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EEG-heart rate connectivity changes after sensorimotor rhythm neurofeedback training: Ancillary study

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Abstract

Objectives: Neurofeedback can induce long-term changes in brain functional connectivity, but its influence on the connectivity between different physiological systems is unknown. The present paper is an ancillary study of a previous paper that confirmed the effect of neurofeedback on brain connectivity associated with chronic pain. We analysed the influence of neurofeedback on the connectivity between the electroencephalograph (EEG) and heart rate (HR).

Methods: Seventeen patients diagnosed with fibromyalgia were divided into three groups: good sensorimotor rhythm (SMR) training responders (n = 4), bad SMR responders (n = 5) and fake training (SHAM, n = 8). Training consisted of six sessions in which participants learned to synchronize and desynchronize SMR power. Before the first training (pre-resting state) and sixth training (post-resting state) session, open-eye resting-state EEG and electrocardiograph signals were recorded.

Results: Good responders reduced pain ratings after SMR neurofeedback training. This improvement in fibromyalgia symptoms was associated with a reduction of the connectivity between the central area and HR, between central and frontal areas, within the central area itself, and between central and occipital areas. The sham group and poor responders experienced no changes in their fibromyalgia symptoms.

Conclusions: Our results provide new evidence that neurofeedback is a promising tool that can be used to treat of chronic pain syndromes and to obtain a better understanding of the interactions between physiological networks. These findings are preliminary, but they may pave the

KEYWORDS
EEG; Heart rate; Neurofeedback; Sensorimotor rhythm; Functional connectivity; Fibromyalgia
Introduction

The brain is a complex network of dynamic connections between local and distant brain areas [72]. Interregional neural communication is thought to be accompanied by a synchronization of oscillations between different brain regions [22]. This synchronization can be analysed by means of functional connectivity, which is a measure of the statistical dependency between activity in different brain regions. In recent years, investigations in the field of functional connectivity have been extended from relations between brain regions, to integration with peripheral systems [5,30]. These investigations have included an analysis of the interactions between different physiological signals (for example, electromyography, electrocardiography (EKG), electroencephalography (EEG), electrodermal activity, etc.) as a biomarker of neuropathological and mental states [5,27,41,61]. The underlying rationale is that the human body consists of an integrated network, where multi-component systems continuously interact through various feedback mechanisms to optimize the function of organs [5]. For example, it has been demonstrated that brain functional connectivity is related to cardiovascular homeostasis at rest [1,10,15,58].

Neurofeedback (NFB) is a non-invasive technique whose objective is that individuals learn to regulate certain parameters of cortical activity such as amplitude, frequency and/or coherence of EEG signal [28]. The main learning mechanism underlying NFB is operant conditioning [20]. During NFB, individuals learn to modify their cortical activity through the visual or acoustic information (feedback) that acts as a reinforcement in training [20,68]. Many studies have shown both structural [24] and functional [56] changes in brain networks after NFB training [2,49,50,55]. The influence of NFB training is not limited to neural activations related to a single trained channel, but changes the functional connectivity involving other brain areas, extending throughout the brain [70]. For example, it has been found that NFB training in sensorimotor rhythm (SMR, 12–15 Hz) in C3 and C4 decreases functional connectivity between frontal and temporal electrodes [11]. Moreover, the influence of NFB training extends beyond the brain and can affect peripheral systems. Studies have found that SMR NFB training increased heart rate variability (HRV) and decreased heart rate (HR) in healthy participants [4,52,53]. Thus, modifying brain activity through NFB can cause changes in heart rate, reflecting the synchronization of the two systems. However, these studies were conducted under the assumption that the brain and cardiac systems are correlated, but they were not considered as two interconnected nodes that belong to the same network. If we consider that the physiology of the human body is a complex interconnected network, NFB should lead to changes in the functional connectivity between remote nodes.

