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Targeted limbic self-neuromodulation for alleviating central sensitization symptoms in fibromyalgia

Ayelet Or-Borichev[1,3*†], Yulia Lerner[1,2,3†], Yael Hamrani[1], Guy Gurevitch[1,3], Netali Mor[1,3], Maayan Doron[1,4], Noam Sarna[4], Jacob N. Ablin[3,5], Talma Hendler[1,2,3,4] and Haggai Sharon[1,2,3,6]

Abstract

Background Fibromyalgia (FM), involving somatic, cognitive, and affective domains is often regarded as a hallmark central sensitization syndrome. Despite limited current therapeutic options, emerging understanding of its neural underpinnings offers the potential of applying novel neuromodulation strategies. Specifically, limbic dysregulation underlying abnormalities in pain modulation and somatic-affective processing, has been shown to play a key role in FM. Here, we assessed the long-term efficacy of targeted limbic self-neuromodulation for improving clinical disease burden in FM.

Methods Forty-seven patients with FM participated in a double-blind, randomized, dual-control study employing a novel specialized neurofeedback probe representing amygdala activity. Patients underwent 10 sessions of either genuine neurofeedback training (NFT = 21), or sham neurofeedback training (NFS = 13), or treatment as usual (TAU = 13). Disease severity and symptom burden were assessed using the Symptom Severity Score (SSS), along with other questionnaires administered before and after treatment. A clinical follow-up was performed 10–12 months post-intervention.

Results NFT led to a significant immediate and long-term reduction in the SSS ($F_{(2,40)} = 7.32$, $p = 0.00$, $\eta p2 = 0.27$) and the Fibromyalgia Impact Questionnaire (FIQ) ($F_{(2,40)} = 9.85$, $p = 0.00$, $\eta p2 = 0.33$), alongside multidomain short- and long-term clinical benefits. NFS resulted in a long-term reduction in pain but did not affect other disease measures or overall disease burden. The TAU group showed no clinical improvements.

Conclusions Our findings support the intimate involvement of limbic brain areas in the pathophysiology of FM and suggest that targeted neuromodulation offers a novel, mechanism-based approach for managing multidomain symptoms in FM.

Trial registration This study was preregistered with the National Institutes of Health (NIH). Registration number: NCT02146495. Name of trial registry: Targeted Limbic Self-modulation as a Potential Treatment for Patients Suffering From Fibromyalgia https://clinicaltrials.gov/study/NCT02146495.

Keywords Brain-based therapy, FMRI-informed EEG model, Non-invasive intervention, Chronic pain relief, Fibromyalgia management

†Ayelet Or-Borichev and Yulia Lerner contributed equally to this work.

*Correspondence:
Ayelet Or-Borichev
ayeletorb@gmail.com
Full list of author information is available at the end of the article

Background

Fibromyalgia (FM) is a chronic pain syndrome affecting approximately 2–4% of the general population, characterized by widespread pain and a range of constitutional, affective, cognitive, and somatic symptoms [1, 2]. The core neural mechanism underlying FM is associated with central sensitization (CS), a pathological state of the central nervous system that heightens reactivity to minor or even subthreshold nociceptive inputs, leading to pain hypersensitivity [3]. Beyond pain amplification, CS is associated with network-level brain abnormalities, particularly within the limbic system [4, 5], which plays a critical role in regulating the cognitive and affective dimensions of pain perception and processing [6, 7]. This neural hyperactivity extends beyond pain pathways, contributing to the broad and diverse range of symptoms commonly observed in FM, such as fatigue, insomnia, emotional dysregulation, cognitive impairments, and oversensitivity to chemical and environmental stimuli [7].

Extensive neuroscientific evidence supports the classification of FM as a brain-based disorder involving abnormal pain processing, altered neurotransmitter levels, and dysfunctional neural connectivity [8, 9]. However, the precise pathogenesis of FM remains largely unknown, limiting the development of targeted, mechanism-based treatments. As a result, existing therapeutic approaches, including pharmacological interventions and non-invasive techniques such as transcranial magnetic stimulation (TMS) and transcutaneous electrical nerve stimulation (TENS), primarily focus on alleviating chronic pain. While TMS and TENS have shown promising results in pain reduction with minimal chronic side effects [10–13], these treatments remain pain-centered rather than mechanism-driven, overlooking the broader spectrum of FM symptoms, including cognitive dysfunction, fatigue, and affective disturbances.

To address the need for a robust integrative model of FM pathogenesis, a recent theoretical framework [14] suggests that FM arises from an imbalance in affect regulation systems, which imprints a negative bias on incoming stimuli. This dysregulation results in hyperactivation of the salience network, potentially triggering pathological responses in other neural networks and processes. This model highlights abnormalities in emotion regulation as a pivotal element in the pathological cascade leading to pain chronification and other FM symptoms. Accordingly, targeting emotion regulation processes and brain structures such as the limbic system [15, 16], rather than solely focusing on nociception pathways, may offer a promising brain-guided therapeutic approach for FM.

A growing body of evidence implicates functional abnormalities in limbic structures, particularly the amygdala, in the key processes underlying FM. These processes include pain modulation [17, 18], the transition from acute to widespread chronic pain [19, 20, 8], and the regulation of somatic-affective homeostasis, such as sleep and emotional processing [21, 22], all of which are disrupted in FM. Substantial evidence links the amygdala to FM neuropathology, with studies reporting reductions in gray matter volume [23, 24], as well as altered amygdala activity [25, 26] and connectivity [27–29]. The amygdala's role in FM is further reinforced by its inclusion in a validated neurophysiological signature of the disorder, particularly in response to pain-related neural patterns [30]. This cumulative evidence identifies the amygdala as a promising therapeutic target for FM. Accordingly, this study aims to implement a brain-guided therapy designed to modulate amygdala activity in individuals with FM.

One way to noninvasively target brain dysregulation is through neurofeedback (NF), a form of brain-computer interface that utilizes closed-loop reinforced self-neuromodulation (SNM), guided by neural functional representations primarily depicted by fMRI or EEG [31]. Accumulating evidence suggests that significant neural modulation achieved through NF can lead to corresponding mental and behavioral changes, bridging the gap between brain function, mental state, and behavior [31]. However, while fMRI-NF is anatomically accurate [32], it is costly and not widely accessible, limiting its scalability for clinical practice [31]. On the other hand, EEG-based NF, while more scalable, has primarily targeted nonspecific brain probes such as sensorimotor rhythm (SMR), alpha, beta, or theta waves [33, 34]. This approach has shown moderate effectiveness in alleviating FM symptoms [35, 36].

We have previously developed and validated a unique fMRI-informed EEG computational model of amygdala activity known as the Electrical Finger-Print (Amyg-EFP) [37, 38]. This approach combines the high neuroanatomical precision of fMRI with the scalability of EEG [39, 38]. A previous small-scale clinical trial in FM [40] demonstrated that training with this probe resulted in immediate improvement in sleep measures, followed by subsequent improvements in pain scores. However, pain, while a prominent symptom, is not the sole feature of FM and does not necessarily reflect the overall severity or burden of the disease. Moreover, because the limbic system is implicated in several key symptoms of FM, it may modify disease severity across various symptom clusters. Furthermore, nonspecific effects of NF training could confound the true effects of targeted therapy.

To address these gaps, the current study employed amygdala EFP-NF training in patients with FM using a double-blind, dual-controlled procedure. Both a no-training control group and a sham-NF control group were implemented to account for transient clinical and neural

changes, as well as non-specific effects [31, 41]. The primary endpoint was overall disease severity, as measured by the FM Symptom Severity Score (SSS) [42]. By utilizing limbic-focused NF, we aimed to target the core neural dysregulations underlying FM [14] to alleviate its broad symptom spectrum. Accordingly, we selected the SSS as the outcome measure, as it captures the full severity of FM symptoms, extending beyond pain to provide a comprehensive representation of disease burden. We also collected subjective assessments of pain, fatigue, affect dysregulation, and cognitive difficulties using validated questionnaires. In addition, we evaluated the capacity of patients with FM to downregulate the Amyg-EFP signal through NF training. Clinical evaluations were conducted before the intervention, immediately post-intervention, and at a 10–12 month follow-up.

We hypothesized that the NFT group would show a more significant linear reduction in the Amyg-EFP signal and a greater overall downregulation of the signal across NF sessions. Furthermore, we expected that the NFT group would develop independent self-neuromodulation capabilities (i.e., successful modulation without feedback). Finally, we anticipated that successful regulation of the Amyg-EFP signal would correlate with reduced disease severity at long-term follow-up.

Methods

The study design and results are presented in accordance with best practice guidelines. Additionally, the CRED-nf checklist [43] is available in the Supplementary Material (see Additional File 1). The checklist details key methodological parameters, including participant characteristics, NF protocol specifications (e.g., target brain regions, signal processing methods, and training paradigms), control conditions, outcome measures, statistical analyses, and reporting transparency.

Participants

Patients were recruited from the FM clinic at the Institute of Rheumatology and the Institute of Pain Medicine at Tel Aviv Sourasky Medical Center (TASMC). FM diagnosis was established according to the American College of Rheumatology (ACR) 2010 criteria [44] by a board-certified rheumatologist or pain specialist. Eligible participants were Hebrew-speaking adults (ages 18–55) of both genders, experiencing pain levels of 5 or higher on a 10-point scale at least three days a week, with or without medical treatment. Exclusion criteria included the presence of other chronic pain conditions, major neuropsychiatric disorders, or changes in pharmacotherapy within two months prior to recruitment, as well as any planned modifications to treatment during the study period. The study was approved by the Institutional Ethical Review Board, and all participants provided written informed consent before enrollment.

