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Can neurophysiological markers of anticipation and attention predict ADHD severity and neurofeedback outcomes?

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ABSTRACT

Neurophysiological measures of preparation and attention are often atypical in ADHD. Still, replicated findings that these measures predict which patients improve after Neurofeedback (NF), reveal neurophysiological specificity, and reflect ADHD-severity are limited.

Methods: We analyzed children's preparatory (CNV) and attentional (Cue-P3) brain activity and behavioral performance during a cued Continuous Performance Task (CPT) before and after slow cortical potential (SCP)-NF or semi-active control treatment (electromyogram biofeedback). Mixed-effects models were performed with 103 participants at baseline and 77 were assessed for pre-post comparisons focusing on clinical outcome prediction, specific neurophysiological effects of NF, and associations with ADHD-severity.

Results: Attentional and preparatory brain activity and performance were non-specifically reduced after treatment. Preparatory activity in the SCP-NF group increased with clinical improvement. Several performance and brain activity measures predicted non-specific treatment outcome.

Conclusion: Specific neurophysiological effects after SCP-NF were limited to increased neural preparation associated with improvement on ADHD-subscales, but several performance and neurophysiological measures of attention predicted treatment outcome and reflected symptom severity in ADHD. The results may help to optimize treatment.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD), one of the most prevalent childhood psychiatric disorders (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015), is characterized by the core symptoms of inattention and hyperactivity/impulsivity. Children with ADHD are significantly impaired in their daily functioning at home and in school, and the problems often persist in adulthood (for a review see Franke et al. (2018)).

Comparisons between participants with and without ADHD show differences in oscillatory brain activity (Barry, Clarke, & Johnstone, 2003) and event-related potentials (ERP) (Albrecht et al., 2013;

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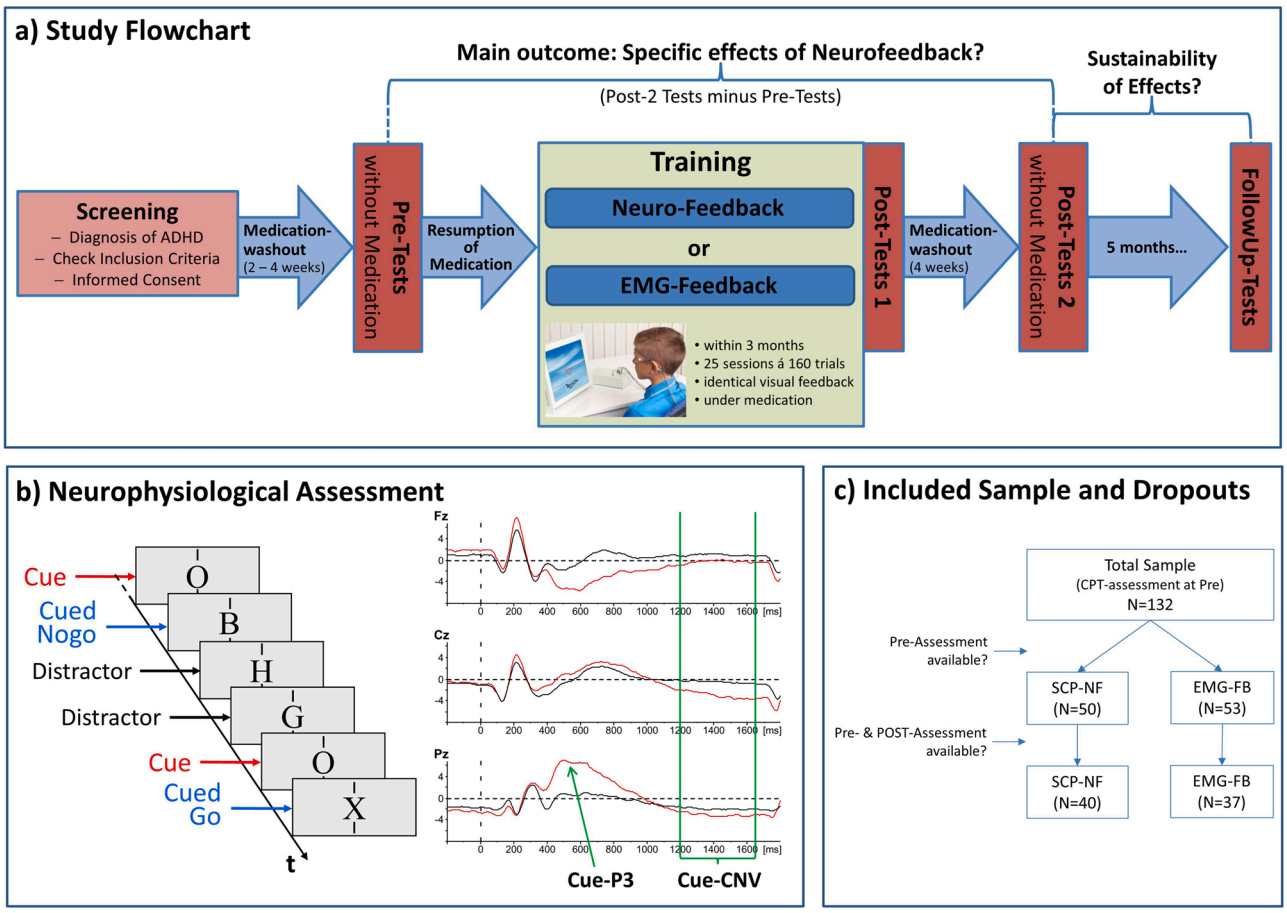

Fig. 1. a) The study flow chart shows the sequence of assessments (red), medication wash-out (blue) and the training block (green). The assessment started with a Screening followed by medication washout and Pre-Tests. The trainings were performed within 3 months, followed by a Post-1 test. After medication washout for four weeks, the Post-2 testing was conducted, followed five months later by the Follow-up assessment. The comparison between Pre and Post-2 may indicate specific effects of NF, and the comparison Post-2 with Follow-up tests for stability of effects. Adapted from Holtmann et al. (2014).
b) The CPT consists of a sequence of briefly presented letters (stimulus onset of 150 ms with a stimulus-onset asynchrony of 1650 ms). Only if the Cue ("O") is followed by the Target ("X"), a button-press is required. In particular, cued nontargets (red) require inhibiting a prepared response, while cued targets (blue) require execution. Distractors never require preparation or response (adapted from Albrecht et al. (2013)). The ERP waveforms show brain-electrical activity to Cues (black) and Distractors (red) at Pre-assessment in the total sample (N=103).
c) From the total sample tested with the CPT before SCP-NF or EMG-BF were administered (N = 132), almost ¾ obtained good data quality at Pre-assessment and were included in the prediction analysis. Of these, again almost ¾ hat also data from Post-assessment available. Dropout-rates did not differ between treatments (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013). Atypical activity in ERP components in ADHD is associated with inhibition, preparation, and attention orientation (Kaiser et al., 2020). Although these differences between groups are not sufficiently validated and robust to serve as markers for diagnosis, they might have prognostic value (Arns, Heinrich, & Strehl, 2014). For example, previous studies showed that excess theta activity was associated with favorable treatment response to stimulant medication (Ogrim et al., 2014) and EEG-neurofeedback (Arns, Drinkenburg, & Leon Kenemans, 2012; Gevensleben et al., 2009).

Non-pharmacological treatment options which refer to neurophysiological deviations such as neurofeedback (NF) may ameliorate the ADHD core symptoms, especially for proximal raters. Several meta-analyses reported significantly higher symptom reduction compared to passive or semi-active control groups (for details see Bussalb et al., 2019; Catala-Lopez et al., 2017). However, there is still a debate regarding the specificity of NF treatments, and the limited effects seen by probably blinded raters despite more promising effects for standard NF protocols including slow cortical potential (SCP) NF (Cortese et al., 2016).

NF aims at learning to self-regulate certain parameters of the neurophysiological brain activity by means of EEG biofeedback. The rationale for improving the core symptoms of ADHD through NF is based on training self-regulation of neurophysiological parameters such as theta/beta, SMR, or SCPs, which are associated with the regulation of alertness, attention, and behavioral control. A recent meta-analysis of ERPs in ADHD showed significant deviation in late cognitive processes associated ERPs, such as Cue-P3, NoGo-P3, and contingent negative variation (CNV) amplitudes (Kaiser et al., 2020).

