Observational Study

# Modification of Alpha Brain Oscillatory Activity in Fibromyalgia After Very Low Intensity Transcranial Magnetic Stimulation

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**Background:** Fibromyalgia (FM) is a chronic disease, with no effective treatments for this disorder. The origin is suspected to be a misprocessing of signals in the central nervous system. One of the experimental treatments is very low intensity transcranial magnetic stimulation (LITMS) used to perform central neuromodulation.

**Objectives:** The main objective was to characterize the differences in oscillatory brain processing before and after LITMS in FM and compare the results with healthy controls.

**Study Design:** This is an interventional study with control group, which shows how the treatment with LITMS could modify brain oscillatory activity and be useful for the improvement of symptoms in FM patients.

**Methods:** Thirty-three women with FM and 14 healthy controls are studied using magnetoencephalography recording, and mechanical stimuli are applied before and after treatment with transcranial magnetic stimulation. Changes in different brain areas and a specific brain frequency are studied, and the results are analyzed within and between patients, before and after treatment.

**Results:** In the FM group, an increase in alpha brain oscillatory activity was observed mainly in the dorsolateral prefrontal cortex (DLPFS), and more pronounced in the left hemisphere ($P = 0.03$). In addition, there was a significant improvement in the FM impact questionnaire in the patients ($P < 0.01$). When comparing patients with controls, it is observed that the differences in alpha frequency in this brain area disappear between groups.

**Limitations:** Age difference between patients and controls. Replicating the long-term results.

**Conclusions:** This treatment improves the patients' symptomatology, and also produces statistical changes in alpha brain activity in the DLPFS. Furthermore, a normalization was observed in this frequency and in this area, similar to that of the controls.

**Key words:** Fibromyalgia, transcranial magnetic stimulation, magnetoencephalography, chronic pain, cingulum, insula, prefrontal cortex, oscillatory brain activity, central nervous system, mechanical stimuli

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Fibromyalgia (FM) is a common pathology and is estimated to be 4% of the general population (1). To date, the precise cause of FM is unknown (2). The symptoms associated with FM significantly affect the patient's quality of life (3) and can result in extensive use of health care services (4).

Accumulating evidence suggests that the underlying cause of FM pain is the result of abnormal pain processing in neuromodulation processes, especially in the central nervous system, possibly due to a central sensitization process (5). It has been observed on experimentally induced pain that these patients have a lower pain threshold, as stimulus intensity is needed to evoke pain (6)

Therefore, a better understanding of the neurophysiological underpinnings of FM is essential to develop new treatments (7). Unfortunately, current treatments are not very effective, mainly using drugs, such as analgesics or antidepressants, and nonpharmacological drugs, such as exercise or cognitive-behavioral therapy (8). Several studies (9-12) have shown that repetitive high-intensity transcranial magnetic stimulation (TMS) can be effective in the treatment of FM. The effect of TMS on pain severity in various conditions, including FM, has been investigated (13-15). Although the use of very low intensity TMS (LITMS) has been less investigated in the field of FM, there is already evidence of its usefulness in this condition, even in the long term (16,17). While TMS applies magnetic fields from 1 Tesla upward, and locally applied, LITMS uses femtotesla intensities, frequencies close to 8 Hz, and holocranially (16). Due to the type of stimulus used with LITMS, low intensity, noninvasive signal repetition, and with a physiological frequency similar to the alpha rhythm, this type of stimulation may be better aligned with the pathophysiology of FM. Our working hypothesis is that the application of LITMS produces changes in brain oscillatory activity, restoring adaptive modulation to pain.

The main objective of the present work was to characterize the differences in alpha oscillatory brain processing before and after several sessions of LITMS in the insula, dorsolateral prefrontal cortex (DLPFC, and cingulum. The second objective was to compare the results obtained between patients and controls in each of the brain areas. The third and final aim was to test whether patients also improved on a scale related to FM symptoms, the Fibromyalgia Impact Questionnaire (FIQ).

## Methods

### Patients

The inclusion criteria were the following:

- Patients (FM) had received a diagnosis of FM according to the criteria of the American College of Rheumatology (18). They were adult women between 18 and 65 years of age.
- Controls (FC) were adult women between 18 and 65 years of age. All the patients were healthy people, without any type of pathology that could interfere with the results.

