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RESEARCH

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Individual brain regulation as learned via neurofeedback is related to affective changes in adolescents with autism spectrum disorder

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Abstract

Background Emotions often play a role in neurofeedback (NF) regulation strategies. However, investigations of the relationship between the induced neuronal changes and improvements in affective domains are scarce in electroencephalography-based studies. Thus, we extended the findings of the first study on slow cortical potential (SCP) NF in autism spectrum disorder (ASD) by linking affective changes to whole-brain activity during rest and regulation.

Methods Forty-one male adolescents with ASD were scanned twice at rest using functional magnetic resonance imaging. Between scans, half underwent NF training, whereas the other half received treatment as usual. Furthermore, parents reported on their child's affective characteristics at each measurement. The NF group had to alternatingly produce negative and positive SCP shifts during training and was additionally scanned using functional magnetic resonance imaging while applying their developed regulation strategies.

Results No significant treatment group-by-time interactions in affective or resting-state measures were found. However, we found increases of resting activity in the anterior cingulate cortex and right inferior temporal gyrus as well as improvements in affective characteristics over both groups. Activation corresponding to SCP differentiation in these regions correlated with the affective improvements. A further correlation was found for Rolandic operculum activation corresponding to positive SCP shifts. There were no significant correlations with the respective achieved SCP regulation during NF training.

Conclusion SCP NF in ASD did not lead to superior improvements in neuronal or affective functioning compared to treatment as usual. However, the affective changes might be related to the individual strategies and their corresponding activation patterns as indicated by significant correlations on the whole-brain level.

Trial registration This clinical trial was registered at drks.de (DRKS00012339) on 20th April, 2017.

Keywords Slow cortical potentials, Neurofeedback, Autism spectrum disorder, Emotion regulation, Functional magnetic resonance imaging

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Background

Autism spectrum disorder (ASD) constitutes a pervasive neurodevelopmental disorder which onsets during childhood and comprises deficits in communication and interaction abilities as well as atypical, repetitive behavior [1]. A variety of therapeutic approaches exists, each focusing on different symptoms [2, 3].

A particular family of treatment approaches based on a system- and network-level understanding of ASD includes the application of non-invasive neuromodulation techniques [4]. Among these, transcranial direct current [5–7] and magnetic stimulation [8–10] have been more widely explored in the past. In contrast, neurofeedback (NF) is a neuromodulatory intervention without external stimulation.

Patients undergoing NF, train their voluntary control over certain characteristics of their brain activity. While reviews on the application of electroencephalography-based (EEG) NF for the treatment of attention-deficit/hyperactivity disorder (ADHD) have yielded mixed results [11, 12], there is a specific recommendation for slow cortical potentials (SCPs) NF [13].

SCP NF has been successfully applied for the treatment of ADHD in children [14–16], adolescents [17] and adults [18]. These very slow EEG fluctuations (typically below 1 Hz) are related to the excitability threshold of the upper cortical layers, where SCP negativity corresponds to increased cortical excitability and SCP positivity to decreased cortical excitability [19]. However, the utility of NF for the treatment of ASD in general has been questioned [24].

This criticism is based on the high comorbidity of ASD with ADHD with estimates ranging from 37 to 85% [25] rendering it difficult to assign symptom improvements to either of the disorders separately. However, previous research using EEG NF in ADHD and ASD often focused on attention deficits [11, 26] while studies on the emotional and empathic components are largely missing. The recently conducted first study on SCP NF in ASD reported positive effects on ASD-specific symptomatology [27], but also showed the complex influence of the ADHD-related problems regarding attention, hyperactivity and impulsivity [28]. Overall, transdiagnostic similarities between ASD and ADHD encompass deficits in emotion regulation, emotion recognition, attention, cognitive flexibility, inhibition, reward processing, working memory, organization and planning [29, 30]. Different severity patterns of emotion recognition and regulation impairments between children and adolescents with and without ASD and/or ADHD have also been found [31–33]. In regards to empathic capabilities, individuals with ASD showed deficits in cognitive empathy, but not in affective empathy [35, 36]. Despite emotion regulation research in ASD still being in its infancy, the importance and efficacy of therapeutic approaches incorporating emotion regulation training for ASD are already evident [38, 39].

On a neuronal level, investigations via resting-state (RS) functional magnetic resonance imaging (fMRI) revealed lower average absolute global connectivity in children and adolescents with ASD compared to typically developing controls [42]. A meta-analysis on differences in resting activity between individuals with and without ASD quantified via regional homogeneity (ReHo; a measure sensitive to brain activity and local connectivity), amplitude of low-frequency fluctuations (ALFF; activity within a certain frequency band) and cerebral blood flow, reported robust over-activation in language-related and motor areas as well as under-activation in the default mode network [43]. A large-scale, multi-center study reported a cluster reaching from the left posterior insula to the operculum showing decreases in voxel-matched homotopic connectivity (i.e., symmetric connectivity), ReHo and degree centrality (a measure of global connectedness) [44]. A second cluster was located in the right dorsal superior frontal cortex and showed increases in fractional ALFF (fALFF; an amplitude-normalized version of ALFF), ReHo and degree centrality [44].

Even though SCPs are a common NF target and further constitute suspected contributors to the blood-oxygenation-level-dependent (BOLD) signal [20, 21], only few studies investigated the neural processes accompanying SCP self-regulation using fMRI. Hinterberger, Veit [45] showed that during transfer runs (training runs without feedback for decoupling regulation success from the feedback procedure) SCP negativity is related to wide-spread activation in fMRI. In turn, SCP positivity was associated with widespread deactivation.

