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Volitional limbic neuromodulation exerts a beneficial clinical effect on Fibromyalgia

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ABSTRACT

Volitional neural modulation using neurofeedback has been indicated as a potential treatment for chronic conditions that involve peripheral and central neural dysregulation. Here we utilized neurofeedback in patients suffering from Fibromyalgia - a chronic pain syndrome that involves sleep disturbance and emotion dysregulation. These ancillary symptoms, which have an amplificating effect on pain, are known to be mediated by heightened limbic activity. In order to reliably probe limbic activity in a scalable manner fit for EEG-neurofeedback training, we utilized an Electrical Finger Print (EFP) model of amygdala-BOLD signal (termed Amyg-EFP), that has been successfully validated in our lab in the context of volitional neuromodulation.

We anticipated that Amyg-EFP-neurofeedback training aimed at limbic down modulation would improve chronic pain in patients suffering from Fibromyalgia, by reducing sleep disorder improving emotion regulation. We further expected that improved clinical status would correspond with successful training as indicated by improved down modulation of the Amygdala-EFP signal.

Thirty-Four Fibromyalgia patients (31F; age 35.6 ± 11.82) participated in a randomized placebo-controlled trial with biweekly Amyg-EFP-neurofeedback sessions or sham neurofeedback ($n = 9$) for a total duration of five consecutive weeks. Following training, participants in the real-neurofeedback group were divided into good ($n = 13$) or poor ($n = 12$) modulators according to their success in the neurofeedback training. Before and after treatment, self-reports on pain, depression, anxiety, fatigue and sleep quality were obtained, as well as objective sleep indices. Long-term clinical follow-up was made available, within up to three years of the neurofeedback training completion.

REM latency and objective sleep quality index were robustly improved following the treatment course only in the real-neurofeedback group (time × group $p < 0.05$) and to a greater extent among good modulators (time × sub-group $p < 0.05$). In contrast, self-report measures did not reveal a treatment-specific response at the end of the neurofeedback training. However, the follow-up assessment revealed a delayed improvement in chronic pain and subjective sleep experience, evident only in the real-neurofeedback group (time × group $p < 0.05$). Moderation analysis showed that the enduring clinical effects on pain evident in the follow-up assessment were predicted by the immediate improvements following training in objective sleep and subjective affect measures.

Abbreviations: ACR, American College of Rheumatology; Amyg, EFP- Amygdala-Electrical Fingerprint.

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Our findings suggest that Amyg-EFP-neurofeedback that specifically targets limbic activity down modulation offers a successful principled approach for volitional EEG based neuromodulation treatment in Fibromyalgia patients. Importantly, it seems that via its immediate sleep improving effect, the neurofeedback training induced a delayed reduction in the target subjective symptom of chronic pain, far and beyond the immediate placebo effect. This indirect approach to chronic pain management reflects the substantial link between somatic and affective dysregulation that can be successfully targeted using neurofeedback.

1. Introduction

Volitional neuromodulation, known as neurofeedback (NF), allows individuals to exert control over neural activity by bridging between mental states and neural signal modulation (Sitaram et al., 2017). Such bridging may be necessary to preserve somatic-affective homeostasis; maintaining stability of the internal bodily environment and related subjective experience in response to environmental challenges (Barrett and Simmons, 2015).

Chronic somatic disorders often involve impaired homeostatic regulation that is mediated by disturbed neural function (Di Lernia et al., 2016a; Elman and Borsook, 2016; Smallwood et al., 2013). It has been suggested that NF can be used to modulate neural probes supporting homeostatic regulation, and may therefore be particularly suitable for treating somatic-affective homeostasis related disorders such as insomnia and chronic pain (Arns and Kenemans, 2014; deCharms et al., 2005). However, it remains unclear to what extent the NF effects demonstrated in such disorders are mediated by improved homeostasis, as opposed to non-specific, placebo-like processes (Thibault et al., 2016).

Fibromyalgia is a highly prevalent and difficult to treat chronic pain syndrome characterized by widespread pain, intimately related to maladaptive dysregulated homeostatic processes of sleep and emotion regulation (Choy, 2015; Hamilton et al., 2008; Hassett et al., 2008 Häuser et al., 2015). The pain chronicity in Fibromyalgia was suggested to be a multistep process that involves the breakdown of several control mechanisms, mainly mood regulation and sleep quality (Choy, 2015). In accordance, manifestations of aberrant sleep in Fibromyalgia and related disorders include increased sleep latency, reduced sleep efficiency (Diaz-piedra et al., 2014), decreased REM latency, increased REM percent (Moldofsky, 2001; Riemann, 2007) and reduced deep sleep periods (Choy, 2015). Chronic impairments in sleep have thus been suggested to result in enhanced "allostatic load"- the increased energetic expenditure an organism is required to endure as a result of being forced to adapt to adverse psychosocial or physical situations (McEwen, 2000, 2006; Sapolsky, 2007). This allostatic accumulation may lead to further neural, physiological and behavioral abnormalities, as well as subsequent pain facilitation, resulting in a vicious cycle (Borsook et al., 2012). Accordingly, Fibromyalgia is considered a prototype of the "central sensitization syndrome"; hypersensitivity of the central nervous system that is assumed to underlie a spectrum of complex psychiatric and somatic conditions including posttraumatic stress disorder (PTSD), tension type headache and premenstrual dysphoric disorder (Yunus, 2008, 2007). The common denominator of these disorders could be impaired homeostasis manifested in sleep disturbance and emotion dysregulation.

A key factor regulating both sleep and emotion is amygdala activity (Goldstein-Piekarski et al., 2015; Wager et al., 2008). Indeed, Fibromyalgia patients display altered limbic functionality as indicated by neural activity and connectivity studies (Cifre et al., 2012; Dehghan et al., 2016; Jensen et al., 2012) as well as reductions in gray matter volume within the amygdala (Burgmer et al., 2009; Lutz et al., 2008). Interestingly, limbic abnormalities have also been demonstrated in sleep deprivation (Ben-Simon et al., 2015; Yoo et al., 2007) as well as in "central sensitization syndrome" disorders such as PTSD (Hendler et al., 2003; Shin et al., 2006). We therefore hypothesized that neuromodulation of limbic activity using NF would benefit patients suffering from Fibromyalgia.

Numerous studies have demonstrated that using real-time fMRI-NF, healthy individuals can successfully modulate their limbic activity and present behavioral changes related to the targeted brain probe (for review see Sitaram et al., 2017). Clinical studies have further demonstrated similar results using amygdala driven fMRI-NF across several homeostatic/central sensitization disorders such as PTSD (Nicholson et al., 2017), borderline personality disorder (Paret et al., 2016) and major depression (Young et al., 2017a,b).

In chronic pain, two studies examined the efficacy of real-time-fMRI-NF by targeting the rACC (rostral Anterior Cingulate Cortex); a major node in the affective aspect of the so called pain matrix (deCharms et al., 2005; Guan et al., 2015). Results of these studies showed an improvement in ongoing pain following rt-fMRI-NF training, claiming an effect of rACC down regulation on pain perception. However, due to small sample sizes in both studies and at least in one study (i.e. deCharms et al., 2005), lack of replication and proper control (deCharms, 2012), the clinical benefit of NF for chronic pain should be supported by further evidence (Jensen et al., 2014).

