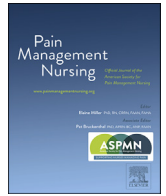




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## Effects of Neurofeedback on Fibromyalgia: A Randomized Controlled Trial

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## ABSTRACT

**Background:** Fibromyalgia is a chronic widespread pain condition that is associated with sleep disturbances and cognitive impairments. Neurofeedback has been demonstrated to improve pain, sleep quality, and fatigue. However, few studies have examined the effect of neurofeedback for patients with fibromyalgia.

**Aim:** To determine the effects of neurofeedback on pain intensity, symptom severity, sleep quality, and cognitive function in patients with fibromyalgia.

**Design:** This study was a randomized controlled trial.

**Method:** Eighty participants were randomized to a neurofeedback group (N = 60), receiving sensorimotor and alpha rhythm feedback for 8 weeks, or a telephone support group (N = 20).

**Results:** Results from the generalized estimating equation modelling revealed significant group-by-time interactions for Brief Pain Inventory pain severity ( $B = -1.35$ ,  $SE = 0.46$ ,  $p = .003$ ) and pain interference ( $B = -1.75$ ,  $SE = 0.41$ ,  $p < .001$ ), Revised Fibromyalgia Impact Questionnaire total scores ( $B = -16.41$ ,  $SE = 3.76$ ,  $p < .001$ ), sleep onset latency ( $B = -25.33$ ,  $SE = 9.02$ ,  $p = .005$ ), and Psychomotor Vigilance Test error ( $B = -1.38$ ,  $SE = 0.55$ ,  $p = .013$ ) after adjustments for age, sex, duration of illness, and group differences at baseline.

**Conclusions:** An 8-week neurofeedback training regimen of sensorimotor rhythm and alpha brain waves significantly improved pain severity and interference, fibromyalgia symptom severity, sleep latency, and sustained attention in patients with fibromyalgia.

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Fibromyalgia is a condition characterized by widespread pain (Wolfe et al., 1990), memory problems, sleep disturbances (Wu et al., 2017), and cognitive impairment (Wu et al., 2018). Fibromyalgia frequently co-occurs with irritable bowel syndrome (Moshiree et al., 2007), fatigue, depression, anxiety disorders (Anderson et al., 2012; Arnold et al., 2006; Miro et al., 2015), and

poor quality of life (Jacobson et al., 2014). Moreover, patients with fibromyalgia exhibit significantly higher risks of coronary heart disease events (Tsai et al., 2015) and mortality (Andersson, 2004) compared with people without fibromyalgia.

Effective treatments for fibromyalgia are lacking. Pharmacologic agents, such as serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and gabapentinoids, have only moderate efficacy, and pure opioids have not shown promising effects in patients with fibromyalgia (Northcott, Guymmer, & Littlejohn, 2017). Nonpharmacologic treatments are favored over pharmacologic

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therapies (Clauw, 2009, 2014; Theoharides et al., 2015) because pharmacologic therapies can cause severe adverse effects (Häuser et al., 2012; Straube et al., 2010). Neurofeedback, known as electroencephalographic biofeedback, teaches individuals to self-regulate their brain waves and intervenes at the central nervous system level (Chiang & Kang, 2012). As the pathophysiologic mechanisms that are involved in the etiology of fibromyalgia include central sensitization with dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis (Desmeules et al., 2003; Yunus, 2007), neurofeedback may potentially be a treatment option.

Decreased alpha brain waves and increased beta and theta brain waves were found in patients with chronic pain (Jensen et al., 2013). Alpha neurofeedback training has been demonstrated to reduce anxiety (Plotkin and Rice, 1981), improve cognitive processing speed (Angelakis et al., 2007), and improve executive function performance (Angelakis et al., 2007; Hanslmayr et al., 2005; Zoefel et al., 2011). Brain wave recordings over the sensorimotor cortex (involving both the sensory and motor cortical areas) revealed a markedly distinctive oscillatory pattern in a frequency range of 12–15 Hz, which is termed sensorimotor rhythm (SMR) (Chiang & Kang, 2012; Howe & Sterman, 1972; Sterman & Wyrwicka, 1967). SMR training significantly improves sleep, cognitive function, learning, and memory in healthy individuals and patients with insomnia (Hoedlmoser et al., 2008; Schabus et al., 2014). A previous randomized controlled trial (RCT) reported significant improvements in pain, fatigue, depression, anxiety, fibromyalgia symptom severity, and health-related quality of life following SMR neurofeedback among women with fibromyalgia (Kayiran et al., 2010). However, the study by Kayiran et al. (2010) investigated a small, all-female sample.

Given that the effect of alpha neurofeedback has not been investigated in patients with fibromyalgia and that the effects of neurofeedback on sleep and cognitive function have not been investigated in patients with fibromyalgia, further investigations in this population are warranted. Because pain is bidirectionally associated with both sleep (Aili et al., 2015) and cognitive function (Attal et al., 2014), we hypothesized that SMR and alpha wave neurofeedback training would improve sleep quality and cognitive function, which would in turn reduce pain and symptom severity in patients with fibromyalgia. This parallel-group, RCT evaluated the effects of neurofeedback on pain intensity, symptom severity, sleep quality, and cognitive function among men and women with fibromyalgia.

