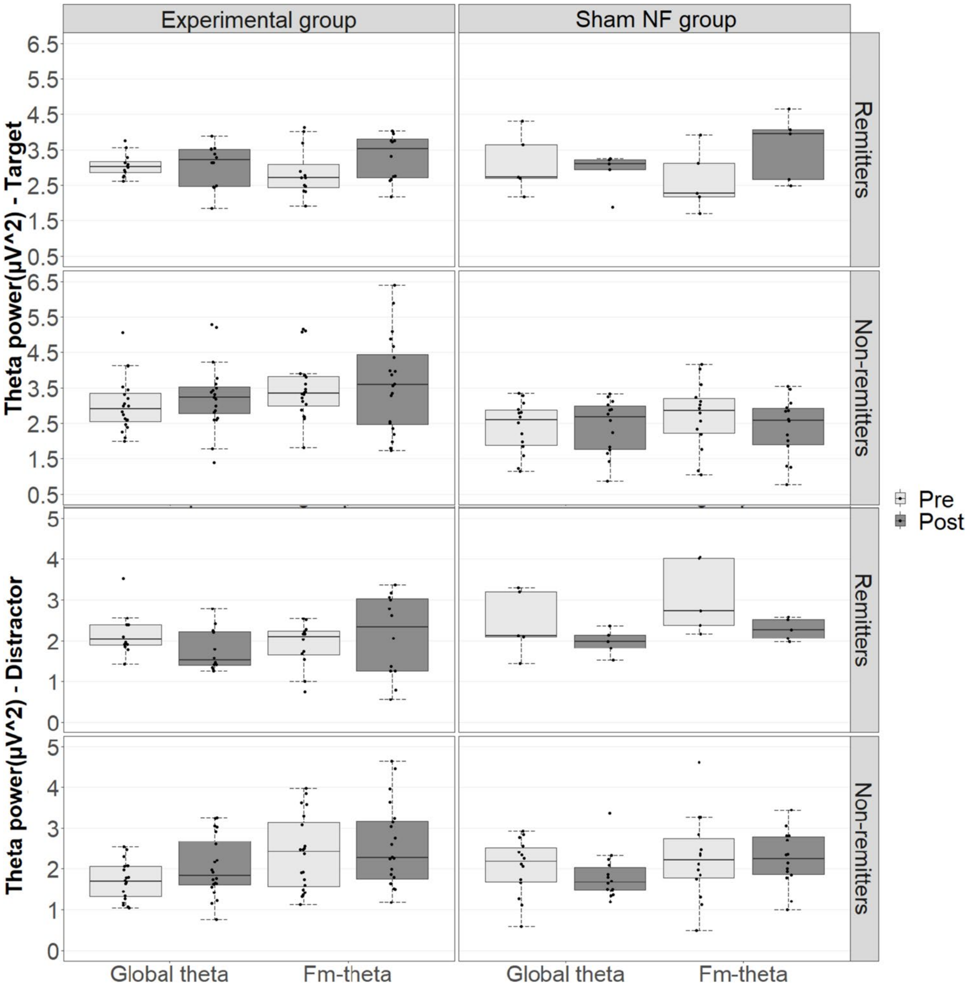


Fig. 5 Box plots for accuracies in the Oddball task. Note: Accuracies are presented for both the experimental (left) and sham NF group (right), and within this for target (left) and distractor (right) conditions. The figure is further divided into remitters (top row) and non-remitters (bottom row). Data are shown before (pre-treatment in light gray) and after (post-treatment in dark gray) TBR neurofeedback training