We investigated potential treatment-induced changes in several affective characteristics on a subjective level via parental questionnaires to gain further knowledge on emotion regulation in ASD. Neuronal outcome measures at rest were assessed using three models previously related to alterations in brain connectivity and activity of individuals with ASD [42–44]. First, the percent amplitude of fluctuation (PerAF) model was used for assessing resting brain activity [47], constituting a less artifact-prone and easier to interpret derivative of (f) ALFF [43, 44]. Second, average brain-wide connectivity was assessed via global functional connectivity (GFC; [48]), a continuous and thus more sensitive alternative to degree centrality [44]. Third, ReHo [49, 50] was assessed as measure of local activity and connectivity [43, 44], placing itself conceptually between PerAF and GFC.

Finally, we conducted a brain regulation task in the MRI scanner, based on suggested links between SCPs and the BOLD signal [21, 45], in which the participants had to apply the regulation strategies learned, and investigated potential relationships between whole-brain activation corresponding to SCP regulation and affective changes.

Methods

Experimental design

Participants were randomly allocated to either 24 sessions of SCP NF or treatment as usual (TAU). SCP feedback was calculated from the fronto-central electrode located according to the extended 10–20 EEG system and presented on a screen as graphical object of the participants' choice. The participants' goal was to gain volitional control over their brain activity. This was visualized by moving the object up or down via changes in SCP positivity or negativity. For details on the NF training protocol, EEG artifact correction, feedback presentation, etc. see Konicar, Radev [27]. In order to assess neuronal and subjective changes, fMRI and psychometric data were acquired before the first and after the last treatment session in both groups.

Participants

Potential male adolescent (12–17 years) participants with a diagnosis of ASD (according to the German version of the Autism Diagnostic Interview—Revised (ADI-R) [51] and/or the Autism Diagnostic Observation Schedule, version 2 (ADOS-2) [52] were recruited and invited to a screening. The subsequent inclusion criteria were right-handedness and an IQ above 70 (if no previous IQ was available, an age-adequate test was administered as part of the screening process) [53, 54]. The recruitment was restricted to male adolescents due to the prevalence of ASD in this population. Participants were excluded in case of relevant psychiatric, neurological or internal conditions (head injuries, major axis I diagnosis of psychosis, obsessive–compulsive disorder, severe motor or vocal tics, Tourette syndrome, severe depression with suicidality) or MRI contraindications. Previous NF experience and current participation in pharmacological studies were not allowed. Concomitant psychosocial and pharmacological treatments were permitted if kept constant throughout study participation.

Psychometric assessment

We used the Emotion Regulation Checklist (ERC [55]) and the Griffith Empathy Measure (GEM [56]) to gather parental reports of the participants' development regarding their affective and empathic abilities. The Emotion Regulation (ER) and Lability/Negativity (LN) subscales of the ERC were analyzed separately, with the former quantifying expression and self-awareness of emotions as well as empathy, and the latter mood lability and anger dysregulation. We concentrated on the Cognitive Empathy (CE) subscale of the GEM, since this ability was shown to be diminished in adolescents with ASD in contrast to affective empathy [35].

Since the frequent co-occurrence of ADHD constitutes the major point of discussion in the application of NF to patients with ASD, the "Diagnostic System for Psychiatric Disease in Children and Adolescent, parent-rated version 2" for ADHD (DISYPS-II [57]) was used to quantify the respective characteristics (henceforth "ADHD score"). The ADHD score was calculated, age-corrected and transformed to the "standard nine" (stanine) score.

FMRI acquisitions

We positioned the participants in the MRI scanner and fixated their heads using foam cushions. Eight minutes of RS data was acquired as the first functional scan to avoid potential task-related carryover effects. The participants were instructed to lie with their eyes open, look at a crosshair, let their mind wander and not to think of anything in particular.

In the SCP neurofeedback group only, after completing the training, a short brain regulation task was recorded in 2 min 42 s. This was done in order to investigate activation corresponding to the application of the SCP regulation strategies on a whole-brain level. The visual cues matched the SCP transfer run. Participants were instructed to apply their regulation strategies: A triangle pointing upwards ("Up" condition) indicated application of the strategy developed to induce negative SCP shifts and a triangle pointing downwards ("Down" condition) indicated application of the strategy developed to produce positive SCP shifts. The conditions were presented 5 times each for 8 s in a pseudo-randomized order interleaved with baselines of the same duration. Since the baseline in the SCP transfer run was only 2 s long and had no visual indicator, we added a crosshair of the same size and color scheme as the triangles for the fMRI run. There was no indication of the currently achieved regulation and, contrary to the SCP transfer run, no reward was given after regulation trials.

Measurements were performed on a Siemens Magnetom Prisma 3 T machine (Siemens, Erlangen, Germany) with the same sequence as in Moessnang, Schäfer [58] due to the previous successful application in a comparable population: echo/repetition time = 30/2000 ms, 3 mm isotropic resolution (+25% gap), 33 slices with 64×64 voxels (field of view = $192 \times 192 \times 123$ mm),

bandwidth = 2365 Hz/Px. Prospective acquisition correction (PACE) was used for online motion correction.