It has been observed that chronic pain causes profound changes to the brain and peripheral systems [3,57]. For example, patients with chronic pain exhibit a sympathetic predominance which explains a higher heart rate, [39,44,54,71] and an increase in EEG connectivity between central and frontal areas, [16,25] compared to healthy controls. NFB is a potential non-pharmacological treatment for the management of chronic pain conditions [8,31,33,34,43,73]. Modulating SMR is a procedure commonly used in NFB, which has been found to impact well-being in people with chronic pain [32,33]. The rationale is to reduce the connectivity and over-activation of lower beta rhythm (12–15 Hz) that patients with chronic pain exhibit in the resting-state over motor, somatosensory and frontal areas [25,26,40]. Similarly, feedback research has shown that increasing heart rate variability is related to enhancement of the SMR and has a positive effect on psychological health in patients with fibromyalgia [40,41]. Nevertheless, the effect of SMR NFB training on heart rate remains unexplored in patients with fibromyalgia. As previous studies have found that SMR NFB training is related to changes in HR activity [23,24], so SMR NFB training should decrease functional connectivity between somatosensory and motor-related areas and HR activity [16,25].

This is an ancillary study to a previous paper (Terrasa et al. [67]), which aims to provide new data about the benefits of NFB in the treatment of chronic pain and the changes in EEG-HR connectivity associated with the improvement seen after training in patients with chronic pain. If we consider that the physiology of the human body comprises a complex interconnected network, then acting on one of these individual systems should lead to changes in the dynamics of other physiological systems and reorganize the characteristics of the physiologic network. We chose to investigate functional connectivity between somatosensory areas and heart rate due to studies that show the bidirectional relation between SMR NFB and HR. Moreover, SMR NFB has been used successfully in the treatment of chronic pain. We hypothesize that SMR NFB training decreases functional connectivity of electrodes located in somatosensory and motor-related areas with other brain areas and HR activity.

Methods

Participants

Seventeen right-handed female patients (aged 54.94 ± 10.11 years) with a diagnosis of fibromyalgia were recruited from the Asociación Granadina de Fibromialgia (AGRAFIM) in Granada (Spain). The diagnosis of fibromyalgia was confirmed following the American Rheumatology College Criteria [76]. The exclusion criteria were having been diagnosed with fibromyalgia for less than 1 year, being pregnant, exhibiting vision or auditory deficits, and having neurological or psychiatric diseases (except depression). Thirteen of the
seventeen patients had a diagnosis of depression. Participants continued to take regular medications, including analgesic/myorelaxant (88.24%), antidepressant (76.47%), and anxiolytic (70.59%) medications during the experiment, but were asked to avoid the use of any other non-pharmacological therapy. The study was conducted in accordance with the Declaration of Helsinki (1991) and approved by the Ethics Committee of the Balearic Islands (Spain). Written informed consent was obtained from the participants after the experimental procedure was explained to them.

**Procedure**

The procedure was explained in detail in Terrasa et al. (2020) [67]. Patients were sequentially assigned to either SMR NFB training (SMR, \( n = 9 \)) or a control group that received false feedback during the training (SHAM, \( n = 8 \)). All participants completed several questions about demographics, and self-reported questionnaires: Beck Depression Inventory (BDI-II) [6], Fibromyalgia Impact Questionnaire (FIQ) [7] and Short-form Health Survey (SF-36) composed of 9 dimensions: “physical functioning”, “role limitations: physical”, “role limitations: emotional”, “vitality”, “mental health”, “social functioning”, “pain”, “general health perception” and “change in health” [75]. The NFB training program consisted of 6 sessions divided into 3 sessions per week for 2 weeks. Before the first training session (Pre-resting state) and before the start of the sixth training session (Post-resting state), the State-Trait Anxiety Inventory (STAI-S) [64] questionnaire was completed and open-eye resting-state EEG and EKG signals were recorded for 7 min. At the end of first and sixth SMR NFB training sessions, patients were asked to rate their perceived pain using a numerical scale ranging from 0 to 100 (Pain Assessment Session).

Briefly, the goal of the EEG NFB task was to move a ball and hit a target localized on the right or left side of the computer screen using the Cursor Task module of the BCI2000 platform [60]. The participants endeavoured to synchronize (by increasing power amplitude) and desynchronize (by decreasing power amplitude) the SMR at sensory-motor-related electrodes (C3, CP1, and CP5) to move the ball to the target.