Despite the potential of this treatment option, the high cost of real-time fMRI NF severely limits its use in community settings. Even when available, the number of training sessions for each individual ends up being restricted by equipment availability. Moreover, traditional criteria for MRI compatibility may result in the exclusion of a significant subset of patients. To overcome such difficulties, we recently introduced a novel approach that combines the advantages of fMRI and EEG, i.e., high anatomical resolution and widespread availability, respectively. Our technology is based on an fMRI-driven EEG computational model, that reflects amygdala activation and supporting regulation networks (i.e. limbic and salience systems) as depicted in simultaneous EEG/fMRI recording, termed here "Amygdala-Electrical Fingerprint" (Amyg-EFP) (Keynan et al., 2016; Meir-Hasson et al., 2016, 2014). In a series of validation studies on a separate group of healthy participants, we have shown that NF training employing the Amyg-EFP signal as a probe, resulted in improved targeting of the amygdala BOLD (Blood-oxygen-level dependent) signal in a subsequent fMRI session (Keynan et al., 2016). Further, we have recently demonstrated that repeated session of Amyg-EFP-NF resulted in enhanced amygdala-BOLD down regulation and amygdala-vmPFC functional connectivity (Keynan et al., in press).

Utilizing Amyg-EFP for the first time in the clinical domain we have conducted a multisession, double-blind, placebo-controlled NF trial in patients suffering from Fibromyalgia. The goal was to train individuals to down-modulate the Amyg-EFP signal and to examine the training effect on chronic pain as well as on ancillary symptoms related to somatic and affective regulation. We obtained subjective assessment of pain, sleep and affect dysregulation, as well as objective measures of sleep quality. Of the numerous manifestations of aberrant sleep in Fibromyalgia, our focus was on REM latency, which is known to be related to amygdala activation (Luppi et al., 2004; Nofzinger et al., 2004) and affective dysregulation in mood disorders (Kupfer, 1976; Palagini et al., 2013).

We hypothesized that: (1) Fibromyalgia patients in the real-NF group would exhibit greater down modulation of the Amyg-EFP signal than the control group. (2) Given that our training probe was limbic and not classically related to the core pain processing network (Apkarian et al., 2005), we expected that the Amyg-EFP-NF training would differentially improve ancillary symptoms related to homeostasis as demonstrated by sleep and affect impairments. Moreover, we expected these changes to be accompanied by improvement in chronic pain symptoms. (3) Individual

differences in treatment outcome improvement would correspond to NF success.

2. Materials and methods

2.1. Participants

Patients were recruited from the Fibromyalgia clinic of the Institute of Rheumatology and from the Institute of Pain Medicine at Tel Aviv Medical Center in Israel. All patients had a diagnosis of Fibromyalgia according to the American College of Rheumatology (ACR) 2010 criteria (Wolfe et al., 2011) which was confirmed by a clinical interview and physical examination by an expert rheumatologist or pain specialist. Exclusion criteria included other chronic pain syndromes, major neuropsychiatric illness and recently changed/initiated pharmacotherapy. Patients were randomly assigned using a computerized algorithm to either sham-EFP or true NF interventions, with an a-priori ratio of 1:2 favoring the latter. This ratio was determined in order to allow for subgrouping of the true intervention group into good and poor NF modulators. Blinding was performed using in-house computer software and a file containing participant's group affiliation was examined only when NF data collection had ended. Thus, participants, care providers and clinicians assessing outcomes were all blinded to treatment.

In total, 136 Fibromyalgia patients underwent initial screening during which ninety-three subjects were excluded: seventy-four did not wish to participate for various personal reasons and nineteen did not meet the ACR 2010 criteria. Forty-three participants underwent randomization and were allocated randomly to real or sham NF intervention. This resulted in 31 participants allocated to the real NF group and 12 participants allocated to the sham group. Of the 31 participants that were allocated to the real NF group, 6 dropped out, resulting in 25 participants (24 females) that underwent the full real Amyg-EFP NF treatment. Of the 12 participants allocated to the sham NF group, 3 dropped out, resulting in 9 (7 females) participants that underwent the full sham NF treatment, totaling 34 Fibromyalgia patients who completed the main procedure (age = 35.62 ± 6.1, 31 females, 79% retention, see Table 1).

Table 1
Baseline characteristics of the sample. VAS- visual analog scale, FIQ-Fibromyalgia Impact Questionnaire, BDI-Beck's Depression Inventory, STAI T-Trait Anxiety Inventory, PSQI- Pittsburgh Sleep Quality Index.

	Amyg-EFP-NF M±S.D	Sham-NF M±S.D	T/ Fisher's Exact Test	P-value
Gender	1M 24F	2M 7F		0.16
Age	35.5 ± 12.6	35.9 ± 10.6	0.08	0.93
Time from diagnosis (years)	4.3 ± 4.1	4.1 ± 4.4	0.12	0.9
SSRI/SNRI (%)	16	33.33		0.35
Gabapentinoids (%)	24	33.33		0.67
Cannabis (%)	20	22.22		1
Analgesics (%)	8	0		1
Miscellaneous (%)	12	11		1
Pain (VAS, McGill, FIQ pain)	2.73 ± 0.9	2.88.73 ± 1.1	0.41	0.68
Affect (STAI-T, BDI, FIQ anxiety, FIQ depression)	2.53 ± 0.7	2.84 ± 0.7	1.02	0.32
Sleep experience (PSQI, FIQ fatigue)	4.17 ± 0.9	3.93 ± 1.0	0.69	0.49
REM latency (min)	76.67 ± 35.2	90.0 ± 34.5	0.97	0.34
Composite Sleep Score (sleep latency, sleep efficiency, REM latency, Deep Sleep percent, REM sleep percent)	−0.09 ± 0.43	0.13 ± 0.28	1.4	0.17

2.2. General procedure

The study was conducted at the Sagol Brain Institute, Tel Aviv Sourasky Medical Center and was approved by the Institutional Ethical Review Board. All participants provided written informed consent before entering the study.

Prior to the NF treatment course, patients underwent a "Pre-NF" (pre) assessment that included a clinical evaluation, disease-related questionnaires, and one night of home sleep monitoring using an ambulatory sleep device (WatchPAT-200; Itamar Medical). Patients then underwent ten biweekly sessions of either real-NF or sham-EFP. After completing the NF course patients underwent "Post NF" (post) assessment, conducted within one week of the last NF session. This evaluation was identical to the baseline assessment (see Fig. 1).

Follow-up assessment: As part of a new study, examining the feasibility of a new NF technique, we re-contacted subjects who participated in the study. We were able to reach 32 subjects 16.2 ± 8.72 months who completed the NF course (real-NF group = 23, the two participants who were not available for follow-up were in the "good modulators" subgroup, for details regarding characteristics of this sample see Table S2). We used this opportunity for an exploratory assessment of long-term effects of the original study using the same outcome questionnaires (see outcome measures). Importantly, during the time of this follow up, subjects were still blinded to the type of treatment they received (real or sham- NF). Of note, all analyses of the follow-up assessment included time from the end of treatment as a covariate to account for variability across participants (see statistical analysis). Also at this time point, no marked difference in pharmacological treatment were observed between real NF and sham groups (see Table S2).

2.3. Neurofeedback procedure

NF treatment course protocol included ten NF sessions, each session was composed of training either using an auditory interface (sessions one, three and five), an animated scenario interface (sessions two, four and six) or both (sessions seven, eight nine and ten in the same order across sessions) (see Fig S1A). Missing more than two NF sessions, out of a total of ten, was determined as a criterion for exclusion. Five participants from the real-NF group missed two sessions.

