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Neurofeedback impacts cognition and quality of life in pediatric focal epilepsy: An exploratory randomized double-blinded sham-controlled trial

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ABSTRACT

Objective: Children with epilepsy experience cognitive deficits and well-being issues that have detrimental effects on their development. Pharmacotherapy is the standard of care in epilepsy; however, few interventions exist to promote cognitive development and to mitigate disease burden. We aimed to examine the impact of two different modalities of neurofeedback (NFB) on cognitive functioning and quality-of-life (QOL) measurements in children and adolescents with controlled focal epilepsy. The study also explored the effects of NFB on clinical outcomes and electroencephalography (EEG) quantitative analysis.
Methods: Participants (n = 44) with controlled focal epilepsy were randomized to one of three arms: sensorimotor rhythm (SMR) NFB (n = 15), slow cortical potentials (SCP) NFB (n = 16), or sham NFB (n = 13). All participants received 25 sessions of intervention. The attention switching task (AST), Liverpool Seizure Severity Scale (LSSS), seizure frequency (SF), EEG power spectrum, and coherence were measured at baseline, postintervention, and at 3-month follow-up.
Results: In children and adolescents with controlled focal epilepsy, SMR training significantly reduced reaction time in the AST ($p = 0.006$), and this was correlated with the difference of change for theta power on EEG ($p = 0.03$); only the SMR group showed a significant decrease in beta coherence ($p = 0.03$). All groups exhibited improvement in QOL ($p = <0.05$).
Conclusions: This study provides the first data on two NFB modalities (SMR and SCP) including cognitive, neurophysiological, and clinical outcomes in pediatric epilepsy. Sensorimotor rhythm NFB improved cognitive functioning, while all the interventions showed improvements in QOL, demonstrating a powerful placebo effect in the sham group.

1. Introduction

Epilepsy is often comorbid with other cognitive and behavioral issues that are more disabling than seizures [1]. Community-based studies document the prevalence of such neurobehavioral comorbidities in epilepsy, which are divided into psychiatric, cognitive, and social categories [2]. A significant potential complication of epilepsy is impairment in some aspect of objectively assessed cognition including intelligence, language, visuoperception, learning and memory, executive function, and/or processing speed [3]. Pediatric epilepsy is particularly challenging because of neurodevelopmental comorbidities associated with the underlying pathology which are then compounded by antiepileptic drug (AED) side effects. Quality of life (QOL) in pediatric epilepsy is often more affected by issues associated with social and family life and academic performance and achievement, than by the occurrence of

Abbreviations: NFB, neurofeedback; SMR, sensorymotor rhythm; SCP, slow cortical potentials; QOL, quality of life; AST, attention switching task; LSSS, Liverpool Seizure Severity Sclae; SF, seizure frequency.

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seizures [4]. Yet, AEDs only target seizure occurrence and may worsen other QOL factors.

An option for cognitive and QOL issues is neurofeedback (NFB), or electroencephalography (EEG) biofeedback, a form of brain–computer interface whereby electrical activity from cortical areas is registered and processed using signal analysis methods. The aggregated neuronal activity is measured and transformed in real-time to visual and auditory feedback presented to patients, enabling them to self-regulate the activity of specific brain areas associated with behaviors or symptoms in a relatively individualized way. Theoretical NFB mechanisms have emerged from learning theories, especially associative learning theory, which includes principles of classical and operant conditioning. The use of NFB to treat epilepsy dates back to the early 1970s [5], with subsequent studies showing that seizure frequency could be reduced in most patients who were trained to decrease slow frequencies in the 3 to 8 Hz range while rewarding those contained within the 9 to 18 Hz range [6]. Low side effects in existing studies and clinical experience suggest that NFB is safe, though safety has not been systematically investigated [7].

Sensorimotor rhythm (SMR or μ rhythm) and slow cortical potentials (SCPs) are two NFB techniques with demonstrated efficacy in epilepsy [8–11]. A specific archiform rhythm of the sensorimotor cortex (corresponding to C3-Cz-C4) in awake participants which is supressed by thinking about or performing movement in the contralateral hand, SMR has a frequency of 12–20 Hz with a spectral peak of 12–15 Hz. It seems to originate from inhibitory thalamocortical circuits [12], hence its potential to regulate hyperexcitability.

Slow cortical potentials are slow event-related direct-current shifts of the EEG. When large cortical neuron assemblies depolarize, they lead to SCPs in the electrical negative direction and reduced excitation thresholds; when they repolarize, they lead to SCPs in the positive direction and a rise in excitation thresholds [13,14]. Hence, negative SCP shifts increase the firing probabilities of a cell assembly, whereas positive SCP shifts inhibit this activity [15]. The slow electrical shifts between positive and negative phases may help regulate attention [16] and other neurological functions as the cortical assemblies have a prominent role in cortico-striato-thalamo-cortical feedback loops [14,17]. For example, frontocentral contingent negative variation (CNV) is a well-studied SCP reflecting cognitive activation and preparation; it is typically reduced in children with ADHD compared with healthy controls [13], and children with ADHD who received SCP-NFB training had an increase in CNV and improved ADHD symptoms [18]. Slow cortical potential NFB has also shown long-term effectiveness in epilepsy [19], demonstrating that SCP training can reduce seizure frequency and severity [20,21]. In epilepsy, the most accepted hypothesis refers to the ability to generate cortical positivity (elevating excitation thresholds), and to carry over this skill into conditions without continuous feedback can serve as a seizure-controlling factor [22].