The exclusion criteria were the following:

- Patients suffering from other medical conditions different from FM, such as cancer, tumors, rheumatic diseases, or major psychiatric illness.
- Patients were asked to suspend their medication for the 2 months prior to scanning. Its intention was to prevent interference of the medication in the study results and to unify the sample as much as possible. This suspension included any medication, except conventional analgesics (opiates derivates were not allowed).

A total of 33 women (FM) and 14 women controls (FC) were recruited voluntarily who met the inclusion and exclusion criteria. The average age, in years, was 42.0 (standard deviation [SD] = 8.0) for patients and 23.9 (SD = 6.0) for controls. The baseline average of clinical characteristics of patients with FM patients is reported in Table 1. All patients signed an informed consent, which was approved by the Ethics Local Committee in June 2018 (19).

### Protocol

All patients were diagnosed with FM by a neurologist and a rheumatologist, who determined whether or not they met the inclusion and exclusion criteria. It was expected to see changes before and after the 5 sessions of LITMS in both groups separately and between groups. Five sessions were determined in a previous study (16) as the necessary and sufficient number to produce a beneficial and significative change in the clinic. Beyond that number, the results were maintained invariably.

For both studies (20,21), before magnetoencephalography (MEG) acquisition, all patients answered the FIQ questionnaire related to their state of health. Subsequently, the pain threshold was identified under medical supervision. Increasing pressure steps were applied with the pneumatic stimulation system at the selected tender point, which was the right epicondyle. A mechanical stimulation device was developed specifically for that purpose (Fig. 1). The protocol used includes trains of pulses of a duration of 1- and 2-second interpulse interval. In that case, mechanical pressure was the method chosen to determine the pain thresh-

old. The Flow Diagram shows the protocol followed for each patient (patients and controls) (Fig. 2).

## MEG Recordings

Neurophysiological data were acquired using a 306-channel Vectorview MEG system (102 magnetometers, 204 planar gradiometers) (Elekta AB, Stockholm, Sweden), placed inside a magnetically shielded room (VacuumSchmelze GmbH, Hanau, Germany) at the Center for Biomedical Technology (CTB), Madrid, Spain. The head shape was obtained using a 3-dimensional Fastrak digitizer (Polhemus, Colchester, Vermont) (22). Continuous estimation of head position was used during the recording to track head movements. Finally, a vertical electrooculogram of the left eye was used to capture blinks and eye movements. MEG data were acquired using a sampling rate of 1,000 Hz and a bandpass filter between 2 Hz and 45 Hz. That band was selected as frequencies under 2 Hz have a lot of biological activity interference, and above 45 Hz, there is noise and no useful information. The recordings were processed offline using a spatial-temporal signal space separation algorithm (22). The algorithm was also used to correct the head movements of the patient during the recording.

## Somatosensorial Stimulation

The International Association for the Study of Pain (IASP) guidelines were taken into account to define the pressure range delivered. Maximum pressure was chosen to be approximately twice the 4 kg/cm$^2$ IASP guideline pain threshold. This upper limit was set as a safety measure

Table 1. *Characteristics of the patients (group mean ± SD). Fatigue was measured with respect to a VAS of 0-10.*

| Time Since Diagnosis (y) | Number of Tender Points | Daily Sleep Hours | Years of Pain | Fatigue |
|---|---|---|---|---|
| 4.8 ± 2.3 | 16.2 ± 2.0 | 5.3 ± 1.3 | 7.3 ± 2.5 | 7.2 ± 0.8 |

Abbreviation: SD, standard deviation; VAS, visual analog scale.