FMRI preprocessing

Unless mentioned otherwise, preprocessing was conducted using Statistical Parametric Mapping, version 12 (SPM12). In a combined first step, physiological artifacts were reduced using PESTICA [59] and slice-wise motion correction was performed with SLOMOCO [60]. This advanced motion correction approach was chosen as adolescents show markedly more in-scanner motion than adults. Slice-timing was corrected to the temporally middle slice. Each paradigm's acquisitions were realigned together for each participant. A population-specific normalization template was created using the CerebroMatic toolbox [61] with spatially adaptive non-local means and hidden Markov random field filtering for increased homogeneity over the whole age range. Affine regularization was performed to the standard ICBM template for European brains with parameters downscaled by a factor 10 for better local fitting, as some brains showed unreasonable inflation without regularization. Thus, tissue distributions were age-adjusted but the localization of the regions were approximately in standard space. The original voxel size was used for reslicing [62]. The BrainWavelet toolbox [63] was employed for non-linear artifact correction providing additional mitigation of motion and other types of artifacts. The "threshold" parameter was set to "15" due to the application to unsmoothed data and "chsearch" to "harsh" to be more sensitive towards slow artifacts. The data was finally smoothed with a Gaussian kernel with full width at half maximum (FWHM) of 3 times the voxel size.

FMRI modelling

An adapted CompCor approach [64, 65] and the Friston-24 model [66] were utilized for reduction of any residual physiological or movement-related artifacts in the brain regulation task and RS data. The latter was further band-limited to 0.01–0.10 Hz using frequency regressors [67]. Based on the filtered RS time series, three voxelwise models were set up: PerAF to quantify brain activity, GFC for brain-wide connectivity and ReHo for local activity and connectivity. Since the calculation of ReHo leads to spatial smoothing, this model was applied to the unsmoothed and filtered data. Afterwards, the ReHo maps were smoothed with a FWHM of 2 times the voxel size achieving smoothness similar to PerAF and GFC. Finally, ReHo and GFC were Fisher z-transformed before group analysis.

The brain regulation task was modeled using the 1st-level module in SPM12. The conditions ("Up"/"Down") were used as regressors. The CompCor and Friston-24 time series were set as nuisance signals. In addition, the equivalent of SCP differentiation between changes in negativity and positivity was calculated as the difference between the "Up" and "Down" conditions (henceforth "fMRI differentiation"). The autocorrelation model was set to "FAST" [68].

Statistical inference

Questionnaire data was analyzed using linear mixed effects models (LMEs). Interactions between "treatment group", "time" (factors) and "ADHD baseline score" (covariate) were analyzed and dropped if non-significant. The LMEs also included participants as random intercepts.

Whole-brain inference was conducted using the 2nd-level module in SPM12. "Treatment group"-by- "time" and "time" effects were analyzed in one model per RS measure. Contrasts for within-group effects were further estimated in case of non-significant interactions. Correlations of regulation direction-specific activation and fMRI differentiation with the ERC and GEM score changes were of interest for the brain regulation task. Family-wise error-corrected results are reported at the cluster- (primary threshold $p \leq 0.001$) or peak-level. Influences of ADHD were controlled for with the pre-training ADHD scores as covariate.

Associations between the RS findings and questionnaire score changes over time were investigated on an exploratory basis using partial correlation (Pearson or Spearman, depending on a visual check of the distributions, corrected for treatment group; median cluster values were extracted using the MarsBaR toolbox 0.44).

In case of significant correlations between activation in the brain regulation task and questionnaire score changes, the latter were subsequently correlated with the average amount of SCP regulation corresponding to the activation contrast achieved during the third and last quarter (six days each) of NF training. These periods showed the strongest regulation or were closest to the second MRI session [27]. This way, we checked whether NF training success was related to score changes (c.f., Heinrich, Gevensleben [69]).

All tests (including neuroimaging models [70]) were two-sided and multiplicity-corrected to $p \leq 0.05$. To correct for the number of questionnaire scales/RS models/brain regulation task correlations, we employed an in-house developed algorithm based on the dependency-adjusted D/AP approach [71] (see supplement for implementation).

Results

Participants

Out of 94 adolescents who were interested in participating in the study, 53 could not be enrolled (21 due to personal reasons, eleven due to neurological reasons or sub-threshold IQ, nine due to MRI contraindications, six were out of the target age range, six were left-handed). This resulted in a sample of 41 adolescents with an ASD diagnosis of which 21 were randomized into the SCP NF and 20 into the TAU group. Complete RS data and brain regulation task data was available for 36 and 20 participants respectively (three participants did not participate in the second session for personal reasons, two had to be excluded due to compromised data quality and one due to missing compliance). Baseline data of our sample is provided in Table 1, longitudinal data and comparisons are provided in Table 2.

The results of the SCP regulation training, ASD core symptoms longitudinally quantified via the Social