General procedure

Participants were divided into three groups: (1) a genuine NF treatment (NFT) group, (2) a placebo-control group receiving sham NF (NFS) based on artificially generated, irrelevant EFP signals, and (3) a treatment-as-usual (TAU) control group with no intervention. Sample size estimation was informed by previously published findings from Goldway et al. [40], which demonstrated long-term clinical improvements in FM-related symptoms, including emotional ($d=0.79$), sleep ($d=1.05$), and pain indices ($d=1.10$). To estimate the overall FM disease burden, a composite effect size was calculated by averaging these values, yielding a mean effect size of $d=0.98$. A formal a priori power analysis was conducted using G*Power v3.1.9.2 for a one-way ANOVA design, with $\alpha=0.05$ and power $(1-\beta)=0.80$, indicating that a minimum of 14 participants per group would be sufficient to detect a statistically reliable effect. Participants were randomly assigned in a blinded manner using a 2:1:1 allocation ratio, favoring the NFT group to ensure adequate power for treatment efficacy analysis. The target sample included 28 participants in the NFT group and 14 each in the NFS and TAU control groups. Fifty-seven participants were screened and randomized in a blinded manner (NFT: $n=28$; NFS: $n=15$; TAU: $n=14$). Blinding was maintained using custom in-house software and was only lifted following completion of data acquisition. The overall attrition rate was 17.5%, resulting in a final sample of 47 participants for analysis (NFT: $n=21$; NFS: $n=13$; TAU: $n=13$).

Both NF intervention groups (NFT and NFS) completed a ten-session training course, conducted two to three times per week. Clinical outcomes were measured using validated clinical questionnaires (see Clinical Assessment section below) at three time points: baseline (pre-test), immediately after the intervention (post-test), and 10–12 months following the completion of NF training (follow-up). The TAU group continued with their standard treatment regimen as prescribed by their pain specialists, without any additional training or intervention. They underwent the same clinical evaluations as the NFT and NFS groups, assessed at baseline, after approximately 2–3 months (to match the NF intervention timeline), and again 10–12 months after the second evaluation (follow-up).

Amyg-EFP-NF training protocol

Patients were trained to modulate their Amyg-EFP signal using a 3D audio-visual animated interface that provided real-time feedback. This virtual scenario, simulating a

hospital waiting room, featured animated characters that displayed agitation or relaxation in response to changes in the EFP signal amplitude [45]. For the sham group, feedback was generated from a randomized artificial signal, calibrated to yield an approximate 52% success rate per session. This approach was designed to avoid excessively rewarding experiences [40] while minimizing frustration [46].

Each NF cycle included three phases: a Watch/baseline period (60 s), a Regulate period (120 s), and a Washout period (30 s) (see Fig. 1B). In the Watch/baseline phase, participants passively observed and listened to the feedback interface, which maintained at a constant 75% unrest level (determined by the sound volume and the number of agitated avatars). During the Regulate phase, patients were instructed to identify and implement a mental strategy to reduce the scenario's unrest level. Participants could choose any mental strategy [40, 47], enabling them to actively explore techniques that effectively modulated the target signal. After each NF run, patients reported the mental strategy they had used. In the Washout phase, participants were presented with a sequence of three-digit numbers and were asked to mentally count the occurrences of identical digits within each block. Each NF run included two complete cycles of these three conditions, lasting a total of 7 min. An EFP-NF session consisted of four NF runs (Fig. 1B). At the beginning of each session, a 2-min resting-state EEG recording was obtained. At the end of each session, a 2-min transfer run was conducted, during which patients re-applied their most effective strategy while viewing a black screen in a feedback-free environment (Fig. 1B). For more detailed information, refer to Additional File 2.

Clinical assessment

Our primary outcome measure was overall disease burden, assessed using the SSS [42]. To capture the diverse manifestations of FM, we also utilized the following scales and subscales: the Fibromyalgia Impact Questionnaire (FIQ) [48] to evaluate disease burden, and the Widespread Pain Index (WPI) [42] to quantify pain distribution. Chronic fatigue was measured using the FIQ-fatigue sub-score, while anxiety symptoms were assessed using the Trait Anxiety Inventory (STAI-T) [49]. Cognitive symptoms were evaluated with the SSS-cognitive sub-score (SSS-Cog) [42].

Statistical analyses

To ensure the validity of our statistical models, we first confirmed that there were no pre-existing differences between groups across all clinical indices.

To assess clinical efficacy within each group, we applied repeated-measures ANOVA with measurement time points (pre, post, and FU) as a within-subject variable. To test differences between groups, we employed a linear mixed-models analysis. The model included a between-subjects fixed Group factor (NFT, NFS, and TAU), a covariate for measurement time point (MTP; pre, post, and follow-up), and clinical self-report scores as the dependent variable. Planned contrasts were conducted to compare the genuine NF group against each control group (NFT vs. NFS and NFT vs. TAU) at different intervals (post–pre and follow-up-pre).

All statistical analyses were performed using IBM SPSS, version 23, Statistica version 12 (StatSoft, Inc), and MATLAB 2017b. All reported p-values are two-tailed. Assumptions of sphericity were tested using Box's test for equality of covariance matrices and Levene's test for equality of variances. Where sphericity assumptions were violated, corrected statistics and p-values were used.

To control for confounding factors, we compared satisfaction levels and mental strategy use between the NFT and NFS training groups. The Additional Files 2 + 3 provide detailed information on these analyses.

Results

Participants

Attrition rates were 17.5% (10 patients). In total, 47 patients were included in the final analyses (age = 35.72 ± 10.18, 39 females, 82% retention, see Table 1). Forty-three patients participated in the follow-up evaluation, with four opting out for personal reasons

(See figure on next page.)

Fig. 1 Experimental Design. **A** Patients underwent a clinical assessment by a certified specialist and were then randomly assigned to either a treatment-as-usual (TAU) group or an NF intervention group (NFT or NFS). A "Pre-NF" assessment, including clinical evaluations, was conducted, followed by ten sessions of Amyg-EFP-NF training, performed 2–3 times per week. A "Post-NF" assessment, identical to the baseline evaluation, was conducted within 1–2 weeks after the NF course. The entire intervention process lasted 8–10 weeks. The TAU group underwent similar assessments at the beginning and end of a 2–3 month period. A follow-up clinical assessment was conducted 10–12 months later. **B** NF training protocol: Patients underwent a brief clinical evaluation at the beginning and end of each session. Each session started with a 2-min EEG resting-state recording. Training involved down-regulating the Amyg-EFP signal using a 3D animated scenario of a virtual waiting room that changed based on EFP signal amplitude. Each NF cycle included: *Watch* (60 s), *Regulate* (120 s), and *Washout* (30 s). Each NF cycle included these conditions, repeated twice in each 7-min NF run. The EFP-NF session comprised four NF runs, followed by a 2-min transfer run where patients applied their most effective strategy without feedback

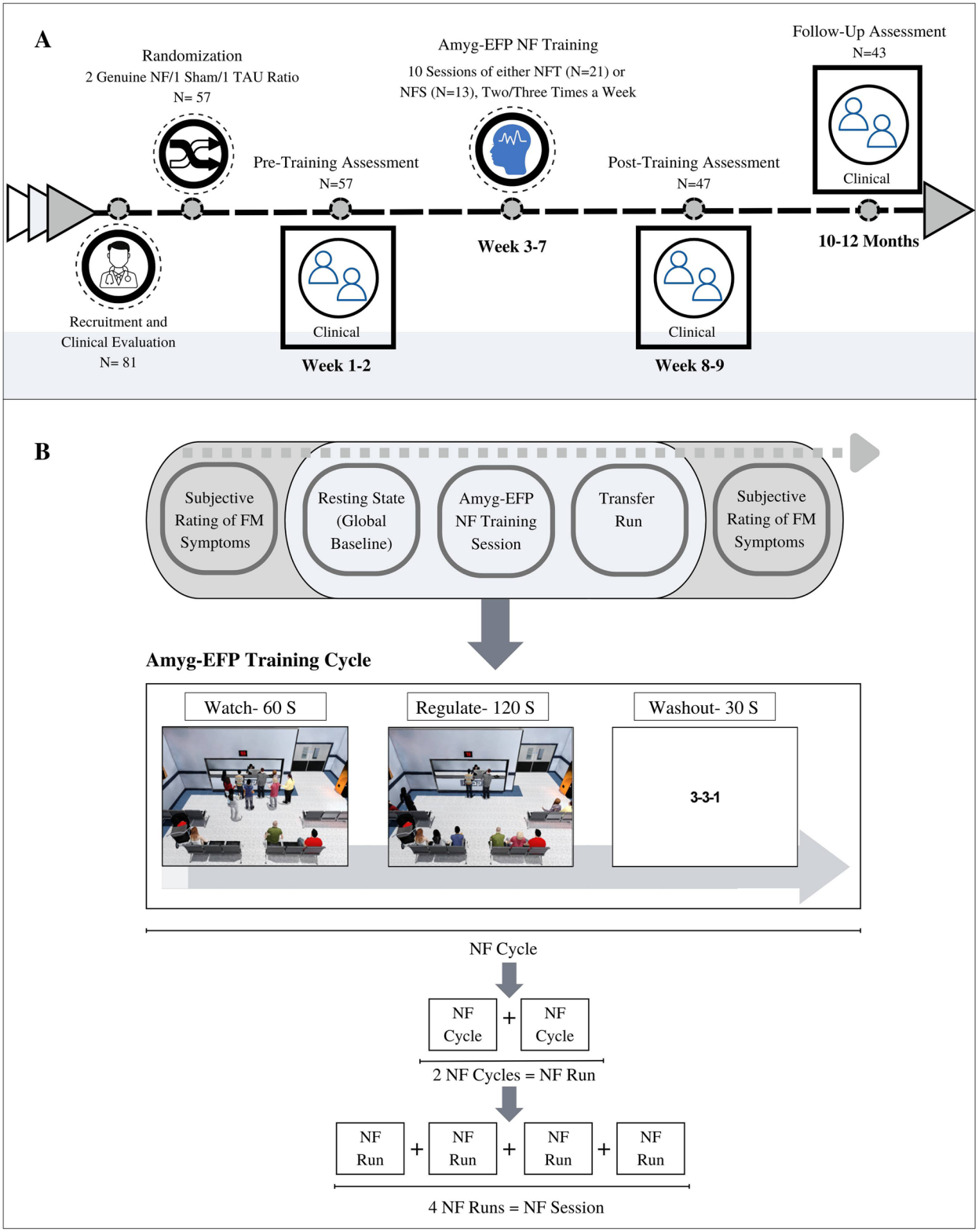

Fig. 1 (See legend on previous page.)