As mentioned, participates were trained to downregulate their Amyg-EFP using two interfaces for feedback: 1. An auditory interface in which the neural signal correlated with the volume of a soft piano tune (Kinreich et al., 2014), and 2. a 3D audio-visual animated scenario in which the neural signal is correlated with the level of unrest in a scenario where virtual characters in a waiting room become impatient, leave their seats and gesture loudly at the front desk receptionist (Cohen et al., 2016) (for illustration see Fig S1B and video S1). The decision to use two different interfaces aimed to encourage broad exploration of mental strategies, which can potentially lead to better regulation abilities. As the advantage of multi-modal stimuli has been demonstrated in various contexts of perceptual learning (Gibson and Maunsell, 1997; Kriegstein and Giraud, 2006; Shams and Seitz, 2008) and were suggested to strengthen integrative processes (van Atteveldt et al., 2014), we decided to introduce participants to varied feedback environments that would potentially maximize their regulation performance. Within each session, NF trials contained two conditions: rest and regulate. Participants were instructed to modulate the interface only during the regulate condition. The real-NF group received feedback reflecting their Amyg-EFP signal level modulation while the control group received feedback reflecting a pre-recorded Amyg-EFP signal obtained from another successful participant in the real-NF group, indicating approximately 85 percent success in each session. EFP signal for the sham NF condition was obtained from different participants in accordance with the relevant order of sessions and feedback modality. This method of producing a sham signal enabled us to control for "NF general effects" such as *control* (applying mental strategies in the attempt to modulate the presented neural pattern),

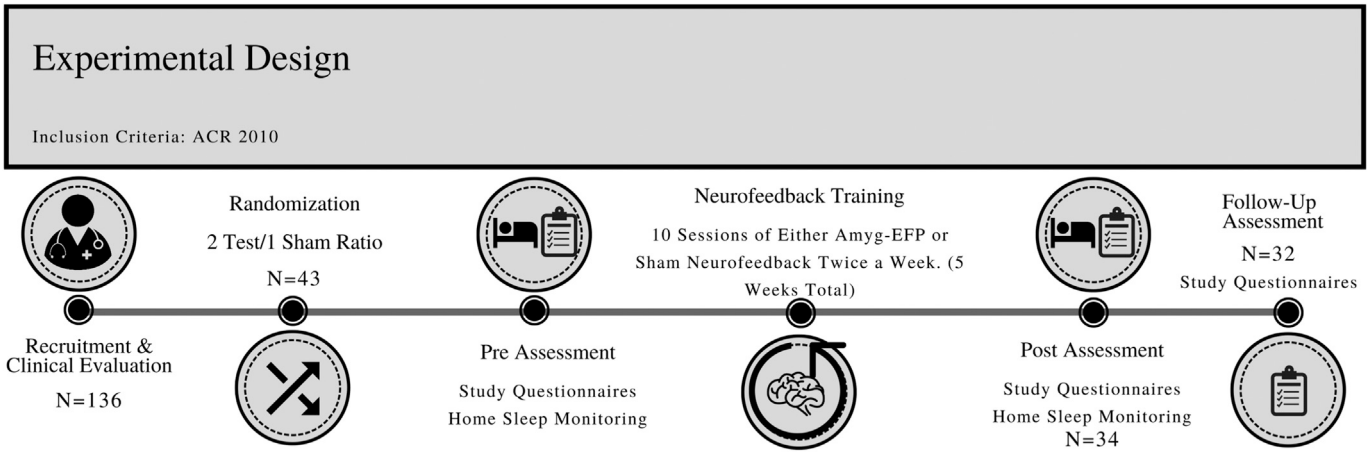

Fig. 1. Experimental design.

reward (valuation of positive/negative outcomes of applied strategies) and *Learning* (the consolidation of associations between reward feedback cues and neural activity patterns) (Sitaram et al., 2017).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.11.001.

2.4. EEG acquisition and on-line calculation

EEG data was acquired using the V-Amp™ EEG amplifier (Brain Products™, Munich Germany) and the BrainCap™ electrode cap with sintered Ag/AgCI ring electrodes (Falk Minow Services™, Herrsching-Breitburnn, Germany). Electrodes were positioned according to the standard 10/20 system. The reference electrode was between Fz and Cz. Raw EEG signal was sampled at 250 Hz and recorded using the Brain Vision Recorder™ software (Brain Products). Amyg-EFP amplitude was calculated based on data recorded from the Pz channel using an in-house algorithm (Meir-Hasson et al., 2016, 2014). See supplementary material for more details.

2.5. NF success measure

Similar to previous studies (Cohen et al., 2016), success in Amyg-EFP signal downregulation was assessed by calculating a personal effect size (Cohen's *d*) of each subject in each trial using the following formula:

$$\text{Effect size} = \frac{\text{mean rest} - \text{mean regulate}}{\sqrt{(SD\ rest^2 + SD\ regulate^2)}}$$

As the neural target was Amyg-EFP down regulation, a desired result would be lower "regulate" than "rest" values, resulting in a bigger (more positive) effect size (see Fig S1C for a graphic description).

Overall success (across all sessions) was evaluated using a *global NF score:* we first calculated z-scores for the effect size for each NF session for each interface. Using these z-scores, we then calculated the mean effect size across all sessions.

In order to assess the contribution of success in NF to changes in clinical status, we wished to cluster the real-NF group into two subgroups based on their performance. Clustering was based on relative difference within the real-NF group. To this end, we used the popular k-means algorithm that clustered the two subgroups based on effect sizes from all the sessions. This clustering was further validated by median split of the *global NF score,* resulting in two sub-groups: good (n = 13, 13 female) and poor (n = 12, 11 female) modulators. To assess the improvement in NF learning over sessions we calculated the delta between the normalized effect size in the first and last sessions in both interfaces. This was labeled the *NF learning index.*

2.6. Outcome measures

Self-report measures: In order to assess the patient's condition in three core symptoms of Fibromyalgia (pain, sleep experience and affect) we used the following validated self-report questionnaires: Fibromyalgia impact questionnaire (FIQ) (Burckhardt et al., 1991), trait anxiety inventory (STAI-T) (Spielberger et al., 1970), Beck depression inventory (BDI) (Beck et al., 1961), the Pittsburgh sleep quality index (PSIQ) (Buysse et al., 1989) and the McGill pain questionnaire (Melzack, 1975), which also includes a Visual Analogue Scale (VAS). To tackle the overlap evident across these questionnaires, three compound scores were computed from all subscales reflecting pain, sleep experience, and affect. The compound scores were based on reliability tests, indicating the overall consistency of a measure by representing the proportion of systematic variation in a scale. Each scale was constructed using the combination of self-report scales that provided the highest reliability score, measured using Cronbach's alpha (Cronbach, 1951; Tavakol and Dennick, 2011). *Affect* was assessed using mean normalized score of the STAI-T questionnaire, the BDI questionnaire, and the anxiety and depression subscales of the FIQ questionnaire (Cronbach's alpha = 0.76). *Sleep experience* was assessed using normalized score of the PSIQ and the fatigue subscale of the FIQ questionnaire (Cronbach's alpha = 0.77). *Pain* was assessed using VAS and general score of the McGill pain questionnaire and subscales of the FIQ for pain (Cronbach's alpha = 0.91).

Sleep assessment: One-night sleep monitoring was performed up to one week before and after the NF training course using the WachPAT-200 device. This device is based on recordings of peripheral arterial tone, along with pulse rate, actigraphy, and pulse oximetry. The WachPAT-200 was shown to accurately detect sleep versus wakefulness (Hedner et al., 2004), to differentiate light and deep sleep, and to detect REM sleep (Bresler et al., 2008; Hedner et al., 2011; Herscovici et al., 2007).

REM latency (i.e. time span between the start of sleeping and the start of the first REM episode) was used as the main sleep outcome measure due to prior work demonstrating a robust link between increased REM latency and mood regulation disorders (Palagini et al., 2013). To assess sleep more globally, we created an index composed of several features known to be important for sleep in Fibromyalgia. This index reflected increased sleep latency (time between going to bed and falling asleep), reduced sleep efficiency (the ratio of the total time spent asleep compared to the total amount of time spent in bed) and lack of proper deep sleep (quantified using "deep sleep percent" and "REM sleep percent", i.e. the ratio of the total time spent in deep/REM sleep out of the total sleep time) (Spaeth et al., 2011). Each measure was standardized and given a positive or negative coefficient, reflecting its contribution to the sleep abnormality in Fibromyalgia: sleep latency (−1), sleep efficiency (+1), REM latency (+1), deep sleep percent (+1) and REM

sleep percent (−1). The average of these weighted and standardized scores was defined as the *composite sleep score*.