Neuropsychological-based treatments to reduce seizures and improve QOL in epilepsy have not been validated, although one review reported cognitive and motor improvements in patients who had the greatest seizure reduction following NFB [23]. However, importantly, most of the literature to date has been in adult populations. Little is known regarding the efficacy of NFB in pediatric epilepsy, as no randomized controlled study of NFB for pediatric epilepsy has been published to date [7].

A recent review on behavioral interventions in epilepsy included neurofeedback as a behavioral modality for seizure control and improvements in multiple QOL and cognitive domains [24]. It has been speculated that hyperexcitable cortical circuits leading to worsened QOL and cognition could be reorganized by NFB-based EEG entrainment, thereby leading to symptom control; both SMR and SCP may alter information processing in such networks by enabling inhibitory mechanisms. Sensorimotor rhythm intervention led to improvements in both QOL and attention measures in fibromyalgia, a disorder with impaired intracortical inhibition [25] highlighting the role of an inhibitory EEG frequency on symptom modulation [26].

We hypothesized that SMR and SCP neurofeedback protocols (30-minute sessions, 5 consecutive days/week over five weeks) would improve cognitive performance and QOL in patients with controlled focal epilepsy compared with sham NFB in a within-group design. Our secondary aim was to explore neurophysiological changes as well as seizure frequency and severity.

2. Methods

2.1. Trial design

This was an exploratory randomized, double-blinded, sham-controlled, 3-arm parallel-group (SMR, SCP, and sham NFB) clinical trial. This study was approved by the Bioethics and Research Committees of the Biomedical Research Institute (Aguascalientes, Mexico), and the Ethics Committee of De Montfort University (Leicester, United Kingdom). Written informed consent from each participant's parent or legal guardian was obtained; all participants assented to participate.

2.2. Participants

Study subjects were recruited from local epilepsy clinics and referrals from neurological centers at the Neuromodulation Center NEOCEMOD in Aguascalientes City, Mexico. Eligibility criteria for inclusion were (1) aged 10–18 years old; (2) proven focal epilepsy with seizures originating within networks usually limited to one hemisphere (defined as clinical seizures plus presence of unilateral interictal EEG findings in accordance with the ILAE classification system [27]); (3) pharmacoresponsive focal epilepsy as defined by no seizures in the last 3 months and no more than one seizure in the last 6 months; (4) AED treatment during the last 12 months; (5) cognitive difficulties in school as reported by parents and/or poor school performance; (6) Mini-Mental Status score > 23; and (7) normal vision and hearing function (as assessed by standardized testing) and ability to receive and understand visual and auditory feedback stimuli.

Exclusion criteria were (1) presence of psychogenic nonepileptic seizures; (2) idiopathic focal or generalized epilepsy; (3) previous epilepsy surgery or craniotomy; (4) history of recent stupor or coma; (5) active intracranial infection; or (6) neurodegenerative diseases. Participants were required to stay on a stable AED regimen during intervention and follow-up periods. While the inclusion criteria limited seizure frequency for enrollment, once patients had given their consent they were not dropped out if they had more seizures during the trial.

2.3. Interventions

Each of the three interventions were given for 5 consecutive days per week over 5 weeks for a total of 25 sessions.

The SMR NFB protocol was implemented using the ProComp Infiniti Encoder, an 8-channel, battery-powered system for real-time data acquisition (Thought Technology, Montreal). The signal was amplified using a preamplified EEG-Z sensor, with a recording electrode placed at Cz with reference to linked earlobes. The preset feedback parameters were as follows: inhibit theta (4–7 Hz) at least 20% below participant's automated calculated threshold, reinforce SMR (12–15 Hz) 80% of the time, and inhibit high beta (25–35 Hz) to at least 20% below their threshold. The automatic threshold calculation is based on a moving 30-second window average; the threshold moves to maintain the required average percentage of success for inhibition/excitation within that period. Based on the changing window average, the threshold may adjust once every 2 s by 0.2-microvolt increments to the value maintaining success 80% of the time.

Sensorimotor rhythm training sessions consisted of 8 trials of 3 min each, intertrial interval of 30 s, and the whole SMR NFB session lasted

approximately 30 min. The visual display for participants included a puzzle with three bars representing each frequency band. One piece of the puzzle was open, and bars turned green whenever the participant achieved the parameters for 0.5 s, indicating a positive reward. This was reinforced by an auditory stimulus presented as a bell. In addition, by opening subsequent puzzles, the participant could see a numerical reward of the points he or she earned.

The SCP NFB protocol followed previously described methods. Negative/positive SCP trials were equally presented in random order. Each trial lasted for 8 s (2-second baseline period, 6-second feedback period), and intertrial interval was set to 5 ± 1 s [18]. Feedback was calculated from Cz, with reference placed on both earlobes with the EEG-Z3™ preamplified sensor for low frequency (0.01 Hz–1 kHz) and DC (0 Hz–1 kHz) modes. To identify muscle artifact from flickering, a second electrode was placed on the temporal area. Finally, as a reference, the third electrode was placed on Pz. Vertical eye movements, recorded from electrodes above and below the left eye, were corrected online using regression-based algorithms [28]. Artifact thresholds were set to ±100 μV in the EEG channel and ±200 μV in the electrooculogram (EOG) channel. The first 15 of the 75 trials were at a 1:1 channel that inhibited 50% of the stimuli and rewarded 50% of the rest. The objective of this exercise was to allow a learning opportunity for participants to control their inhibition and reward cortical shifts. The channel changed to 3:1 after 15 trials inhibiting 66% and rewarding 33%. Thereafter, the participant learned to inhibit negativity. Each session consisted of 75 trials. The visual display for participants included a balloon moving up the screen when the goal was to activate the stimulus, or a submarine moving down when the goal was to inhibit the stimulus.