Table 1 Baseline characteristics of the sample

	NF-Treatment (NFT) M ± S.D	NF-Sham (NFS) M ± S.D	Treatment-as-usual (TAU) M ± S.D	ANOVA F Value	*P* Value
Demographics					
Gender	2 M 19F	5 M 8F	1 M 12F		0.057
Age	35.76 ± 9.67	37.00 ± 10.09	34.38 ± 11.65	0.207	0.814
Baseline level of clinical characteristics					
Time from diagnosis (years)	7.52 ± 3.35	9.00 ± 5.74	7.07 ± 4.42	0.697	0.504
General severity (FIQ)	8.09 ± 1.57	7.15 ± 1.46	7.00 ± 1.63	2.49	0.094
General influence (FIQ)	8.61 ± 1.28	8.15 ± 1.51	7.92 ± 2.56	0.672	0.516
Pain (VAS, WPI)	0.20 ± 0.67	−0.15 ± 0.57	−0.17 ± 0.97	1.380	0.262
Affect (STAI-T)	48.29 ± 7.72	50.15 ± 8.75	51.38 ± 13.41	0.420	0.660
Pharmacological baseline level					
SSRI/SNRI (%)	17	12	22		0.111
Gabapentinoids (%)	9	10	16		0.103
Cannabis (%)	34	29	31		0.896
Analgesics (%)	7	9	13		0.675
Miscellaneous (%)	12	14	20		0.518

FIQ Fibromyalgia Impact Questionnaire, *STAI* TTrait Anxiety Inventory, *VAS* Visual Analog Scale, *WPI* Widespread Pain Index

(N at follow-up: NFT = 18, NFS = 13, TAU = 12; refer to Fig. 1A).

Group baseline characteristics were compared using a chi-square or Kruskal–Wallis test for categorical variables, and an ANOVA F-test for continuous variables. No significant differences were noted in demographic, clinical, or pharmacological baseline characteristics.

Amyg-EFP-NF clinical outcome

Overall FM disease burden—symptom severity scale

The NFT group showed a significant immediate and long-term improvement in overall disease severity ($F_{(2,40)} = 7.32$, $p = 0.00$, $\eta p2 = 0.27$). Specifically, the post-treatment vs. pre-treatment difference was significant (mean difference = −1.19 ± 0.32, $p = 0.00$, $\eta p2 = 0.41$, 95% CI: −1.86 to −0.52), and the FU vs. pre-treatment difference was also significant (mean difference = −1.78 ± 0.53, $p = 0.00$, $\eta p2 = 0.36$, 95% CI: −2.90 to −0.67; see Table 2), consistent with our hypothesis. The NFT group exhibited a 19 percent overall improvement, while no clinical improvement was found in either the NFS or TAU control groups at any time point (see Table 2 and Fig. 2A). The mixed-model analysis using the SSS as the dependent variable showed a significant group-by-time interaction effect ($F_{(2,91)} = 3.36$, $p = 0.039$). Planned contrasts revealed no significant difference between the NFT group and the control groups immediately post-intervention. However, in line with our hypothesis, genuine NF training resulted in significantly greater long-term improvements, with the NFT group showing a significant improvement compared to the NFS (mean difference = −1.55 ± 0.75, $t_{(44)} = -2.08$, $p = 0.04$, 95% CI: −3.06 to −0.04) and TAU (mean difference = −1.48 ± 0.75, $t_{(44)} = -1.98$, $p = 0.05$, 95% CI: −2.99 to −0.03) groups (see Table 2 and Fig. 3A).

Auxiliary questionnaires and secondary measures

FIQ—The NFT group showed a significant reduction of 17 percent in the FIQ-final score immediately after the intervention, with a further reduction of 22 percent at follow-up ($F_{(2,40)} = 9.85$, $p = 0.00$, $\eta p2 = 0.33$). The post vs. pre difference was significant (mean difference = −11.42 ± 2.91, $p = 0.00$, $\eta p2 = 0.43$, 95% CI: −17.50 to −5.34), as was the FU vs. pre difference (mean difference = −14.79 ± 3.87, $p = 0.00$, $\eta p2 = 0.42$, 95% CI: −22.87 to −6.71) (see Table 2). The NFS group also exhibited an immediate improvement of 19 percent, but this effect did not persist in the long term, and, in fact, symptoms worsened over time. No immediate or long-term clinical effects were observed in the TAU group (see Table 2 and Fig. 2B). The linear mixed-model analysis revealed a significant interaction between Group (NFT, NFS, and TAU) and measurement time points (MTP: pre, post, and FU), indicating a more substantial reduction in the NFT group. Planned contrasts further confirmed that the NFT group demonstrated greater immediate and long-term improvement compared to the TAU group, but not when compared to the sham condition (see Table 2 and Fig. 3B).

WPI—No significant between-group differences were found, as indicated by the non-significant interaction between Group and time-point. However, when assessed separately, the NFT group showed a significant

Table 2 An immediate and long-term clinical efficacy in each group separately

BETWEEN-GROUP EFFECTS												WITHIN-GROUP EFFECTS								
A priori differences		Group X MTP interaction		Immediate clinical effect (Post–Pre)				Long-term clinical effect (FU-Pre)					MTP Main Effect			Immediate clinical effect (Post–Pre)			Long-term clinical effect (FU-Pre)		
F	*P*	*F*	*P*	NFT vs. NFS		NFT vs. TAU		NFT vs. NFS		NFT vs. TAU			*F*	*P*	ηp^2	*Mean Difference*	*Std. Error*	*P*	*Mean Difference*	*Std. Error*	*P*
				t	*P*	*t*	*P*	*t*	*P*	*t*	*P*										
Symptom Severity Score- SSS																					
2.46	0.10	3.36	0.04	−1.35	0.18	−1.47	0.15	−2.08	0.04	−1.98	0.05	NFT	7.32	0.00	0.27	**−1.19 (−13%)**	0.32	0.00	**−1.78 (−19%)**	0.53	0.00
												NFS	0.22	0.80	0.02	−0.31 (−4%)	0.43	0.49	−0.23 (−3%)	0.50	0.65
												TAU	0.15	0.86	0.01	−0.23 (−3%)	0.71	0.75	−0.30 (−3%)	0.50	0.56
Fibromyalgia Impact Questionnaire- FIQ-Final Score																					
2.12	0.13	6.36	0.00	−0.10	0.92	−3.21	0.00	−1.30	0.21	−3.80	0.00	NFT	9.85	0.00	0.33	**−11.42 (−17%)**	2.91	0.00	**−14.79 (−22%)**	3.87	0.00
												NFS	3.54	0.04	0.23	**−10.99 (−19%)**	2.86	0.00	−6.75 (−11%)	4.85	0.19
												TAU	0.51	0.61	0.04	1.61 (+3%)	2.47	0.53	2.34 (+4%)	2.29	0.33
Widespread Pain Index- WPI																					
0.80	0.92	0.48	0.62	−0.83	0.41	−0.44	0.66	0.34	0.74	−0.68	0.50	NFT	3.55	0.04	0.15	**−1.38 (−13%)**	0.62	0.04	**−2.39 (−23%)**	1.09	0.04
												NFS	4.00	0.03	0.25	−0.54 (−5%)	0.81	0.52	**−2.92 (−28%)**	0.96	0.01
												TAU	0.38	0.69	0.03	−0.85 (−8%)	1.18	0.49	−1.12 (−10%)	1.59	0.50
FIQ-Fatigue																					
3.05	0.06	4.34	0.02	−1.56	0.13	−2.16	0.04	−2.01	0.04	−2.63	0.01	NFT	7.75	0.00	0.28	**−1.38 (−16%)**	0.33	0.00	**−1.64 (−19%)**	0.46	0.00
												NFS	0.19	0.83	0.01	−0.38 (−6%)	0.59	0.53	−0.15 (−2%)	0.59	0.80
												TAU	0.14	0.87	0.01	0.00 (0%)	0.52	1.00	0.22 (+3%)	0.47	0.64
Trait Anxiety Inventory- STAI-T																					
0.86	0.43	1.23	0.30	−1.54	0.13	−1.91	0.06	−1.29	0.20	−0.44	0.60	NFT	10.6	0.00	0.35	**−5.24 (11%)**	0.86	0.00	**−6.60 (14%)**	1.96	0.00
												NFS	0.93	0.38	0.07	**−2.92 (6%)**	1.31	0.05	−2.38 (5%)	2.72	0.40
												TAU	2.44	0.11	0.18	−1.50 (3%)	2.12	0.49	−5.12 (10%)	2.67	0.08
Cognitive symptoms- SSS-cognitive sub-score																					
3.06	0.06	4.62	0.01	−0.50	0.62	−1.00	0.32	−2.57	0.01	−2.30	0.03	NFT	4.05	0.02	0.17	**−0.38 (−18%)**	0.18	0.04	**−0.56 (−26%)**	0.21	0.01
												NFS	1.52	0.24	0.11	−0.15 (−11%)	0.22	0.50	0.23 (+16%)	0.26	0.39
												TAU	0.21	0.81	0.02	−0.08 (−4%)	0.26	0.78	0.07 (+4%)	0.18	0.70