Hitting the ball on the target acts as a positive reinforcement of learning to regulate SMR power [20]. Moreover, the number of trials in which the ball hit the target (percentage of hits) was recorded as the task performance index. The greater the change in SMR power effected by the participant, the greater the performance index achieved. In the first and sixth training sessions, all participants performed the NFB in an MRI scanner and received real feedback on their performance. The remaining four training sessions (second to fifth sessions) were performed in an MRI simulator and only the SMR group received real feedback on the changes in SMR power, while the SHAM group received random feedback.

**Physiological data acquisition and pre-processing**

In this paper, only EEG and EEG-HR functional connectivity results in pre-resting state and post-resting state are presented. The demographic data, psychological variables, EEG power acquired during NFB, fMRI functional connectivity and level of pain experienced were presented in the previous paper [67]. Physiological signals during the resting state were continuously acquired using Ag/AgCl electrodes with a 64-ch QuickAmp amplifier (Brain Products GmbH, Munich, Germany). EEG electrodes were mounted according to the 10/20 montage system, their impedance was maintained at <10 kOhm, and the sampling rate was 1000 Hz. The EKG signals were recorded with one electrode located on the left side of the back (near the heart). Both physiological signals were referenced online to the AFz electrode. EEG pre-processing analysis was performed with the EEGLAB toolbox for MATLAB [13]. The recordings were filtered offline with a 0.1-Hz high-pass filter and 70-Hz low-pass filter. All channels were offline-referenced to the average of the electrodes. EEG waveforms were segmented in epochs of 2 s in duration (a total of 210 epochs were obtained) for analyses. Bad epochs and channels were then eliminated using visual inspection and ±70 mV amplitude difference in the epoch. Thus, nine of sixty-three EEG channels (FPz, AF7, AF8, FT9, FT10, F5, F6, TP7 and TP8) were removed due to faulty recording or because 20% of epochs were rejected. The longest recording had 210 epochs, and the shortest recording had 180 epochs. The mean number of epochs rejected was 12.76, and the standard deviation was 10.92. To equalize the number of epochs between participants, we selected the first 180 epochs after rejection in all recordings.

EKG signals were filtered offline with a 5-Hz high-pass filter and 45-Hz low-pass filter. R–R intervals were extracted from EKG data filtered using the ECGLAB toolbox for MATLAB [9]. Then, Kardia software [46] was used to obtain the weighted average of the HR every 2 s, obtaining a total of 210 HR values.

**Functional connectivity in EEG activity between the central region and other cortical regions**

Functional connectivity analysis was conducted with a self-programmed MATLAB script. First, the power spectral density of the EEG signals was estimated with Welch’s averaged periodogram method using a Hamming window that has a 500-point fast Fourier transformation and does not overlap. Then, coherence was calculated as the functional connectivity index in SMR. This index measures the linear correlation between two EEG signals, \( x(t) \) and \( y(t) \), as a function of the frequency, \( f \). Thus, coherence is the ratio of the cross-power spectral density, \( S_{xy}(f) \), between both signals and their individual power spectral densities, \( S_{xx}(f) \) and \( S_{yy}(f) \):

\[
K_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}}
\]

To reject spurious correlations between cortical sources, the imaginary part of coherence (iCOH) was calculated in each EEG epoch between central electrodes (Fc5, Fc3, Fc1, Fc2, Fc4, Fc6, C5, C3, C1, Cz, C2, C4, C6, C5p, C3p, C1p, C2p, C4p, and C6p) and the rest of the EEG electrodes. The mean iCOH over time was obtained for each link of the central EEG network. We decided to use both right- and left-hemisphere electrodes in the central areas because of the low spatial resolution of the EEG signals and the fact that the use of NFB training over C3, CP1 and CP5 electrodes
shows contralateral desynchronization and ipsilateral synchronization over central areas.

**Functional connectivity between EEG activity and HR**

This analysis was conducted with a self-programmed MATLAB script. The SMR power was calculated in each EEG epoch as the sum of power spectral densities between 12 and 15 Hz in central electrodes. The length of the HR time series was set to be equal to the SMR power time series to eliminate the epochs rejected during EEG pre-processing. Both time series were z transformed to improve normality and stabilize variance. Finally, Pearson correlations were performed between the HR and SMR power of the central electrodes.