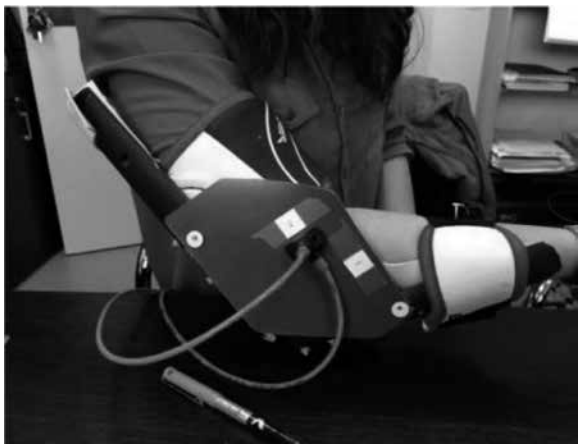

Fig. 1. *Applicator module in the form of an elbow brace and a piston.*

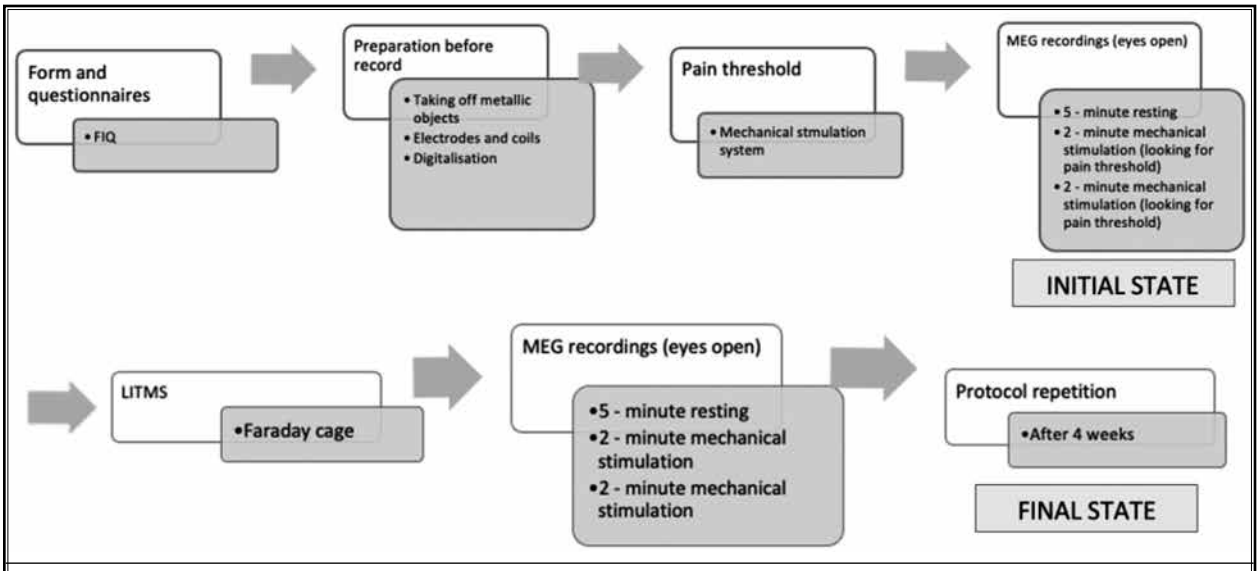


Fig. 2. *Flow Diagram. Showing the steps followed in the protocol.*

and to avoid causing excessive discomfort to patients. The exerted pressure was measured using a Force TenTM FDX Digital Force Gauge (Wagner Instruments, Greenwich, United States). Ten pressure steps that increased linearly from 1.9 kg/cm$^2$ to 7.6 kg/cm$^2$ were considered. That pain level was used afterward in the MEG task. A pneumatic mechanical stimulation system previously developed with the A61B5-00 patent was used to apply pulse trains (Fig. 3). It has an applicator module, which includes an applicator placed on the patient's epicondyle. It is a mechanical piston that applies pressure to the epicondyle. All the components, which are part of the mechanical arm, are made of nonferromagnetic materials to introduce them inside the MEG room.

## TMS of Very Low Intensity

The system LITMS, which was applied, is Brain Waves Minestim® APCM-01. It was assigned the patent WO 2011/098638 and was approved by the Spanish Agency for Medicines and Health Products and with the quality warranty certificate CE0318. Its field intensity is approximately 10 picoTeslas and 50 picoTeslas. The signal applied to the patient's head is a low frequency (8 Hz) square wave with a picoTesla magnetic field (16). A Faraday cage is necessary to protect against disturbances (23) and it is grounded. Brain Waves Minestim® applies weak magnetic fields, permitting continuous and repetitive stimulation as it does not lead to a temperature increasing. The sessions had a duration of 20 minutes with a holocranial location.

## Source Statistics

The SPSS version 26.0 statistical software tool (IBM Corporation, Armonk, NY) was used to apply the statistical model. The statistical test used to contrast the questionnaires was the same as that used to analyze the relative powers found in each brain area, the paired samples t test with 95% confidence interval (CI).

In the case of power analysis, valid data are entered into the statistical model after discarding patients whose acquisition was not performed correctly due to incorrect positioning of the sensors during acquisition. Thus, a total of 35 viable patients, 21 patients and 14 controls, are obtained.