An initial between-group comparison of the first measurement point was conducted for all clinical indices

The 'Between-Groups Effects' section presents the results of the linear mixed-models analysis (Group × MTP interaction), as well as the planned contrasts that examined the distinctions between the genuine NF group and each control group (i.e., NFT vs. NFS and NFT vs. TAU) at different measurement intervals (i.e., post–pre and FU-pre)

The 'Within-Groups Effects' section reports the results of repeated measures ANOVA conducted separately for each group. This section includes post-hoc comparisons for immediate clinical improvement (post vs. pre) and long-term effects (FU vs. pre) for each group. The percentage of immediate and long-term symptom improvement is displayed at the end of each row

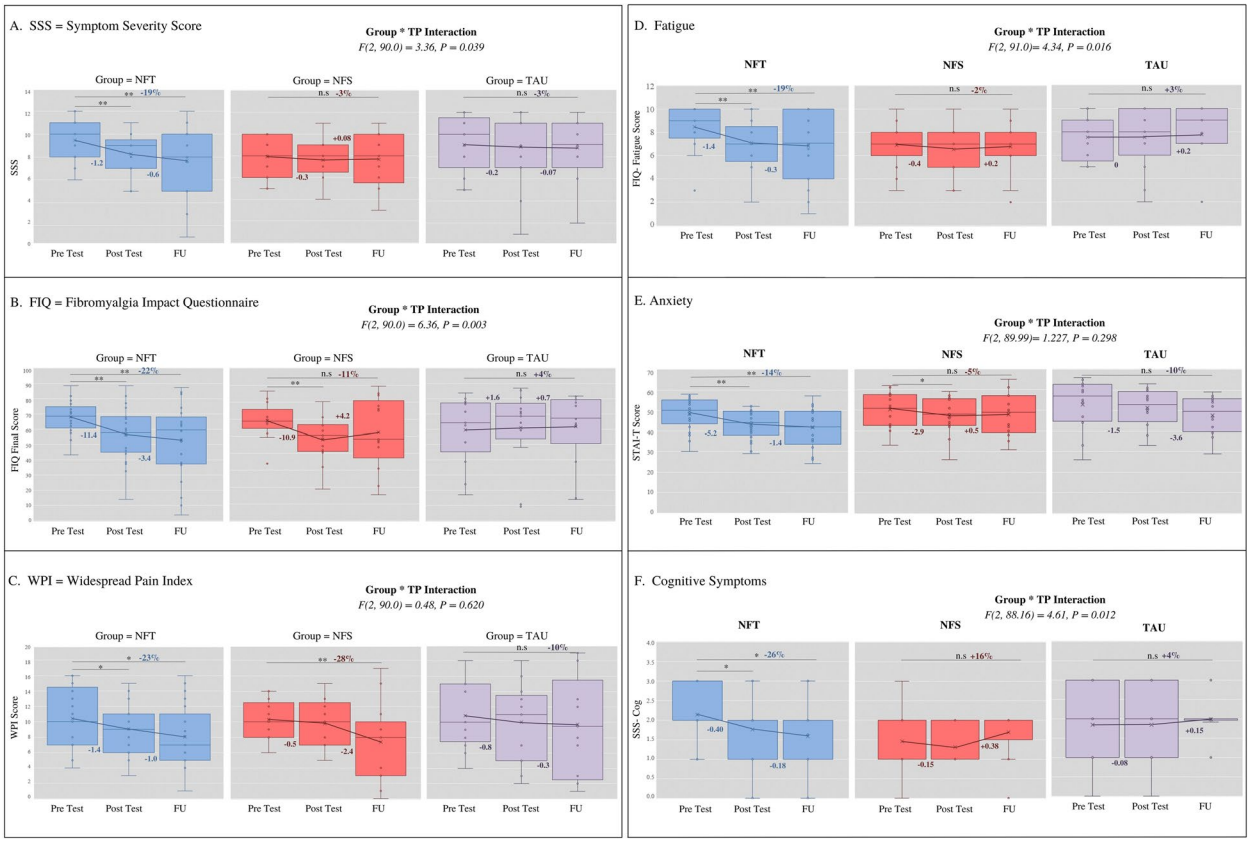

Fig. 2 Feasibility, Immediate and Long-Term Effectivity of Amyg-EFP NF. Several statistical analyses were conducted to assess the immediate and long-term clinical efficacy for each clinical index (A-F). The clinical indices included: **A** symptom severity score (SSS), **B** FIQ-final score index, **C** widespread pain index (WPI), **D** subjective fatigue (FIQ-fatigue), **E** affective state (STAI-T), and (**F**) cognitive symptoms score (SSS-Cog). A linear mixed-model analysis was initially performed to examine the interaction between Group (NFT, NFS, TAU) and measurement time-points (MTP) (pre, post, follow-up), testing between-group differences in overall clinical efficacy. Post-hoc comparisons following ANOVA were then conducted for each group to evaluate immediate improvement (post vs. pre) and long-term effects (follow-up vs. pre). The percentage of symptom improvement over the long term was also calculated for each index and group. The NFT group demonstrated significant long-term effects across all indices. In contrast, the NFS group showed significant long-term effects only for the WPI score, while the TAU group showed none. Significant between-group effects were found for SSS, FIQ-final score, fatigue, and cognitive indices. See Table 2 for detailed results

immediate and long-term effect (23 percent reduction at follow-up). While the NFS group did not achieve immediate improvement in widespread pain, long-term data indicated a 28 percent reduction. The TAU group showed no significant change at any time-point (see Table 2 and Fig. 2C). Planned contrasts indicated no significant differences between the NFT group and the control groups, both immediately post-intervention and at long term (see Table 2 and Fig. 3C).

Fatigue index—The NFT group exhibited a significant long-term improvement of 19 percent in the fatigue index, whereas no immediate or long-term improvements were found in either NFS or TAU groups (see Table 2 and Fig. 2D). The group-by-time-point interaction showed that both sham-NF and no-NF had no significant effect. Post-intervention analysis revealed a significantly greater immediate improvement in the NFT group compared to the TAU group, but not the sham group. As expected, the NFT group displayed significant long-term improvements compared to both the NFS and TAU groups (Table 2 and Fig. 3D).

Anxiety symptoms—There was a significant immediate and long-term reduction in anxiety symptom in the NFT group, with a 14 percent improvement observed at follow-up. In contrast, the NFS group exhibited a significant immediate effect, but only a non-significant long-term improvement of 5 percent. The TAU group did not demonstrate significant immediate or long-term effects (see Table 2 and Fig. 2E). However, the NFT group did not show a significant reduction in anxiety compared to the control groups, as indicated by the non-significant interaction between Group and time-point and the planned contrast analysis (see Table 2 and Fig. 3E).