The sham NFB was identical to the SMR technique, but consisted of a prerecorded NFB session not contingent to the participant's EEG activity.

2.4. Outcomes

Primary efficacy outcome measures were changes in performance on the attention switching task (AST) and changes in QOL on the Impact of Pediatric Epilepsy Scale (IPES) from baseline to postintervention. Secondary outcomes were seizure frequency, seizure severity, and EEG metrics (defined below). Feasibility was evaluated by recruitment and trial completion rates; safety was monitored by a side effects checklist. All outcomes were recorded at baseline, at the end of the 5-week intervention period, and at the 3-month follow-up.

2.4.1. Attention switching task (AST)

The AST is a computerized task applying principles of the Dimensional Change Card Sort (DCCS) task, which measures the ability to adjust behavior in accordance with changing task goals [29]. We used a modified version of the attention switching task (AST), consisting of 64 trials. The parameters measured are as follows: commission and omission errors, accuracy, as well as switch cost and reaction time for each of the categories — number of letters (even vs. odd numbers) and letter category (vowel vs. consonants). Switch costs are calculated by subtracting reaction time of repeat trials from reaction time of switch trials [30].

Each trial started with a cue presented on the computer screen for 500 ms, which was then replaced by a 2000 ms target. The cue could be either a "+" or a "Δ" sign. If the cue was "+", participants were asked to respond by pressing the "L" key if the subsequent target (i.e., group of letters) consisted of an odd number of letters (i.e., 3 or 5) or by pressing the "A" key if an even number (i.e., 2 or 4 letters). If the cue presented before the target was "Δ", participants should instead respond to vowels by pressing the "A" key, and to consonants by pressing the "L" key. If the cue remained the same for two consecutive trials, it was counted as a repeat trial; if not, it was considered a switch trial. Each cue had a 50% probability of being presented.

Children's performances in an attention switching task indicate increased flexibility in their attentional control during development, whereas selective attention processes may contribute to flexible attention switching. Therefore, the AST can be considered a measurement of both attentional functions [31].

2.4.2. Quality of life (QOL)

We used the Impact of Pediatric Epilepsy Scale (IPES) [32], a validated standardized instrument comprised of 11-items typically used in clinical trials for AEDs. The questionnaire was administerd to the subject's parent or guardian. Each item featured a severity score of 0 (not at all) to 3 (a lot) and included the subdomains of academic improvement, social adaptation, and self-esteem.

2.4.3. Seizure frequency (SF)

A seizure diary was used to evaluate SF. The same parent or guardian recorded detailed seizure-related information over the duration of the study period. The diary registered date, time of day, percieved intensity, duration, and time of any seizure. Seizure frequency extracted from diaries was compared between the postintervention and follow-up timepoints. Baseline SF was not available.

2.4.4. Liverpool Seizure Severity Scale (LSSS)

The LSSS was used to quantify participant perceptions of changed seizure severity patterns during the study period. The LSSS consists of 20 items in two categories: perception of control subscale (8 items) and perceived ictal/postictal severity subscale (12 items). Each item is scored on a 1- to 4-point Likert response scale, depending on the response category (e.g., Item 5 titled *Perceived control over attacks* response category is *very good, fairly good, little control, no control*; Item 19 *Time to full recovery* response category is *<1 min, 1–5 min, 6–60 min, >60 min*) [33].

2.4.5. EEG metrics

Awake EEGs (10 min each for eyes open and closed conditions) were recorded at each time point. Standard EEGs were recorded according to the American Clinical Neurophysiology Society recommendations using the 10/20 International System [34]. Data were sampled at a rate of 256 Hz, amplified, and filtered using a bandpass of 0.3–50 Hz. Electroencephalography tracings were treated as continuous data, and offline analysis included bandpass filtering with a low-pass cut-off of 40 Hz and high-pass of 1 Hz, and manual artifact detection and rejection. Fast Fourier transformation (averaged windows of 5 s with 50% overlap) was used to calculate power (μV^2) for the EEG bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), SMR (12–15 Hz), and beta (15–30 Hz) rhythms. As a measure of connectivity, we used pair-wise coherence for C3-Cz and C4-Cz electrodes. Welch's averaged modified periodogram method was used to find the estimated coherence of signal x and y, representing each electrode site.

2.5. Sampling and blinding

Participants were randomly assigned to the intervention groups using a computerized random number generator. The evaluating physician (D.M.) was blinded and independent from the investigator testing the patients. The technician applying NFB was not blinded but did not collect outcome data. Data collectors, as well as investigators performing data analysis (L.M.Q., D.M., M.E.), were blinded. The EEGs were manually cleaned by D.M., who was blinded.

2.6. Statistical analysis

Statistical analysis was performed with SPSS v.20 software (IBM Corp, New York, NY, 2012). The statistical significance level was defined with two-tailed $p < 0.05$. Confidence intervals were defined at the 95% confidence level. Descriptive statistics (mean, frequency, range, and

percentage) were used to describe sociodemographic variables. A mixed 3 × 3 and 3 × 2 analysis of variance (ANOVA) was used for AST, SF, LSSS, and EEG metrics with treatment group as a between-participant variable with three levels (SMR, SCP, and control) and time as a within-participants variable with either two or three levels depending on the measure (baseline, posttreatment, and follow-up). The AST was divided into four variables: letter category reaction time, letter category error rate, letter counting reaction time, and letter counting error rate. A 3 × 3 mixed ANOVA was conducted on each of the AST variables. The Wilcoxon signed-rank test was used to compare the IPES from baseline to postintervention and follow-up, and the Friedman test for the LSSS ordinal scale to compare results across the three treatment time-points (baseline, postintervention, and follow-up). To evaluate changes in brain activity and cognitive outcomes, a regression analysis was used to examine SMR NFB responders as a dependent variable, with mean absolute power per EEG frequency band and reaction time in the AST as dependent variables. Pearson correlation was applied to assess association between those frequencies showing positive changes as a result of NFB and each of the four AST reaction time variables.