In this study, the recordings of the 4 states collected are analyzed to first understand what brain events occur in them. In addition, statistics are applied to the relative powers by frequency obtained in 3 different brain structures, the left and right insula, the left and right cingulum, and the left and right DLPFC. For each area, the alpha (8 Hz to 12 Hz) frequency is evaluated since it is the frequency close to the stimulation frequency, it is also indicative of changes in symptomatological processes in FM.

The sample contains relative power data from patients and controls on 2 different days, before starting treatment and after the end of treatment. Data is obtained from an initial state, before any mechanical stimulation and LITMS sessions, and a final state, where the patient has undergone the full process of mechanical stimulation and LITMS sessions. All records (initial and final) are obtained in a resting state of the patient. These 2 states are the ones used to apply the statistical model to obtain statistically significant results within-patient and between-patient.

The statistical model used is a mean comparison model, t test for related samples. The null hypothesis is that there is no significant difference between the 2 sets of data. It can be rejected if the *P* value obtained is below the 0.05 level of significance. Figure 3 shows a diagram summarizing the records performed and the conditions compared in the statistical analysis.

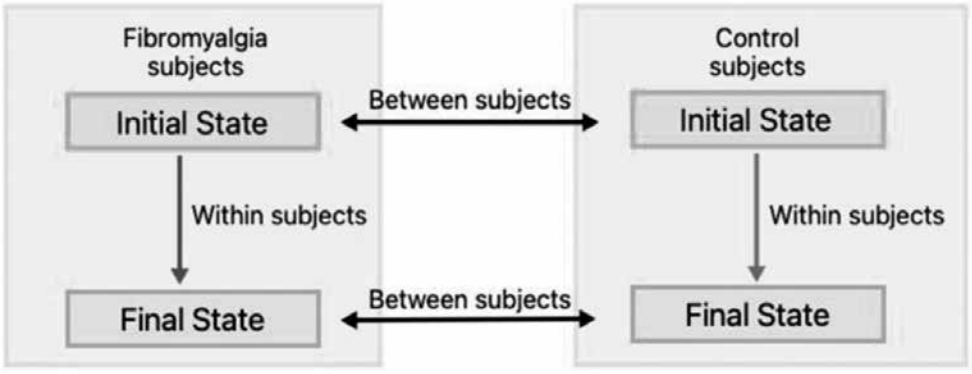


Fig. 3. *Diagram showing the records performed on each patient and the statistical tests performed between the different registers and groups of patients (control and FM).* FM, fibromyalgia.

## Results

### Results of the Initial State of Patients

The results of the patient's initial state are recorded when the patient has not yet undergone either mechanical epicondyle stimulation or LITMS treatment. The brain recording is performed in a resting state. In the initial scores for the FIQ test in patients and controls, the FM patients have higher final scores with a mean value of 69.4 (SD = 17.3), being the mean score of the FC patients 4.4 (SD = 6.19), scores expected as the control group did not present the pathology evaluated.

Regarding the relative powers found in patients and controls in the initial state, Table 2 shows that the mean value of the relative brain powers in the group of FM patients is lower in all the brain areas studied with respect to the values of the FC patients.

A mean comparison model, t test for related samples with a confidence level of 95% is used, so the statistically significant values for rejecting the null hypothesis are at a $P$ value < 0.05.

The significant $P$ values shown in Table 3 for most brain areas (Left DLPFC: $P$ value < 0.01; Right DLPFC: $P$ value = 0.01; Right cingulum: $P$ value < 0.01; Left cingulum: $P$ value < 0.01) indicate a high heterogeneity of relative powers in the alpha band in the initial resting state (before starting mechanical epicondyle stimulation and LITMS) between the control group and FM patients.

### Results of the Final State of Patients

The results of the patient's final state are recorded when the patient has completely finished the mechanical stimulation process and the LITMS. The brain recording is performed in a resting state. In the final scores for the FIQ test in patients and controls, the FM patients have higher final scores with a mean value of 48.8 (SD = 25.0), being the mean score of the FC patients 2.8 (SD = 4.4).

Regarding the relative powers found in patients and controls in the initial state, Table 4 shows that the mean value of the relative brain powers in the group of FM patients is lower in most of the brain areas studied with respect to the values of the FC patients.

A mean comparison model, t test for related samples with a confidence level of 95% is used, so the statistically significant values for rejecting the null hypothesis are at a $P$ value < 0.05.