2.7. Statistical analyses

Analyses were performed using IBM SPSS, version 20, Statistica version 10 (StatSoft, Inc) and MATLAB 2013b. Demographic results were descriptive and expressed as mean ± standard deviation (see Table 1). We compared the baseline characteristics of each group using chi-square or Fisher's exact test for categorical variables, and two-sample *t*-test for continuous variables. All reported p values are two tailed and Bonferroni corrected (Dunn, 1961) with respect to the number of comparisons conducted in each analysis, unless stated otherwise.

2.7.1. Outcome measures

To evaluate treatment effect, we used mainly repeated measures ANOVAs, with between-subject factor of group (Amyg-EFP-NF/sham-EFP). To evaluate NF learning we used NF session (first/last) as within-subject factor and for clinical improvement we used pre/post NF training within-subject factor.

To assess the contribution of NF regulation abilities to the clinical outcome, we categorized the real-NF group into two subgroups according to their success (see above). We then performed repeated measures ANOVA with clinical outcome as dependent variable, with three groups (good modulators/poor modulators and sham-EFP) as between subject factor and time (pre/post NF) as the within subject factor.

When assessing clinical improvement at follow-up, a covariant of time from end of treatment was included in all statistical models. Treatment effects were tested at a two-sided significance level of 0.05. Change in outcome measures was quantified using effect size (Cohen's d) (Cohen, 1992, 1988).

For clinical efficacy assessment, we evaluated the number needed to treat (NNT) for our primary objective sleep outcome measure, REM latency, and for pain reduction. NNT represents the number of patients that need to be treated for one patient to benefit compared with a control (Laupacis et al., 1988). Thus, higher NNT indicates less effective treatment (Cordell, 1999). For normalized sleep, we defined clinical improvement as a patient that had a pre-assessment REM latency of less than 90 min and post-NF assessment of more than 90 min. Reduced pain was defined as at least forty percent decrease in visual analog scale (VAS).

2.7.2. Moderation analysis

To examine whether reduction in pain ratings in the follow-up assessment was due to clinical changes observed at the end of the NF training, we used moderation analysis. This analysis determines whether the size of the effect of some putative causal variable X on outcome Y depends on a moderator variable (Hayes, A. F., 2013). In other words, how the interaction between two independent variables can contribute to the prediction of the outcome variable. Specifically, we applied this concept to examine whether changes in *composite sleep score* moderate the manner by which initial improvement in extra-musculoskeletal symptoms (i.e. *affect* and *sleep experience*) impact pain improvement in the long run. For this moderation analysis we used the bootstrap method of Preacher and Hayes (2004), which enabled estimation of the effects that *composite sleep score* (pre-post), *affect* (pre-post), *sleep experience* (pre-post) and their interaction on pain in the follow-up assessment (post-follow-up). This was done with time from the end of NF training as covariant. We evaluated the contribution of *composite sleep score* as moderator and of each predictor separately, based on 5000 bootstrap samples using SPSS macro version 3 (www.processmacro.org).

3. Results

3.1. Neurofeedback learning and success

In accordance with our first hypothesis, we found improved performance in Amyg-EFP regulation abilities in the last compared to the first training session in the real-NF, but not in the control group (Fig. 2A). A repeated measures ANOVA revealed greater NF learning in the real-NF group compared to the control group [Session × Group interaction $F(1,32) = 9.7$; $p < 0.005$; $d = 1.24$], with first-last session difference significant for the real-NF group only [post hoc pBonferroni<0.0005](for further details regarding results of NF learning see supplementary material).

We then sought to examine whether performance during the first NF sessions were predictive of overall NF regulation performance. To this end, a regression model was built using real-NF group data ($n = 25$). The model's aim was to predict the average effect size of sessions 3–10 using the first two NF sessions. To this end, two predicting variables were entered into the model: the effect size of the first animated scenario session and the effect size of the first auditory session. The final model contained only the animated scenario success index as a single predictor, as its predictive power had a more significant contribution. The auditory success index did not contribute significantly to the model and was thus excluded from its final version. The final model accounted for 16.1% (adjusted R square) of the variance in the dependent variable; overall regulation performance [$F(1,24) = 5.6$; $p < 0.05$] (see Fig. 2B).

3.2. Neurofeedback training outcomes

Our second hypothesis asserted that real-NF training would improve homeostatic indices such as sleep and affect as well as measures of pain (for full details regarding clinical outcomes see supplementary table 1). Notably, one participant from the real-NF group was not included in this analysis, as he did not provide self-report measures in the pre-assessment. Focusing first on subjective measures of *affect*, *sleep experience* and *pain* we did not find any significant effects of NF treatment (all Time × Condition $p > 0.16$). Following our a-priori assumption, we nevertheless tested for the simple effect of time in each group. This analysis revealed two significant results: *affect* was improved in the real-NF group only, and *sleep experience* was improved across both groups ($p < 0.01$; $p < 0.005$ respectively) (Fig. 3A–C).

In contrast, analysis of the objective measures of sleep: REM latency and *composite sleep score* (see methods), indicated greater improvement in real than sham-NF group after treatment. [Time × Condition interaction; REM latency: $F(1,30) = 4.43$; $p < 0.05$; $d = 0.85$, *composite sleep score*: $F(1,30) = 6.81$; $p < 0.05$; $d = 1.05$]. The NNT calculation for normalizing REM latency to at least 90 min, was 2.875. Of note, two subjects were unable to perform one session of objective sleep assessment due to technical difficulties and were thus excluded from the analysis. The two missing datasets belonged to participants from the real-NF group; one from the good modulators and one from the poor modulators subgroup.

3.3. Neurofeedback success relation to clinical outcome

Our third hypothesis predicted that individual differences in NF modulation would be reflected in clinical real-NF group outcome. In contrast to our expectation, there was no significant Time*Sub-group interaction for *affect*, *sleep experience* or pain (all $p > 0.19$).

However, objective outcome measures confirmed our hypothesis for both REM latency [Time × Group, $F(2,29) = 4.46$; $p < 0.05$; $d = 1.15$], and *composite sleep score* [Time × Group, $F(2,29) = 8.1$; $p < 0.005$; $d = 1.4$], showing improvement over time only in good modulators [REM latency; pBonferroni<0.05, *composite sleep score*; pUncorrected<0.05]. We further computed a change index for REM latency and *composite sleep score* (the delta between the 'pre' and 'post' assessment) in order to confirm that improvement in objective sleep indices was greater in good modulators. We then used this index in a one-way ANOVA model. This test confirmed that good modulators improved to a greater degree compared to both the poor modulators or sham group [REM latency, good modulators vs. sham; pBonferroni<0.05, *composite sleep score*, good modulators vs. sham; pBonferroni<0.005, good modulators vs. poor