3. Results

In total, 107 patients were assessed for eligibility, and 44 were enrolled and randomized to the experimental interventions and follow-up, with no dropouts and with 100% adherence (Fig. 1 — CONSORT flow diagram). No participants were excluded by changes in their AEDs or dosage during the clinical trial. All participants tolerated the interventions well; there were no side effects in the NFB or sham interventions reported on the session checklists. Tables 1 and 2 detail baseline demographics and disease characteristics. None of the enrolled participants presented with the diagnosis of childhood epilepsy with centrotemporal spikes (CECTS), nor did localization include central regions (Table 2).

Table 1
Demographic characteristics: by sex, mean age in years (SD), localization of epileptic foci (unknown or localized), and antiepileptic drug (AED) management (monotherapy or polytherapy).

	SMR	SCP	Control
Male/female	7/8	9/7	6/7
Age, years (SD)	14.8 (2.33)	14.8 (2.3)	15 (2.3)
Foci unknown/localized	8/7	9/7	6/7
AED mono/poly	9/6	13/3	8/5

3.1. Effects of SMR and SCP on cognitive function

For the AST letter category reaction time, within-group analysis showed a significant main effect of time for SMR [F (2,82) = 7.043, MSE = 4.5, p = 0.006, η_p^2 = 0.147], and for intervention [F (4,82) = 3.319, MSE = 0.652, p = 0.046, η_p^2 = 0.139], there was no significant interaction effect [F (2,82) = 1.35 MSe = 0.352, p = 0.269]. Pairwise within group comparisons of SMR showed significant improvement in the letter category reaction time from baseline to postintervention (−757 msec, p = 0.015) and from baseline to follow-up (−644 msec, p = 0.04) (Fig. 2).

No significant changes were observed for the letter counting reaction time, letter category error rate, letter counting error rate, or switching time (p > 0.05).

3.2. Effects of SMR and SCP on quality of life

Significant improvements were observed in the QOL (IPES) scores for SMR (Z = −3.035, p = 0.002), and this represented a 1.5-point change in the QOL score. The analysis also revealed a significant improvement in the QOL score for SCP (Z = −3.416, p = 0.001), with a change of 1.9 points. For the sham group, the analysis showed a significant improvement in the QOL score (Z = −2.762, p = 0.006), and a

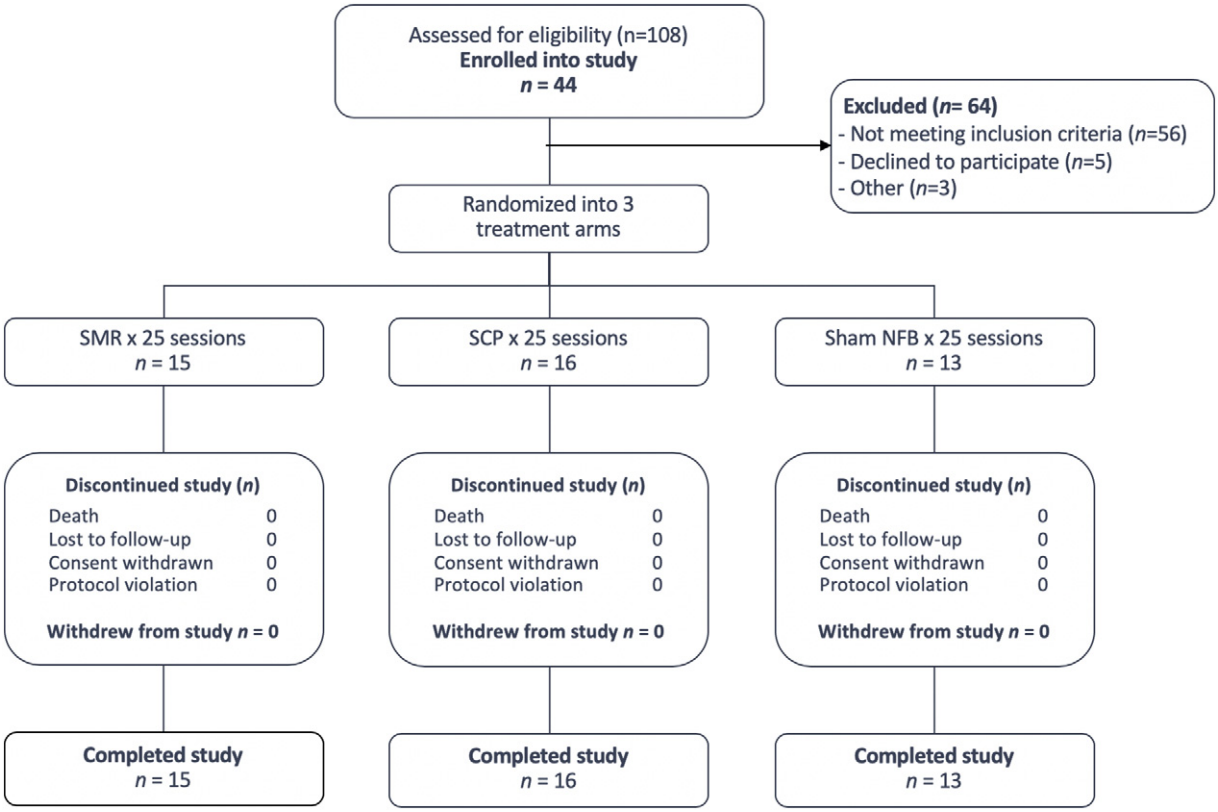

Fig. 1. CONSORT flow diagram. SMR: sensorimotor rhythm; SCP: slow cortical potentials; NFB: neurofeedback. 30 min training × 25 sessions.