Table 1 Baseline characteristics

Score	Neurofeedback	Treatment as usual
N	21	20
Age[1] [years]	14.44 ± 1.90	15.01 ± 1.59
IQ: WISC/WAIS[2]	100.82 ± 17.34	101.57 ± 14.14
IQ: qualitative[3] [median]	average	average
ADI-R[4]: social interaction	12.25 ± 4.90	17.00 ± 7.73
ADI-R[4]: communication and language	10.08 ± 6.17	13.65 ± 5.40
ADI-R[4]: restricted and repetitive behavior	3.67 ± 2.71	3.75 ± 1.23
SRS: total	99.57 ± 26.10	89.50 ± 25.94
SRS: social awareness	12.57 ± 3.22	11.45 ± 4.01
SRS: social cognition	18.38 ± 4.90	15.50 ± 6.01
SRS: social communication	34.95 ± 11.14	30.70 ± 9.32
SRS: social motivation	15.86 ± 5.92	16.25 ± 5.18
SRS: autistic mannerism	17.81 ± 6.59	15.60 ± 6.29
SCQ: total	18.62 ± 7.26	15.10 ± 6.88
SCQ: social interaction	7.05 ± 4.02	5.60 ± 3.76
SCQ: communication	6.86 ± 2.57	6.10 ± 3.09
SCQ: stereotyped behavior	4.52 ± 2.42	3.10 ± 2.47
ASD subtype: deficits in social interaction[5] [n]	5	6
ASD subtype: repetitive behavior and interests[5] [n]	1	2
ASD subtype: deficits in social interaction + repetitive behavior and interests[5] [n]	12	10
ASD subtype: deficits in social interaction + deficits in language[5] [n]	1	1
ASD subtype: deficits in social interaction + deficit in language + repetitive behavior and interests[5] [n]	2	1
DISYPS-II: ADHD total[6] [standard nine]	7.5 ± 0.98	7.10 ± 1.17
DISYPS-II: attention deficits [standard nine]	7.33 ± 1.29	7.20 ± 1.15
DISYPS-II: hyperactivity [standard nine]	6.38 ± 1.77	5.55 ± 2.98
DISYPS-II: impulsivity [standard nine]	7.76 ± 1.09	5.90 ± 3.65
DISYPS-II: competences [standard nine]	3.90 ± 1.55	3.20 ± 1.91

Unless otherwise specified, scores are given as mean ± standard deviation

WISC/WAIS: Wechsler Intelligence Scale for Children/Wechsler Adult Intelligence Scale, *ADI-R:* Autism Diagnostic Interview—Revised, *SRS:* Social Responsiveness Scale, *SCQ:* Social Communication Questionnaire, *ASD:* Autism Spectrum Disorder, *DISYPS-II:* Diagnostic Dystem for Psychiatric Disease in Children and Adolescent, parent-rated version 2, *ADHD:* attention-deficit/hyperactivity disorder

[1] At first magnetic resonance imaging session

[2] WISC/WAIS IQs were available for 11 participants in the neurofeedback and 14 in the treatment as usual group. Two participants in the neurofeedback group had an IQ of 96 and 120, respectively, assessed via the Adaptive Intelligence Diagnostic, version 2

[3] Only one participant in the treatment as usual group was rated "slightly above average", none below

[4] Available for 12 participants in the neurofeedback and ten participants in the treatment as usual group

[5] Clinical observer assessment; no "deficits in language"-only subtype was observed in any group

[6] Combines the "attention deficits", "hyperactivity" and "impulsivity" subscales

Table 2 Changes in emotion regulation, empathy and in-scanner movement

Score	Neurofeedback pre	Neurofeedback post	Treatment as usual pre	Treatment as usual post	p-value
N	21	scores: 21 resting-state: 19 brain regulation task: 20	20	Scores: 20 Resting-state: 17	
Emotion Regulation Checklist: Emotion Regulation	21.19 ± 3.98	23.05 ± 3.23	20.45 ± 5.00	21.15 ± 3.59	Time: 0.0419
Emotion Regulation Checklist: Lability/Negativity	33.71 ± 5.83	30.76 ± 5.34	32.00 ± 7.06	31.65 ± 6.43	Time: 0.0506 ADHD score: 0.0014
Griffith Empathy Measure: Cognitive Empathy	-1.00 ± 9.85	5.33 ± 9.80	0.60 ± 9.20	1.20 ± 8.89	Time: 0.0601
Mean total displacement	2.49 ± 0.88	2.12 ± 0.46	2.01 ± 0.41	2.16 ± 0.42	Interaction: 0.0024 Group: 0.0145

Pre- and post-treatment scores are given as mean ± standard deviation. *ADHD*: attention-deficit/hyperactivity disorder. Tests were conducted with linear mixed effects models

Responsiveness Scale [72] and further information on the exact training protocol are provided in Konicar, Radev [27]. A detailed analysis of the comorbid ADHD symptoms and their influence on attention and expectancy measured via the contingent negative variation (CNV) in the EEG signal is presented in Prillinger, Radev [28].

Psychometric and behavioral analysis

No significant interaction effects were found for any psychometric scale. The ER subscale (higher is better) of the ERC showed a significant improvement of symptoms over both groups, whereas the LN (lower is better) and GEM CE (higher is better) subscales barely fell short of statistical significance. The LN subscale positively correlated with the pre-training ADHD score.

Since the PerAF results indicated a potential relationship with in-scanner movement, the mean of the total displacement output of the SLOMOCO step of RS preprocessing was additionally analyzed via LME to uncover potential further relationships with psychopathology. There was a significant time by group interaction where the SCP NF group showed significantly higher pre-training movement. Total displacement did not correlate with the ADHD score over both scans (Spearman $\rho = -0.05$, $p = 0.6790$). No multiplicity correction was applied in the total displacement analysis.