## Materials and Methods

This was a single-center, parallel-group, assessor-blind RCT. This study was approved by the relevant institutional review board (JIRB N201604055). The full protocol of the trial is available online ([http://my2.tmu.edu.tw/blog.php?user=ptsai&f=blog\\_doc&bid=149854](http://my2.tmu.edu.tw/blog.php?user=ptsai&f=blog_doc&bid=149854)). Each participant provided informed consent before participating in the study.

### Participants and Settings

Data collection and neurofeedback training were performed at the biobehavior laboratory of a university in Northern Taiwan.

Participants were recruited by referral from physicians. Participants were eligible for the study if they were 18 years or older and were diagnosed as having fibromyalgia according to the 2010 American College of Rheumatology criteria for fibromyalgia (Wolfe et al., 2011). Individuals were excluded based on the following criteria: (1) shift work (work that takes place outside traditional daytime hours, including evening, night, and rotating shifts); (2)

medical history of head injury or neurological disorder; (3) present psychopathologic disorder; (4) malignant neoplasm; or (5) pregnancy. The Polysymptomatic Distress Scale (PDS [Wolfe et al., 2011]; was used during a run-in period to confirm the diagnosis of fibromyalgia. A PDS score of  $\geq 13$  was selected as the cut-off score. Therefore, individuals with fibromyalgia were excluded if they had a PDS score  $< 13$ .

### Primary and Secondary Outcomes

The primary outcomes were Brief Pain Inventory (BPI) scores and Fibromyalgia Impact Questionnaire-Revised (FIQR) scores, which were measured before and after treatment. The secondary outcomes were sleep quality and cognitive function, which were measured before and after the treatment period.

### Sample Size

The sample size was estimated based on the expected treatment effect size for the primary outcome. The treatment effect size of neurofeedback training on pain reduction in the eighth week in patients with fibromyalgia is reportedly 1.166 (Kayiran et al., 2010). Assuming a type I error of 0.05, a type II error of 0.1, and an effect size of 1.166, having 16 participants per group achieves a 0.9 power with a 2-sided test, according to a power analysis. Although a total of 32 participants would achieve a power of 0.9, 80 participants were enrolled to allow for subgroup analyses and a 25% dropout rate. A 3:1 ratio was used for enrolling patients in the neurofeedback and control groups. Therefore, 60 patients and 20 patients were enrolled in the neurofeedback and control groups, respectively.

### Randomization Sequence Generation, Concealment, and Blinding

After written consent was obtained and baseline measurements were completed, eligible participants were randomly assigned in a 3:1 ratio using permuted blocks of four assigned to a neurofeedback group ( $n = 60$ ) and a control group ( $n = 20$ ). We adopted an unequal randomization scheme because it enables better recruitment (Lim & In, 2019). An independent research assistant who was not involved in participant recruitment, enrolment, or data collection generated randomization sequences using computerized software. The generated random sequence was concealed in sequentially numbered, opaque envelopes until assigned to participants. To minimize detection bias, an independent research assistant who was blinded to the group assignment collected baseline and post-test data.

### Measurements

#### Baseline Demographics

Baseline demographics and comorbidities included age, sex, body weight, body height, medical history related to fibromyalgia, years of education, marital status, use of pharmacologic therapies, and use of complementary therapies.

#### BPI Short-Form

The BPI-Short Form (BPI-SF) assesses pain in several contexts: worst pain, least pain, average pain, and current pain, graded on a 0–10 scale (Cleeland & Ryan, 1994). A Chinese version of the BPI was used; the coefficient alpha for internal reliability was 0.81 for the severity scale and 0.89 for the interference scale (Ger et al., 1999). The convergent validity of BPI pain severity and pain interference has been demonstrated in patients with cancer (Ger et al., 1999).

For this study, the BPI severity and interference scores were calculated.

#### FIQR

The FIQR is an instrument that assesses the current health status of patients with fibromyalgia in clinical and research settings. This questionnaire comprises three domains: physical function, overall effect of fibromyalgia, and fibromyalgia symptoms (pain, fatigue, unrefreshing sleep, stiffness, anxiety, depression, tenderness to touch, memory, balance, and environmental sensitivity) (Bennett et al., 2009). All 21 questions are graded on a 0-10 numeric scale (no difficulty to very difficult). A higher FIQR score indicates greater symptom severity (Bennett, 2005). The intraclass correlation coefficient for test-retest reliability was 0.91 for the FIQR total score, with a range of 0.84-0.90 in three domains: function, overall impact, and symptoms (Isomura et al., 2017). Internal consistency was demonstrated by a Cronbach's alpha of 0.90 for the total score, with a range of 0.83 and 0.85 for the domains (Isomura et al., 2017). The FIQR total score and three FIQR domain scores exhibited satisfactory concurrent validity when validated with comparable domains in the 36-Item Short-Form Health Survey (Bennett et al., 2009).