Table 2
Individual type of seizures and total AED's dosage per day. Abbreviations: ST: seizure type; CPS: complex partial seizures; TCS: tonic–clonic seizures; AEDs: antiepileptic drugs; CBZ: carbamazepine; OX: oxcarbamazepine; VA: valproic acid; LM: lamotrigine; LV: levetiracetam; DZ: diazepam; PH: phenobarbital; UNK: unknown; TL: temporal left; TR: temporal right; T: temporal; P: parietal.

No.	Condition	Gender	Age	Localization	ST	AED 1	D/24H	AED2	D/24H	AED3	D/24H
1	SMR	M	18	UNK	CPS	NA					
2	SMR	F	15	TL	CPS	CBZ	600	LM	200		
3	SMR	M	13	TL	TCS	OX	600				
4	SMR	F	17	UNK	CPS/TCS	VA	1200	CBZ	900		
5	SCP	F	12	UNK	CPS	VA	1500				
6	SCP	F	13	UNK	CPS/TCS	VA	900	LV	2000	TP	300
7	Control	M	12	TL	CPS	VA	600	LM	200	CBZ	200
8	Control	F	13	UNK	TCS	VA	800				
9	Control	M	16	T/P	CPS/TCS	CBZ	200	LV	1000	DZ	10
10	SMR	F	14	T	CPS	PH	100	LM	100		
11	SCP	M	18	UNK	TCS	LV	1000				
12	SMR	F	12	P	TCS	VA	800				
13	SCP	M	15	T	CPS	VA	1200				
14	Control	M	12	P	TCS	LM	200				
15	SCP	M	12	UNK	CPS	NA					
16	SCP	M	12	T	CPS	PH	800				
17	SMR	M	12	TL	CPS	LV	1000	DZ	10	VA	600
18	SCP	F	12	UNK	TCS	VA	600				
19	Control	F	13	UNK	CPS	VA	800				
20	SMR	M	18	UNK	TCS	VA	800				
21	SMR	F	17	UNK	CPS/TCS	VA	600				
22	SCP	M	14	UNK	TCS	PH	200				
23	SCP	F	15	UNK	CPS	VA	500				
24	SMR	M	16	TL	CPS	VA	1400				
25	Control	F	18	UNK	CPS	VA	400				
26	Control	F	18	UNK	TCS	VA	800				
27	Control	F	14	T	CPS/TCS	VA	600	OX	600	LV	1000
28	SMR	F	18	UNK	CPS	VA	600	LV	1000		
29	SCP	M	18	TL	CPS	LV	1000				
30	Control	M	15	T	CPS	VA	800	PHY	200		
31	SMR	M	13	UNK	CPS	VA	400				
32	SCP	M	16	T	CPS	CBZ	800	DZ	5		
33	SCP	F	14	T	CPS	NA					
34	SMR	F	14	TL	CPS	VA	600	CBZ	100		
35	Control	M	15	T	CPS	LV	1000				
	SCP	M	16	P	TCS	VA	1200	CBZ	400		

(continued on next page)

Table 2 (*continued*)

No.	Condition	Gender	Age	Localization	ST	AED 1	D/24H	AED2	D/24H	AED3	D/24H
36	SMR	M	13	UNK	CPS	PH	200				
37	SCP	M	15	T	CPS	VA	400				
38	Control	F	13	TR	TCS	CBZ	200				
39	SCP	F	18	UNK	CPS	VA	800				
40	SCP	F	18	UNK	CPS	VA	1200				
41	SMR	F	12	UNK	CPS	CBZ	250				
42	Control	F	18	UNK	CPS	VA	600	CBZ	200		
43	Control	M	18	UNK	CPS	CBZ	300				
44											

difference of 1.3 points. The follow-up had the maximum improvement from baseline for all 3 groups. Fig. 3 illustrates the mean IPES by group baseline/follow-up.

3.3. Effects of SMR and SCP on clinical outcomes

There was no significant effect of time ($p = 0.18$) or group ($p = 0.61$), and no significant interaction effect ($p = 0.57$) for any clinical outcome.

There was a trend in the SMR and SCP groups for seizure reduction over time. Seizure frequency difference from postintervention to follow-up showed that SF after SMR dropped by 34.7% from 3.20 ($SD = 1.75$) to 2.10 ($SD = 0.75$); SCP group SF decreased 21.4% from 2.75 ($SD = 1.21$) to 2.16 ($SD = 1.41$); the sham group showed an increase of 11.6% from 2.3 ($SD = 1.87$) to 3 ($SD = 1.26$). In average numbers, the SMR group SF dropped from 3.2 at the end of intervention period to 2.1 by the end of the follow-up, the SCP group from 2.75 to 2.16, and the sham group SF increased from 2.65 to 3.

There were no significant differences in the LSSS in any of the intervention groups: SMR ($\chi^2 = 2.8$, $p = 0.247$), SCP ($\chi^2 = 2.0$, $p = 0.368$), and sham group ($\chi^2 = 2.0$, $p = 0.370$).

3.4. Effects of SMR and SCP on EEG metrics

There was no group or time effect on power for any EEG band (all $ps > 0.05$).

Regarding interhemispheric central coherence (C3-C4), only SMR differed significantly from the other groups, showing a decreased coherence in the beta band for time ($p = 0.04$) and intervention ($p = 0.035$) across all time points (Fig. 4).