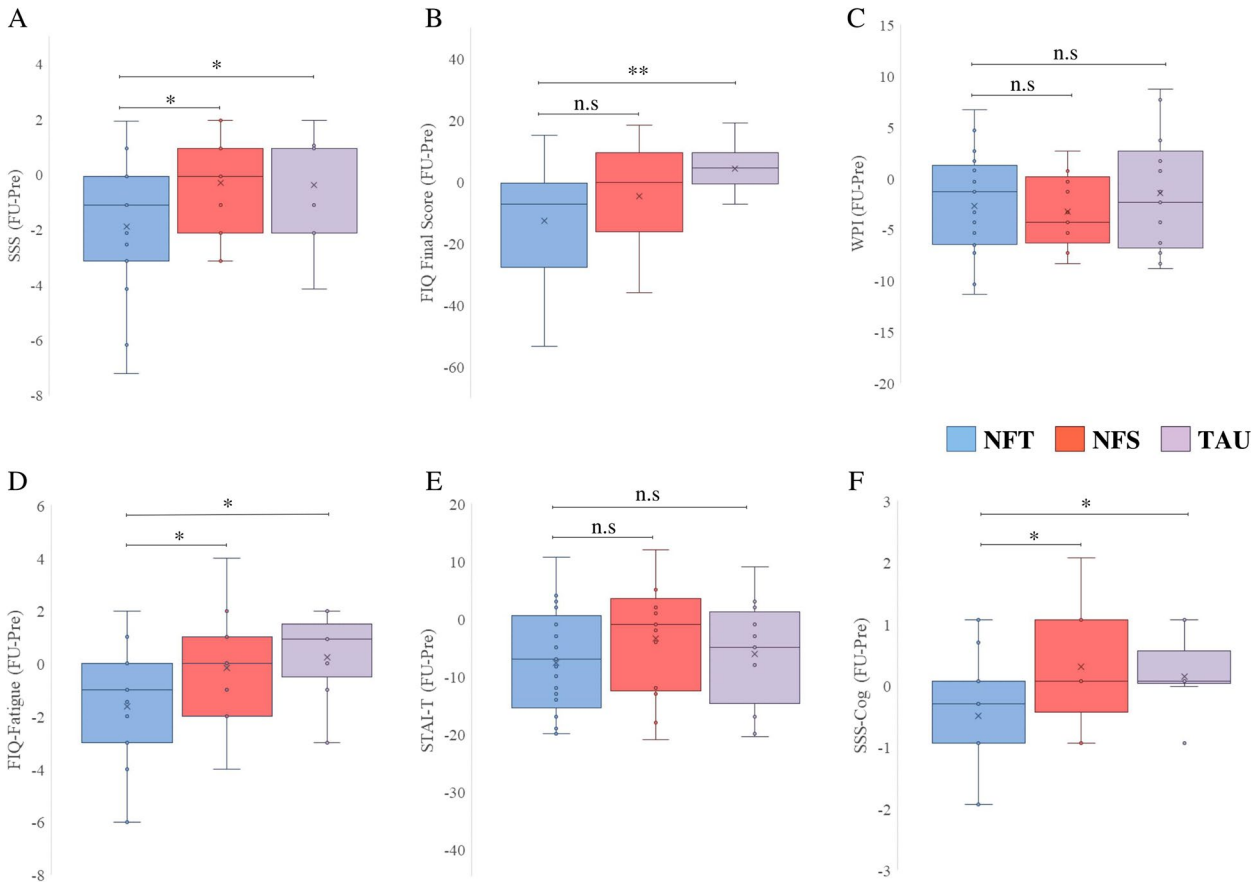

Fig. 3 Long-Term Clinical Efficacy of Amyg-EFP-NF: Inter-Group Comparisons. A planned contrast analysis was conducted to compare the genuine NF group (NFT) with each control group (NFS and TAU) at long-term follow-up (FU-pre) across all clinical outcomes. **A** The NFT group showed greater improvement in symptom severity compared to both the NFS and TAU groups. **B** For the Fibromyalgia Impact Questionnaire (FIQ) final score, the NFT group demonstrated greater improvement than the TAU group, though the difference was not significant when compared to the NFS group. **C** No significant differences were found between groups regarding the Widespread Pain Index (WPI) score. **D** The NFT group showed greater improvement in the FIQ-fatigue score compared to both control groups. **E** There were no significant differences in the STAI-T scores between the groups. **F** Finally, the NFT group exhibited greater improvement in cognitive scores compared to both the NFS and TAU groups

Cognitive symptoms—Separate ANOVA tests showed an immediate and long-term improvement for the NFT group with a 26 percent reduction at follow-up in the cognitive index sub-score (SSS-Cog) (see Table 2 and Fig. 2F). In contrast, neither the NFS nor the TAU groups showed significant changes in cognitive symptoms at any time point. Furthermore, NFT resulted in a greater improvement compared to the control groups (Fig. 2F), as indicated by a significant Group by time-point interaction (see Table 2). While no immediate significant differences were found between NFT and the control groups in the planned contrast analysis, there were significant long-term differences, as expected, with NFT demonstrating greater long-term improvement in cognitive symptoms compared to both control groups (refer to Table 2 and Fig. 3F).

Prediction of long-term symptoms severity reduction

We conducted multiple regression analyses to examine whether immediate improvements in FM-related symptoms—anxiety, fatigue, and pain (WPI)—could predict long-term reductions in FM symptom severity (SSS). This analysis was performed separately for the NFT and NFS groups to distinguish the effects of genuine versus sham NF training. The multiple regression analysis revealed that in the NFT group, immediate improvement in anxiety significantly predicted a long-term reduction in FM symptom severity (SSS) (B = 0.464, $p = 0.034$, 95% CI: 0.024 to 0.550). However, immediate improvements in fatigue (B = 0.01, $p = 0.96$), and WPI (B = 0.32, $p = 0.11$) did not significantly predict long-term improvements in FM symptoms. In contrast, for the NFS group, immediate improvement in WPI negatively predicted long-term reduction in SSS (B = −0.684, $p = 0.010$, 95% CI: −0.719

to −0.123). Furthermore, immediate improvements in fatigue (B = 0.234, $p = 0.341$) and anxiety (B = 0.047, $p = 0.842$) were not significant predictors of long-term symptom reduction in FM.

Self-neuromodulation capacity

The self-neuromodulation effect was assessed by examining the changes in Amyg-EFP signal activity during the active regulation condition compared to the passive observation condition (referred to as "Regulate–Watch"). As anticipated, repeated measures ANOVA unveiled a significant main effect for the 'Condition' variable (Regulate vs. Watch; $F_{(1,32)} = 27.10$, $p = 0.000$, $\eta p^2 = 0.46$), confirming that both the NFT and NFS groups successfully downregulated the Amyg-EFP signal through NF training. However, no significant interaction between the 'Condition' and 'Group' variables was observed ($F_{(1,32)} = 0.216$, $p = 0.645$), indicating that, in contrast to our initial hypothesis, both groups effectively achieved downregulation of the Amyg-EFP signal through NF training.

To evaluate sustainability of this acquired skill, we tested patients' ability to volitionally regulate Amyg-EFP in the absence of online feedback (i.e., the transfer run). A repeated measures ANOVA was conducted with the transfer score (Regulate vs. Baseline) as the dependent variable, groups (NFT/NFS) as the between-subjects factor, and session number (10 sessions) as the within-subjects factor. Contrary to expectations, no significant difference in generalization learning was found in the real-NF and sham-NF groups [Session X Group interaction $F_{(1,32)} = 0.607$, $p = 0.791$, $\eta p2 = 0.019$]. Both real and sham feedback led to successful generalization of the ability to downregulate Amyg-EFP independently of feedback [Mean transfer score across all NF sessions; NFT = −0.198 ± 0.235, $t_{(20)} = -3.76$, $p = 0.001$, CI: −0.299 to −0.082; NFS = −0.214 ± 0.148, $t_{(12)} = -5.21$, $p = 0.000$, CI: −0.304 to −0.124]. An interesting finding emerged when examining the association between the average transfer score across sessions and the average modulation score (Delta: Regulate-Watch). In the NFT group, a positive correlation was found between Amyg-EFP downregulation and transfer scores (r = 0.452, $p = 0.040$). This correlation was specific to the real-feedback group, as no significant relationship was found in the NFS group (r = −0.110, $p = 0.721$; see Fig. 4A).

Learning self-neuromodulation through NF training

Our findings indicate that while both NF groups demonstrated a significant ability to downregulate the Amyg-EFP signal within each session (i.e. modulation effect), only the NFT group showed improvement in the capacity to downregulate the Amyg-EFP across successive sessions (i.e. learning effect). This was evidenced in three ways. First, ANOVA analysis revealed a significant interaction between Condition and Session (1–10 NF sessions) ($F_{(7.80,288)} = 2.155$, $p = 0.033$, $\eta p^2 = 0.063$), which was primarily driven by the NFT group ($F_{(9,180)} = 1.976$, $p = 0.044$, $\eta p2 = 0.090$) but not by the NFS group ($F_{(9,108)} = 1.235$, $p = 0.282$), indicating differential learning trends between the groups. Next, a linear mixed model was employed, incorporating a random intercept and fixed effects of Session, Group, and Group x Session, with the latter being the primary effect of interest. We found a significant Session-by-Group interaction ($F_{(1,84.34)} = 5.39$, $p = 0.02$, 95% CI: 0.0052 to 0.0683), favoring a reduction trend in the NFT group compared to the NFS group. Finally, a main effect for Session was observed only in the NFT group (NFT: $F_{(1,84.08)} = 14.29$, $p = 0.00$; NFS: $F_{(1,8449)} = 0.02$, $p = 0.98$), suggesting that the patients in the test group improved their performance over successive sessions. Indeed, as shown in Fig. 4B, the slope of the NFT group was significant (NFT slope estimate = −0.0370 ± 0.01, $p = 0.000$), while the NFS group slope was not (NFS slope estimate = −0.00023 ± 0.012, $p = 0.985$).

The association between probe regulation and long-term clinical improvement

A Pearson correlation analysis revealed that Amyg-EFP-NF downregulation (average delta; Regulate-Watch) was positively associated with long-term improvements (i.e., FU vs. pre-intervention) in symptom severity (SSS) in the NFT group ($r = 0.434$, $p = 0.049$; Fig. 4C). Similar correlations were found for cognitive dysfunction (NFT group: $r = 0.436$, $p = 0.048$; Fig. 4D) and anxiety (NFT group:

(See figure on next page.)

Fig. 4 Different Dimensions of Amyg-EFP-NF Learning. **A** Association between Amyg-EFP NF capacity and generalization of Amyg-EFP downregulation learning: A positive correlation was observed exclusively in the NFT group, linking average transfer scores (across all sessions) with the average Amyg-EFP downregulation score (Regulate vs. Watch). **B** Global learning success: A mixed linear model analysis of Amyg-EFP NF learning trajectory showed a significant Session by Group interaction effect ($F_{(1,84.34)} = 5.39$, $p = 0.02$, 95% CI: 0.0052 to: 0.0683). This result indicated a linear trend in NF learning favoring the NFT group compared to the NFS group. The association between Amyg-EFP-NF downregulation and long-term clinical improvement. A Pearson correlation analysis revealed that successful Amyg-EFP downregulation (average delta; Regulate-Watch) was assosiated with long-term reductions (FU-pre-intervention) in (**C**) symptom severity (SSS), **D** cognitive dysfunction, and (**E**) emotional dysregulation (STAI-T). These correlations were specific to the genuine Amyg-EFP group and were not observed in the NF-sham group