#### Sleep Quality: Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a self-report measure of sleep quality. The scale is composed of seven components: subjective quality of sleep, sleep onset latency (SOL, minutes), total sleep time, habitual sleep efficiency, sleep disorders, use of sleeping medication, and daytime dysfunction (Buysse et al., 1989). Each component is scored from 0 to 3, with a higher score indicating poorer sleep quality. The summed score of all components ranges from 0 to 21, with optimal sleeping profiles being closest to 0. A global PSQI score  $>5$  yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% ( $\kappa = 0.75$ ,  $p < .001$ ) and test-retest reliability in distinguishing good and poor sleepers (Buysse et al., 1989). The Chinese version of the PSQI, which has been previously validated in a primary care population, was employed. The global score and seven component scores of the Chinese version of the PSQI revealed satisfactory test-retest reliability and demonstrated satisfactory discriminant validity among individuals with primary insomnia (Tsai et al., 2005). A meta-analysis revealed that patients with fibromyalgia had longer subjective SOL (Wu et al., 2017); thus, SOL score was also selected as an outcome in this study.

#### Cognitive Function: Psychomotor Vigilance Test

The standard 3-minute Psychomotor Vigilance Test (PVT) measures of sustained or vigilant attention were performed by recording the response time to visual stimuli, occurring at random inter stimulus intervals. Participants were told to press the start button and single click on the box as soon as possible after the red numbers appear in the box. The red numbers appeared at random times and remain for 2-10 seconds. The 3-minute PVT is reliable, with intraclass correlations and test-retest reliability scores of over 0.8 (Dorrian et al., 2005). The PVT is sensitive and specific to sleep loss (Basner & Dinges, 2011). The mean PVT reaction time (RT) and PVT error (number of false starts) were used in this study.

#### Cognitive Function: Digit Span Test

The Digit Span Tests (DSTs) employed were the Digit Span Forward and the Digit Span Backward tests which were used to assess working memory performance. The longest correct scores were used as measures, with a range of 0-9 for the Digit Span Forward test and 0-8 for the Digit Span Backward test (Wechsler, Coalson, & Raiford, 1997).

## Intervention

### Neurofeedback Training Conditions

Each participant in the neurofeedback group received 20 sessions (600 minutes) of neurofeedback training over an 8-week period. Each treatment session (30 minutes) consisted of 10 trials of neurofeedback enhancement using a ProComp Infinity biofeedback device (Thought Technology Ltd., Toronto, Canada), and each trial lasted for 3 minutes. Electrodes were placed on the C3, C4, and Cz positions for brainwave recording. The thresholds for neurofeedback were initially based on the baseline measurement from the first session. The following formulas were used for SMR training: mean amplitude + (standard deviation/4) for reinforcing SMR, and mean amplitude + (standard deviation/2) for inhibiting theta and beta wave (Cortooos et al., 2010). During each neurofeedback enhancement trial, the participants were told to relax and concentrate on a computer-animated game, which was designed to discontinue if brain wave amplitudes were outside the desired range. Both visual and audio indicators were displayed, as rewards to condition the participants' achievements of control over their electroencephalography (EEG; i.e., achieving the predetermined goals for brain wave amplitudes).

During the first 2 weeks, the participants received four sessions of alpha wave neurofeedback training, during which they were instructed to enhance 8-12 Hz brain waves. Subsequently, the participants attended 12 sessions of SMR wave training during a 4-week period. For SMR training, the participants were taught to enhance 12-15 Hz brain waves and simultaneously inhibit theta (4-7 Hz) and beta (18-22 Hz) brain waves. In the last four sessions over the last 2 weeks, the participants chose to receive either alpha wave or SMR wave training according to their preference. In addition to neurofeedback training, educational materials regarding fibromyalgia were provided to the neurofeedback group.

### Control Condition

To reduce attrition, participants in the control group were provided with educational materials regarding fibromyalgia. To determine the specific treatment effects of neurofeedback, we adopted an attention-control condition. The attention-control condition consisted of weekly telephone support during the 8-week treatment period. The telephone conversation was semi-structured and prescribed to focus on the participant's knowledge regarding the disease, their symptoms, and their concerns. Each telephone call lasted approximately 10 minutes, with 5 minutes of questions and answers regarding the educational materials and a 5-minute debriefing. The educational materials were obtained from <https://www.pfizer.com.tw/mediacalinfo/2010/27/index.html>.

### Treatment Fidelity

All treatment sessions were conducted by one intervener who was an experienced nurse with a Master's degree in Nursing. The intervener was trained and certified by the principal investigator who is a certified biofeedback therapist to deliver the intervention. Before working with the participant, the intervener conducted a practice session with the principal investigator after the training. A manual was developed to detail operating procedures for collected data, intervention, and outcome assessment. Specifically, for ensuring treatment fidelity, a treatment manual detailing essential treatment components with a corresponding checklist of adherence to neurofeedback protocol was used. The intervener was required to complete the checklist of adherence to neurofeedback protocol and to record the treatment duration in minutes for each and every treatment session.