In this randomized controlled trial (RCT) we investigated the clinical effects of SCP-NF training, the predictive value of ERPs associated with attention and preparation, and the neurophysiological changes after treatment end. The primary clinical outcome showed superiority of SCP-NF in comparison to a semi-active control group one month after treatment end, but this effect was lost at six-month follow-up (Aggensteiner et al., 2019; Strehl et al., 2017) which was due to an improvement in the control group. Concerning the effects on attention at a neurophysiological level, a main target of SCP-NF is the CNV which is an event-related slow cortical potential reflecting expectation and cognitive anticipation or motor preparation. The CNV was found to be reduced in children with ADHD (Banaschewski et al., 2003), which was recently confirmed by a meta-analysis showing that the CNV was lower in ADHD with a medium pooled effect size (Kaiser et al., 2020). This is in

line with models supposing a dysfunctional regulation of energetical resources in ADHD (Sergeant, 2000).

Several studies have investigated the impact of SCP-NF on the CNV during a cued continuous performance task (CPT) probing attention and anticipation as well as inhibition. Heinrich, Gevensleben, Freisleder, Moll, and Rothenberger (2004) showed that SCP-NF increased the CNV amplitude while no increase was found in the waiting-list group. This CNV increase was interpreted as a neurophysiological equivalent of improved self-regulation capabilities. A significant correlation between SCP regulation and changes of the CNV amplitude was found by Doehnert, Brandeis, Straub, Steinhausen, and Drechsler (2008). Interestingly, a later study replicated the specific effects of SCP-NF training on the CNV during a cued CPT in a sample of 56 children (Wangler et al., 2011). The predictive value of these attention-associated markers was less systematically studied. For instance, Gevensleben et al. (2009) showed that alpha oscillations were associated with clinical change and Wangler et al. (2011) reported that the baseline CNV predicted treatment outcome after SCP-NF. For this reason, we focus on the CNV, which is also closely related to the slow cortical negativity shifts targeted by the SCP-NF training used here.

Changes of P300 components may also be promising for predicting treatment effects in children with ADHD. The Go-P3 may be rather, in contrast to CNV, associated with unspecific treatment effects also present after an attention skills training (Wangler et al., 2011), while elevated Nogo-P3 was found in another study after frequency-band NF in good but not poor performers (Kropotov et al., 2005). Unfortunately, the CPT conducted in the current study yielded considerably lower numbers of Go- and NoGo- compared to Cue trials which prevented analysing these P300 components in the current study.

In the present multi-level investigation, we explored the associations between behavioral ratings and neuropsychological and -physiological parameters of CPT performance. Second, we evaluated these parameters regarding unspecific and specific effects of SCP-NF in comparison to electromyogram biofeedback (EMG-BF) and their unspecific and specific predictive value regarding treatment outcome.

We hypothesized that CPT performance and attentional and preparatory neurophysiological activity to Cues are associated with symptom severity and can predict clinical outcome. We expected specific treatment effects in terms of enhanced CPT performance and Cue-P3 and CNV amplitudes following SCP-NF compared to EMG-BF (Heinrich et al., 2004; Wangler et al., 2011).

Table 1
Sample characteristics, behavioral ratings and CPT Performance at Pre-assessment.

Measure	SCP-NF (N = 50) Mean (SD)	EMG-BF (N = 53) Mean (SD)	ANOVA
Age (in years)[a]	8.70 (0.89)	8.6 (0.90)	$F_{(1,101)} = 0.19$, p = .66, part. η^2<.01
Sex (% male)[b]	80 %	89 %	$X^2_{(1)} = 1.48$, p = .22
Medication[b]	38 %	45 %	$X^2_{(1)} = 0.56$, p = .45
FBB-HKS (parent)[a]			
Total	1.76 (0.41)	1.73 (0.47)	$F_{(1,85)} = 0.11$, p = .75, part. η^2<.01
Inattention	2.01 (0.48)	1.95 (0.52)	$F_{(1,85)} = 0.34$, p = .56, part. η^2<.01
Hyperactivity	1.44 (0.67)	1.46 (0.71)	$F_{(1,85)} = 0.02$, p = .89, part. η^2<.01
Impulsivity	1.76 (0.69)	1.71 (0.79)	$F_{(1,85)} = 0.08$, p = .78, part. η^2<.01
FBB-HKS (teacher)[a]			
Total	1.42 (0.66)	1.40 (0.74)	$F_{(1,85)} = 0.02$, p = .89, part. η^2<.01
Inattention	1.68 (0.75)	1.68 (0.74)	$F_{(1,85)}$<0.01, p = .99, part. η^2<.01
Hyperactivity	1.09 (,.81)	1.06 (0.89)	$F_{(1,85)} = 0.03$, p = .86, part. η^2<.01
Impulsivity	1.42 (0.95)	1.35 (1.03)	$F_{(1,85)} = 0.10$, p = .76, part. η^2<.01
CPT: Performance			
Hit-RT	531 (107)	511 (93)	$F_{(1,101)} = 0.98$, p = .32, part. η^2 = .01
Hit-RT-SD	181 (73)	169 (70)	$F_{(1,101)} = 0.63$, p = .43, part. η^2<.01
Hit-Rate (%)	90 (11)	85 (12)	$F_{(1,101)} = 4.77$, p = .03, part. η^2 = .05
Commission-Error-Rate	3.3 (6.7)	3.5 (6.2)	$F_{(1,101)} = 0.04$, p = .85, part. η^2<.01
CPT: Cue-P3			
Pz	9.7 (5.5)	10.0 (4.9)	$F_{(1,101)} = 0.09$, p = .76, part. η^2<.01
CPT: Cue-CNV			
Cz	−2.9 (2.6)	−3.1 (2.1)	$F_{(1,101)} = .18$, p = .67, part. η^2<.01

[a] FBB-HKS parents and teacher ratings are available for N = 43 participants who received SCP-NF and N = 44 participants who received EMG-BF.
[b] Ratios were tested with the Chi-squared test.

2. Methods

2.1. Sample

The current analysis dwells on the association of ADHD symptoms with performance and neurophysiological measures of attention and preparation during the Continuous Performance Test (CPT) to gain insights into mechanisms of training-induced improvements. Patients with ADHD combined type according to DSM-IV TR aged 7–9 years were recruited and treated by five German child and adolescent psychiatry outpatient clinics. The diagnosis was verified in a semi-structured clinical interview (Delmo, Weifenbach, Gabriel, Stadler, & Poustka, 1998). The impact of Neurofeedback and EMG-Feedback on ADHD symptom ratings by parents and teachers using the FBB-HKS, and comorbid symptoms as measured by the Strengths and Difficulties Questionnaire (SDQ by Goodman (1997) with German norms by Woerner, Becker, and Rothenberger (2004) were published previously (Strehl et al., 2017).

2.2. Biofeedback interventions

The multicenter intervention study was conducted according to the declaration of Helsinki as a randomized controlled trial comparing SCP-Neurofeedback with EMG-Biofeedback (ISRCTN76187185). For SCP-Neurofeedback, the EEG was registered at electrode CZ with reference to the left mastoid, real-time-preprocessing included ocular correction, artifact rejection, and filtering. EMG-Biofeedback was obtained from two electrodes placed at the upper shoulder area for addressing contraction or relaxation of the left to right musculus supraspinatus. Both SCP and EMG signals were fed back visually including positive reinforcers if a pre-defined regulation criterion was fulfilled.

Both interventions were administered within three months at the outpatient clinics by trained instructors and comprised 25 sessions of four blocks with 40 trials each and were identical in terms of transfer trials, feedback presentation, reinforcement schedules and electrode montage. The general study protocol with further details and primary study outcome is described in previous publications (Aggensteiner et al., 2019; Holtmann, Pniewski, Wachtlin, Worz, & Strehl, 2014; Strehl et al., 2017) (see Fig. 1a).

2.3. Task

The cued CPT modeled after Rosvold, Mirsky, Sarason, Bransome, and Beck (1956) comprises a sequence of 400 letters presented for 150 ms with a stimulus onset asynchrony of 1650 ms. These include N = 80 Cues (“O”), N = 80 targets (“X”), N = 80 frequent distractors (“H”) and further N = 160 distractors (letters B, C, D, F, G, H, J, L with equal probability each). The sequences cued Targets (“O-X” that requires responding) and cued Non-Targets (“O” followed by another letter than

"X" that requires not responding) were presented pseudo-randomized 40 times each (see Fig. 1b).

2.4. EEG recording and processing

During CPT performance, the EEG was continuously recorded from 19 sites of a 10–20 montage and additional electrodes for a vertical and horizontal electro-oculogram with a reference and ground electrode placed at the right and left mastoid via Ag/AgCl ring electrodes and Abralyt ™ electrode cream using TheraPrax ™ amplifiers (neuroConn GmbH, Ilmenau, Germany). The signals were registered from DC to 150 Hz and sampled at 512 Hz.