**Statistical analysis**

After the initial statistical analyses, we observed that participants in the SMR group as a whole could not achieve an average performance above chance level. Therefore, we decided to subdivide the SMR group into good responders (who achieved a mean performance level above 50% success during all the sessions) and poor responders (who achieved a mean performance level under 50% success during all the sessions). Thus, the study was finally conducted with three groups: good SMR responders \((n = 4)\) with 67.76% ± 15.97 successful trials (mean of the six sessions), poor SMR responders \((n = 5)\) with 48.31% ± 7.26 successful trials and sham group \((n = 8)\). Task performance (percentage of success) for each group through the six sessions is shown in Fig. 1.

Statistical analyses were carried out using IBM SPSS Statistics v.23. For self-reported questionnaires (SF-36, BDI-II, and FIQ) one-way analyses of variance (ANOVA) were used to examine differences between groups (good-SMR responders, bad-SMR responders and SHAM). Differences in STAI-S scores were tested using 3 × 2 repeated-measures ANOVA with group as the between-subject factor and resting-state session (Pre-resting state and Post-resting state) as the within-subject factor. For repeated-measures analyses, normal distributions of the measured variables were tested, and Greenhouse-Geisser epsilon corrections were applied to control for violation of the sphericity assumption. When significant effects were found, post hoc analyses were performed using Bonferroni correction.

**Results**

**Demographic and psychological data**

Before SMR NFB training, there were no significant differences between groups with respect to depression (BDI-II) scores, but there was a significant difference in FIQ scores \([F(2, 14) = 4.16, p < .05, \eta^2 = 0.41]\). Bonferroni post hoc analyses of FIQ only showed a non-significant difference between good SMR and poor SMR responders on these scores \((p = .062)\). SF-36 questionnaire analysis showed significant differences between groups in SF36-pain \([F(2, 15) = 4.12, p < .05, \eta^2 = 0.39]\), SF36-general health perception \([F(2, 15) = 5.95, p < .05, \eta^2 = 0.48]\) and SF36-change in health \([F(2, 15) = 7.13, p < .01, \eta^2 = 0.52]\) before SMR NFB training. Bonferroni post hoc analyses of these effects revealed that good-SMR responders had higher scores than poor SMR responders on SF36-pain \((p < .05; 39.7 ± 21.5 and 9.2 ± 12.6, respectively)\), SF36-general health perception \((p < .05, 41.2 ± 14.3 and 12.0 ± 12.5, respectively)\) and SF36-change in health \((p < .01, 43.7 ± 12.5 and 5.0 ± 12.1, respectively)\).

The ANOVA 3 × 2 analysis showed no significant differences on STAI-S scores between groups, resting-state
session or interaction between factors (all \( p < .05 \)). No significant differences in pain perception were found by ANOVA 3 \( \times \) 2 analysis between groups or pain assessment sessions. However, analysis yielded a significant interaction effect of group \( \times \) pain assessment session \([F(2, 14) = 4.103, p < .05, \eta^2 = 0.37]\). The Bonferroni post hoc tests showed that good SMR responders reported a significant reduction in the level of pain experienced between the first and sixth training session (\( p < .05 \)), which was not seen in r either poor-SMR responders or sham participants.

### Functional connectivity in eeg activity between the central region and other cortical regions

A 3 \( \times \) 2 repeated-measures ANOVA on iCOH was performed for each link between the central electrodes and the rest of the EEG electrodes. For clarity, only significant results related to group by session are reported, while the main effects of resting-state session or group are not reported. Table 1 displays the \( F \)s and partial etas of group \( \times \) resting-state session interactions between EEG and HR connectivity.