3.5. Associations between neurofeedback learning and cognitive function

We performed a post hoc exploratory analysis in the SMR group examining the association between NFB learning and cognitive function (letter category reaction time). We found a correlation between the mean difference per EEG bandwidths between baseline and follow-up using the predefined threshold (theta and beta inhibition and SMR reinforcement) and the mean difference in reaction time between baseline and follow-up for the subjects who learned how to succesfully achieve these thresholds.

Exploratory analysis was done for participants in the SMR group who succesfuly learned how to modulate the theta band. There was a positive correlation between the difference in theta power changes from baseline to follow-up and improvements in reaction time ($r^2 = 0.629$, $p = 0.033$), i.e., the lower the theta power, the shorter the reaction time (Fig. 5). However, the two subjects on the right (outliers who performed extremely well) were driving the results; by removing those two subjects the correlation was still positive (in the same direction) but did not reach significance.

4. Discussion

This study showed that (*i*) SMR has positive effects on reaction time in an attentional task, and that the greater the theta band modulation, the greater the change in cognitive performance (improved reaction times); (*ii*) both active and sham NFB interventions showed significant improvements in the QOL (IPES) assessment; (*iii*) SMR and SCP showed a trend for seizure frequency reduction; and (*iv*) SMR training over the vertex reduced EEG beta coherence.

These findings suggest three important conclusions: 1. SMR can improve cognitive performance in participants with pharmacoresponsive focal epilepsy (specifically attention-related), and these changes may be associated with decreased theta band power over sensorimotor cortices; 2. expectations for the treatment (with elaborate interactions embedded in the trial) and positive motivation generated strong placebo effects on subjective measurements, as seen particularly in QOL measures; and 3. SMR training decreased beta connectivity.

4.1. Neurofeedback, cognitive performance, and neurophysiology

Sensorimotor rhythm significantly reduced AST reaction time, and this effect was maintained through the follow-up period. This change was not seen in the other groups. While learning effect can be problematic in interpreting cognitive behavioral tests, this effect would be difficult to aquire for AST because of its psychometric properties [35]. The use of NFB as an operant conditioning paradigm facilitates cognitive functioning [36–38]. Sensorimotor rhythm training has been associated with enhanced cued recall performance [38] and focused attention in healthy individuals [39]. Both cognitive properties are relevant when performing under AST conditions. For SMR training, recording electrode was placed over the sensorimotor cortex; imaging studies have shown the sensorimotor cortex active during movement, understanding, anticipation, organization, planning, motor response, and inhibition [40]. All these functions relate to attention switching paradigm performance. These results are relevant as children with epilepsy can have problems with reaction time under attention-demanding conditions [41]. Moreover, these functional abnormalities have been associated with the presence of slow EEG activity [42]. Sensorimotor rhythm not only improved reaction time, but also was associated with changes in the theta band, demonstrating an interesting association between behavioral response and neurophysiological modulation — specifically, cognitive function improved with decreased theta slowing. As slowing in the theta and delta range reflect encephalopathy (when generalized) or

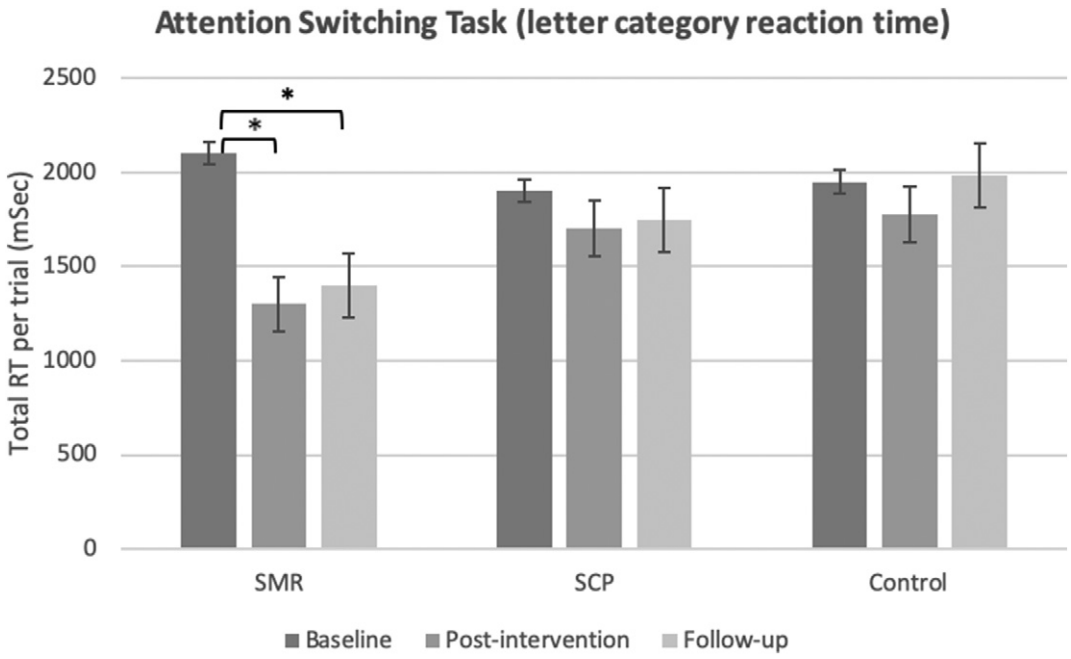

Fig. 2. Total attention switching task reaction time per trial by group, for the letter category variable. Bars indicate standard error of the means. *Statistically significant $p < 0.05$.

focal dysfunction (when focal), this finding is consistent with clinical practice.