Offline processing was performed with Brain Vision Analyzer 2.2.0 (BrainProducts, Gilching Germany). The continuous EEG was filtered with 0.1–30 Hz, 24 db/oct Butterworth filters, broad artefacts were eliminated after visual inspection and heavily affected channels were interpolated using their nearest neighbors, as described by Hjorth (1975). Ocular artefacts were removed as described by Gratton, Coles, and Donchin (1983). Data were re-referenced to the average reference and subsequently checked for remaining artefacts. If amplitudes at any channels exceeded ±150μV, a segment −150 ms to 800 ms was discarded. The continuous data were segmented −200 to 1800 ms around correctly processed Cues; all averages contained at least 10 sweeps. The Cue-P3 was detected as the most positive peak between 300 and 750 ms, and the Cue-CNV was quantified as the mean activity 1200–1650 ms following Cue onset.

2.5. Available EEG samples

From the total sample of N = 132 patients that received either SCP-NF or EMG-BF, 109 had CPT EEG data from the Pre-assessment for analysis of baseline associations between behavioral ratings, CPT performance, and neurophysiological characteristics of Cue-processing. After excluding participants with artefacts in the EEG or poor performance (more than 50 % omission or commission errors), EEG data of N = 103 patients at Pre-assessment (74 % of the total sample) was analyzed (which is included in the association and prediction analyses as long as behavioral ratings were also available; see the descriptive statistics in Table 1 and Fig. 1c).

Altogether 89 subjects also participated in CPT-assessments at Post-2, of which 77 (58 % of the total sample) had acceptable electrophysiological data from both Pre and Post-2 assessments, and were entered in the analyses of specific treatment effects on neurophysiological parameters of Cue processing. The CPT-dropouts with available Pre-assessment data did not differ in age ($F(1, 101) = 0.19$, $p = .66$, part. $\eta 2 < .01$) or sex-ratio ($\chi^2(1) = 1.48$, $p = .22$, see Table 1) nor behavioral ratings from those participants who were included in the analysis.

2.6. Statistics

We analyzed the relationship between ADHD symptom-ratings and CPT Performance and ERP components evoked by Cue-Processing. Linear mixed-effects models were conducted in R with maximum likelihood fit [lme4 package; (Bates, Machler, Bolker, & Walker, 2015)] including separately neurophysiological (Cue-P3 and -CNV at Fz, Cz, and Pz) or performance (hit-rate, reaction time, reaction-time variability, omission and commission errors) parameters set as mean centered within-subject factor fixed effects. Age, medication at pre-assessment, site and sex were added as possible covariates, and intercepts were set as random factors. Additionally, the same analyses were performed with teacher ratings instead of parent ratings as the dependent variable.

Second, neurophysiological and clinical changes from Pre to Post-2 were evaluated in separate GLMs (SPSS 26.0.0.1) with between-subject factor Treatment (SCP-NF vs. EMG-BF) and within-subject factor Change Δ (Pre vs Post-2 treatment). For predicting treatment

Table 2
Association between neurophysiological markers of attention and baseline symptom severity.

FBB-HKS Global scale				FBB-HKS Inattention				FBB-HKS Hyperactivity				FBB-HKS Impulsivity			
Predictors	*Estimates*	*CI*	*p*	*Predictors*	*Estimates*	*CI*	*p*	*Predictors*	*Estimates*	*CI*	*p*	*Predictors*	*Estimates*	*CI*	*p*
(Intercept)	1.03	−0.09 - 2.15	0.076	(Intercept)	1.01	−0.24 - 2.26	0.112	(Intercept)	0.90	−0.75 - 2.55	0.285	(Intercept)	1.29	−0.54 - 3.12	0.168
Age	0.074	−0.03 - 0.18	0.169	Age	0.07	−0.05 - 0.19	0.234	Age	0.08	−0.07 - 0.24	0.301	Age	0.07	−0.11 - 0.24	0.445
Gender	0.024	−0.21 - 0.26	0.843	Gender	0.18	−0.09 - 0.44	0.187	Gender	−0.06	−0.41 - 0.29	0.731	Gender	−0.16	−0.54 - 0.23	0.432
Site	0.022	−0.05 - 0.09	0.530	Site	0.01	−0.07 - 0.09	0.878	Site	0.00	−0.10 - 0.11	0.972	Site	0.10	−0.02 - 0.22	0.092
Medication at pre	−0.06	−0.24 - 0.12	0.531	Medication at pre	0.01	−0.19 - 0.21	0.915	Medication at pre	−0.08	−0.34 - 0.18	0.555	Medication at pre	−0.18	−0.47 - 0.11	0.229
CNV at Fz	−0.01	−0.04 - 0.03	0.720	CNV at Fz	0.01	−0.03 - 0.04	0.658	CNV at Fz	−0.03	−0.08 - 0.02	0.234	CNV at Fz	0.00	−0.05 - 0.06	0.927
CNV at Cz	−0.01	−0.05 - 0.04	0.783	CNV at Cz	0.04	−0.02 - 0.09	0.172	CNV at Cz	−0.05	−0.12 - 0.02	0.172	CNV at Cz	−0.03	−0.10 - 0.05	0.462
CNV at Pz	0.01	−0.03- 0.05	0.702	CNV at Pz	−0.01	−0.06 - 0.03	0.594	CNV at Pz	0.03	−0.03 - 0.09	0.295	CNV at Pz	0.01	−0.06 - 0.08	0.824
CUE P3 at Fz	−0.01	−0.03 - 0.01	0.225	CUE P3 at Fz	0.01	−0.02 - 0.03	0.534	CUE P3 at Fz	−0.03	−0.06 - 0.00	0.079	CUE P3 at Fz	−0.03	−0.07 - 0.00	0.065
CUE P3 at Cz	0.01	−0.02 - 0.03	0.684	CUE P3 at Cz	−0.00	−0.03 - 0.03	0.960	CUE P3 at Cz	0.01	−0.03 - 0.04	0.719	CUE P3 at Cz	0.02	−0.02 - 0.06	0.424
CUE P3 at Pz	−0.02	−0.04 - -0.00	**0.031**	CUE P3 at Pz	−0.00	−0.03 - 0.02	0.730	CUE P3 at Pz	−0.03	−0.06 - -0.01	**0.020**	CUE P3 at Pz	−0.04	−0.07 - -0.01	**0.022**

Δ indicates changes between assessments. CNV: Contingent negative variation, P3: P3. CI: Confidence intervals (95 %).

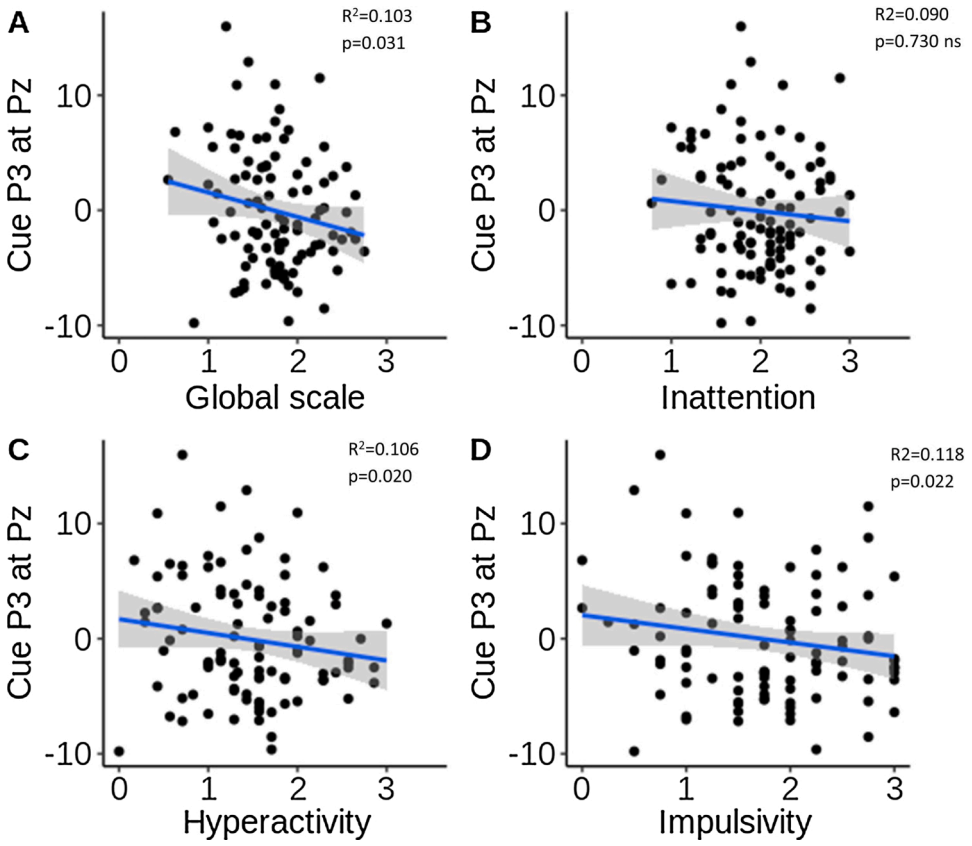

Fig. 2. Baseline measurements: parent-rated ADHD symptoms and Cue P3 at Pz.
A) Association between Cue P3 and Global scale. B) Inattention which was not significant. C) For hyperactivity, and D) For impulsivity. R^2 is adjusted.

outcome we performed a linear mixed-effects models as described above with the change between Post-2 minus Pre for all (Δ) FBB-HKS scales as dependent variables and Age, Sex, and baseline Cue-P3 and CNV as predictors. These analyses were additionally repeated with the CPT performance variables and with clinical changes rated by teachers.