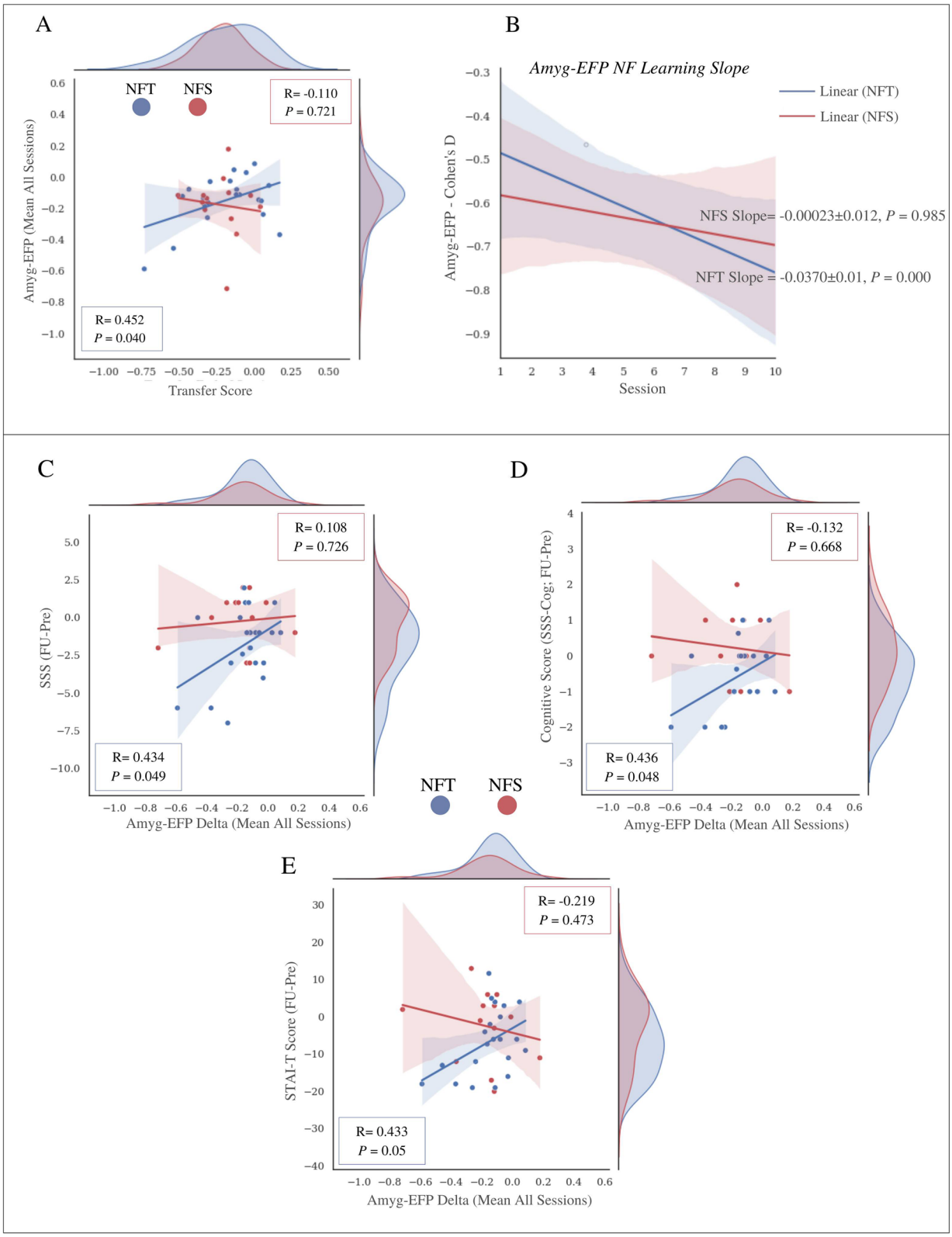

Fig. 4 (See legend on previous page.)

$r=0.433$, $p=0.05$; Fig. 4E). However, no significant correlations were observed with the FIQ-final score ($r=0.339$, $p=0.132$) or FIQ-fatigue ($r=0.363$, $p=0.106$). Due to the modest sample size, we refrained from correcting for multiple comparisons. Importantly, these associations were not observed in the sham group (NFS group; SSS: $r=0.108$, $p=0.726$; Cognitive dysfunction: $r=-0.132$, $p=0.668$; Anxiety: $r=-0.219$, $p=0.473$; Fig. 4C-E).

Methodological validations

To prevent any bias resulting from potential frustration, we examined satisfaction levels within the NF training groups (NFT and NFS). As expected, both NF groups reported high satisfaction levels with their participation, with no significant differences between the groups (Additional File 3: Table S1 presents all relevant values for the t-tests). Furthermore, to ensure that the observed clinical and brain changes were not merely due to the mental strategies employed during NF training, we verified that there were no significant differences in strategy preferences between the groups (see Additional File 3: Figure S1 and Table S2). Interestingly, the results indicated that patients in both groups tended to prefer mental strategies characterized by detachment from the interface, combined with traits of low arousal and positive valence.

Discussion

The goal of the current study was to evaluate both the clinical and neural effects of a NF treatment employing a disease-relevant, fMRI-informed EEG probe, the amygdala-EFP, in patients with FM. To this end, we collected clinical, narrative, and electrophysiological data before and after ten sessions of genuine NF, sham NF, or a no-intervention group. This approach allowed us to examine time-related effects (via the TAU group) and non-specific intervention effects (via the NFS group) (Figs. 2, and 3 and Table 2).

Our results revealed that only the NFT group experienced prolonged and robust clinical improvements across an extensive range of FM-related symptoms, spanning somatosensory, affective, and cognitive domains. These improvements were reflected in a significant reduction in overall disease severity, as assessed by the SSS. In contrast, the NFS group did not exhibit sustained clinical improvements, with the exception for improvement in long-term reported widespread pain. The TAU group displayed no immediate or long-term clinical benefits.

The clinical benefits observed in the genuine NF group were distinct from the effects of the sham intervention in two critical aspects. First, the clinical effects in the NFT group were not only sustained but also enhanced over time (one-year follow-up) across all assessed FM symptoms (Fig. 2 and Table 2). This is in contrast to the transient benefits seen in the sham group, with the exception for subjective pain scores. The phenomenon observed in our study, where clinical effects following real NF training persist and even intensify over time, while most benefits from sham learning are temporary, aligns with findings from other NF studies, including those on various brain pathologies [40, 50, 51]. Thus, comparing the clinical effects between real and sham NF at long-term follow-up provides a clearer distinction between target process effects and the non-specific effects of sham NF.

Secondly, and more importantly, the clinical benefits observed in the genuine NF group extended beyond affective-nociceptive indices to encompass a broad range of cognitive functions, constitutional symptoms (fatigue), and overall disease severity (Figs. 2, and 3). This finding is significant not only within the internal control of this NF trial but also in comparison to conventional FM treatments. Cognitive and fatigue-related impairments, which represent a major burden in FM, not only fail to improve with pharmacological treatments but often worsen due to medication-induced cognitive decline and increased fatigue [8, 52]. Despite being the standard therapeutic approach, pharmacological interventions provide symptom-oriented rather than mechanism-driven relief, leading to only modest clinical effects and posing substantial risks of adverse side effects [53, 54]. Similarly, while non-invasive neuromodulation techniques such as TMS and TENS have demonstrated efficacy in reducing pain symptoms with minimal chronic side effects, their effects remain largely confined to the somatosensory domain, failing to address the broader cognitive and affective dysfunctions that contribute significantly to FM's disease burden [10–13]. A key advantage of NF over existing treatment modalities is its ability to facilitate self-directed neuroplasticity. Unlike pharmacological treatments, TMS and TENS interventions, which rely on external stimulation, NF enables patients to actively regulate their brain activity, fostering intrinsic, self-sustained learning and long-term neural adaptation within pathological circuits [31, 55, 41]. This capacity for endogenous modulation may underlie the sustained therapeutic effects observed in this and other NF studies [40, 50, 51].

Interestingly, the treatment-specific improvements observed in the NFT group, including enhancements across multiple FM-relevant domains and, crucially, in the total SSS, a key measure of overall disease burden, were obtained despite no significant difference in long-term pain relief between the genuine and sham NF groups. Given that pain is a hallmark symptom of FM, this finding challenges the traditional focus on pain as the primary target for FM interventions. Instead, it suggests that other symptom dimensions are equally

critical in determining overall disease severity and should receive greater clinical attention. It may be more accurate to view pain within FM as a part of a network of interrelated symptoms that influence one another [14, 56]. Supporting this perspective, Goldway et al. [40] found that long-term pain relief in patients with FM was predicted by immediate improvements in somatic-affective homeostasis metrics, such as sleep quality and affective state, following Amyg-EFP-NF training. This aligns with a growing body of evidence highlighting the reciprocal relationship between affective dysregulation, particularly emotion regulation deficits, and the maintenance of chronic pain [57, 58]. This evidence further supports the theoretical framework proposed by Pinto et al.[14], which posits that affect-regulation dysfunction leads to persistent activation of the brain's salience network, which triggers some of the basic biological mechanisms underlying FM symptoms, and in turn, feeds back into the negative imbalance of emotional regulation. According to this model, interventions targeting emotional regulation may yield benefits not only for affective symptoms but also for pain modulation and other FM-related impairments. Our findings provide empirical support for this framework in two key ways. First, the significant clinical improvements observed in the NFT group following NF training targeting the amygdala, a central node in emotional regulation, suggest that restoring balance in this system can disrupt the pathological cycle underlying FM's broad symptomatology. Notably, the correlation between NF success in the NFT group and long-term clinical benefits across multiple clinical domains (Fig. 4C-E) further strengthens the causal link between Amyg-EFP training and sustained symptom relief. Second, immediate reduction in anxiety, a key marker of emotional dysregulation, predicted long-term improvements in FM symptoms, but only in the genuine NF group. This finding reinforces the hypothesis that affect-regulation dysfunction plays a fundamental role in FM pathophysiology. In contrast, immediate pain relief did not predict long-term improvement in overall disease severity in the NFT group and even negatively predicted long-term outcomes in the sham group. These findings further support the notion that pain in FM is not the central defining feature of the syndrome but rather a component of a complex interplay of interrelated symptoms [14, 56]. In conclusion, the observed multi-domain and sustainable clinical improvements achieved by targeting affect-regulation processes highlight the significant therapeutic potential of mechanism-driven therapies that address the specific pathogenesis of FM, as opposed to traditional symptom-oriented treatments.