Another interesting finding was the decrease in interhemispheric beta coherence over the sensorimotor cortices (C3-Cz-C4) in the SMR group. Increased beta connectivity can be considered the result of persistent disruptive cortical activity that impacts some cognitive functions, as observed in adults with histories of poor academic performance and delayed recall [43]. Moreover, a recent meta-analysis showed that cognitive dysfunction is associated with alterations of functional connectivity within and between neurocognitive networks, particularly hyperconnectivity between the default mode network (DMN), the frontoparietal network (FPN), and the salience network (SN) [44]. By understanding the proposed mechanism of action behind SMR, one can postulate that the decrease observed in beta hyperconnectivity may be the result of enhanced thalamocortical inhibitory transmission and concurrent cortical SMR generation.

4.2. Placebo effect and quality of life

Participants in each group showed significant improvements in QOL as measured by the IPES scale. Perhaps most interesting is the robust effect on QOL in those receiving sham NFB, suggesting the role of nonspecific "placebo effects". Placebo effects have been long recognized in AEDs trials [45] as well as medical device and technology trials [46]. Placebo is often considered the effect of an "inert substance" or "sham intervention", but our study suggests that this characterization is misleading. In a broad sense, placebo effects are improvements in patients' symptoms that are attributable to their participation in the therapeutic encounter (or experimental setting), with its rituals, symbols, and interactions [47]. The influence of the experimental environment, the symbols associated with the intervention, and personal interactions can dramatically enhance the effectiveness of sham interventions in a controlled trial. In fact, this effect has been described to extend to family

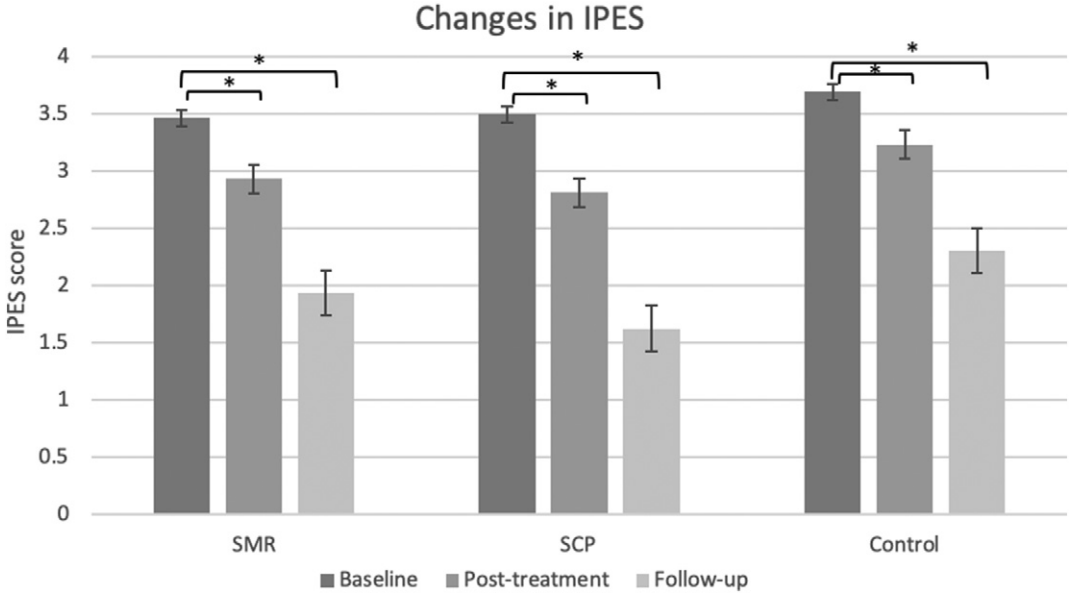

Fig. 3. Mean Impact of Pediatric Epilepsy Scale (IPES) global score from baseline to follow-up by group. Bars indicate standard error of the means. *Statistically significant $p < 0.05$.

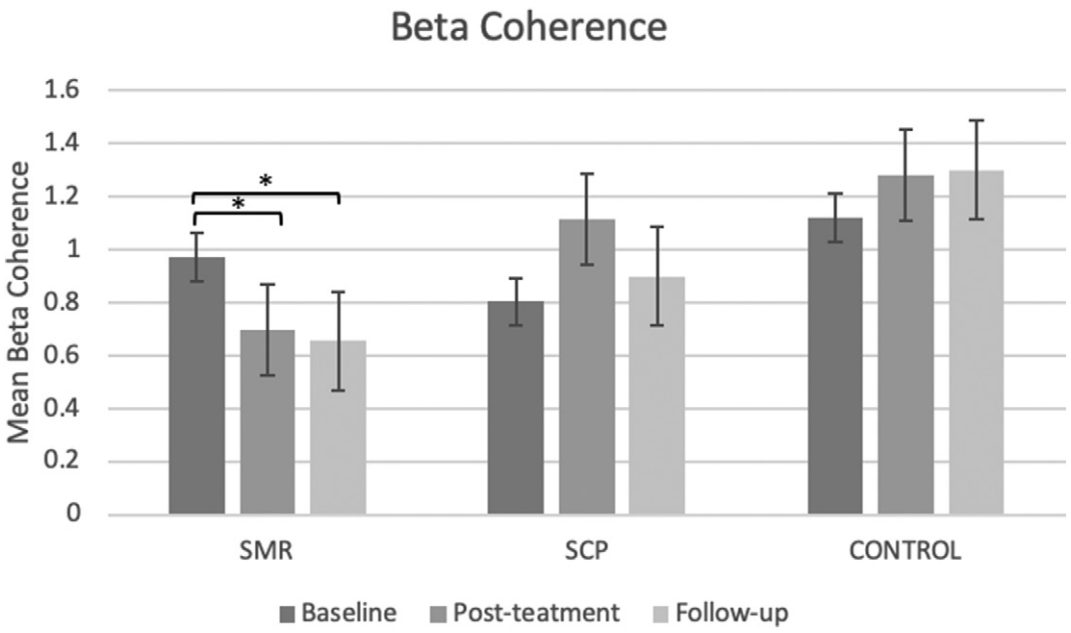

Fig. 4. Mean change in EEG beta coherence (coherence ± SD) per group. Bars indicate standard error of the means. *Statistically significant $p < 0.05$.

members, whereby their feelings and perceptions about the experimental intervention may influence their judgements about effectiveness, and anticipation, excitement, and behavioral changes of family members favor a positive patient response independent of any placebo effect on the patient [48]. Unfortunately, we did not conduct posttrial interviews exploring the parents' and children's perceptions of the trial.