The significant $P$ values that were observed in Table 3 are not observed in the relative powers recorded for the same brain structures in the final state (Table 5), which could indicate that there has been a remission of differences between the 2 groups.

Table 2. *Summary of the descriptive statistical results obtained for the different brain areas of the initial recording state (before mechanical stimulation of the epicondyle and application of the TMS treatment) for both groups, FM and FC.*

| Brain Structure | FM Patients | FC Patients |
|---|---|---|
| Left DLPFC | | |
| Average (Standard Error) | 0.1285 (± 0.003) | 0.1495 (± 0.007) |
| Median (Min-Max) | 0.1280 (0.1045-0.1622) | 0.1428 (0.1173-0.2018) |
| SD | 0.01548 | 0.02709 |
| Right DLPFC | | |
| Average (Standard Error) | 0.1292 (± 0.004) | 0.1527 (± 0.008) |
| Median (Min-Max) | 0.1279 (0.1010-0.1781) | 0.1456 (0.1095-0.2108) |
| SD | 0.01846 | 0.03160 |
| Right Cingulum | | |
| Average (Standard Error) | 0.1352 (± 0.005) | 0.1742 (± 0.013) |
| Median (Min-Max) | 0.1335 (0.1016-0.1963) | 0.1568 (0.1208-0.2556) |
| SD | 0.0230 | 0.0487 |
| Left Cingulum | | |
| Average (Standard Error) | 0.1344 (± 0.005) | 0.1682 (± 0.011) |
| Median (Min-Max) | 0.1298 (0.0951-0.1962 | 0.1541 (0.1243-0.2489) |
| SD | 0.0259 | 0.0419 |
| Right Insula | | |
| Average (Standard Error) | 0.1714 (± 0.009) | 0.1754 (± 0.011) |
| Median (Min-Max) | 0.1562 (0.1157-0.2632) | 0.1750 (0.1309-0.2343) |
| SD | 0.0426 | 0.0349 |
| Left Insula | | |
| Average (Standard Error) | 0.1691 (± 0.008) | 0.1736 (± 0.011) |
| Median (Min-Max) | 0.1554 (0.1245-0.2504) | 0.1725 (0.1270-0.2283) |
| SD | 0.0389 | 0.0366 |

Abbreviations: FM, patient group; FC, control group; DLPFC, dorsolateral prefrontal cortex; SD, standard deviation; TMS, transcranial magnetic stimulation.

### Comparative Results Between the Initial State and the Final State for Both Groups of Patients

Data extracted from the FIQ showed a general improvement in the patient's symptomatology (Fig. 4). After 5 sessions of stimulation (final state), almost 70%

of the cases improved. Before the LITMS (initial state) only 5 of 33 patients had a score lower of 50, mean score was 70 (range: 26-94) and after the LITMS (final state) 18 of 33 patients have a score lower of 50, mean 48 (range: 9-97). Applying a t test statistical model for related samples with a 95% CI we obtain a *P* value < 0.01.

Table 3. *Results of the application of the statistical model used, t test for related samples, at alpha frequency (8-12 Hz) for different areas of the brain with a 95% CI in the initial state.*

| Brain Structure | *P* value |
|---|---|
| Left DLPFC | < 0.01* |
| Right DLPFC | 0.01* |
| Right Cingulum | < 0.01* |
| Left Cingulum | < 0.01* |
| Right Insula | 0.07 |
| Left Insula | 0.14 |

* Statistically significant *P* value.
Abbreviations: DLPFC, dorsolateral prefrontal cortex; CI, confidence interval.

The results shown for the FC patients before (initial state) and after LITMS (final state) are not statistically significant. Before treatment the mean score is 4 (range 0-16) and after treatment the mean score is 3 (range 0-12).

Regarding the changes produced in the relative power of each cerebral areas, a mean comparison model, t test for related samples with a confidence level of 95% is used, so the statistically significant values for rejecting the null hypothesis are at a *P* value < 0.05.

Table 6 shows a statistically significant *P* value in the left DLPFC for the frequency of alpha in the group of patients. This indicates that there are statistically significant differences between the power found in the initial state and the power found at the end of LITMS, so that the LITMS applied has probably produced a change in the modulation of the signal at the level of this brain structure. This difference between the values can be seen in Tables 2 and 4, and Fig. 5, with the power in the left DLPFC this brain structure being lower in alpha in the initial state and higher in the final state.