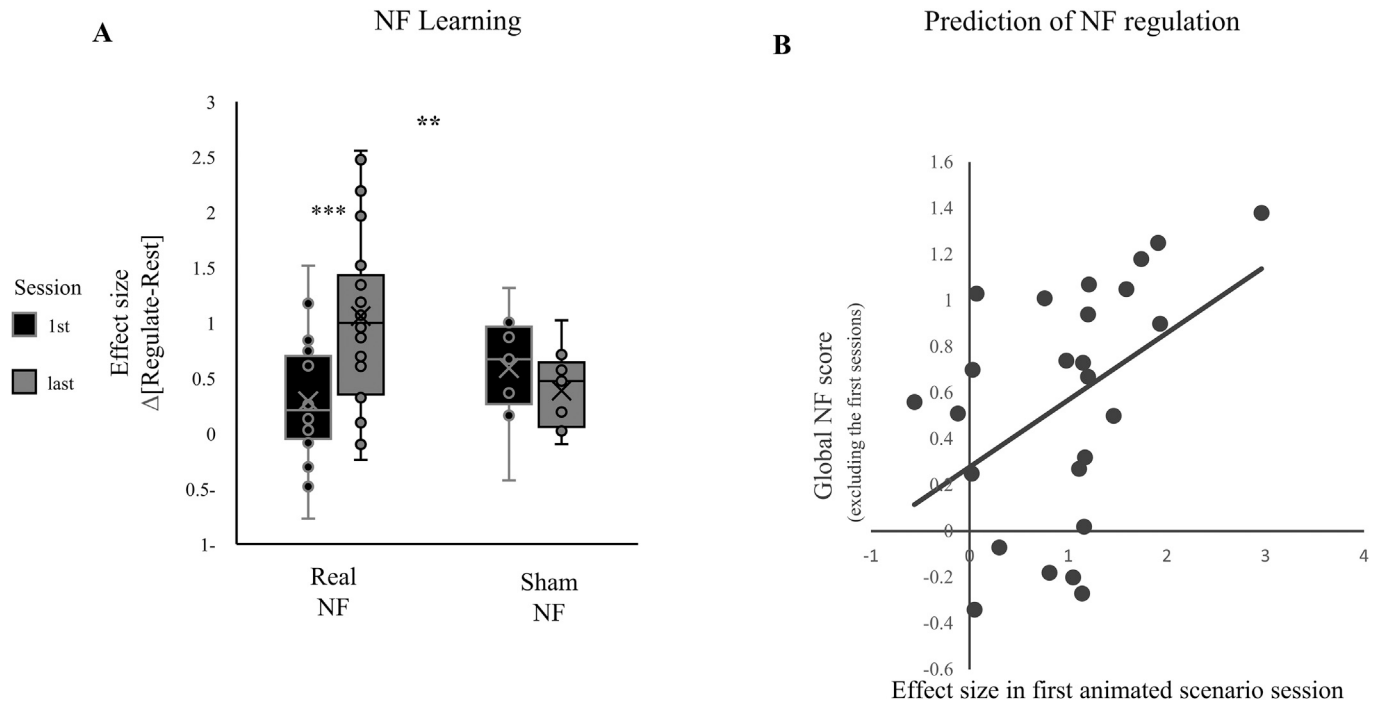

Fig. 2. NF learning. a. Effect size for NF learning index in the first and last training sessions (black and gray boxes, respectively), per group (real-NF/sham-EFP), with box plot displaying significant interaction of Session × Condition and simple effect of session only for the real-NF group, showing greater learning effect at the last session compared to the first. *b.* Scatterplot of the relation between effect size in the first animated scenario session and the average learning effect size across all the other sessions (3–10), showing significant positive correlation (r = 0.44, Adjusted Rsqr = 0.16, $p < 0.05$), thus pointing to a predictive value of the first animated scenario session with regard to later NF success. This analysis is based on data from 25 real NF group participants. **p < 0.005, ***$p < 0.0005$. Bonferroni post hoc correction.

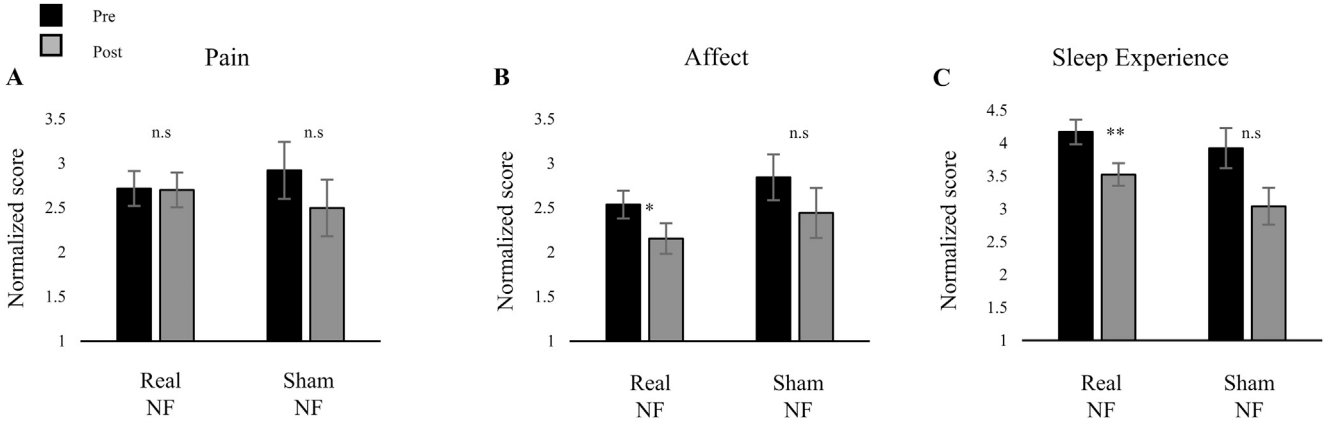

Fig. 3. Change in self-report readouts, pre to post assessment. a. *Pain* readout (VAS, McGill general score, FIQ pain) pre/post NF training. Bar graphs display no main effect of time, nor interaction of Time × Condition. b. *Affect* readout (STAI-T, BDI, FIQ anxiety, FIQ depression) pre/post NF training. Bar graphs show simple effect for time (pre/post NF) only for the real-NF group, without Interaction of Time × Condition. c. *Sleep experience* readout (PSQI, FIQ fatigue) pre/post NF training. Bar graphs show simple effect for time (pre/post NF) for both groups, without Interaction of Time × Condition. Error bars represent SEM. *p < 0.05; **p < 0.005. Bonferroni post hoc corrections. This analysis is based on data from 33 participants, 24 from the real NF group and 9 from the sham NF group.

modulators; pBonferroni<0.05] (Fig. 5A,B). The Number Needed to Treat per NF success subgroups for normalized REM latency, were 2.4 for good modulators and 3.67 for poor modulators.

3.4. Follow-up clinical outcome and their relation to immediate neurofeedback effect

To assess the long-term clinical impact of Amyg-EFP-NF treatment, we performed an unplanned assessment of self-report measurements 16.2 ± 8.72 months following NF training, focusing on the subjective measures of *pain, affect* and *sleep experience.* We used a repeated measures ANOVA, with time (post-NF/follow-up) as within subject variable, condition (Amyg-EFP/Sham-EFP) as between subject variable and time elapsed since the end of the NF training as a covariant. This analysis demonstrated that *pain* and *sleep experience* were improved at follow-up relative to post-NF only in the real-NF group, while *affect* showed a marginally significant effect (*pain:* Time × Condition [$F(1,28) = 6.7$, $p < 0.05$; $d = 1.1$], post-hoc for time effect in real-NF group, pBonferroni<0.05, *sleep experience:* Time × Condition [$F(1,28) = 5.02$; $p < 0.05$; $d = 0.92$]; post hoc-test for time effect in real-NF group, pBonferroni<0.05, *affect:* Time × Condition [$F(1,28) = 3.69$; $p = 0.065$; $d = 0.79$]) (Fig. 4A–C).