### Table 1  Significant F-test results and partial eta values of 3 \( \times \) 2 repeated-measures ANOVAs for each network physiology node.

| Node | \( F(2,14) \) | \( \eta^2 \) | \( F(2,14) \) | \( \eta^2 \) |
|------|---------------|-------------|---------------|-------------|
| Fp1Cz | 9.61**        | 0.58        | 4.52*         | 0.39        |
| Fp1Fc2 | 7.87**        | 0.53        | 4.12*         | 0.43        |
| Fp1C5 | 7.69**        | 0.52        | 8.18**        | 0.54        |
| F3C4 | 4.12*         | 0.37        | 5.29*         | 0.43        |
| F3Fc1 | 4.83*         | 0.41        | 5.15*         | 0.42        |
| F3Cp2 | 4.95*         | 0.41        | 5.56*         | 0.44        |
| F3C2 | 4.11*         | 0.37        | 6.16*         | 0.47        |
| C3Fz | 4.07*         | 0.37        | 3.75*         | 0.35        |
| C4O1 | 4.57*         | 0.40        | 6.30*         | 0.47        |
| C4F1 | 6.82**        | 0.49        | 4.99*         | 0.42        |
| C4F1 | 4.95*         | 0.41        | 6.21*         | 0.47        |
| C4Cp3 | 5.11*         | 0.42        | 4.16*         | 0.37        |
| P4Fc1 | 5.75*         | 0.45        | 7.29**        | 0.51        |
| O2Fc1 | 3.96*         | 0.36        | 5.55*         | 0.44        |
| F7Fc1 | 4.10*         | 0.37        | 3.80*         | 0.35        |
| F8Fc1 | 4.52*         | 0.43        | 4.12*         | 0.37        |
| FzCf3 | 4.23*         | 0.38        | 4.78*         | 0.41        |
| FzCp2 | 6.67**        | 0.49        | 4.13*         | 0.37        |
| FzC1 | 6.07*         | 0.46        | 6.64*         | 0.40        |
| FzC4 | 4.21*         | 0.38        | 8.74**        | 0.56        |
| CzO2 | 4.18*         | 0.37        | 4.98*         | 0.42        |
| CzF1 | 3.90*         | 0.36        | 7.34**        | 0.51        |
| CzPo7 | 3.87*         | 0.36        | 5.02*         | 0.42        |
| O2Fc1 | 4.91*         | 0.41        | 4.87*         | 0.41        |
| Fc1Fc2 | 5.02*         | 0.42        | 4.32*         | 0.38        |
| Fc1Poz | 7.37**        | 0.51        | 4.01*         | 0.36        |
| Fc1AF4 | 4.60*         | 0.40        | 4.01*         | 0.36        |
| Fc2AF3 | 5.13*         | 0.42        | 5.07*         | 0.42        |
| Fc2Po8 | 4.47*         | 0.39        | 3.78*         | 0.35        |
| Fc5F2 | 3.80*         | 0.35        | 4.82*         | 0.41        |
| Fc5HR | 4.10*         | 0.37        | 8.10**        | 0.54        |
| Cp5Cp4 | 4.09*         | 0.37        | 4.20*         | 0.38        |
| Cp6Po3 | 4.59*         | 0.40        | 4.40*         | 0.39        |
| C6P7 | 3.75*         | 0.35        | 4.50*         | 0.39        |
| F1Fc3 | 6.11*         | 0.47        | 5.69*         | 0.45        |
| F1Cpz | 4.74*         | 0.40        | 3.94*         | 0.36        |
| C1AF3 | 5.96*         | 0.46        | 4.54*         | 0.39        |
| P1C5 | 4.91*         | 0.41        | 6.24*         | 0.47        |
| AF4Fc3 | 3.86*         | 0.36        | 5.10*         | 0.42        |
| Fc3Po8 | 4.79*         | 0.41        | 4.13*         | 0.37        |
| Cp3C5 | 5.08*         | 0.42        | 6.78**        | 0.49        |
| Po3C6 | 9**           | 0.56        | 4.73*         | 0.40        |
Fc5F2 and Fc5AF3) than sham responders in the post-resting-state session.

Post hoc analysis of the interaction comparing pre- and post-resting-state sessions in each group yielded significant differences in 42 links in good SMR responders, 30 links in poor SMR responders and only 11 links in the sham group (Fig. 2). In summary, good SMR responders had decreased iCOH in central-frontal, central-central, central-parietal and central-occipital links in post-resting-state sessions. Poor SMR responders presented a random pattern of increases and decreases between central, frontal and occipital links in the post-resting-state session. Finally, the sham group mainly had increased iCOH on some central-frontal, central-central, central-parietal and central-occipital links in the post-resting-state session. Thus, NFB training changed resting EEG functional connectivity more than the SHAM training condition, and good performance in SMR modulation was related to a decrease in iCOH after training.