Table 4. *Summary of the descriptive statistical results obtained for the different brain areas of the final recording state (before mechanical stimulation of the epicondyle and application of the LITMS) for both groups of patients, FM and FC.*

| Brain Structure | FM Patients | FC Patients |
|---|---|---|
| Left DLPFC | | |
| Average (Standard Error) | 0.1360 (± 0.005) | 0.1489 (± 0.006) |
| Median (Min-Max) | 0.1359 (0.07199-0.1886) | 0.1396(0.1228-0.1968) |
| SD | 0.02421 | 0.02504 |
| Right DLPFC | | |
| Average (Standard Error) | 0.1356 (± 0.005) | 0.1498 (± 0.008) |
| Median (Min-Max) | 0.1341 (0.07242-0.1930) | 0.1355(0.1178-0.2055) |
| SD | 0.02609 | 0.03111 |
| Right Cingulum | | |
| Average (Standard Error) | 0.1447 (± 0.007) | 0.1639 (± 0.011) |
| Median (Min-Max) | 0.1447 (0.07093-0.2194) | 0.1424 (0.1143-0.2544) |
| SD | 0.0341 | 0.0447 |
| Left Cingulum | | |
| Average (Standard Error) | 0.1431 (± 0.007) | 0.1563 (± 0.010) |
| Median (Min-Max) | 0.1439 (0.0719-0.2201) | 0.1389 (0.1163-0.2427) |
| SD | 0.0332 | 0.0388 |
| Right Insula | | |
| Average (Standard Error) | 0.1807 (± 0.011) | 0.1765 (± 0.008) |
| Median (Min-Max) | 0.1683 (0.076-0.3115) | 0.1719 (0.1268-0.2202) |
| SD | 0.0549 | 0.0272 |
| Left Insula | | |
| Average (Standard Error) | 0.1734 (± 0.010) | 0.1776 (± 0.009) |
| Median (Min-Max) | 0.1727 (0.0725-0.3039) | 0.1780 (0.1314-0.2480) |
| SD | 0.0490 | 0.0307 |

Abbreviations: FM, patient group; FC, control group; DLPFC, dorsolateral prefrontal cortex; SD, standard deviation; LITMS, low intensity transcranial magnetic stimulation.

## Discussion

FM is a prevalent condition that significantly affects patients' quality of life. At present, there is no objective diagnostic tool and current treatment options have limited efficacy (7,8). In the present study, we have obtained brain responses after the application of LITMS, repeated weekly (5 sessions), in a group of patients with FM and in a control group of healthy patients. The main findings fall into 2 categories, the between-patients results (between groups, patients, and controls) and the within-patients results (within the same group). On the one hand, in the between-group results, we observed that the alpha power for the left and

right DLPFC and the left and right cingulate brain structures, after full treatment, matched the powers that at baseline appeared different, eliminating the differences in relative signal power between the 2 groups. On the other hand, in the intrapatient results, it is observed that there is a modulation of the alpha signal in the left DLPFC, which increases the relative power of this signal. In addition, an improvement in the symptoms of this disease is observed, as evidenced by the FIQ.

Although brain stimulation has been widely used to modulate cortical excitability and treat patients, there remains inter- and intra-individual variability in the effects (24,25). To minimize this variation as much as possible, in our study, comparisons were made before and after treatment, as well as comparisons with healthy patients, also before and after treatment.

Pain is a multidimensional experience and is therefore the product of complex network interactions between brain regions, and this activity can interact with and modulate other networks. Within this complex configuration, the DLPFC is considered a key region in pain processing. Although it is not the only structure positively associated in pain processing, as it is also part of other areas, such as the primary and secondary somatosensory cortex, insula, cingulum, or thalamus (26), the DLPFC is considered a key node in the networks involved in nociceptive processing and pain modulation (27,28).

The functions of the DLPFC should not be attributed to single brain regions. The DLPFC is a key node in at least 3 brain networks: it sits between the extrinsic mode network (EMN) (29) and the default mode network (DMN) (30,31) interface, and is a key node in the cognitive control network (32). The EMN is thought to be a generalized network that allocates cognitive resources to any cognitive task or sensory processing of the external environment. The DMN, in contrast, is active in the absence of any overt stimulus or task, and is thought to be related to internal environmental monitoring and introspection. In fact, the DLPFC is thought to act as a switch and interface between rapid eye movement and DMN (33).