### Study Procedures and Data Collection

Patients who satisfied the eligibility criteria were placed on the waiting list and entered a 1-week run-in period during which PDS scores were assessed. Patients who scored 13 and above on the PDS were enrolled in the study. The baseline measurements included demographics, pain (i.e., BPI), fibromyalgia symptom severity (i.e., FIQR), sleep quality (PSQI), and cognitive function (i.e., PVT and DST). After the 8-week neurofeedback training period, all participants participated in a posttest session, during which measurements of pain, fibromyalgia symptom severity, sleep quality, and cognitive function were assessed. All baseline and posttest measurements were analyzed by assessors who were blinded to the participants' group assignments.

### Statistical Analyses

Differences in baseline data were determined using Mann–Whitney U-tests, chi-squared tests, and *t* tests for independent samples. Comparisons of group means at baseline, posttest one, and posttest two for normally distributed primary and secondary outcomes were performed using independent *t* tests. The effect size (Cohen's *d*) was calculated for each outcome variable.

An intention-to-treat analysis was performed to determine the effectiveness of neurofeedback training. All unavailable posttest values were imputed using the mean imputation method. The between-group differences in outcome variables at baseline and posttest were examined using an independent *t* test. The treatment

effect sizes for all outcome variables were estimated by calculating Cohen's *d* for the pretest-to-posttest change scores.

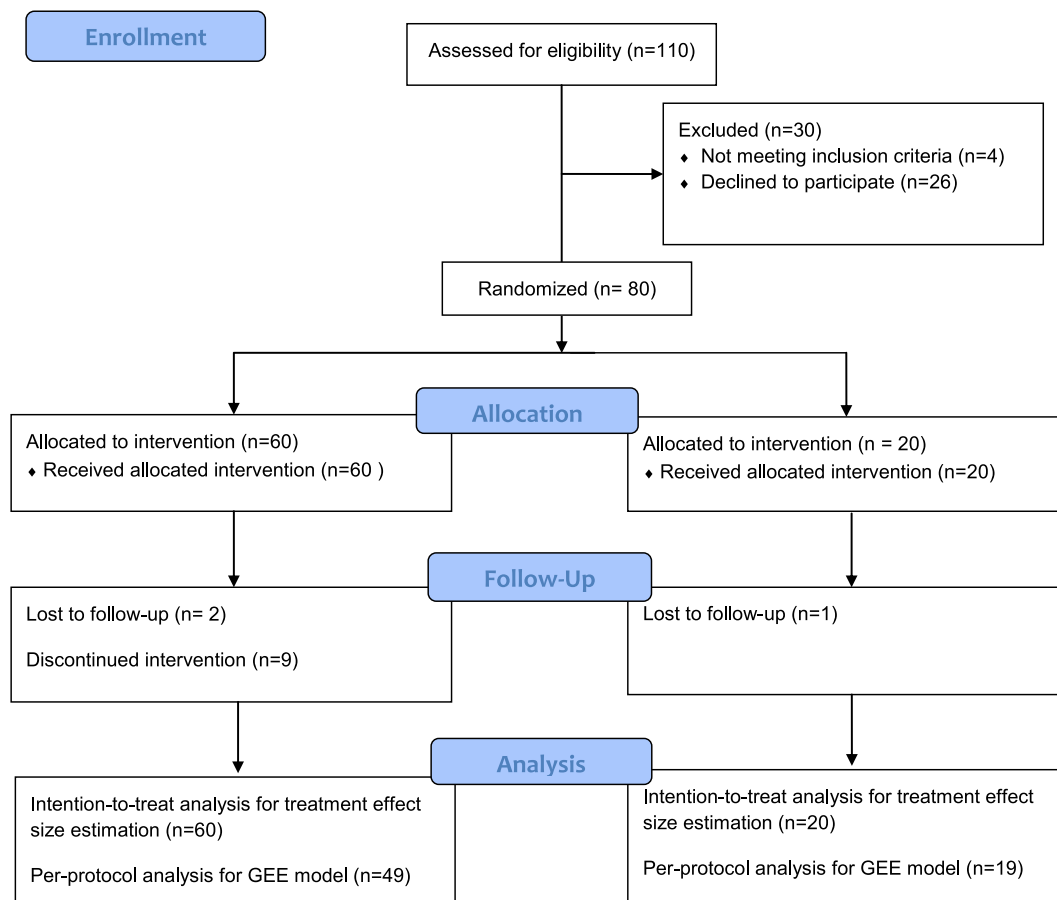
To determine the efficacy of neurofeedback training on primary and secondary outcomes, the differences in outcome variables were analyzed using a generalized estimating equation (GEE) through per-protocol analysis. The outcome variables were adjusted for baseline scores and for demographics and comorbidities that differed significantly at baseline. The baseline Beck Anxiety Inventory score was also adjusted in the GEE model because of its possible effects on outcomes.

### Results

#### Demographics Variables Between Neurofeedback and Control Groups

The flow chart in [Figure 1](#) indicates the number of participants who were screened and considered eligible for the study, the number of those who withdrew, and the reasons for withdrawal. A total of 80 patients with fibromyalgia aged 21 to 82 (mean = 47, SD = 13.1) participated in the study. As can be seen in [Table 1](#), the majority of the participants in both groups were female with a college level education or higher. No significant differences were identified in the demographic variables ( $p > .05$  for all) between groups, except that the percentage of female participants was higher in the neurofeedback group ( $p = .006$ ); the results are reported in [Table 1](#).