Functional connectivity between EEG activity and HR

The functional connectivity between SMR power in central electrodes and heart rate reached significant group × resting-state session interactions in the Fc5, Fc4, C6 and Cp6 electrodes (Table 1). Bonferroni post hoc tests showed that good SMR responders decreased their connectivity in Fc5HR, Fc4HR and C6HR links in post-resting-state sessions (Fig. 3). However, poor SMR responders increased their connectivity in C6HR in the post-resting-state session. The sham group showed no significant differences in functional connectivity between central electrodes and heart rate.

Fig. 4

Bonferroni post hoc tests between groups showed that good SMR responders had higher SMR power-HR connectivity of SMR power on Fc5HR and C6HR than poor SMR responders in the pre-resting-state session. Moreover, good SMR responders showed higher SMR power-HR connectivity in the Fc5HR group than in the sham group. No significant differences between groups in the pre-resting-state session in Fc4HR and C6HR or differences between groups in the post-resting-state session were found.

Discussion

The aim of this study was to provide novel data about the benefits of NFB in the treatment of chronic pain pathologies and the changes in EEG-HR connectivity associated with the improvement seen in patients with chronic pain after the training. A cohort of patients with fibromyalgia was randomly assigned to an SMR training group or to a sham group. The analyses of task performance during the six sessions revealed that 4 out of 9 participants in the SMR training group were able to achieve a success rate above 50%. Good SMR responders reduced their perceived pain after SMR NFB training, while the SHAM group and bad SMR responders did not reduce their pain level. Good SMR responders showed reduced connectivity between central and frontal areas, within the central area itself, between central area and occipital area and between the central area and heart rate activity after SMR NFB training. However, the sham group showed increases in EEG functional connectivity, while the poor SMR responder group showed both decreases and increases in EEG functional connectivity. In relation to connectivity between central SMR activity and heart rate activity, good SMR responders decreased their connectivity in Fc5HR, Fc4HR and C6HR links after NFB training, while poor SMR responders increased functional connectivity in C6HR links after NFB training. These results support the view that NFB training induced changes in functional connectivity between cortical regions and between brain and peripheral autonomic activities, and that these changes are associated with improvements in patients with chronic pain. Specifically, it was observed that SMR NFB training reduced functional connectivity between EEG activity in the central cortical region (situated over motor and sensory areas), and heart rate. Moreover, functional connectivity changes remained stable during the resting-state evaluation.

Good SMR responders learned to successfully synchronize and desynchronize the SMR through the sessions, which was not achieved by the sham group and poor responders. Success in the SMR NFB training appears to be associated with relief of pain, because only good SMR responders decreased their perceived pain after the training. Previous research has linked SMR NFB training with reductions in anxiety [23], although this was not shown in our study.

Thus, the neural correlate of good SMR responders was a decrease in functional connectivity of central regions with frontal, parietal, and occipital regions and with nodes within the central region itself pertaining to the SMR when comparing pre- and post-resting-state sessions. On the other hand, poor SMR responders showed an unclear pattern of increases and decreases in EEG functional connectivity of central activity with frontal and occipital nodes and within the central region itself, while the sham group showed increased functional connectivity of the central region with frontal, parietal and occipital nodes, although these changes only affected eleven links. It is well known that patients with chronic pain show overactivation in frequency ranges between 12 and 15 Hz over central areas in the resting state [36,59,65,74], as well as strengthened connectivity of
somatosensory regions with brain regions involved in pain processing [12,21,29]. Our EEG results are consistent with previous fMRI results, as SMR NFB altered the EEG connectivity in electrodes closely localised to somatosensory and motor-related areas in the resting state. These results are supported by previous studies showing that SMR NFB training reduces the coherence of central electrodes with other EEG areas [37,51]. Moreover, our results seem to indicate that a decrease in the connectivity of central areas with other brain regions could be related to the effectiveness of NFB training in providing pain relief [8,34,38,45]. SMR NFB training and relief of pain could be related to the learning of an EEG pattern characterized by reduced connectivity between central areas and areas related to pain processing, while an EEG pattern characterized by random connectivity could reflect difficulties in training in NFB. To our knowledge, there are no previous studies testing how NFB training could modulate the connectivity between central and peripheral systems, considering heart rate as another node. It is well known that HR has an effect on EEG activity [63,69]. For example, Prinsloo et al. (2011) [48] observed that HRV biofeedback training induces higher theta/beta