Resting-state models

Over both groups, an increase in RS activity was found in the ventral anterior cingulate cortex (ACC). Within the TAU group, a further increase was detected in the right precentral gyrus. Another cluster of increased resting activity over both groups stretching into the medial and inferior temporal gyrus (ITG) did not survive correction for the number of models. Upon visual inspection (see Fig. 1), the result in the precentral gyrus might be particularly biased by baseline differences. LMEs of the median values extracted from the clusters were run (treatment group, time and their interaction as factors, the ADHD score as covariate, random intercept per participant). These confirmed the time effect for the ACC ($p = 0.0006$) and temporal gyrus ($p = 5.4E\text{-}6$) and indicated a baseline difference ($p = 0.0326$), time ($p = 3.5E\text{-}5$) and interaction effects ($p = 0.0020$; all uncorrected) for the precentral gyrus. The ADHD score had no significant influence in either model. Details are presented in the upper section of Table 3 and left column of Fig. 1.

Since precentral gyrus activation might be indicative of movement, the PerAF values of each region were Pearson partially correlated (corrected for measurement, treatment group and their interaction) with the mean total displacement (thresholded at 1.5 times the interquartile range due to potential outliers) and the pre- and post-training ADHD scores on an exploratory basis. Indeed, significant relationships with total displacement were found for all results ($r = [0.24, 0.49]$, $p = [0.0479, 1.6E\text{-}5]$; all p-values for the ADHD score > 0.45). The thresholded mean total displacement values were then used as additional covariate in a repeated analysis. All results survived this control for in-scanner movement with one further cluster for the TAU group in the triangular gyrus (not significant after multiplicity adjustment; see Additional file 1: Table S3, upper section). Given the homogeneous effect on all investigated regions, the influence of total displacement was also investigated on a whole-brain level, resulting in weak but widespread patterns of correlations and anti-correlations (Additional file 1: Figure S3).

Exploratory analyses revealed correlations between changes in the LN subscale and the middle/ITG cluster