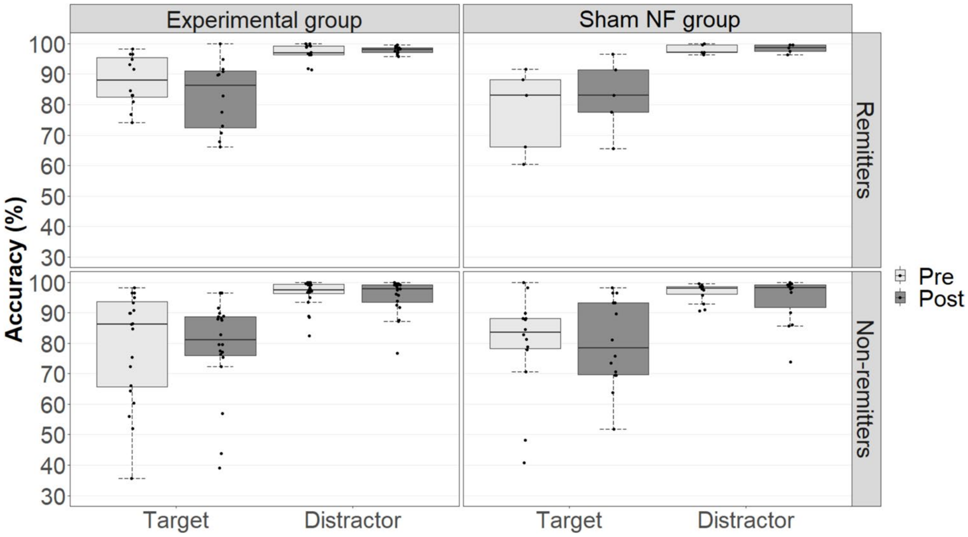
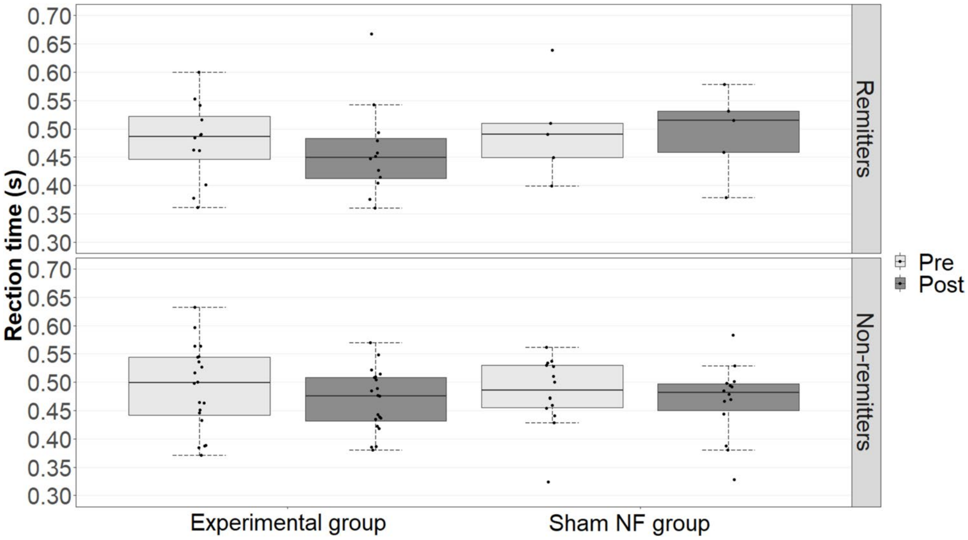


Fig. 6 Box plots for reaction times in the Oddball task. Note: Reaction times are presented for both the experimental (left) and sham NF group (right), and within this for target (left) and distractor (right) conditions. The figure is further divided into remitters (top row) and non-remitters (bottom row). Data are shown before (pre-treatment in light gray) and after (post-treatment in dark gray) TBR neurofeedback training



Limitations

One of the primary limitations of this study is the significant exclusion rate, which affected the number of participants available for the final analyses. In particular, for the analysis of error dynamics (during and after errors), the original availability of 142 dropped due to incomplete data sets to only 30 participants with sufficient data on errors, which brings the challenge of reduced statistical power and the possibility of biased retention. Possible reasons for the incomplete data include technical problems with the oddball test at one site and that the selected measurements were not the primary outcomes of the study. Additionally, EEG measurements in children with ADHD are prone to artifacts making it challenging to obtain useful EEG data for analysis. Furthermore, the analyses included more non-remitters compared to remitters, which can introduce a potential bias of non-remitters and could skew the results; observed effects might be primarily driven by the non-remitters, who were more likely to make enough errors to qualify for retention. A final limitation is the likelihood of statistical error: The low number of participants increases the risk of false negative error and the lack of correction for multiple tests increases the risk of false positives. Hence, it is important to be cautious in generalizing these results to other children with ADHD.