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**Fig. 3** Means of differences and standard errors of significant differences ($p < .05$) in central EEG links between post- and pre-SMR resting-state sessions. The symbols indicate if increases and decreases in common links between groups were equal or different (# good $\neq$ SHAM; ~ good $\neq$ bad; + good = bad).
ratios in the frontal, central and parietal areas. Similarly, HRV NFB training increases SMR levels in central localizations, and SMR NFB training produces a decrease in HR [4,52]. Thompson and Thompson (2009) [70] support the existence of neural synergy between physiological systems, which proposes that NFB performed at Cz will affect not only activity in the central region but also affects whole physiological networks (in both central and autonomic nervous systems). This study is the first to show that NFB in central areas could induce long-term changes in functional connectivity related to an improvement in chronic pain symptoms, not only regarding EEG activity but also regarding heart rate. Some studies indicate that brain areas related to pain processing and neuronal networks involved in cardiovascular regulation are closely integrated [17,19,42,62]. Moreover, a recent study demonstrated that altered primary somatosensory cortex connectivity of patients with fibromyalgia is related to heart rate variability [35]. Studies of the somatic aspects of patients with chronic pain patients have shown that the autonomic state of patients with fibromyalgia is characterized by increased sympathetic and decreased parasympathetic tone in the resting state [44,54,71] with consequent increased heart rate than in healthy volunteers.

Previous studies showed that NFB can modify heart rate in healthy volunteers [4,52]. We expected similar results in patients with chronic pain, who indeed showed changes in the functional connectivity between central brain regions and HR, at least diminished in good SMR responders. Nevertheless, the connectivity changes in Fc5HR and Cp6HR links should be considered with caution because these links showed differences between groups in the pre-resting-state session. The differences in baseline EEG-HR connectivity are difficult to explain. A tentative explanation could be related with a higher pain impact over frontal and central cortical regions, which could be preferentially involved in NFB learning [16,25]. In general, our findings suggest that physiological networks could be shaped by experience-driven modulation of SMR NFB, and training could cause long-term changes in the interactions between physiological systems. Moreover, our results also suggest that patients with fibromyalgia show altered functional connectivity between the somatosensory cortex and the heart. This means that central

Fig. 4  Means and standard errors of significant differences (p < .05) in connectivity between EEG activity and heart rate between post- and pre-SMR sessions.
and autonomic physiological alterations, which occur in chronic pain disorders, might influence each other.

The design of the current study entails some shortcomings; therefore, its findings should be interpreted with caution. First and most importantly, the sample size was small (the statistical power was 50.98% considering \( f = 0.25, \alpha = 0.05 \) and correlation of repeated measures = 0.4), which makes the findings only preliminary. Secondly, the fact that all participants took regular medication during NFB training could have biased the results; hence, the possible effects of medication on the connectivity changes observed in this study should be further explored. Finally, the quality of the reinforcement used in the NFB training was not controlled and this could reduce the rate of successful self-regulation of SMR power. Previous studies have shown that the use of a motivationally relevant reinforcement can increase the effectiveness of NFB training \([14,47,66]\). Future research controlling the quality of the reinforcement could increase the proportion of participants who learn to self-regulate SMR power by NFB successfully.

Our results are an extension of previous results published \([67]\) providing new evidence that NFB training is a promising tool that can be used in the treatment of chronic pain syndromes and to obtain a better understanding of the interactions between physiological networks. Beyond the limitations of the study, these results may pave the way for future methodologically more robust studies showing the capacity of neurofeedback to modulate the connectivity between the central and peripheral systems. Moreover, our results indicate that the analysis of the central-peripheral network could help in the treatment of patients with chronic pain and to investigate its physiological basis. This work opens two new research lines: the effect of NFB on the connectivity between different physiological systems and the relationship of physiological networks with chronic pain symptoms.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any professional, commercial or financial relationships that could be construed as a potential conflict of interest.

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