Of the 80 participants recruited, 68 (85%) completed the study. The attrition rate was not significantly different between the two



**Figure 1.** Consort flow chart. GEE = generalized estimating equation.



**Table 1**  
Baseline Characteristics of Participants and Controls Between the Neurofeedback and Control Groups

Demographic Variables	NFG		CG		p
	n = 60		n = 20		
	n	%	n	%	
Age (mean ± SD)	48.6	13.5	42.2	10.9	.055
Female	57	95.0	14	70.0	.006
BMI (mean ± SD)	21.9	3.9	23.8	5.1	.094
Duration of pain (years; mean ± SD)	9.8	12.1	8.7	7.6	.644
Duration since FMS diagnosis (month; mean ± SD)	28.2	36.3	26.9	31.3	.879
Education					
≤ High school	16	26.7	6	30.0	.793
College	39	65.0	11	55.0	
≥ Graduate school	5	8.3	3	15.0	
Marital status, n (%)					
No	18	30.0	10	50	.239
Yes	35	58.3	9	45	
Divorced	7	11.7	1	5	
Medical history					
CHD	6	7.5	4	20.0	.242
Insomnia	3	3.8	0	0.0	.569
Depression	21	26.3	4	20.0	.272
Anxiety	7	8.8	2	10.0	.838
Panic	2	2.5	0	0.0	.560
Dry eyes	3	3.8	0	0.0	.308
Migraine	1	1.3	1	5.0	.380
Rheumatic disease	4	5.0	1	5.0	1.0
BAI (mean ± SD)	22.5	12.7	20.9	12.9	.610
BDI (mean ± SD)	21.1	13.2	19.8	14.0	.720
Medication history					a
Analgesics	14	23.3	6	30.0	.190
Topamax	32	53.3	9	45.0	.250
Pregabalin (Lyrica)	27	45.0	7	35.0	.155
Clonazepam (Rivotril)	5	8.3	1	5.0	.364
Antidepressants	15	25.0	3	15.0	.538
Complementary hypnotic therapy	16	26.7	7	35.0	.170
Acupuncture	10	12.5	0	0.0	.059
Rehabilitation	9	11.3	0	0.0	.103
Traditional Chinese medicine	13	16.3	4	20.0	1.0

FMS = Fibromyalgia; NFG = Neurofeedback group; CG = Control group; BMI = Body mass index; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory.

groups. With the exception of unavailable posttest values resulted from attrition, the data of the participants who retained in the study was intact. All demographic and baseline data were not significantly different between participants who withdrew from the study ( $N = 12$ ) and those who retained in the study ( $N = 68$ ) (all  $p > .05$ ; data not shown). The participants in the neurofeedback group received, on average, 17.9 ( $SD = 1.8$ ) treatment sessions, with a mean total length of 539.5 minutes ( $SD = 53.3$ ); 49 participants (81.7%) in the neurofeedback group completed the 20 training sessions.

#### Between-Group Differences in Primary Outcomes at Baseline and Posttest

We determined the differences in primary outcomes between groups at baseline and posttest as well as the change in score from baseline to posttest (Table 2). As can be seen in Table 2, the change scores of BPI pain severity, BPI pain interference, FIQR total score, FIQR function domain score, and FIQR symptom domain score were significantly higher in the neurofeedback group compared with the control group (Cohen's  $d = -0.83, -0.96, -1.05, -0.61, \text{ and } -1.18$ , respectively).

#### Between-Group Differences in Secondary Outcomes at Baseline and Posttest

Table 3 summarizes the between-group differences in sleep quality and cognitive function at baseline and posttest.

At baseline, the SOL in the neurofeedback group ( $51.42 \pm 58.78$  minutes) was significantly longer than in the control group ( $27.50 \pm 18.53$  minutes;  $p = .007$ ). The change score of the PSQI was not significantly different between groups ( $p = .406$ , respectively), whereas the change score of SOL was significantly higher in the neurofeedback group than in the control group ( $p = .006$ ).

Of the four cognitive function measures, only PVT error, a measure of sustained attention, was significantly different between groups at baseline ( $p = .007$ ). The change score of PVT error differed significantly between groups ( $p = .028$ ).

#### Efficacy of Neurofeedback for Fibromyalgia

We used the GEE model to examine the efficacy of neurofeedback training on reducing pain and fibromyalgia symptom severity and improving sleep quality and cognitive function after adjustment for age, sex, duration of diagnosis, baseline Beck Anxiety Inventory, and outcome baseline scores with significant group differences (Table 4). The results of the GEE analyses revealed a significant group effect ( $B = 1.78, SE = 0.82, p = .030$ ), and a significant group-by-time interaction effect on the BPI pain severity score ( $B = -1.35, SE = 0.46, p = .003$ ). The GEE analyses revealed significant time ( $B = 1.50, SE = 0.61, p = .014$ ), group ( $B = 2.06, SE = 0.78, p = .008$ ), and group-by-time interaction ( $B = -1.75, SE = 0.41, p < .001$ ) effects on the BPI pain interference score.