Contrary to our expectations, both real and sham NF groups successfully downregulated their Amyg-EFP signal during NF training. However, two key findings indicate a distinct learning pattern in the NFT group. First, only the NFT group showed a significant linear progression in NF performance, indicating a progressing learning process (Fig. 4B) [59]. Second, a unique correlation emerged exclusively in the NFT group between two critical measures of NF success – the ability to generalize NF learning (transfer score) and NF capacity (the difference between Regulate and Watch; Fig. 4A). These results imply that although both groups demonstrated short-term modulation success, only genuine feedback established a strong and lasting connection between these learning mechanisms.

This complex pattern may be explained by the role of the feedback interface in shaping the modulation learning process. Specifically, our paradigm was designed to establish an affective context conducive to emotional regulation [60]. Implementing this process-specific contextual interface likely provided implicit guidance for utilizing strategies relevant to emotional regulation (see Additional File 3: Figure S1 and Table S2). This would also explain why clinical benefits in the NFS group were either absent or short-lived, as their improvements were sporadic and lacked the consolidation necessary for long-term, context-independent learning, as seen in the NFT group.

This study has several limitations. First, replication in a larger, more gender-diverse sample with a broader age range is necessary to assess the reproducibility and generalizability of the observed clinical effects. Second, given the central role of emotional regulation in FM pathophysiology and the amygdala-targeted approach of this study, a key limitation is the reliance on anxiety as the sole measure of affect dysregulation. Future research should incorporate a broader range of assessments, including intrinsic (e.g., heart rate variability) and extrinsic emotion regulation measures, to provide a more comprehensive understanding of affective dysfunction in FM. Additionally, a methodological limitation of this study is the potential for an enhanced placebo effect due to the implicit induction of mental strategies tailored to emotional regulation. When considering both desired and undesired effects, one must carefully navigate the delicate trade-off between improving NF learning outcomes (see Additional File 3: Figure S2) and generating a robust placebo effect. To better delineate the mechanisms underlying NF learning, future studies should consider alternative control conditions that involve regulating a distinct brain target rather than sham-EFP feedback [41, 61]. Specifically, an optimal NF control condition should differ from the Amyg-EFP NF group not only in anatomical locus but also in the targeted neural process [61]. This approach would help to dissociate between target-specific effects and general NF training effects [31, 62].

Conclusions

This double-blind, randomized, double-controlled clinical trial with long-term follow-up demonstrates that targeting neural circuits implicated in affective dysregulation, a core element in FM and central sensitization pathogenesis, can lead to broad and sustainable clinical improvements. Given its scalability, including potential home-based applications, this neuromodulation approach has the potential to transform current FM treatment, offering a viable alternative to pharmacological therapies that have shown only limited success. Furthermore, this method holds promise for broader application in other brain-based disorders conceptualized as central sensitization syndromes, where affect-regulation imbalances contribute to stress-induced symptom amplification beyond chronic pain.

Abbreviations

Amyg-EFP	Amygdala Electrical-Finger-Print
BOLD	Blood-oxygen-level-dependent
CS	Central sensitization
FM	Fibromyalgia
FIQ	Fibromyalgia Impact Questionnaire
FU	Follow-up
fMRI	Functional MRI
MTP	Measurement time-point
NF	Neurofeedback
NFS	NF sham
NFT	NF treatment
SNM	Self-neuromodulation
SSS	Symptom Severity Score
SSS- Cog	SSS-cognitive sub-score
TASMC	Tel Aviv Sourasky Medical Center
STAI-T	Trait Anxiety Inventory
TAU	Treatment as usual
WPI	Widespread Pain Index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04138-3.

Additional file 1. CRED-NF Checklist Summary. Description of data: Summary of the checklist compliance for NF studies, including registration, blinding, and control groups. Additional file 2. Methods. Method S1. The Amyg-EFP Model. Method S2. EEG Acquisition and Online Calculation. Method S3. Animated Scenario Feedback Generation. Method S4. Evaluation of Clinical Feasibility. Method S5. Long-term Improvement in Symptoms Severity: Prediction Analysis. Method S6. Evaluation of NF Learning Success. Figure S1. Fig. S1. The amygdala-electrical fingerprint (Amyg-EFP) prediction model. Additional file 3. Methodological Validations. Methodological Validation S1. Satisfaction Level Analysis. Methodological Validation S2. Mental Strategies Analysis. Methodological Validation S3. Effectiveness of Amyg-EFP-NF: Proportion of NF Successful Modulators. Figures S1-S2. Tables S1-S2. Fig. S1. Exploration of Mental Strategies. Fig. S2. Proportion of Good and Poor Amyg-EFP-NF Modulators. Table S1. Satisfaction Level Regarding the NF-Intervention. Table S2. Mental Strategies Classification and Examination of Between-Groups Difference.

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Authors' contributions

AOB and YL contributed equally to this study and share first authorship. AOB, YL, JNA, TH, and HS were involved in the conceptualization and design of the study. AOB carried out validation, formal analysis, data acquisition and interpretation, as well as project administration, and visualization. YH and GG were responsible for software development, validation, formal analysis, and data curation. NM, MD, and NS contributed to data acquisition and formal analysis. JNA assisted with conceptualization, data interpretation, and patient provision. YL, TH, and HS supervised the study and contributed to funding acquisition. AOB drafted the original manuscript, and YL, TH, and HS handled review and editing. All authors read and approved the final manuscript.

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Data availability

The datasets generated and analyzed during the current study are not publicly available due to medical confidentiality and since participants did not consent to having their data publicly published. The unidentified data (e.g. data spreadsheet) that support the findings of this study are available from the corresponding author on reasonable request (A.O.B).

Declarations

Ethics approval and consent to participate

The study protocol received approval from the Institutional Ethical Review Board of Tel Aviv Sourasky Medical Center (TASMC), reference number 0044–14-TLV. Written informed consent was obtained from all participants prior to their enrollment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Sagol Brain Institute, Tel-Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 6423906, Israel. [2]Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv 6997801, Israel. [3]Faculty of Medical and Health Sciences, Tel-Aviv University, Tel-Aviv 6997801, Israel. [4]Gershon H. Gordon Faculty of Social Sciences, School of Psychological Sciences, Tel-Aviv University, Tel-Aviv 6997801, Israel. [5]Internal Medicine, Tel-Aviv Sourasky Medical Center, Tel-Aviv 6423906, Israel. [6]Institute of Pain Medicine, Department of Anesthesiology, Critical Care and Pain, Tel-Aviv Sourasky Medical Center, Tel-Aviv 6423906, Israel.

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References

1. Wu Y-L, Chang L-Y, Lee H-C, Fang S-C, Tsai P-S. Sleep disturbances in fibromyalgia: A meta-analysis of case-control studies. J Psychosom Res. 2017;96:89–97.
2. Wolfe F, Rasker JJ. The evolution of fibromyalgia, its concepts, and criteria. Cureus. 2021;13(11):e20010. https://doi.org/10.7759/cureus.20010.
3. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3):S2–15.
4. Ji R-R, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003;26(12):696–705.
5. Spisák T, Pozsgay Z, Aranyi C, Dávid S, Kocsis P, Nyitrai G, et al. Central sensitization-related changes of effective and functional connectivity in the rat inflammatory trigeminal pain model. Neuroscience. 2017;344:133–47.