The fact that no participant was lost to follow-up suggests that participants (and parents) might have developed a positive expectancy to the intervention and an attachment to the staff and technicians involved in the experiment as the same technician provided all training sessions. Converging evidence substantiates the view that placebo responses are complex psychoneurobiological phenomena involving the activation of distinct brain areas, particularly those associated with reward, expectations, and anxiety regulation [49]. Associative learning (conditioning) and conscious and nonconscious expectancy formation are the two main psychological mechanisms that contribute to the placebo effect [50]. In this study, it could be argued that both NFB interventions and the sham group carried an especially elaborate ritualistic experience (e.g., electrode placement, EEG traces being displayed, and video game-like interactions). There is evidence suggesting the existence of an enhanced placebo effect for devices and medical procedures; this phenomenon cannot be ignored because of its relevance for the appropriate interpretation of medical technology trials [51].

Surprisingly, participants in the sham group reported improvements in QOL despite no changes in clinical outcomes. This type of in-trial behavior might represent a phenomenon called "experimental subordination" [52] which is driven by the subject's desire to please investigator expectancies. On the other hand, it might also suggest that support groups or group activities with ritualistic elements might improve QOL for patients with epilepsy in broad ways not captured by specific clinical outcomes.

That said, our study showed a trend toward seizure frequency improvement (which is more objective than QOL measures) after the treatment ended toward the follow-up period, where both NFB groups' seizure frequencies somewhat improved while the sham group worsened. This may point to placebo's time-limited effects on neuroplasticity and seizure frequency compared with that of NFB, although our study may have been underpowered to detect significant changes.

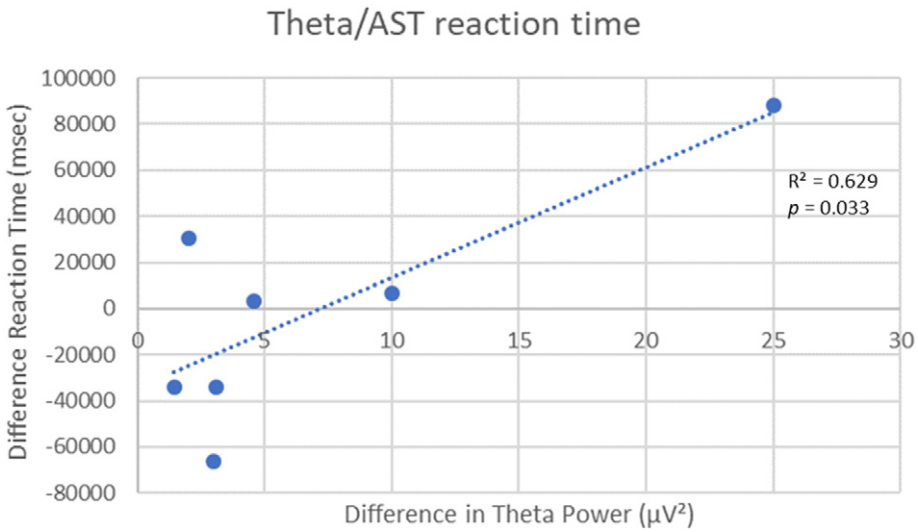

Fig. 5. Scatterplot of positive correlation between the difference of average AST reaction time in msec versus difference in EEG theta power.

4.3. Limitations

The main limiltation of the study is a small sample size which means the trial is best understood as an underpowered exploration, and results should be interpreted cautiously. The lack of clinical efficacy observed in seizure frequency and intensity might be attributable to lack of power due to this limited number of participants and the use of a Likert scale (LSSS) for intensity, especially as a trend for seizure frequency reduction was observed in the SMR group but was less evident for the SCP intervention. Also important to consider is that these subjects had AED-controlled epilepsy, which might obscure the potential benefits of both NFB techniques in reducing ictal activity. Another limitation was the number of sessions in the SCP group. Previous SCP studies averaged 125 trials [53]. In the present study, the training period was 75 trials per session, a modification for feasibility and acceptability based on the expected attention-span in a pediatric population. However, the SCP group may not have had enough training trials to develop the necessary learning and consolidation for an operant conditioned effect on cortical inhibition.

Despite these limitations, this study provides the first data on two NFB modalities (SMR and SCP) including cognitive, neurophysiological, and clinical outcomes in pediatric epilepsy. While all previous NFB investigations in epilepsy focused on adults, our study provides valuable information specifically in children with controlled focal epilepsy. Neurofeedback may be a safe, noninvasive intervention that might be used in conjunction with pharmacotherapy in this population. The results from this trial may be used for power/sample size calculations in future studies; an adequately powered clinical trial might help to elucidate the real impact of NFB on seizure control. Neurofeedback should also be explored further as an integrative treatment for comorbidities associated with pediatric epilepsy.

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Declaration of competing interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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