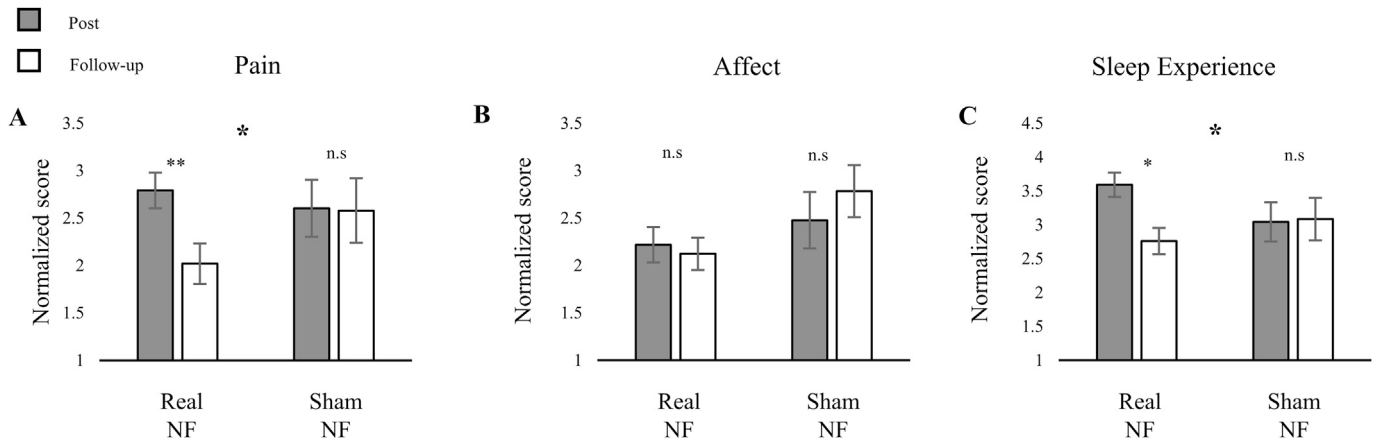

Fig. 4. Change in self-report readouts, post-NF to follow-up assessment a. *Pain* readout, post NF/follow-up. Bar graphs show Interaction of Time × Condition and simple effect for time (post NF/follow-up) only for the real-NF group. b. *Affect* readout, post NF/follow-up. Bar graphs show marginal Interaction of Time × Condition ($p = 0.065$) but no simple effect for time (post NF/follow-up). c. *Sleep experience* readout. Bar graphs show interaction of Time × Condition and effect for time (post NF/follow-up) only for the real-NF group. Error bars represent SEM. *$p < 0.05$; **$p < 0.005$. Bonferroni post hoc corrections. Values are presented with covariate of time from end of the study at level of 15.8 months. This analysis is based on data from 31 participants, 22 from the real NF group and 9 from the sham NF group.

Lastly, to account for the relation between immediate clinical outcome following treatment and the long-term effect of pain reduction, we applied moderation analysis using a custom-made regression model (see methods). This analysis examined the manner by which immediate homeostasis related outcomes of *sleep experience, affect* and *composite sleep score* predict long-term pain reduction (Fig. 6). This analysis revealed that improvement in *composite sleep score* following NF training was predictive of *pain* reduction in the follow-up assessment [$B = 0.91$; $p = 0.01$; 95% CI (0.21, 1.6)]; and that the interaction between improvement in *composite sleep score* and subjective *affect* post NF training had an additional, significant contribution to the prediction of *pain* reduction at follow-up [$B = 1.9$; $p < 0.05$; 95% CI (0.19, 3.68)]. In contrast, self-reported *sleep experience* did not have any predictive power for long-term *pain* reduction and was not moderated by *objective sleep* score. Importantly, time elapsed from the end of NF training to follow-up assessment was used as a covariant and did not significantly contribute to the model. These results suggest that when both objective sleep and affective symptoms were improved initially, pain intensity in the follow-up assessment was improved to the greatest extent, strengthening the idea that long-term pain alleviation relies on improvements in homeostatic indices.

4. Discussion

The goal of the current study was to utilize a disease-relevant fMRI-based EEG-NF in a clinical population and to assess NF training effects on somatic-affective homeostasis measures such as sleep quality, subjective affect and chronic-pain. To this aim, we applied ten sessions of Amyg-EFP-NF (or sham-NF) in a randomized placebo control manner in a cohort of Fibromyalgia patients. We were able to demonstrate improved NF regulation abilities in the real NF group, followed by a robust immediate improvement in objective measures of sleep quality (NNT for normalized REM latency was 2.875). Immediately after NF training, we found no improvement in chronic pain. However, exploratory long-term follow-up conducted 16.2 ± 8.72 months after the completion of the NF course revealed delayed improvement in chronic pain and sleep reports when compared to the end of treatment. Importantly, pain improvement at follow-up could be predicted by improvement in objective sleep

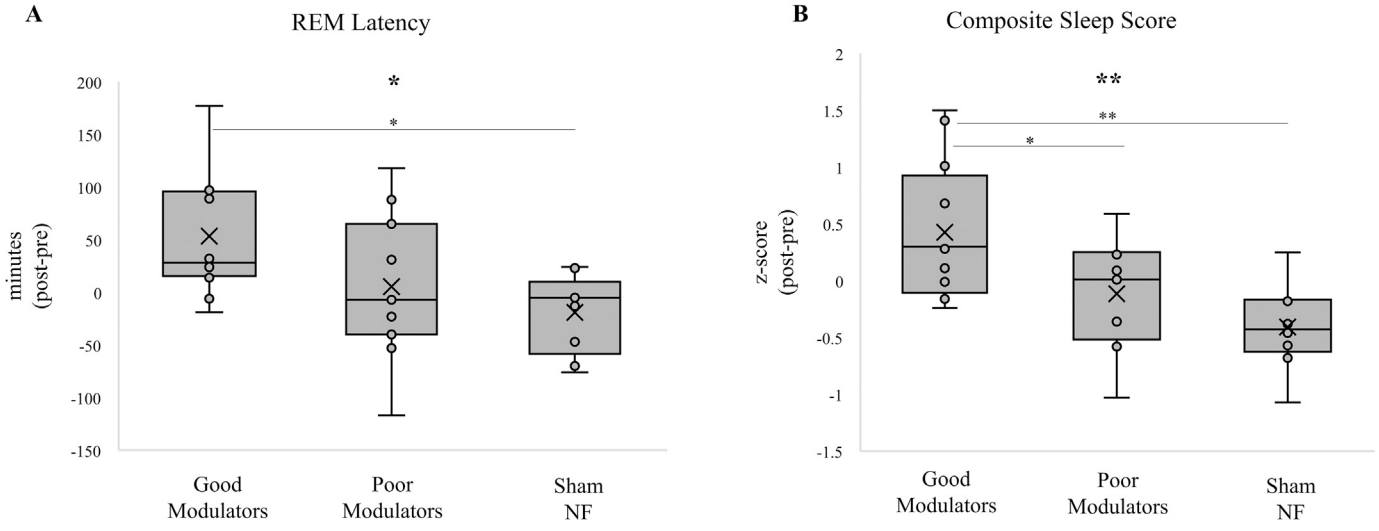

Fig. 5. Objective sleep changes over time. Difference between post and pre-NF, per subgroup (good modulators/poor modulators/sham) *a.* REM latency. Box plot displaying significant effect for group. Post hoc tests show significant difference between good modulators and sham. *b.* Composite Sleep Score (see methods). Box plot displaying significant effect for group. Post hoc tests show significant difference between good modulators and sham and between good and poor modulators. *$p < 0.05$; **$p < 0.005$. Bonferroni post hoc corrections. This analysis is based on data from 32 participants, 23 from the real NF group and 9 from the sham NF group.