Further, we assessed the specificity of the SCP-NF using a linear mixed model with the differences Δ between Pre and Post-2 for the FBB-HKS scales as dependent variables and Δ Cue-P3 and Δ CNV (Post-2 minus Pre) as predictors, controlling for Age and Sex. Significant interactions were further explored applying a Johnson-Neyman simple slope analysis (R package "interactions", Long (2019)).

Finally, we evaluated the role of CNV-changes in the SCP-NF group only, by classifying participants into SCP-NF CNV-responders or CNV-non-responders aiming at identifying baseline differences in the CNV-responder group. To meet the criteria of CNV-responder participants had to show a CNV improvement at Post-2 assessment. We compared both groups by means of ANOVA or chi-square tests when appropriate for all above-mentioned variables.

3. Results

At Pre-assessment no group differences were found in behavioural ratings with the FBB sores (all $p > .56$, part. $\eta 2 < .01$). CPT performance was similar in both groups with the exception of a slightly lower hit-rate in patients receiving EMG-BF ($F_{(1,101)} = 4.77$, $p = .03$, part. $\eta^2 = .05$). The Cue-P3 and –CNV with the expected maxima at parietal and centro-parietal sites showed no significant differences between treatment groups (see Table 1 for data from the total sample with Pre-assessment available).

3.1. Association of neurophysiological parameters of Cue-Processing and symptom severity at baseline

We found a significant negative association between the Cue P3 amplitude at its topographical Pz maximum with the parent-rated FBB global scale ($F_{(1,103)} = 4.66$, $p = 0.031$), with hyperactivity ($F_{(1,103)} = 5.38$, $p = 0.020$) and impulsivity ($F_{(1,103)} = 5.23$, $p = 0.022$), but not with inattention ($F_{(1,103)} = 0.11$, $p = 0.730$, see Table 2 and Fig. 2), which was not present for teacher ratings (all $p > .273$, see supplement S1). No significant associations were found for the CNV amplitude at baseline with any of the variables.

With regard to the behavioral performance in the CPT task, no significant associations were found with the parent ratings (all $p > .217$, supplement S2). However, teacher ratings showed significant associations with lower hit rates, lower reaction time, and higher reaction time variability (RTV) which were associated with higher global symptom severity, and inattention. Further, hyperactivity was associated with RTV only (for details see supplement S3).

3.2. Evaluation of overall treatment effects

The comparison between Pre and Post-2 assessment was based on sub-samples of patients with available Pre and Post-2 assessment data that received SCP-NF (N = 40) or EMG-BF (N = 37) training. The groups did not differ in age ($F_{(1,75)} = 0.71$, $p = .40$, part. $\eta^2 < .01$) or sex-ratio ($\chi^2_{(1)} = 2.60$, $p = .11$, see Table 3). Exploratory multivariate analyses of FBB-ratings from parents (available from N = 41 receiving SCP-NF and N = 43 that got EMG-BF), and age from Pre-assessment and between-subject factor Group and CPT-Dropout (CPT data available vs. unavailable at Post-2) revealed no main effects of CPT-Dropout (Wilk's $\lambda = .95$, $F_{(5,76)} = 0.89$, $p = .49$, part. $\eta^2 = .06$), Group (Wilk's $\lambda = .99$, $F_{(5,76)} = 0.10$, $p = .99$, part. $\eta^2 < .01$) and no interaction of Group × CPT-

Table 3
Treatment-Effects (Change from Pre to Post-2 assessment).

Change (Post-2 - Pre)	SCP-NF (N = 40) Mean (SD)	EMG-BF (N = 37) Mean (SD)	ANOVA (Group × Time)
Age (in years)[a]	8.74 (0.93)	8.6 (0.92)	$F_{(1,75)} = 0.71$, $p = .40$, part. $\eta^2 < .01$
Sex (% male)[b]	75 %	89 %	$X^2_{(1)} = 2.60$, $p = .11$
FBB-HKS (parent)[a]			
Global	−0.48 (0.39)	−0.25 (0.45)	$F_{(1,65)} = 5.00$, $p = .03$, part. $\eta^2 = .07$
Inattention	−0.55 (0.51)	−0.25 (0.53)	$F_{(1,65)} = 5.28$, $p = .03$, part. $\eta^2 = .08$
Hyperactivity	−0.47 (0.45)	−0.32 (0.57)	$F_{(1,65)} = 1.28$, $p = .26$, part. $\eta^2 = .02$
Impulsivity	−0.35 (0.54)	−0.12 (0.64)	$F_{(1,65)} = 2.06$, $p = .11$, part. $\eta^2 = .04$
FBB-HKS (teacher)[b]			
Global	−0.20 (0.61)	−0.21 (0.49)	$F_{(1,53)} < 0.01$, $p = .96$, part. $\eta^2 < .01$
Inattention	−0.26 (0.54)	−0.19 (0.59)	$F_{(1,53)} = 0.22$, $p = .64$, part. $\eta^2 < .01$
Hyperactivity	−0.12 (0.87)	−0.18 (0.55)	$F_{(1,53)} = 0.09$, $p = .76$, part. $\eta^2 < .01$
Impulsivity	−0.22 (0.89)	−0.31 (0.77)	$F_{(1,53)} = 0.14$, $p = .71$, part. $\eta^2 < .01$
CPT-Performance			
Hit-RT	65 (111)	50 (79)	$F_{(1,75)} = 0.47$, $p = .50$, part. $\eta^2 < .01$
Hit-RT-SD	72 (103)	51 (79)	$F_{(1,75)} = 0.94$, $p = .34$, part. $\eta^2 = .01$
Hit-Rate (%)	−3.2 (11.3)	2.4 (10.9)	$F_{(1,75)} = 4.80$, $p = .03$, part. $\eta^2 = .06$
Commission-Error-Rate	−0.8 (3.5)	−1.5 (5.1)	$F_{(1,75)} = 0.38$, $p = .54$, part. $\eta^2 < .01$
CPT: Cue-P3			
Pz	−1.8 (5.3)	−1.8 (5.4)	$F_{(1,75)} < 0.01$, $p = .97$, part. $\eta^2 < .01$
CPT: Cue-CNV			
Cz	1.1 (2.8)	1.5 (2.5)	$F_{(1,75)} = 0.37$, $p = .55$, part. $\eta^2 < .01$

[a] Available for N = 35 with SCP-NF and N = 32 with EMG-BF.
[b] Available for N = 29 with SCP-NF and N = 26 with EMG-BF.

Dropout (Wilk's $\lambda = .99$, $F_{(5,76)} = 0.23$, $p = .95$, part. $\eta^2 = .02$).

3.2.1. Behavioral ratings

Parents in both groups rated improvements on all symptom scales (see Fig. 3 for confidence intervals with $p = .05$), with higher improvement in Global- and inattention-scores following SCP-NF (both $F_{(1,65)} \geq 5.00$, $p = .03$, part. $\eta^2 \geq .07$). Teacher ratings also revealed improvements in both intervention groups, but no superiority of SCP-NF (all $F_{(1,65)} < 1$, $p > .64$, part. $\eta^2 < .01$). This result closely resembles the outcome from the total sample of the study as reported by Strehl et al. (2017).

3.2.2. Reaction-Time

Performance data was missing for 3 subjects that received SCP-NF and 3 with EMG-BF training. Reaction times were slower at Post-2 assessment (Time: $F_{(1,79)} = 30.5$, $p < .01$, part. $\eta 2 = .28$), and did not differ between groups (Group: $F_{(1,79)} = 0.37$, $p = .55$, part. $\eta 2 < .01$ and Time × Group: $F_{(1,79)} = 0.22$, $p = .64$, part. $\eta 2 < .01$, see Table 3 and Fig. 4).