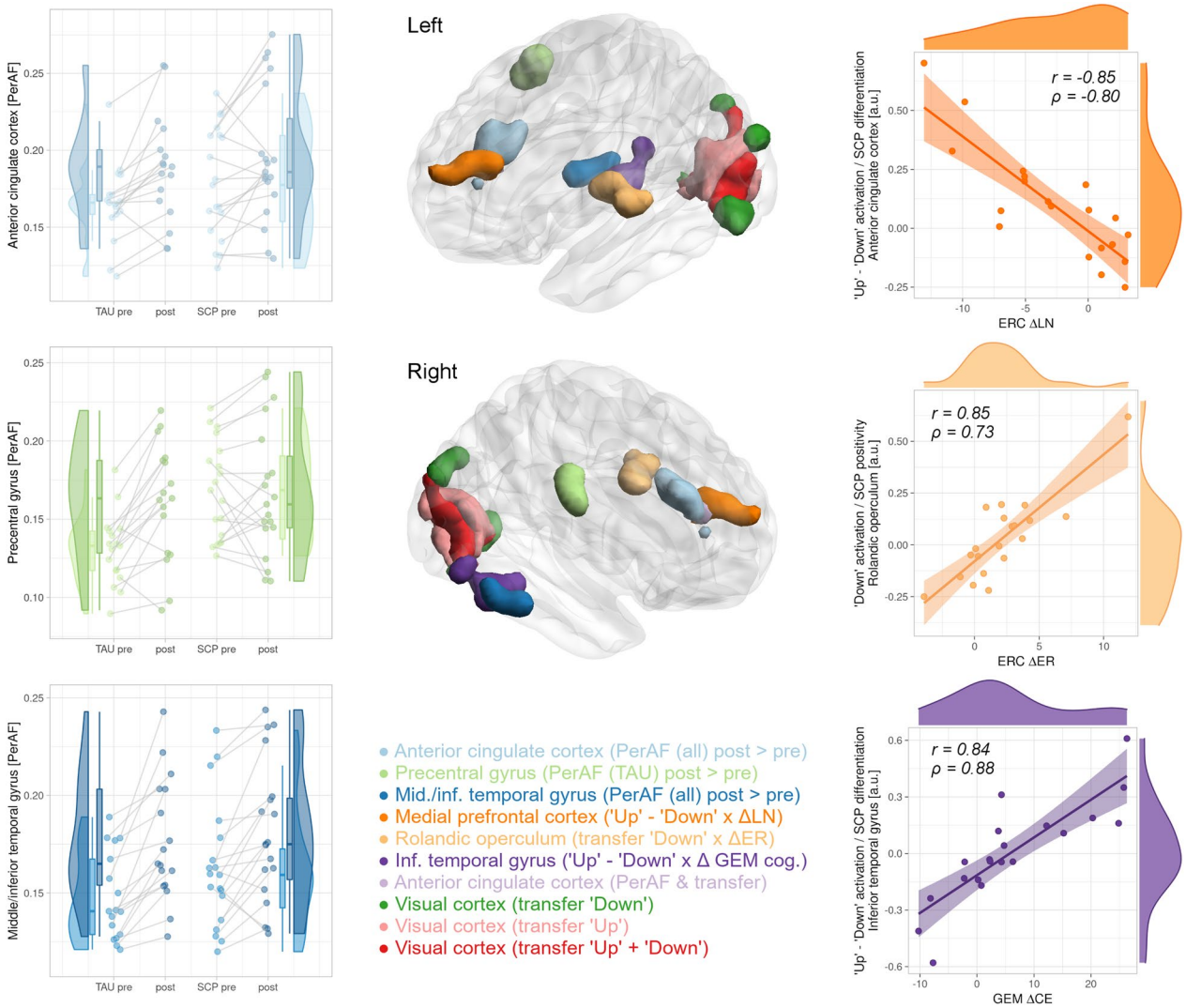

Fig. 1 Results of the resting brain activity and brain regulation task analyses. The increase in the percent amplitude of fluctuations (PerAF) of the anterior cingulate cortex over both, the slow cortical potentials (SCP) neurofeedback and treatment as usual (TAU) group, is visualized in the top-left diagram. The middle-left diagram shows a PerAF increase in the precentral gyrus of the TAU and generally higher values in the SCP group. The bottom-left plot shows the PerAF changes over both groups in the temporal gyrus with stronger increases in the TAU group. The right scatter plots show the correlation of the brain regulation task (Pearson's r corresponding to the parametric analysis as implemented in Statistical Parametric Mapping and Spearman's due to potential outliers): The difference between the "Up" and "Down" conditions (i.e., fMRI differentiation) was anticorrelated with changes on the Lability/Negativity (ERC ΔLN) subscale of the Emotion Regulation Checklist. The SCP positivity condition correlated with changes on the Emotion Regulation (ERC ΔER) subscale. Changes on the Griffith Empathy Measure Cognitive Empathy (GEM ΔCE) subscale again significantly correlated with fMRI differentiation. The whole-brain 3D models were created using BrainNet Viewer 1.7 [73]

from both groups (Spearman $\rho = 0.41$, $p = 0.0133$). The GFC and ReHo models yielded no significant effects.

Brain regulation task

During the "Up" and "Down" conditions (corresponding to the induction of negative and positive SCP shifts, respectively), primary and secondary visual areas were activated. No significant difference was found between the two conditions (i.e., no significant fMRI differentiation). Rolandic operculum activation (stretching into the anterior insula and the Heschl gyrus) during the "Down" condition significantly correlated with increases in ER after training. FMRI differentiation in the ITG showed a significant correlation with changes in CE. A further cluster barely missing corrected significance was detected for the correlation of higher fMRI differentiation in the ventral ACC and improvements in LN. The baseline ADHD score had no significant influence on any

Table 3 Results of the whole-brain resting-state analysis and brain regulation task

Model/condition	Contrast	Coordinates			Cluster size	p-value	p_{corr}-value	Region
		x	y	z				
Resting-state								
PerAF	post > pre	63	− 34	− 16	56	0.0481	0.1356	Middle/inferior temporal gyrus
PerAF	post > pre	12	29	32	140	0.0003	0.0008	Anterior cingulate cortex
PerAF	TAU: post > pre	60	− 31	− 19	peak	0.0433	0.1225	Middle/inferior temporal gyrus
PerAF	TAU: post > pre	57	− 10	47	96	0.0033	0.0098	Precentral gyrus
Brain regulation task								
Down	mean > 0	− 18	− 82	− 16	543	1.8E-9	4.8E-9	Primary/secondary visual cortex
Down	mean > 0	− 18	− 82	− 16	peak	5.7E-5	0.0001	
Up	mean > 0	6	− 79	− 10	816	2.3E-12	5.9E−12	
Up	mean > 0	6	− 79	− 10	peak	0.0021	0.0056	
Down	ERC ΔER > 0	− 39	− 13	14	141	0.0026	0.0104	Rolandic operculum, insula, superior temporal gyrus
Down	ERC ΔER > 0	45	− 4	− 13	peak	0.0381	0.2683	Insula
Up-Down	ERC ΔLN < 0	− 12	35	20	112	0.0066	0.0515	Anterior cingulate/medial prefrontal cortex
Up	GEM ΔCE > 0	54	− 49	− 22	72	0.0215	0.2974	Inferior temporal gyrus
Up-Down	GEM ΔCE > 0	51	− 46	− 16	157	4.2E−4	0.0068	Inferior temporal gyrus

Resting-state: The PerAF results are provided here (see supplement for those additionally corrected for total displacement). Brainregulation task: The mean activation per condition (mean > 0) and the correlation with psychometric score changes (ERC ΔER > 0, ER ΔLN < 0, GEM ΔCE > 0) are shown. All models were corrected for the baseline attention-deficit/hyperactivity disorder(ADHD) score. The coordinates need to be seen as rough orientation only due to a study-specific normalization. The p-values werecorrected for the investigated models/contrasts. *PerAF*: percent amplitude of fluctuation, *TAU*: treatment as usual, *SCP*: slowcortical potentials neurofeedback, pre/post: measurement before/after intervention, Up: up-regulation, Down: down-regulation,Up-Down: difference between up- and down-regulation; *ERC ΔER*: Emotion Regulation Checklist Emotion Regulation subscale change; *ERC ΔLN*: Emotion Regulation Checklist LIability/Negativity subscale change; *GEMΔCE*: Griffith Empathy Measure Cognitive Eempathy subscale

model. For details, see the lower section of Table 3 and right column of Fig. 1.

The only notable correlation with SCP shift amplitudes was found for the change in CE and the average differentiation achieved during the last quarter of the NF training (Spearman: $\rho = 0.35$, $p = 0.1184$; all other $|\rho| < 0.15$, $p > 0.53$) but was not significant.

Discussion

In this work, we used fMRI to assess the resting brain activity of adolescents with ASD and parental reports of their affective functioning before and after receiving SCP NF or TAU. In addition, the SCP NF group performed an in-scanner brain regulation task where the participants had to apply their regulation strategies after undergoing NF training. Using the whole-brain regulation data, we found relationships between the activation during regulation and improvements in different affective domains.