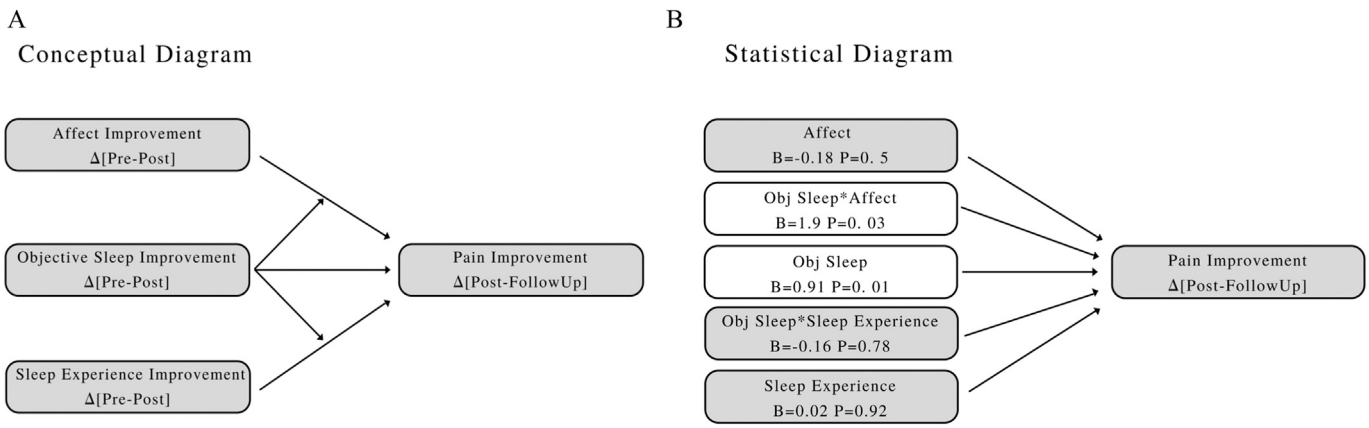

Fig. 6. Pain improvement in follow-up session: moderation analysis of follow-up pain improvement. a. Conceptual Diagram: the moderation model was designed to examine how objective sleep improvement, reflected by Composite Sleep Score (see methods), predicts long-term pain reduction and how this index moderates the contribution of *affect* and *Sleep experience* on this pain alleviation. b. Statistical illustration of the moderation. This analysis is based on data from 30 participants, 21 from the real NF group and 9 from the sham NF group.

observed immediately after NF training and its interaction with improved affective symptoms.

We have previously shown that healthy individuals can learn to down modulate the Amyg-EFP signal after short NF training and that this modulation corresponds to altered BOLD activity of the amygdala (Keynan et al., 2016). Here, we elaborate this concept by demonstrating that Fibromyalgia patients were also able to down modulate their Amyg-EFP signal via repeated NF sessions, thus proving the relevance of our novel imaging approach to limbic neuromodulation in a clinical set-up.

Notably, when comparing pre-intervention to follow-up assessment, NNT for 40% reduction in pain intensity (measured using visual analog scale) was 3.14. This result indicates relatively high clinical effectiveness, in comparison to common pharmacotherapy; e.g. Milnacipran was reported to have NNT of 8.5 (Cording et al., 2015), Duloxetine 7.2, and Pregabalin 8.6 (Bellato et al., 2012). As current treatment guidelines for chronic pain in general, and Fibromyalgia in particular, emphasize the value of multimodal interventions (Häuser et al., 2015; Nüesch et al., 2013) these results seems to carry high clinical relevance.

4.1. Limbic function and chronic pain

In contrast with previous NF studies in the context of chronic pain (deCharms et al., 2005; Guan et al., 2015), we employed a limbic probe for neuromodulation rather than targeting a traditional 'pain matrix' region (Apkarian et al., 2005). This decision was informed by accounts suggesting a critical role for the limbic system in chronic pain. Animal models demonstrated that amygdala hyperactivity generates enhanced feedforward inhibition of the medial prefrontal cortex, causing impaired cortical control that supports persistent activation of pain mechanisms (Neugebauer, 2015; Neugebauer et al., 2004). In humans, structural and functional limbic abnormalities predict transition from acute to chronic pain (Mansour et al., 2013; Vachon-Presseau et al., 2016). These findings support the idea that emotional states, underlined by limbic structures, may play a crucial role not only in pain perception and modulation, but also in its chronification (Baliki et al., 2012; Bushnell et al., 2013; Hashmi et al., 2013).

These propositions are nicely integrated in a recent theoretical framework which ascribes a main role for the limbic system in perceiving and maintaining bodily homeostasis; sensory information indicating the current state of the body is integrated in the limbic cortex and projected forward to construct an affect. According to this approach, aberrant perceptions regarding bodily states may hamper this process and can therefore cause chronic physical burdens, known as allostatic load, resulting in mental and physical illnesses such as depression (Barrett et al., 2016) and chronic pain (Di Lernia et al., 2016b). Guided by this conceptualization, we aimed to improve limbic modulation and therefore related homeostatic functions using Amyg-EFP-NF. Indeed, our results suggest that improved limbic regulation resulted in distinct clinical improvement in sleep that later manifested in long-term pain relief (see Fig. 6).

4.2. Sleep as a mediator in pain treatment

Sleep abnormalities are among the most common complaints in chronic pain in general, and are a major extra-musculoskeletal symptom in Fibromyalgia specifically (Häuser et al., 2008; Yunus, 2007). Often more prominent than pain itself, sleep disorders have been suggested to be one of the main processes contributing to pain chronicity (Choy, 2015; Yunus, 2007). Accordingly, we found that improvement in objective indices of sleep immediately after the NF training predicted improvement in chronic pain at long term follow-up (Fig. 6). Moreover, we demonstrated that when both objective sleep and affective symptoms were improved at the end of the NF training, pain at long term follow-up was improved to the largest extent.

These results are in line with prior evidence that effective pharmacological and nonpharmacological therapies often improve both sleep quality and pain severity in Fibromyalgia patients. Treatment with sodium oxybate, a sleep modifier used to treat narcolepsy, led to improved pain ratings, correlated with decreased sleep disturbance (Moldofsky et al., 2010; Russell et al., 2009b; Spaeth et al., 2012). Likewise, pregabalin, an FDA approved medication for Fibromyalgia also has a beneficial effect on sleep (Mease et al., 2008; Russell et al., 2009a). Interestingly, some evidence suggests a positive effect for melatonin, commonly used as a sleep aid, to support pain relief in Fibromyalgia (de Zanette et al., 2014; Hussain et al., 2011; Reiter et al., 2007). Further, cognitive behavioral therapy was shown to improve subjective sleep as well as pain catastrophizing, anxiety and depression (Martínez et al., 2014).

Taken together, these findings support the suggestion that sleep may mediate the association between emotional symptoms and pain via amygdala functionality; It is well established that affective disorders such as anxiety and depression are highly comorbid with sleep dysregulation (Alvaro et al., 2013; Pires et al., 2016; Tsuno et al., 2005). Therefore, it was suggested that impaired sleep triggers unregulated aversive emotional processing by hampering affect reactivity and emotion regulation (Anderson and Platten, 2011; Krause et al., 2017; Minkel et al., 2012). Importantly, a key role is attributed to amygdala dysregulation in

this maladaptive emotional processing, mainly via impaired connectivity with the pre-frontal cortex (Goldstein and Walker, 2014; Motomura et al., 2013; Prather et al., 2013; Simon et al., 2015; Yoo et al., 2007). Moreover, the amygdala, together with the anterior cingulate cortex and anterior insula, form the salience-detection network that discriminates between stimuli of different emotional valence. Following insufficient sleep this network displays non-specific, over generalizing responses to emotional cues (Goldstein and Walker, 2014). Importantly, structural and functional alterations in brain regions of the salience and emotional arousal networks are consistently evident in patients with chronic visceral pain (Mayer et al., 2015), leading to the claim that chronic pain can be considered, at least in part, as a condition of altered responsive salience (Borsook et al., 2013). Disordered sleep has also been indicated as exacerbating pain chronicity by interfering with normal processing of interoceptive information; enabling awareness to our body state (Craig, 2003; Ewing et al., 2017). Indeed, a recent paper on Fibromyalgia patients demonstrated that objective sleep measures mediate the relation between pain intensity and level of anxiety and depression (Diaz-piedra et al., 2014). Altogether, our results support the idea that improvements in sleep may have a beneficial effect on chronic pain by restoring control mechanisms of homeostasis, which in turn breaks the vicious cycle of chronic pain, sleep disturbance and mood abnormalities (Choy, 2015).