The GEE analyses revealed significant time ( $B = 14.95, SE = 6.20, p = .016$ ), group ( $B = 21.42, SE = 5.96, p < .001$ ), and group-by-time

**Table 2**  
Pain Levels and Fibromyalgia Symptoms Between the Two Groups (NFG, n = 60; CG, n = 20)

	Group		Difference Between Means		Treatment Effect Size
	NFG	CG	(95% CI)	<i>p</i>	Cohen's <i>d</i>
<b>BPI pain severity</b>					
Baseline	5.16 ± 1.77	4.40 ± 2.09	-0.19 to 1.72	.115	
Posttest	3.80 ± 1.80	4.24 ± 1.67	-1.39 to 0.52	.370	
Change score	-1.41 ± 1.52	-0.01 ± 1.84	-2.27 to -0.52	.002	-0.83
Effect size	0.76	0.08			
<b>BPI pain interference</b>					
Baseline	5.81 ± 2.21	5.11 ± 3.26	-0.91 to 2.31	.379	
Posttest	4.02 ± 2.71	4.72 ± 3.17	-2.24 to 0.83	.362	
Change score	-2.00 ± 2.29	-0.26 ± 1.18	-2.60 to -0.90	<.001	-0.96
Effect size	0.72	0.12			
<b>FIQR total score</b>					
Baseline	55.08 ± 17.69	47.30 ± 23.12	-2.06 to 17.63	.120	
Posttest	38.39 ± 23.36	44.63 ± 20.91	-18.50 to 6.01	.313	
Change score	-17.53 ± 17.29	-1.47 ± 12.83	-24.80 to -7.32	.001	-1.05
Effect size	0.37	0.06			
<b>FIQR function</b>					
Baseline	34.35 ± 22.77	25.65 ± 25.42	-3.35 to 20.75	.155	
Posttest	22.59 ± 22.25	24.68 ± 22.17	-14.09 to 9.90	.729	
Change score	-11.06 ± 21.38	0.32 ± 15.40	-22.78 to -0.62	.038	-0.61
Effect size	0.25	0.02			
<b>Overall FIQR</b>					
Baseline	10.65 ± 6.49	9.65 ± 6.88	-2.39 to 4.39	.558	
Posttest	7.88 ± 6.71	9.00 ± 6.78	-4.76 to 2.51	.539	
Change score	-2.96 ± 4.93	-0.37 ± 4.97	-5.26 to 0.08	.057	-0.52
Effect size	0.21	0.05			
<b>FIQR symptoms</b>					
Baseline	65.73 ± 15.91	58.15 ± 21.19	-1.33 to 16.50	.094	
Posttest	45.86 ± 22.56	54.63 ± 19.27	-20.49 to 2.94	.140	
Change score	-21.69 ± 20.67	-2.58 ± 9.76	-29.02 to -9.21	<.001	-1.18
Effect size	0.45	0.09			

NFG = Neurofeedback group; CG = Control group; BPI = Brief Pain Index; FIQR = Revised Fibromyalgia Impact Questionnaire.

**Table 3**  
Differences in Sleep Quality and Cognitive Function Outcome Variables Between Groups (NFG, n = 60; CG, n = 20)

	Group		Difference Between Means		Treatment Effect Size
	NFG	CG	(95% CI)	<i>p</i>	Cohen's <i>d</i>
<b>Sleep quality</b>					
<b>PSQI</b>					
Baseline	14.40 ± 3.93	12.20 ± 4.07	-1.33 to 2.62	.516	
Posttest	13.75 ± 3.45	12.05 ± 3.63	-1.98 to 2.29	.888	
Change score	-2.29 ± 3.11	-1.58 ± 3.24	-2.41 to 0.99	.406	-0.22
Effect size	0.09	0.02			
<b>SOL (minutes)</b>					
Baseline	51.42 ± 58.78	27.50 ± 18.53	6.59 to 41.25	.007	
Posttest	31.03 ± 29.35	31.68 ± 32.60	-16.99 to 15.68	.937	
Change score	-24.65 ± 56.12	3.56 ± 25.03	-54.95 to -1.14	.006	-0.65
Effect size	-0.12	-0.08			
<b>Cognitive function</b>					
<b>DST forward</b>					
Baseline	8.78 ± 0.58	9.95 ± 0.22	-0.43 to 0.10	.070	
Posttest	8.84 ± 0.51	8.89 ± 0.46	-0.33 to 0.21	.669	
Change score	0.10 ± 0.47	-0.05 ± 0.52	-0.11 to 0.42	.241	0.31
Effect size					
<b>DST backward</b>					
Baseline	5.72 ± 1.72	6.60 ± 1.73	-1.77 to 0.01	.050	
Posttest	6.00 ± 1.66	6.79 ± 1.58	-1.67 to 0.09	.079	
Change score	0.39 ± 1.60	0.16 ± 1.39	-0.61 to 1.07	.585	0.15
Effect size	-0.08	-0.06			
<b>PVT reaction time</b>					
Baseline	369.80 ± 220.60	334.20 ± 87.74	-63.60 to 138.50	.282	
Posttest	313.20 ± 68.20	311.30 ± 58.07	-34.20 to 38.14	.914	
Change score	-71.02 ± 232.5	-20.75 ± 49.42	-161.1 to 60.60	.159	-0.30
Effect size	0.17	0.15			
<b>PVT error</b>					
Baseline	5.82 ± 0.37	5.78 ± 0.22	0.37 to 2.21	.007	
Posttest	5.73 ± 0.20	5.73 ± 0.17	-0.48 to 0.58	.858	
Change score	-0.12 ± 0.36	-0.05 ± 0.13	-2.70 to 0.16	.028	-0.47
Effect size	0.15	0.13			

NFG = neurofeedback group; CG = control group; PSQI = Pittsburgh Sleep Quality Index; SOL = sleep onset latency; DST = Digit Span Test; PVT = Psychomotor Vigilance Test.