Affective symptom improvements and the potential influence of regulation strategies

Changes in resting activity and affective improvements over both groups without any interaction effects indicate unspecific positive effects of SCP NF and TAU. Furthermore, while localized correlations between brain activation during regulation and improvements on all investigated affective scales point towards an influence of NF, these improvements did not significantly correlate with SCP regulation measure used (i.e., the SCP shifts produced in the same direction for which the correlations with fMRI activation were detected). Heinrich, Gevensleben [69] likewise concluded universal improvements of emotional and behavioral self-regulation after successfully applying SCP NF in ADHD without finding correlations of training outcomes and symptom improvements. A possible interpretation of these findings may ascribe the affective improvements not to the achieved SCP regulation but to the application of regulation strategies. The correlation between fMRI differentiation and activation during the "Down" condition with affective improvements could indeed point towards highly individual activation patterns and strategies. In line with this speculation, Hasslinger, D'Agostini Souto [74] identified emotional strategies as one class of common regulation approaches in SCP NF when treating ADHD. Using the same classifications, strategies from the emotional domain were also frequently reported in this study (see supplement of [27]). Furthermore, ER is known to often be a key factor in the development of successful regulation strategies [75, 76]. It, however, should be noted that any comparison to NF training outcomes strongly depends on the definition of learning and the quantification of the regulation success.

The support of the experimenters needs consideration in regards to the origin of the correlation between fMRI differentiation in the right ITG and improvements in CE. Empathic comments after negative performance feedback were shown to decrease negative feelings [77]. The participants might have unintentionally related verbal positive reinforcement to their regulation strategies ultimately resulting in CE improvements. In a comparable scenario, the experimenters' empathy was concluded to be a potential driving factor of subjective improvements in the sham group of a NF study in primary insomnia [78]. While the weaker correlation of the "Up" condition alone appears to support this hypothesis, the stronger effect for the fMRI differentiation is probably the best argument against such an additional unintentional effect.

In addition, the TAU group might have improved due to the supportive clinical counseling received, leading to no significant therapeutic advantage of SCP NF. The positive correlation between the LN subscale and the ADHD baseline score corroborates the well-documented emotion dysregulation in ADHD [79–81]. The stronger reduction of in-scanner head movement (total displacement) in the SCP group might result from the requirement to sit still for a longer time over repeated NF sessions.

The anterior cingulate cortex and emotional negativity

Similar to improvements on the psychometric level, we found an increase in ACC resting activity quantified as PerAF over both groups. Smaller gray matter volume (potentially presenting as decreased resting activity after structural normalization) as well as decreased metabolic rate in the ACC of individuals with ASD have been reported [82, 83]. A lack of activation in the ACC was also found for a stroop task in ADHD and related to the symptoms of inattention and impulsivity [85], which are likely shared between ADHD and ASD [86]. The increased ACC resting activity could thus constitute a treatment-induced compensatory effect.

Beyond changes in PerAF, the ventral part of the ACC also showed a negative correlation between fMRI differentiation and the change in the LN subscale of the ERC extending into the medial prefrontal cortex. The ACC is known to be related to repetitive behavior in ASD [87] but also to cognitive inflexibility in depression [88, 89]. The latter is potentially also represented in the LN subscale [90], providing further evidence that behavioral flexibility might be reflected in neuronal flexibility of the ACC.

The inferior temporal gyrus and cognitive empathy

General as well as regionally specific alterations in temporal lobe structures related to ASD are well known [91,

92]. Smaller gray matter volume of the right ITG was previously related to a higher probability of an ASD diagnosis [93]. Reduced gray matter volume of the left ITG was also detected in children with low-functioning ASD [94] and related to communication skills [95]. Similar to the ACC, smaller gray matter volume in the ITG might be related to less activity after structural normalization, relating our finding of an increase after NF training to compensatory processes. The positive correlation of PerAF changes in the rITG cluster with changes in emotional negativity (LN subscale) would imply a worsening in emotional negativity accompanying an increase in ITG activity. This, however, is in contradiction with our other findings and might be owed to the exploratory nature of the analysis.

Besides the temporal lobe results found at rest, which did not survive correction for the number of models, we also identified a positive correlation between fMRI differentiation in the right ITG and improvements in CE. Laterality of this correlation as well as specificity for cognitive compared to affective empathy are supported by findings in unilateral mesial temporal lobe epilepsy [97] and personal/impersonal emotional imagery [98].

The Rolandic operculum and emotion regulation

The correlation between the "Down" condition (SCP positivity) and the increase in the ER score mostly covers the posterior Rolandic operculum reaching to the insula and superior temporal gyrus. This particular result might be explained by the role of the Rolandic operculum in language encoding [100] and emotion processing [101]: Reduced activation was found in the left Rolandic operculum of adults with ASD compared to neurotypical individuals regarding speech [102]. The Rolandic operculum further showed increased activation during emotion induction with happy compared to sad music [103]. Similar results were obtained for the superior temporal gyrus of children with low-functioning autism and age-matched controls using speech recordings of their parents and each child's favorite song containing vocals [104]. These previous findings suggest two possible conclusions related to NF: First, our reported activation related to improvements on the ER subscale was evoked by self-induced positive mood, possibly in combination with sound imagination. Second, less severe language deficits facilitated the development of strategies involving inner speech, which had a positive impact on ER.

On the role of SCP positivity in particular, we can only make an indirect assumption: Better SCP differentiation was previously associated with less relaxation when trying to produce negative SCP shifts [105], suggesting that the potentially induced positive mood is a side effect of more relaxation when trying to produce positive shifts.