3.2.3. Reaction-Time Variability

Reaction-Time Variability increased from Pre to Post-2 assessments (Time: $F_{(1,79)} = 37.12$, $p < .01$, part. $\eta 2 = .32$) similarly for both groups (Group: $F_{(1,79)} = 0.02$, $p = .88$, part. $\eta 2 < .01$ and Time × Group: $F_{(1,79)} = 0.09$, $p = .76$, part. $\eta 2 < .01$).

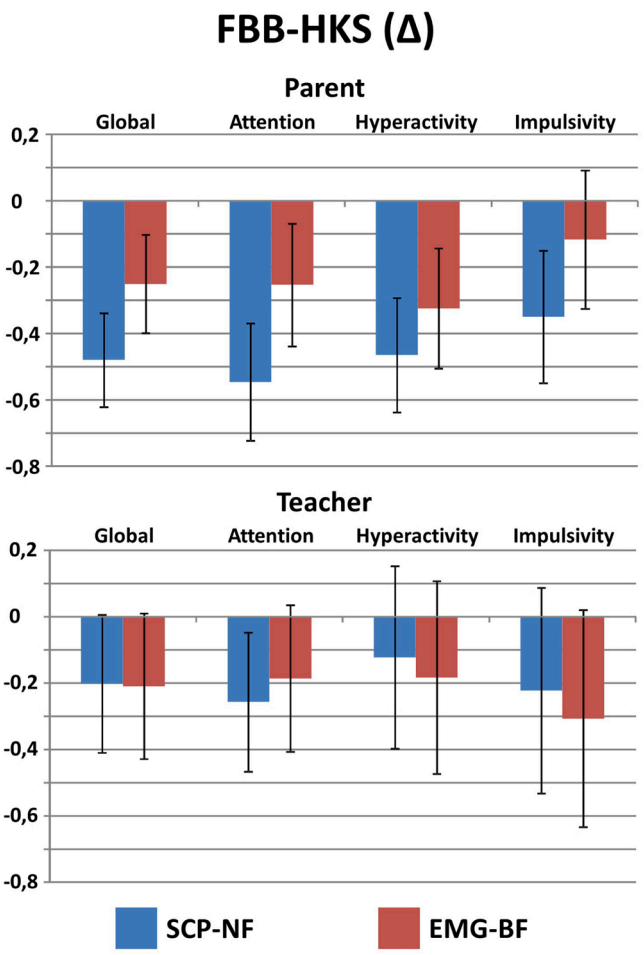

Fig. 3. Following treatment, parents rated reduced symptom scores changes (Δ) for all FBB-HKS scales. For global and inattention scores improvement were significantly larger after SCP-NF than after EMG-BF. Teachers also rated improvements for the global and inattention scales, but no differences between intervention groups are eminent.

3.2.4. Accuracy

Hit-Rate decrease in those receiving SCP-NF compared to EMG-BF ($F_{(1,75)} = 4.80$, $p = .03$, part. $\eta^2 = .06$), while Commission-Errors remain similarly stable in both groups ($F_{(1,75)} = 0.38$, $p = .54$, part. $\eta^2 < .01$).

3.2.5. Cue-P3

The Cue-P3 amplitude was tested at its Pz maximum and was smaller at Post-2 assessment (Time: $F_{(1,75)} = 8{,}4$ $p < .01$, part. $\eta 2 = .10$). No group differences in change from Pre- to Post-2 assessment were significant (Time × Group: $F_{(1,75)} < 0.01$, $p = .97$, part. $\eta^2 < .01$, see Table 3 and Fig. 5).

3.2.6. Cue-CNV

The slow-wave CNV mean amplitude tested at its Cz maximum was reduced in the Post-2 compared to the Pre-assessment (Time: $F_{(1,75)} = 19.0$, $p < .01$, part. $\eta 2 = .20$). No differences between intervention groups in CNV-change were significant (Time × Group: $F_{(1,75)} = 0.37$, $p = .55$, part. $\eta^2 < .01$).

3.3. Prediction of clinical outcome with neurophysiological and neuropsychological parameters at baseline

Regarding CPT performance, an interaction emerged with group and reaction time (RT) as a predictor for decreased parent-rated inattention

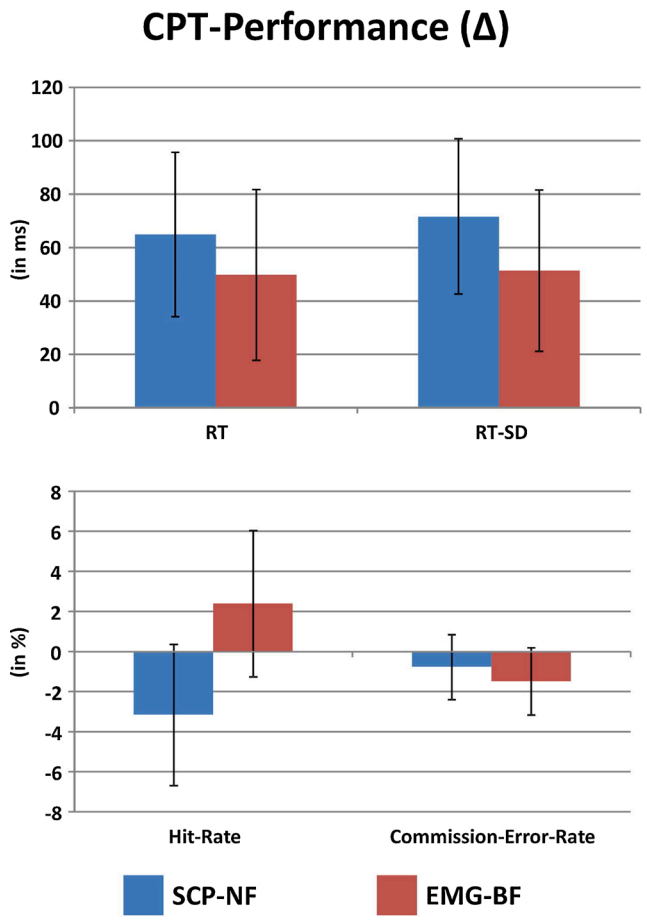

Fig. 4. Means and confidence intervals (p = .05) of changes (Δ) from Pre- to Post-2 assessments of the main performance parameters. Reaction times (RT) and RT-variability (RT-SD) were significantly elevated in the Post-2 compared to Pre-assessment. As a trend, Hit-Rate worsened in SCP-NF and Commission-Error-Rate improved in the EMG-BF group (both p = .10).

symptoms ($F_{(1,80)}$ = 5.30, p = .021), and decreased teacher-rated impulsivity ($F_{(1,80)}$ = 5.58, p = .018). Post-hoc analysis showed that the effect was driven by the EMG-BF group for parent-rated inattention improvement (t=-2.61, p = .01) and not for the SCP-NF group (t = 0.36, p = .72), indicating that faster RT at baseline predicted significant improvement of inattention in the EMG-BF group (Fig. 6A). However, faster RT at baseline predicted improvement of impulsivity rated by teachers in the SCP-NF group (t=−2.94, p < .001) but not in the EMG-BF group (t = .69, p = .49) (Fig. 6B). A trend was also seen for RT-Variability predicting inattention rated by parents ($F_{(1,80)}$ = 3.49, p < .062) irrespective of groups (Fig. 6C). Moreover, more commission errors predicted improvements following SCP-NF and EMG-BF in parent-rated hyperactivity ($F_{(1,80)}$ = 4.33, p = .037,see Fig. 6D).

Cue-related activity at baseline showed a group-specific predictive value for Cue-P3 at Pz [interaction with group, $F_{(1,67)}$ = 6.62, p = .010]. Post-hoc analyses suggested that larger Cue-P3 tended to predict more improvements in teacher-rated inattention for those receiving SCP-NF (t = 1.94, p = .06), but in contrast less improvement following EMG-BF (t=-1.82, p = .07) (Fig. 6E). Furthermore, an interaction emerged between group and Cue-CNV at Cz which predicted improvement in teacher-rated inattention ($F_{(1,67)}$ = 5.95, p = .015). This interaction was driven by the EMG-BF group (t=-2.43, p = .02) indicating that a larger (that is more negative) CNV at Cz at baseline predicted decrease of teacher-rated inattention symptoms (Fig. 6F).