**Table 4**  
Effects of the Neurofeedback Intervention on Outcome Variables (GEE Model) (NFG, n = 49; CG, n = 19)

	B	SE	(95% CI)	p
BPI—pain severity				
Posttest	1.30	0.84	−0.35 to 2.95	.123
NFG	1.78	0.82	0.17 to 3.38	.030
Group × time	−1.35	0.46	−2.26 to −0.45	.003
BPI—pain interference				
Posttest	1.50	0.61	0.30 to 2.69	.014
NFG	2.06	0.78	0.54 to 3.58	.008
Group × time	−1.75	0.41	−2.55 to −0.94	<.001
FIQR total score				
Posttest	14.95	6.20	2.79 to 27.11	.016
NFG	21.42	5.96	9.75 to 33.09	<.001
Group × time	−16.41	3.76	−23.79 to −9.03	<.001
PSQI				
Posttest	−0.77	1.51	−3.73 to 2.19	.611
NFG	1.11	1.26	−1.36 to 3.58	.378
Group × time	−0.81	0.85	−2.47 to 0.85	.339
SOL <sup>a</sup>				
Posttest	29.89	13.55	3.33 to 56.46	.027
NFG	33.65	11.68	10.76 to 56.54	.004
Group × time	−25.33	9.02	−43.00 to −7.65	.005
DST forward				
Posttest	−0.19	0.24	−0.66 to 0.28	.427
NFG	−0.24	0.18	−0.60 to 0.12	.193
Group × time	0.14	0.13	−0.12 to 0.40	.284
DST backward				
Posttest	−0.03	0.65	−1.31 to 1.25	.961
NFG	−0.73	0.73	−2.17 to 0.71	.318
Group × time	0.21	0.38	−0.53 to 0.96	.573
PVT reaction time				
Posttest	36.52	37.64	−37.26 to 110.30	.332
NFG	77.46	67.30	−54.44 to 209.36	.250
Group × time	−52.02	31.58	−113.91 to 9.87	.100
PVT error <sup>b</sup>				
Posttest	2.02	0.68	0.69 to 3.35	.003
NFG	2.01	0.79	0.47 to 3.55	.011
Group × time	−1.38	0.55	−2.46 to −0.29	.013

GEE = generalized estimating equation; NFG = neurofeedback group; CG = control group; BPI = Brief Pain Index; PSQI = Pittsburgh Sleep Quality Index; FIQR = Revised Fibromyalgia Impact Questionnaire; SOL = sleep onset latency; DST = Digit Span Test; PVT = Psychomotor Vigilance Test; BAI = Beck Anxiety Inventory. Controlled for age, sex, duration of diagnosis, and baseline BAI score in the GEE model.

<sup>a</sup> Also controlled baseline SOL.

<sup>b</sup> Also controlled baseline PVT error.

interaction ( $B = -16.41$ ,  $SE = 3.76$ ,  $p < .001$ ) effects on the total FIQR score.

For the PSQI global score, no significant time effects, group effects, or group-by-time interaction effects were observed on the PSQI global score ( $p > .05$  for all). For the SOL, the GEE analyses revealed significant time ( $B = 29.89$ ,  $SE = 13.55$ ,  $p = .027$ ), group ( $B = 33.65$ ,  $SE = 11.68$ ,  $p = .004$ ), and group-by-time interaction ( $B = -25.33$ ,  $SE = 9.02$ ,  $p = .005$ ) effects on SOL.

The GEE analyses revealed a significant time effect ( $B = 2.02$ ,  $SE = 0.68$ ,  $p = .003$ ), group effect ( $B = 2.01$ ,  $SE = 0.79$ ,  $p = .011$ ), and group-by-time interaction effect ( $B = -1.38$ ,  $SE = 0.55$ ,  $p = .013$ ) on PVT error. The results of the GEE analyses are reported in Table 4.

## Discussion and Conclusion

The present study revealed that patients with fibromyalgia who received neurofeedback training exhibited significantly greater improvements in pain severity, pain interference, fibromyalgia symptom severity, sleep latency, and sustained attention compared with patients in the control group.