6. Crofford LJ. Chronic pain: where the body meets the brain. Trans Am Clin Climatol Assoc. 2015;126:167.
7. Burke AL, Mathias JL, Denson LA. Psychological functioning of people living with chronic pain: A meta-analytic review. Br J Clin Psychol. 2015;54(3):345–60.
8. Häuser W, Ablin J, Fitzcharles M-A, Littlejohn G, Luciano JV, Usui C, et al. Fibromyalgia Nat Rev Dis. 2015;1(1):1–16.
9. Pinto AM, Geenen R, Palavra F, Lumley MA, Ablin JN, Amris K, Branco J, Buskila D, Castelo-Branco M, Crofford LJ, Fitzcharles M. An updated overview of the neurophysiological and psychosocial dimensions of fibromyalgia–a call for an integrative model. 2020. Preprint at https://www.preprints.org/manuscript/202007.0224/v1.
10. Toh EY, Ng JS, McIntyre RS, Tran BX, Ho RC, Ho CS, et al. Repetitive transcranial magnetic stimulation for fibromyalgia: an updated systematic review and meta-analysis. Biopsychosoc Med. 2022;84(4):400–9.
11. Sun P, Fang L, Zhang J, Liu Y, Wang G, Qi R. Repetitive transcranial magnetic stimulation for patients with fibromyalgia: a systematic review with meta-analysis. Pain Med. 2022;23(3):499–514.
12. Amer-Cuenca JJ, Badenes-Ribera L, Biviá-Roig G, Arguisuelas MD, Suso-Martí L, Lisón JF. The dose-dependent effects of transcutaneous electrical nerve stimulation for pain relief in individuals with fibromyalgia: a systematic review and meta-analysis. Pain. 2023;164(8):1645–57.
13. García-López H, Calle-Ortega F, García-Robles P, del-Rey RR-, Obrero-Gaitán E, Cortés-Pérez I. Effectiveness of transcutaneous electrical nerve stimulation improves pain intensity, disability and quality of life in patients with fibromyalgia syndrome: a systematic review with meta-analysis. Disabil Rehabil. 2024;46(26):6323–33.
14. Pinto AM, Geenen R, Wager TD, Lumley MA, Häuser W, Kosek E, et al. Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia. Nat Rev Rheumatol. 2023;19(1):44–60.
15. Denny BT, Inhoff MC, Zerubavel N, Davachi L, Ochsner KN. Getting over it: Long-lasting effects of emotion regulation on amygdala response. Psychol Sci. 2015;26(9):1377–88.
16. Berboth S, Morawetz C. Amygdala-prefrontal connectivity during emotion regulation: A meta-analysis of psychophysiological interactions. Neuropsychologia. 2021;153: 107767.
17. Zaldivar A, Krichmar JL. Interactions between the neuromodulatory systems and the amygdala: exploratory survey using the Allen Mouse Brain Atlas. Brain Struct Funct. 2013;218:1513–30.
18. Neugebauer V. Amygdala pain mechanisms. Pain control. 2015;227:261–84.
19. Baliki MN, Apkarian AV. Nociception, pain, negative moods, and behavior selection. Neuron. 2015;87(3):474–91.
20. Choy EH. The role of sleep in pain and fibromyalgia. Nat Rev Rheumatol. 2015;11(9):513–20.
21. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Neural mechanisms of emotion regulation: evidence for two independent prefrontal-subcortical pathways. Neuron. 2008;59(6):1037.
22. Goldstein-Piekarski AN, Greer SM, Saletin JM, Walker MP. Sleep deprivation impairs the human central and peripheral nervous system discrimination of social threat. J Neurosci. 2015;35(28):10135–45.
23. Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, et al. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. Psychosom Med. 2009;71(5):566–73.
24. Jensen KB, Srinivasan P, Spaeth R, Tan Y, Kosek E, Petzke F, et al. Overlapping structural and functional brain changes in patients with long-term exposure to fibromyalgia pain. Arthritis Rheum. 2013;65(12):3293–303.
25. Dehghan M, Schmidt-Wilcke T, Pfleiderer B, Eickhoff SB, Petzke F, Harris RE, et al. Coordinate-based (ALE) meta-analysis of brain activation in patients with fibromyalgia. Hum Brain Mapp. 2016;37(5):1749–58.
26. Hsiao F-J, Chen W-T, Ko Y-C, Liu H-Y, Wang Y-F, Chen S-P, et al. Neuromagnetic amygdala response to pain-related fear as a brain signature of fibromyalgia. Pain The. 2020;9:765–81.
27. Cifre I, Sitges C, Fraiman D, Muñoz MÁ, Balenzuela P, González-Roldán A, et al. Disrupted functional connectivity of the pain network in fibromyalgia. Psychosom Med. 2012;74(1):55–62.
28. Jensen KB, Loitoile R, Kosek E, Petzke F, Carville S, Fransson P, et al. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. Mol. Pain. 2012;8:1744–8069–8–32.
29. Makowka S, Mory L-N, Mouthon M, Mancini C, Guggisberg AG, Chabwine JN. EEG Beta functional connectivity decrease in the left amygdala correlates with the affective pain in fibromyalgia: A pilot study. PLoS ONE. 2023;18(2): e0281986.
30. López-Solà M, Woo C-W, Pujol J, Deus J, Harrison BJ, Monfort J, et al. Towards a neurophysiological signature for fibromyalgia. Pain. 2017;158(1):34–47.
31. Sitaram R, Ros T, Stoeckel L, Haller S, Scharnowski F, Lewis-Peacock J, et al. Closed-loop brain training: the science of neurofeedback. Nat Rev Neurosci. 2017;18(2):86–100.
32. Lubianiker N, Paret C, Dayan P, Hendler T. Neurofeedback through the lens of reinforcement learning. Trends Neurosci. 2022;45(8):579–93.
33. Kayıran S, Dursun E, Dursun N, Ermutlu N, Karamürsel S. Neurofeedback intervention in fibromyalgia syndrome; a randomized, controlled, rater blind clinical trial. Appl Psychophysiol Biofeedback. 2010;35:293–302.
34. Wu Y-L, Fang S-C, Chen S-C, Tai C-J, Tsai P-S. Effects of neurofeedback on fibromyalgia: a randomized controlled trial. Pain Manag Nurs. 2021;22(6):755–63.
35. Santoro M, Cronan T. A systematic review of neurofeedback as a treatment for fibromyalgia syndrome symptoms. J Musculoskelet Pain. 2014;22(3):286–300.
36. Hesam-Shariati N, Chang WJ, Wewege MA, McAuley JH, Booth A, Trost Z, et al. The analgesic effect of electroencephalographic neurofeedback for people with chronic pain: a systematic review and meta-analysis. Eur J Neurol. 2022;29(3):921–36.
37. Keynan JN, Cohen A, Jackont G, Green N, Goldway N, Davidov A, et al. Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. Nat Hum Behav. 2019;3(1):63–73.
38. Meir-Hasson Y, Keynan JN, Kinreich S, Jackont G, Cohen A, Podlipsky-Klovatch I, et al. One-class FMRI-inspired EEG model for self-regulation training. PLoS ONE. 2016;11(5): e0154968.
39. Meir-Hasson Y, Kinreich S, Podlipsky I, Hendler T, Intrator N. An EEG fingerprint of fMRI deep regional activation. Neuroimage. 2014;102:128–41.
40. Goldway N, Ablin J, Lubin O, Zamir Y, Keynan JN, Or-Borichev A, et al. Volitional limbic neuromodulation exerts a beneficial clinical effect on Fibromyalgia. Neuroimage. 2019;186:758–70.
41. Paret C, Goldway N, Zich C, Keynan JN, Hendler T, Linden D, et al. Current progress in real-time functional magnetic resonance-based neurofeedback: Methodological challenges and achievements. Neuroimage. 2019;202: 116107.
42. Galvez-Sánchez CM, De la Coba P, Duschek S, Reyes del Paso GA. Reliability, factor structure and predictive validity of the Widespread Pain Index and Symptom Severity scales of the 2010 American College of Rheumatology criteria of fibromyalgia. J Clin Med. 2020;9(8):2460.
43. Ros T, Enriquez-Geppert S, Zotev V, Young KD, Wood G, Whitfield-Gabrieli S, et al. Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist). Brain. 2020;143:1674–85.
44. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011;38(6):1113–22.
45. Cohen A, Keynan JN, Jackont G, Green N, Rashap I, Shani O, et al. Multimodal virtual scenario enhances neurofeedback learning. Front Robot AI. 2016;3:52.
46. Schabus M. Reply: On assessing neurofeedback effects: should double-blind replace neurophysiological mechanisms? Brain. 2017;140(10):e64-e.
47. Keynan JN, Meir-Hasson Y, Gilam G, Cohen A, Jackont G, Kinreich S, et al. Limbic activity modulation guided by functional magnetic resonance imaging–inspired electroencephalography improves implicit emotion regulation. Biol Psychiatry. 2016;80(6):490–6.
48. Burckhardt CS, Clark Sa, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J. rheumatol. 1991;18(5):728–33.
49. Spielberger CD, Gonzalez-Reigosa F, Martinez-Urrutia A, Natalicio LF, Natalicio DS. The state-trait anxiety inventory. Rev Interam Psicol. 1971;5(3 & 4):145–58.
50. Zilverstand A, Sorger B, Slaats-Willemse D, Kan CC, Goebel R, Buitelaar JK. fMRI neurofeedback training for increasing anterior cingulate cortex activation in adult attention deficit hyperactivity disorder. An exploratory randomized, single-blinded study. PLoS One. 2017;12(1):e0170795.

51. Anil K, Hall SD, Demain S, Freeman JA, Ganis G, Marsden J. A systematic review of neurofeedback for the management of motor symptoms in Parkinson's disease. Brain Sci. 2021;11(10):1292.
52. Mease PJ, Arnold LM, Crofford LJ, Williams DA, Russell IJ, Humphrey L, et al. Identifying the clinical domains of fibromyalgia: contributions from clinician and patient Delphi exercises. Arthritis Care Res (Hoboken). 2008;59(7):952–60.
53. Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, et al. AAPT diagnostic criteria for fibromyalgia. J Pain. 2019;20(6):611–28.
54. Thieme K, Mathys M, Turk DC. Evidenced-based guidelines on the treatment of fibromyalgia patients: are they consistent and if not, why not? Have effective psychological treatments been overlooked? J Pain. 2017;18(7):747–56.
55. Thibault RT, MacPherson A, Lifshitz M, Roth RR, Raz A. Neurofeedback with fMRI: A critical systematic review. Neuroimage. 2018;172:786–807.
56. Suñol M, Payne MF, Tong H, Maloney TC, Ting TV, Kashikar-Zuck S, et al. Brain structural changes during juvenile fibromyalgia: relationships with pain, fatigue, and functional disability. Arthritis Rheumatol. 2022;74(7):1284–94.
57. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci. 2013;14(7):502–11.
58. Koechlin H, Coakley R, Schechter N, Werner C, Kossowsky J. The role of emotion regulation in chronic pain: A systematic literature review. J Psychosom Res. 2018;107:38–45.
59. Pusic MV, Boutis K, Pecaric MR, Savenkov O, Beckstead JW, Jaber MY. A primer on the statistical modelling of learning curves in health professions education. Adv Health Sci Educ. 2017;22:741–59.
60. Cavazza M, Charles F, Gilroy SW, Porteous J, Aranyi G, Raz G, Keynan NJ, Cohen A, Jackont G, Jacob Y, Soreq E. Integrating virtual agents in BCI neurofeedback systems. InProceedings of the 2014 Virtual Reality International Conference. VRIC'14 (New York, NY: Association for Computing Machinery). https://doi.org/10.1145/2617841.2620713.
61. Lubianiker N, Goldway N, Fruchtman-Steinbok T, Paret C, Keynan JN, Singer N, et al. Process-based framework for precise neuromodulation. Nat Hum Behav. 2019;3(5):436–45.
62. Emmert K, Kopel R, Sulzer J, Brühl AB, Berman BD, Linden DE, et al. Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated? Neuroimage. 2016;124:806–12.

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