3.4. Specific association of clinical improvements

Mixed model analyses showed a significant interaction between group and CNV changes from Pre to Post-2 assessment at Pz ($F_{(1,77)}$ = 4.44, p = .03), and as a trend also at Cz, $F_{(1,77)}$ = 2.81, p = .07) for parent-rated improvement of inattention. Further, a significant interaction between group and CNV changes at Cz ($F_{(1,77)}$ = 4.99, p = .03, and as a trend also at Pz, $F_{(1,77)}$ = 3.51, p = .07) was found for improvement of impulsivity. Separate post-hoc analyses for each group yielded a trend for an association between increased CNV and improved inattention in the SCP-NF group (t=−1.953, p = .051, but not for impulsivity, t = 0.956, p = .34). This pattern suggests that those participants in the SCP-NF group who improved their CNV amplitude from Pre- to Post-2 assessment, improved more on parent-rated inattention, which was not seen in those patients receiving EMG-BF. For details see Table 4 and Fig. 7.

Concerning the teacher ratings, group interacted with the CNV change at Cz for hyperactivity improvement ($F_{(1,63)}$ = 4.94, p = .026). In line with the parent ratings, this association suggests that the increase of the CNV was differently associated with clinical improvement in the two groups. The association was significant for SCP-NF group but not for the EMG-BF group in a separate post-hoc analysis for each group (SCP-NF t=−2.20, p = .03, and EMG-BF t = .83, p = .41). Nevertheless, no significant association was found for the global score or for inattention rated by teachers. Additionally, an increase of the P3 at Pz for Pre to Post-2 was also associated with clinical improvement, but only for impulsivity rated by teachers (p = .03). For details see Supplement S4.

3.5. Differences between CNV- responders and non-responders

37.5% percent (n = 15) of the participants were classified as CNV-Responders, whereas 25 were non-responders. The responder group showed reduced hit rates ($F_{(1,39)}$ = 4.55, p = .039) and a reduced CNV at baseline ($F_{(1,39)}$ = 12.834, p < .001). All the other variables did not differentiate between CNV-responders and non-responders (Table 5).

4. Discussion

Neurofeedback can be an effective training for treating ADHD. Identifying those patients that may benefit most reliably would make an important step towards improving its effectiveness, but evidence that allows predicting treatment outcome early on is currently rare.

To this end, we investigated the predictive value of ERP and behavioral markers of attention and anticipation during a sustained attention task by investigating the possible underlying mechanisms in a large multicenter randomized controlled trial. We further assessed the specificity of neurophysiological changes after SCP-NF treatment. As neurophysiological variables, we chose the ERP components evoked by cues in a CPT which showed in previous studies a predictive value and specific changes after SCP-NF.

As a main outcome, we found that the Cue P3 at its parietal (Pz) maximum was negatively associated with ADHD core symptoms except for inattention. The CNV did not show any significant association with baseline symptom severity. These findings are partially in line with a recent meta-analysis that reported higher effect sizes compared to healthy controls for the Cue P3 than for the CNV (Kaiser et al., 2020). Furthermore, we did not find any significant association between ERP components and teacher ratings at baseline. This might be related to the reduced symptom severity rated by teachers (Sollie, Larsson, & Morch, 2013; Strehl et al., 2017) and that parent ratings might be more sensitive to the children's symptoms (Cheung et al., 2016; Du Rietz et al., 2016). Interestingly, behavioral performance of the CPT task was associated with teacher ratings only. Specifically, reduced hit rates, slower reaction times and higher RTV were associated with global symptoms and inattention rated by teachers at baseline. Additionally, hyperactivity was further associated with higher RTV. This result is in line with the current

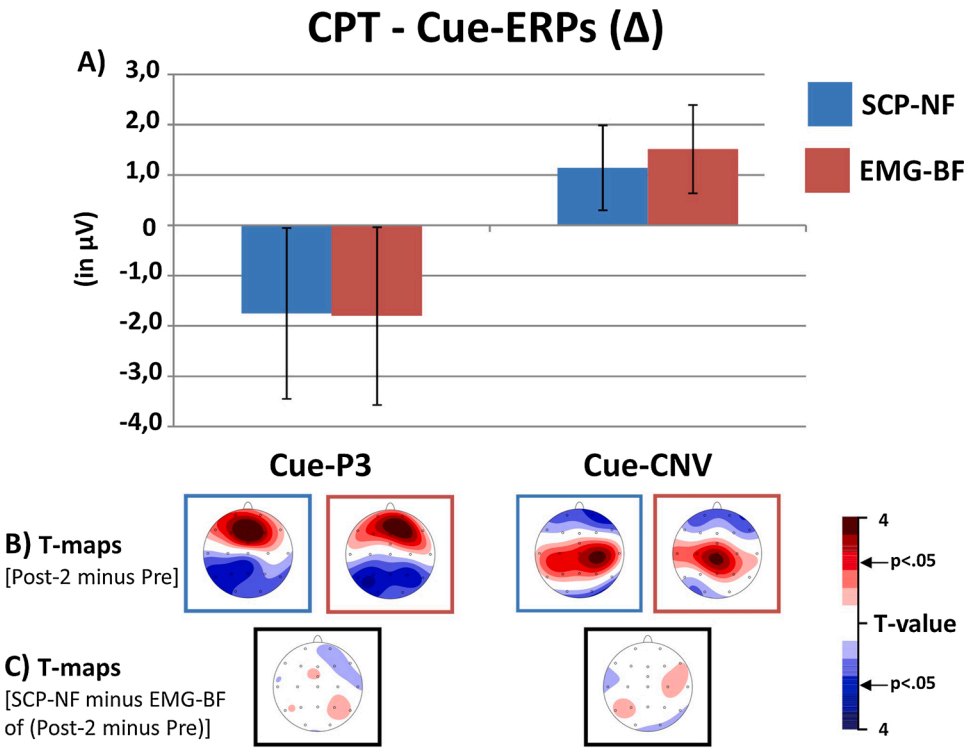

Fig. 5. Analyses of ERPs associated with Anticipation and Preparation following Cues. A) In Post-2 compared to Pre-assessment, both Cue-P3 and –CNV had significantly diminished amplitudes (i.e. changes (Δ) for Cue-P3 were of negative and Cue–CNV were of positive amplitude), which was similarly the case in both groups (see confidence intervals with p = .05 at the respective Cz and Pz maxima). B) Exploratory T-maps of the within-subject change Post-2 minus Pre from Cue-P3 and -CNV: the difference between Post-2 minus Pre-assessment in Cue-P3 amplitude was significantly negative at posterior sites and more positive at frontal sites, while the difference in CNV amplitudes was significantly positive over central sites. C) Exploratory T-Maps of the between-subject comparison between SCP-NF and EMG-BF of Change (Post-2 minus Pre): no differences between interventions were significant.