4.3. Clinical perspective of Amyg-EFP-NF

The demonstration that a low-cost mechanism-based EEG-NF treatment can be clinically valuable in Fibromyalgia patients carries significant hope for this poorly managed syndrome. As expected, not all patients exhibited the same learning capacity. Previous reports have linked differences in NF performance to behavioral/clinical improvement (Kim et al., 2015; Wen et al., 2013; Zuberer et al., 2015), affirming the basic assumption that NF trains neural regulation, which alters behavior and improves clinical outcome (Thibault et al., 2018). Here too, we observed that participants that presented enhanced Amyg-EFP regulation skills also displayed a more robust sleep related clinical improvement at the end of the NF training.

Results from the full NF protocol analysis (see Fig. S1) indicted that some participants in the real-NF group were unable to regulate their Amyg-EFP signal better than sham-group participants. This result corresponds to previous findings which suggested that a significant percent of the population (10–50%) are unable to volitionally change their brain activity (Alkoby et al., 2018; Allison and Neuper, 2010; Jeunet et al., 2016). In previous studies, NF treatment efficiency was successfully predicted using behavioral factors such as control belief (Witte et al., 2013), motivation, mood (Nijboer et al., 2010, 2008), memory (Daum et al., 1993; Roberts et al., 1989; Wangler et al., 2011) or by EEG markers such as resting-state alpha (Wan et al., 2014) or beta (Nan et al., 2015) (for detailed review see Alkoby et al., 2018). However, in our sample prediction was unsuccessful using behavioral, neural or clinical factors. Nonetheless, and as has been previously demonstrated (Neumann and Birbaumer, 2003; Weber et al., 2011), the first NF session, in this case, of animated scenario, was predictive for the overall NF regulation abilities (see Fig. 2B). We suggest that this quality might be due to the more enjoyable, engaging and relatable nature of the animated scenario interface (Cohen et al., 2016) as well as its multi-modality. As this interface was deliberately designed to provoke limbic activity and user engagement, we were pleased to observe that it could effectively predict treatment success.

Importantly, the pattern of clinical change observed here taps into the important issues of NF's late effect (see Fig. 5). This subject was the focus of a recent study by Rance et al. (2018) that reported that in two clinical populations (OCD and Tourette Syndrome), symptoms kept improving up to 80 days from the end of the NF training. The authors point out that a similar pattern of results is evident in previous NF studies at the behavioral (Amano et al., 2016), clinical (Schnyer et al., 2015) and neural (e.g Harmelech et al., 2013; Robineau et al., 2017; Yuan et al., 2014) levels.

Two mechanisms are suggested to underlie these latent effects. The first is behavioral: much like other coping skills, such as those acquired by cognitive behavioral therapy (also demonstrated to have a latent effect e.g. Carroll et al., 1994; Goldstein et al., 1989; Piacentini et al., 2011), NF can turn into a skill that is integrated into daily life. Hence, as time goes by, it is possible that trainees continue to practice the new skill they acquired and thus symptoms and neural regulation continue to improve. The second mechanism suggested relates to neural learning principles: over time, consolidation and reconsolidation processes that underlie learning paradigms such as NF are likely to take place (Kandel et al., 2014). As these processes occur regardless of practice, synchronization, or desynchronization of the targeted brain process may increase over time (Rance et al., 2018).

The results we report here are consistent with Rance et al's. suggestion regarding the late effect of NF. However, our results concern a longer time duration than reported in previous papers and contain notable variance in sampling time. Although we controlled for this variable in the relevant analyses by employing it as a covariate, ideally this should be factored in prospectively.

Our results also relate to the current discussion regarding the strong placebo effect of NF intervention (Thibault and Raz, 2017). A recent study that significantly contributed to this discussion, conducted by Schabus et al., used a full-length, widely accepted, EEG-NF protocol (increasing 12–15 Hz rhythm over the sensorimotor cortex) to improve the clinical status of insomnia patients. Results of this study showed no advantage to NF-treatment over sham treatment (Schabus et al., 2017). Similarly, we observed non-differential effect in subjective reports at the end of the NF training. However, as we targeted a specific neural probe, we witnessed an immediate effect on *objective* sleep measures related to NF training success, as well as long term clinical improvement evident in the real-NF group only.

Interestingly, although a connection between modulation success and clinical outcome was observed, we could not find a correlation between these two measures. This may echo the suggestion by Ramos-Murguialday et al. (2013), that the nature of the relation between NF learning and behavioral/clinical outcomes should not necessarily be a linear one. Learning to control NF may follow similar principles as the learning of motor skills. As such, patients may acquire these "skills" via NF training, which then become part of their behavioral repertoire. Accordingly, one would expect that the acquisition of the skill by itself, rather than the level of proficiency, has the crucial effect on clinical outcomes.

4.4. Methodological considerations

We acknowledge that certain aspects of this study could be improved and hope that further research will untangle aspects that remained unsolved. The first issue is NF learning: In a recent study we demonstrated that healthy trainees were able to down-modulate their Amyg-EFP signal better than active control after four Amyg-EFP-NF session (see Keynan et al., in press). However, in the current study, participants showed improved Amyg-EFP regulation only at the final session (see Fig. S1). This slow learning process might be a characteristic of the unhealthy populations in this study (as was briefly discuss in Schabus et al., 2017) or, alternately, might be due to the combination of different feedback interfaces that introduced additional challenges. By interleaving two interfaces, we hoped to provide an engaging training set-up for repeated sessions. However, in fact, this NF protocol might have been counter-productive to effective learning. Further, the relation between NF regulation and clinical outcome could have been better accounted for using transfer trials, which was unfortunately unavailable. Moreover, to fully control for effects of NF-reward related processes (Emmert et al., 2016; Sitaram et al., 2017) it would be preferable to use complete matching of success rates between the sham to real NF. Likewise, we believe that further studies may apply additional control groups regulating a different brain probe rather than sham-EFP. Such an approach could help support the claim that targeting a specific domain, as done using the Amyg-EFP,

indeed produces specific and differential results. Clearly, we hope that the results presented here will be replicated in a bigger sample size and include more elaborate and quantifiable measures of pain such as quantitative sensory testing or central pain modulation, that could potentially better characterize a relation between pain modulation and NF learning. Lastly, in order to fully account for the relation between amygdala regulation and improved clinical outcome, fMRI scans in future studies would be beneficial.

5. Conclusions

Using a randomized, double-blind, placebo-controlled design with outcome measurements of homeostasis (sleep and affect) and pain, and accounting for measures of learning (good versus poor modulators), we show that Amyg-EFP-NF can serve as a scalable non-pharmacological, non–invasive treatment for individuals suffering from Fibromyalgia. By examining the therapeutic potential of limbic modulation in the specific case of Fibromyalgia, this study further serves to support the clinical potential of mechanism-driven fMRI driven EEG-NF approaches that target specific neural processes relevant to different disease states, thus promising to be a highly accessible therapeutic tool, both in medical settings as well as in the patient's home environment.

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Declaration of interest

Prof. Hendler and Prof. Intrator are inventors of related patent applications entitled "Method and system for use in monitoring neural activity in a subject's brain" (US20140148657 A1, WO2012104853 A3, EP2670299 A2). This does not alter the authors' adherence to neuroimage policies. Mr. Goldway, Dr. Ablin, Mr. Lubin, Mr. Zamir, Mr. Keynan, Miss. Or-Borichev, Prof. Cavazza, Dr. Charles, Dr. Brill, Dr. Ben-Simon, and Dr. Sharon all reported no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.11.001.

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