Neurofeedback is a training method for the self-regulation of brainwaves using EEG feedback signals (Chiang & Kang, 2012) and

can be used to reduce the severity of pain and pain-associated symptoms in patients with chronic pain (Patel et al., 2020). Our neurofeedback training protocol focused on two types of brain wave: SMR and alpha waves. SMR waves are associated with a calm body but an active mind, which is often depressed and affected by anxiety, panic, chronic pain, migraine, and attention-deficit disorders (Egner et al., 2004; Reiner, 2008). Alpha waves are beneficial for relaxation and self-regulation (Chiang & Kang, 2012). Studies have reported that SMR neurofeedback was efficacious for reducing the frequency of headaches among patients prone to migraines (Stokes & Lappin, 2010) and in improving sleep and cognitive function among patients with chronic pain (Chiang & Kang, 2012; Hoedlmoser et al., 2008; Schabus et al., 2014). The pathophysiologic mechanisms of fibromyalgia include CNS dysregulation and central sensitization involving the HPA axis (Desmeules et al., 2003). Alpha brain wave neurofeedback has been demonstrated to balance HPA self-regulated moods, including decreasing anxiety and alleviating depressive symptoms (Peng et al., 2015). Furthermore, alpha wave neurofeedback reportedly shortens the duration of sleep latency and alleviates chronic pain (Emmert et al., 2017). Our findings demonstrate that an 8-week training program of SMR and alpha wave neurofeedback was efficacious in decreasing pain and fibromyalgia symptom severity. We did not observe significant improvements in sleep quality, determined by the PSQI global score. However, neurofeedback significantly shortened sleep latency among patients with fibromyalgia. This result accorded with findings that SMR neurofeedback training significantly reduced sleep latency in healthy participants (Hoedlmoser et al., 2008). The observed neurofeedback-induced improvements in sleep latency may have contributed to the improvements in pain severity and pain interference among patients with fibromyalgia.

Impairments in cognitive performance associated with fibromyalgia have been identified in several domains, including executive function, learning memory, working memory, attention, and psychomotor speed (Wu et al., 2018). SMR neurofeedback training enhancement had an association with improved overnight memory, determined using the Wechsler memory scale, in healthy participants (Schabus et al., 2014). SMR neurofeedback training has also exhibited positive effects in the attention domain of cognitive function in individuals with attention-deficit/hyperactivity disorder (Bink, van Nieuwenhuizen, Popma, Bongers, & van Boxtel, 2015). The present study demonstrated that SMR neurofeedback combined with alpha training improved cognitive function, measured using the PVT. The PVT is a valid neuropsychiatric test for behavioral alertness in populations with sleep loss and is a test for sustained vigilance and attention (Basner & Dinges, 2011). The PVT is a validated test for assessing cognitive function in patients with sleep disturbances (Dorrian et al., 2005). However, we only observed improvements in PVT error and not in PVT RT, DST forward and backward, or PVT RT after neurofeedback training. Perceived sleep quality (PSQI global score) was not significantly improved after 8 weeks of neurofeedback training. Because sleep disturbances are associated with poor cognitive function, future studies are required to further explore the modalities involved in reducing sleep disturbances to improve cognitive function among patients with fibromyalgia.

A study on SMR neurofeedback treatment in patients with insomnia revealed that 360 minutes of neurofeedback treatment (24 minutes × 15 sessions) significantly improved overnight memory (Schabus et al., 2014). In patients with fibromyalgia, an SMR neurofeedback training dosage of 600 minutes (30 minutes × 5 sessions for 4 weeks, and follow up until 24 weeks) was effective in improving pain and psychological symptoms (Kayiran et al., 2010). In Kayiran's study, the largest treatment effects were observed at 4 weeks, and the effects were reduced in the

follow-up period. Therefore, the long-term effects of neurofeedback warrant further investigation. The present study included a neurofeedback training program with 20 sessions (600 minutes) over 8 weeks using alpha and SMR brainwave training, and we similarly demonstrated a significant reduction in pain intensity, the alleviation of fibromyalgia symptoms, and improvements in sustained attention among participants with fibromyalgia. It is important to note, however, that we were unable to determine the dose-dependent effect of neurofeedback for symptom improvements in fibromyalgia. Future RCTs should compare the effects of neurofeedback of different treatment durations to determine the optimal dosage of neurofeedback for the fibromyalgia population. It is also suggested that future meta-analyses of the effects of neurofeedback for chronic pain in general, or fibromyalgia in particular should incorporate a dose-response analysis.

Neurofeedback is a promising noninvasive treatment for fibromyalgia-associated pain and symptoms. The findings of this study can inform patients with fibromyalgia and clinicians. More research is necessary to confirm the effect and optimal dosage of neurofeedback for sleep improvement in the fibromyalgia population. In conclusion, this RCT study demonstrates the efficacy of neurofeedback for improving pain, overall symptom severity, SOL, and sustained attention in patients with fibromyalgia.

### Limitations

Several limitations must be addressed. First, although neurofeedback was effective for alleviating fibromyalgia symptoms, no EEG data were collected; thus, we could not examine the associations between reductions in symptoms and EEG changes. Second, not all participants completed all intended treatment sessions. However, because less than 20% of the participants in the neurofeedback group did not complete the total treatment (600 minutes), we were unable to determine the amount of neurofeedback training necessary to achieve a significant effect on outcomes. Thus, a treatment duration of at least 600 minutes of neurofeedback is recommended for people with fibromyalgia. Finally, the long-term effects of neurofeedback in patients with fibromyalgia were not investigated in this study.

### Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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