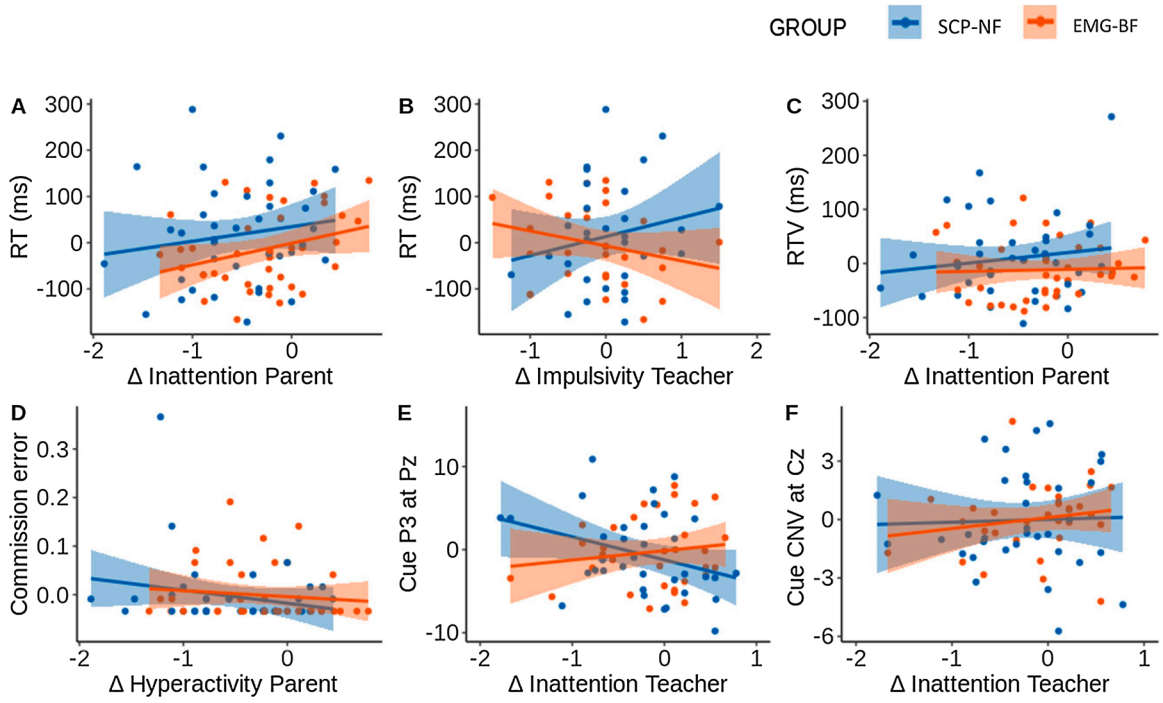

Fig. 6. Associations between mean-centered CPT parameters at baseline and clinical outcome; Δ indicates changes between Pre and Post-2 assessments. Negative values for clinical changes indicate improvement at Post-2. A) Reaction time (RT) showed a significant group interaction (p = .018). Faster RT at baseline predicted significant inattention improvement in the EMG-BF group only (p = .01). B) Faster RT at baseline predicted impulsivity improvement rated by teachers, particularly for the SCP-NF group (p < .001) and not for the EMG-BF (p = .49). C) Reaction time variability (RTV) showed a trend for group interaction. D) More commission errors predicted symptom improvement for parent ratings. E) Larger Cue-P3 predicted improvements in teacher ratings for those receiving SCP-NF. F) Larger CNV at Cz predicted higher symptom improvement in the EMG-BF only.

literature (for review see Kofler et al., 2013). Strikingly, these associations with behavioral markers of attention were only found for teachers and not for parent ratings. We speculate that the CPT task might resemble more a classroom-like setting in which teachers are more sensitive.

Concerning the predictive value of ERP and behavioral markers of attention and anticipation, various group interactions emerged. Faster reaction time at baseline predicted more clinical improvement rated by

Table 4
Mixed model for CNV changes and clinical changes.

FBB-HKS Global scale (Δ)				FBB-HKS Inattention (Δ)				FBB-HKS Hyperactivity (Δ)				FBB-HKS Impusivity (Δ)			
Predictors	*Estimates*	*CI*	*p*	*Predictors*	*Estimates*	*CI*	*p*	*Predictors*	*Estimates*	*CI*	*p*	*Predictors*	*Estimates*	*CI*	*p*
(Intercept)	−0.14	−1.40 - 1.13	0.831	(Intercept)	0.08	−1.43 - 1.58	0.921	(Intercept)	−0.17	−1.64 - 1.29	0.817	(Intercept)	−0.61	−2.37 - 1.14	0.493
Age	0.04	−0.07 - 0.16	0.458	Age	0.03	−0.11 - 0.18	0.636	Age	0.03	−0.10 - 0.17	0.620	Age	0.09	−0.08 - 0.25	0.390
Gender	0.17	−0.10 - 0.45	0.222	Gender	0.13	−0.20 - 0.45	0.447	Gender	0.15	−0.17 - 0.47	0.349	Gender	0.34	−0.04 - 0.72	0.078
Medication at pre	−0.02	−0.23 - 0.19	0.880	Medication at pre	−0.01	−0.26 - 0.24	0.949	Medication at pre	0.05	−0.19 - 0.30	0.668	Medication at pre	−0.17	−0.46 - 0.13	0.266
Group	−0.30	−0.51 - -0.10	**0.004**	Group	−0.33	−0.57 - -0.08	**0.009**	Group	−0.21	−0.45 - 0.03	0.085	Group	−0.40	−0.69 -0−0.12	**0.005**
Δ CNV at Fz	0.02	−0.02 - 0.06	0.235	Δ CNV at Fz	0.05	−0.00 - 0.09	0.057	Δ CNV at Fz	0.01	−0.03 - 0.06	0.581	Δ CNV at Fz	−0.01	−0.06 - 0.05	0.804
Δ CNV at Cz	−0.02	−0.08 - 0.05	0.607	Δ CNV at Cz	−0.05	−0.13 - 0.03	0.235	Δ CNV at Cz	−0.03	−0.10 -0.05	0.469	Δ CNV at Cz	0.07	−0.02 -0.16	0.112
Δ CNV at Pz	0.03	−0.03−0.08	0.368	Δ CNV at Pz	0.06	−0.01 - 0.13	0.080	Δ CNV at Pz	0.02	−0.05 - 0.09	0.546	Δ CNV at Pz	−0.05	−0.13 - 0.03	0.236
Δ CUE P3 at Fz	−0.02	−0.05 - 0.01	0.256	Δ CUE P3 at Fz	−0.01	−0.05 - 0.03	0.521	Δ CUE P3 at Fz	−0.03	−0.06 - 0.01	0.168	Δ CUE P3 at Fz	−0.02	−0.06 - 0.03	0.386
Δ CUE P3 at Cz	0.00	−0.04 - 0.04	0.958	Δ CUE P3 at Cz	−0.01	−0.06 - 0.03	0.560	Δ CUE P3 at Cz	0.03	−0.01 - 0.07	.0189	Δ CUE P3 at Cz	−0.01	−0.06 - 0.04	0.663
Δ CUE P3 at Pz	−0.00	−0.04 - 0.03	0.801	Δ CUE P3 at Pz	0.01	−0.02 - 0.05	0.491	Δ CUE P3 at Pz	−0.01	−0.05 - 0.02	0.484	Δ CUE P3 at Pz	−0.03	−0.07 - 0.01	0.188
Group X Δ CNV at Fz	−0.03	−0.10 - 0.04	0.403	Group X Δ CNV at Fz	−0.07	−0.15 - 0.01	0.097	Group X Δ CNV at Fz	−0.02	−0.10 - 0.06	0.614	Group X Δ CNV at Fz	0.04	−0.05 - 0.14	0.358
Group X Δ CNV at Cz	0.00	−0.08 - 0.09	0.927	Group X Δ CNV at Cz	0.09	−0.01 - 0.20	0.077	Group X Δ CNV at Cz	−0.04	−0.14 - 0.06	0.456	Group X Δ CNV at Cz	0.13	−0.25 - -0.01	**0.038**
Group X Δ CNV at Pz	−0.01	−0.09 - 0.07	0.850	Group X Δ CNV at Pz	0.11	−0.20 - -0.01	**0.030**	Group X Δ CNV at Pz	0.06	−0.03 - 0.15	0.204	Group X Δ CNV at Pz	0.10	−0.01 - 0.22	0.072
Group X Δ CUE P3 at Fz	0.01	−0.03 - 0.05	0.619	Group X Δ CUE P3 at Fz	0.02	−0.03 - 0.06	0.529	Group X Δ CUE P3 at Fz	−0.00	−0.05 - 0.05	0.976	Group X Δ CUE P3 at Fz	0.02	−0.04 - 0.07	0.522
Group X Δ CUE P3 at Cz	−0.01	−0.06 - 0.04	0.643	Group X Δ CUE P3 at Cz	−0.01	−0.07 - 0.05	0.721	Group X Δ CUE P3 at Cz	−0.03	−0.09 - 0.02	0.264	Group X Δ CUE P3 at Cz	0.02	−0.05 - 0.09	0.590
Group X Δ CUE P3 at Pz	0.01	−0.03 - 0.05	0.755	Group X Δ CUE P3 at Pz	−0.01	−0.06 - 0.04	0.706	Group X Δ CUE P3 at Pz	0.00	−0.04 - 0.05	0.871	Group X Δ CUE P3 at Pz	0.05	−0.01 - 0.11	0.089

Δ indicates changes between assessments. CNV: Contingent negative variation. CI: Confidence intervals (95 %).
Significant effects (p<.05) are printed **bold**.