The precentral gyrus at rest

Lastly, we found an increase in resting activity in the right motor cortex of the TAU group, which was biased by a baseline difference. The unspecific correlations to the amount of in-scanner head motion, the fact that motion decreased in the SCP NF but PerAF increased in the TAU group and the effect surviving a correction for motion on group-level, speak against movement-related motor activity as sole cause. Altered connectivity of motor regions [107, 108] as well as motor impairments [109] are known in ASD. Higher visuomotor impairment was associated with increased ALFF in the precentral cortex, among other regions [110]. Furthermore, ASD without ADHD was shown to be related to increased and ADHD to decreased gray matter in the precentral gyrus among other regions [111, 112]. Assuming that the baseline difference in precentral gyrus PerAF is reflecting more deficits/higher symptom severity in pre-treatment measures in the SCP NF group (i.e., increased movement, higher SRS scores), the observed increase in the TAU group cannot be seen as a positive therapeutic effect.

Limitations

Some results barely missed statistical significance after multiplicity adjustment, but were deemed relevant in relation to others and thus further discussed. Despite correcting for in-scanner head movement far beyond the standard procedure in multiple steps, residual artifacts are likely present in the data, as can be concluded from the correlation with the RS models (see Additional file 1: Figure S1). However, since the PerAF findings survived an additional control for the quantified motion on group-level, in-scanner movements unlikely are the cause of our findings. A potential preventive approach to further reduce head motion in future studies might be the low-demand video "Inscapes" [113]. The brain regulation data could only be reasonably acquired in the NF group and after the training, so all conclusions drawn from the data are necessarily purely correlational. We also kept the acquisition as short as possible expecting increasing movement and decreasing attention throughout each session.

During the brain regulation task, we could not check whether participants really applied the strategies learned. Concurrent EEG recordings were not possible but would have been of little use in this case since, on average, our participants did not gain control over the SCP signal in the absence of feedback (27).

Conclusion

SCP NF as well as TAU led to unspecific positive effects over both treatment groups. These effects comprise increases in resting activity in regions known to be affected in ASD and improvements in several affective domains. The affective improvements correlated with the activation corresponding to SCP regulation in comparable regions. The neuronal effects were, however, largely unrelated to the achieved degree of SCP regulation during NF training. Besides corroborating the role of regional alterations and affective functioning in ASD, our findings suggest that the application of distinct NF regulation strategies rather than SCP NF itself leads to affective symptom improvements. Future research is needed to clarify the distinct influences of SCP positivity and negativity as well as the role of individual regulation strategies.

Abbreviations

(f)ALFF	(Fractional) amplitude of low-frequency fluctuations
ACC	Anterior cingulate cortex
ADHD	Attention-deficit/hyperactivity disorder
ADI-R	Autism Diagnostic Interview—Revised
ADOS-2	Autism Diagnostic Observation Schedule, version 2
ASD	Autism spectrum disorder
BOLD	Blood-oxygenation-level-dependent
CE	Cognitive Empathy subscale of GEM
CNV	Contingent negative variation
DISYPS-II	Diagnostic System for Psychiatric Disease in Children and Adolescent, parent-rated version 2
EEG	Electroencephalography
ER	Emotion Regulation subscale of the ERC
ERC	Emotion Regulation Checklist
FEW	Family-wise error
fMRI	Functional magnetic resonance imaging
FWHM	Full with at half maximum
GEM	Griffith Empathy Measure
GFC	Global functional connectivity
ITG	Inferior temporal gyrus
LME	Linear mixed effect
LN	Lability/Negativity subscale of the ERC
NF	Neurofeedback
PACE	Prospective acquisition correction
PerAF	Percent amplitude of fluctuations
ReHo	Regional homogeneity
RS	Resting-state
SCP	Slow cortical potential
SPM12	Statistical Parametric Mapping, version 12
TAU	Treatment as usual
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children

Supplementary Information

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Additional file 1: **Table S1**. False-positive rates of three multiplicity correction approaches. **Table S2.** Overview of the psychometric and behavioral data. **Table S3.** Results of the whole-brain resting-state analysis and brain regulation task with and without control for movement on group level and Sidak correction. **Figure S1**. Correlation between resting-state models and SLOMOCO total displacement.

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Author contributions

LK, LP and RL conceptualized the study. LK acquired the funding. LK, RL and MK planned the MRI measurements. MK conducted the MRI measurements with support from LK, KP, RD and KD. KP, RD, KD and LK performed the NF training and monitored the collection of the questionnaire data. MK analyzed the data presented in this manuscript and compiled the original draft. KP, LK and RL preformed the administrative tasks for this study. PP and RL provided the resources for this study. PP, LP and RL supervised the study. All authors read and approved the final manuscript.

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Availability of data and materials

Due to reasons of data protection, the preprocessed data is available only upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The overall clinical trial and all parts presented here were conducted in accordance with the Declaration of Helsinki and the good scientific practice guidelines of the Medical University of Vienna. The project was approved by the institutional review board (EK-Nr.: 1850/2015). Informed assent was given by the participants and informed consent was provided by the parents/legal guardian.

Consent for publication

Not applicable.

Competing interests

Rupert Lanzenberger received travel grants and/or conference speaker honoraria within the last three years from Bruker BioSpin MR and Heel, and has served as a consultant for Ono Pharmaceutical. He received investigator-initiated research funding from Siemens Healthcare regarding clinical research using PET/MR. He is a shareholder of the start-up company BM Health GmbH since 2019.

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