For future studies on the analysis of TBR neurofeedback on resting and task-related theta activity, the following recommendations are suggested to address these limitations: (i) conducting standalone studies focusing exclusively on TBR neurofeedback, rather than integrating it into multimodal treatment to isolate effects of the intervention on theta activities, (ii) improving data quality during EEG data recording with children to minimize EEG artifacts, (iii) limitation of the number of measures to pre-treatment, post-treatment and follow up to reduce the risk of missing datasets and the burden on participants, (iv) employment of advanced analyses techniques such as source a estimations or independent component analysis instead of relying solely on scalp measures to differentiate resting theta activity and fm-theta.

Implications

Nevertheless, this study highlights an important implication: the need to refine neurofeedback protocols to more precisely target specific theta-band activity in specific networks underlying rest or cognitive control. Currently, most EEG neurofeedback protocols do not target network-specific brain activity, instead relying on scalp measures. This approach faces challenges related to the inverse problem, including the potential for multiple sources, volume conduction, and the ambiguity of different source configurations producing similar scalp EEG patterns (Pascual-Marqui et al., 1999). Consequently, it remains challenging to determine the precise neural sources of the observed EEG signals and accurately target specific brain activities.

One solution would be simultaneous bimodal fMRI and EEG neurofeedback protocols to combine the advantages of high spatial and temporal resolutions. However, this approach has its own challenges, e.g. regarding the scalability for treatment. Cury et al. (2020) proposed an elegant model for hybrid EEG-fMRI neurofeedback using a sparse representation to predict fMRI signals from EEG data to enhance accuracy and efficiency of EEG neurofeedback, which could be applied to other protocols as well and help in differentiating between theta activity related to cognitive control (fm-theta) and drowsiness (resting theta activity).

Another solution might be decoded neurofeedback, which arose from critics who pointed out that neurofeedback lacked specificity. Decoded neurofeedback is an advanced neurofeedback technique that uses machine learning algorithms to decode and modulate specific brain activity patterns associated with certain cognitive states or behaviors (Shibata et al., 2019; Taschereau-Dumouchel et al., 2021). This means that unlike traditional neurofeedback, decoded neurofeedback provides feedback based on complex, multidimensional representations of brain activity. Examples of decoded neurofeedback with EEG and in the clinical domain are for instance the study by Bu et al. (2019), who assessed this novel approach in brain activity patterns associated with smoking cue reactivity on nicotine addiction. Results showed a significant decrease in the number of cigarettes smoked per day, including an average reduction of 40% in the experimental group compared to 14% in controls at 4 months' follow up. Another study used decoded neurofeedback during a virtual reality flight simulation, with the effect of improved performance and arousal regulation (Faller et al., 2018).

Conclusion

Future research should focus on improving the specificity of EEG neurofeedback protocols in general and TBR neurofeedback specifically to achieve sustained reductions in resting-state theta activity without adversely affecting fm-theta during cognitive tasks applying advanced methods in clinical trials as done with fMRI neurofeedback.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10484-024-09675-w.

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Author contributions S.E.-G. had the idea of the work and contributed to the design, she supervised the analysis, and mainly wrote the manuscript. J.K. took over the further processing of the data, the analyses and the visualization, as well as parts of the manuscript drafting. H.v.D. took over the pre-processing of the data. R.dB. and L.E.A. shared the data of the original ICAN study, advised on the work. M.A. had the idea and contributed to the design, advised on the work. All authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest S.E.-G, J.K., H.v.D., R.dB. declare that they have no conflict of interest. They also declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. L.E.A. has contracts to carry out research from Yamo, Maplight, Supernus and consult in CHADD and Yamo. L.E.A. also uses amplifiers from Thought Technology and Brainmaster, ADHD Suite from TT, EEger software, EEG equipment from BRC. L.E.A also uses broad-spectrum micronutrients and placebo from Hardy Nutritionals. M.A. is scientific adviser and shareholder to Sama Therapeutics, and scientific adviser to Synaeda Research and Neumarker.

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