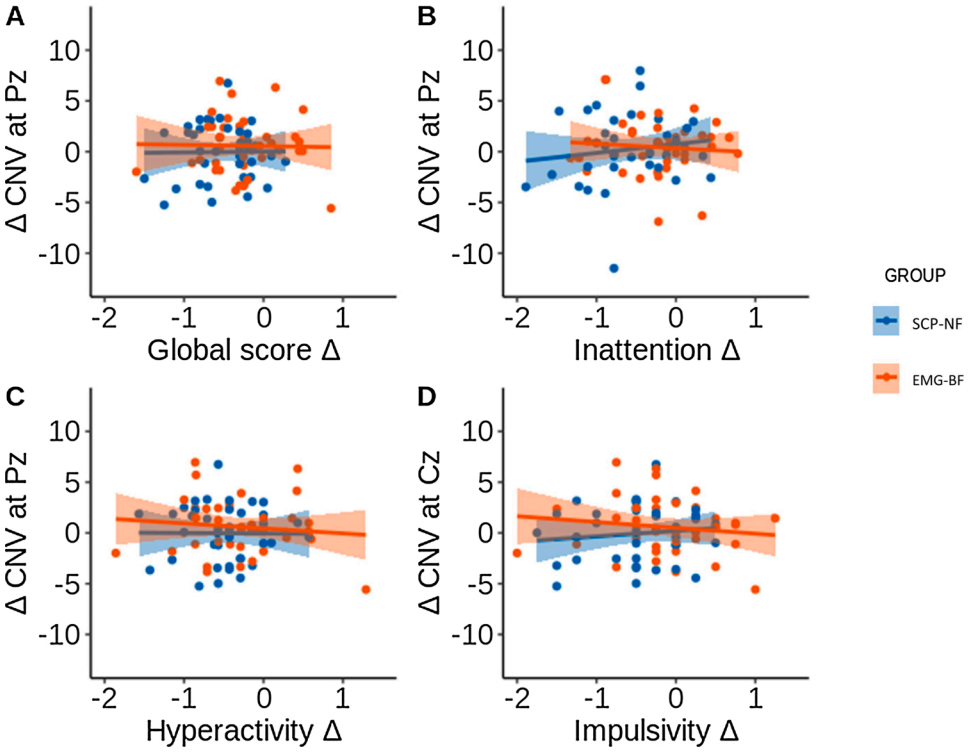

Fig. 7. Associations between mean-centered CNV and clinical changes rated by parents; Δ indicates changes between Pre and Post-2 assessments. Negative values indicate larger (that is more negative) CNV at Post-2. Negative values for clinical changes indicate improvement at Post-2. ns; not significant. A) No association between Δ CNV and Δ global scale. B) Significant group x CNV at Pz interaction ($p = .03$). Only the SCP-NF group showed an association with larger CNV at post-2 and inattention improvement. C) No association between Δ CNV and Δ hyperactivity. D) Significant group x CNV at Cz interaction ($p = .03$). Only the SCP-NF group showed an association with larger CNV at post-2 and impulsivity improvement.

Table 5
Baseline differences between SCP-NF responders and non-responders.

Measure	CNV RE (N = 15) Mean (SD)	CNV non-RE (N = 25) Mean (SD)	ANOVA
Age (in years)[a]	8.66 (0.88)	8.7 (0.97)	$F_{(1,39)} = 1.36$, $p = .71$
Sex (% male)[b]	80 %	89 %	$X^2_{(1)} = 0.00$, $p = 1$
FBB-HKS (parent)			
Total	1.79 (0.45)	1.75 (0.48)	$F_{(1,39)} = 0.09$, $p = .55$
Inattention	1.91 (0.45)	2.02 (0.44)	$F_{(1,39)} = 0.433$, $p = .76$
Hyperactivity	1.57 (0.57)	1.49 (0.72)	$F_{(1,39)} = 0.134$, $p = .51$
Impulsivity	1.90 (0.67)	1.60 (0.63)	$F_{(1,39)} = 1.90$, $p = .17$
FBB-HKS (teacher)			
Total	1.30 (0.78)	1.54 (0.64)	$F_{(1,33)} = 0.93$, $p = .34$
Inattention	1.49 (0.65)	1.87 (0.78)	$F_{(1,33)} = 2.09$, $p = .15$
Hyperactivity	1.17 (1.00)	1.06 (0.83)	$F_{(1,33)} = 0.115$, $p = .73$
Impulsivity	1.12 (0.97)	1.61 (0.97)	$F_{(1,33)} = 1.95$, $p = .17$
CPT: Performance			
Hit-RT	530 (104)	515 (116)	$F_{(1,39)} = 0.16$, $p = .69$
Hit-RT-SD	167(100)	174 (55)	$F_{(1,39)} = 0.09$, $p = .75$
Hit-Rate (%)	88 (9)	94(8)	$F_{(1,39)} = 4.55$, $p = .039$
Commission-Error-Rate	0.933 (1.43)	1.08 (1.84)	$F_{(1,39)} = 0.69$, $p = .79$
CPT: Cue-P3			
Pz	10.54 (6.00)	899 (4.9)	$F_{(1,49)} = 0.72$, $p = .379$
CPT: Cue-CNV			
Cz	−1.13 (2.01)	−4.25 (2.48)	$F_{(1,39)} = 23.10$, $p < .001$

RE = Responder and non-RE = non-responder. RE were considered if participants showed a CNV improvement at Post-2 assessment.
[b] Ratios were tested with the Chi-squared test.

parents' for the inattention subscale in the EMG-BF group, and more impulsivity improvement rated by teachers' in the SCP-NF group. More commission errors predicted higher parent-rated hyperactivity improvement regardless of group. Faster reaction time at baseline was also predictive for teacher rated impulsivity in the SCP-NF group. Although these results are exploratory and heterogeneous, they might help to understand who is more responsive to SCP-NF. With regard to neurophysiological activity, we could not replicate the findings of (Wangler et al., 2011). Contrary to our expectations, higher CNV at baseline did only predict clinical improvement in the EMG-BF control group, but not so for the SCP-NF group. Instead, a larger Cue P3 at baseline tended to predict inattention improvement rated by teachers in the SCP-NF group only.

Regarding specific effects after SCP-NF, we failed to support earlier findings of increased CNV amplitude at a group level after SCP-NF training during a CPT task (Heinrich et al., 2004; Wangler et al., 2011). However, the CNV decrease at Pz and Cz interacted significantly with group, showing that the increase of the CNV negativity was associated with more clinical improvements for inattention and impulsivity symptoms rated by parents in the SCP-NF group. This might suggest a specific effect for those who were able to recruit more attentional resources at the Post-2 assessment. In general and at a group mean level, our results might point to a rather unspecific component of effects observed after both the SCP-NF and EMG-BF training, but when taking into consideration the CNV changes from Pre to Post-2, a group by CNV interaction emerged. A similar effect, but restricted to the hyperactivity subscale, was also found for teacher ratings, which may indicate a specific effect after SCP-NF. Importantly, and despite the smaller sample size of the analyzed group, the clinical outcome of this sub-sample for our neurophysiological outcomes resembled the findings of the whole sample (Strehl et al., 2017), suggesting that it was not biased.

Contrary to our expectations, performance and electrophysiological parameters of Cue processing were diminished at Post-2 assessment after both SCP-NF and EMG-BF interventions. This was eminent in slower and more variable reaction times to cued targets and diminished Cue-P3 and –CNV amplitudes - and may indicate motivational difficulties after prolonged laboratory sessions that occupied a considerable part of our patient's free time rather than some fancy elaborated neural efficacy after treatments. These findings are in line with the results of Doehnert et al. (2008) who argued that a repetitive and to the patients probably boring test battery without sufficient motivation or reward salience might be associated with reduced engagement and consequently less

functional neurophysiological activity. Additionally, one SCP-NF study with healthy adults obtained similarly diminished CNV, but importantly in light of stable or even better CPT-performance after 8 NF sessions. As discussed by Gevensleben et al. (2014), under these circumstances the reduced CNV at post-assessment might therefore reflect less effort needed after NF training to complete the same task with comparable performance. We thus consider in line with Doehnert et al. (2008) that mainly motivational difficulties might be responsible for the limited CPT outcome at Post-2 assessment.

As a new finding, our data indicated that parent ratings of improvements in attention impulsivity and teacher ratings of hyperactivity were associated with improvements in Cue-CNV amplitude only in the group receiving SCP-NF; suggesting a possibly specific mode of action. Further exploratory analysis showed that those participants who improved their CNV after SCP-NF had lower hit rates and reduced CNV at baseline. This might suggest that these participants might benefit more from the SCP-NF treatment and underlines recent efforts to individualize NF training (Bioulac et al., 2019). However, these results should be interpreted with caution since the responder group comprised only 15 participants and require replication before definitive conclusions or even suggestions towards an individualized NF treatment protocol can be given.

5. Limitations

The generalization of our results is limited by different factors among which we consider as most important the reduced quality of EEG data and therefore a higher CPT-Dropout rate of participants. Only 58 % of the complete sample could be analyzed. The main reasons were insufficient quality of EEG data but missing measurements as well. It is worth noting, that the quality of the CPT assessment might suffer from the possible lack of motivation due to the high amount of EEG assessments and tests.

6. Conclusion

Across clinical and neurophysiological outcomes, some neurophysiological and behavioral markers of attention at baseline were associated with symptom severity. Importantly, we found that aspects of CPT Performance, Cue-P3 and -CNV predicted specific treatment outcomes which may help to tailor the treatment to individuals in the future. Moreover, we observed specific effects after SCP-NF in those participants who improved their CNV after training.

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Declaration of Competing Interest

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