Given the compelling evidence that the structure and function of the DLPFC reflects chronic pain states, and that the DLPFC is involved in pain regulation, it is feasible that this brain region could serve as a therapeutic target. Indeed, several studies (34,35) have shown that noninvasive brain stimulation of this region can effectively control pain, whether acute or chronic.

In particular, repetitive TMS of the left DLPFC has shown promise as a treatment for chronic pain disorders (36,37). Another type of noninvasive brain stimulation, transcranial direct current stimulation of the left DLPFC in healthy patients, has also been shown to increase pain tolerance and improve performance on a

Table 5. *Results of the application of the statistical model used, t test for related samples, at alpha frequency (8-12 Hz) for different areas of the brain with a 95% CI in the final state.*

| Brain Structure | *P* value |
|---|---|
| Left DLPFC | 0.09 |
| Right DLPFC | 0.10 |
| Right Cingulum | 0.12 |
| Left Cingulum | 0.25 |
| Right Insula | 0.16 |
| Left Insula | 0.42 |

Abbreviations: DLPFC, dorsolateral prefrontal cortex; CI, confidence interval.

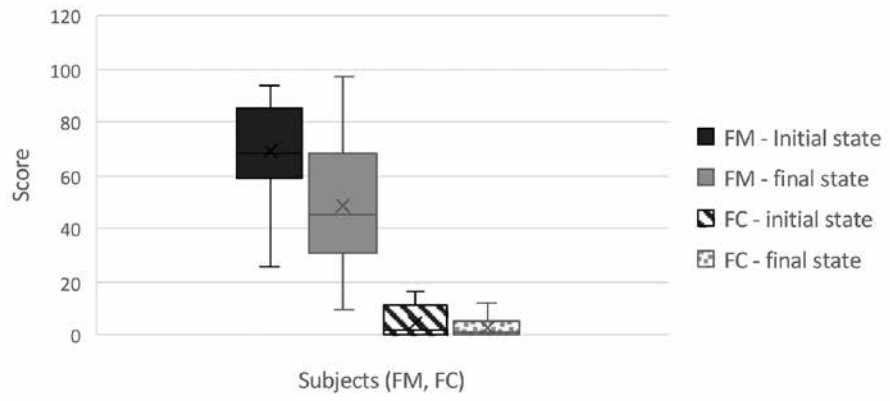


Fig. 4. *Box-and-whisker plot representing the initial state (before starting LITMS) and the final state (at the end of LITMS) of the FIQ test score of FM patients and controls; 95% CIs error bars are included.*
LITMS, low intensity transcranial magnetic stimulation; FIQ, Fibromyalgia Impact Questionnaire; CIs, confidence intervals; FM, patient group; FC, control group.

cognitive task, consistent with the role of the DLPFC in cognitive processes and pain modulation (38).

Equally interesting is the fact that neural oscillations play an important role in the integration and segregation of brain regions that are important for brain functions, including chronic pain (39-41). Similar to this study, other studies (5,41) have considered chronic pain as a disorder associated with central nervous system reorganization. Previous studies (39,40,42) have shown that patients with chronic pain exhibit abnormal neural oscillations. In particular, it has been hypothesized that alpha oscillations are involved in chronic pain (43-46). We hypothesize, as in previous studies, that alpha oscillations are reduced in FM due to disinhibition associated with pathological cortical arousal in chronic pain (47), indicating dysfunction of inhibitory neurotransmitters (48). Inspired by these previous studies (39,49-52), which found a relationship between alpha frequency and pain sensitivity, we investigated this relationship in our data. We found that functional changes also occur at the level of the left DLPFC in alpha frequency before and after LITMS treatment in patients. Furthermore, differences between patients and controls show a tendency to equalize relative power in the bilateral DLPFC and in the cingulate cortex (another area as we have seen involved in the pain circuitry) also after treatment. Previously, alpha oscillations in the context of pain have been investigated in depth in healthy patients. Most of these studies (15,53) have provided evidence of pain perception in the presence of suppressed alpha oscillations for phasic pain. Also, tonic pain of longer duration, which may represent a precursor to chronic pain, suppresses alpha oscillations (54-58).

In a previous study, Lim et al (59) investigated the presence of abnormal brain rhythms in low- and high-frequency bands during the resting state in FM patients and their relationship to the clinical pain symptom. Spontaneous activity was recorded by MEG in 18 women with FM and 18 healthy control patients. They observed that FM patients showed a slowing of the dominant alpha peak. In addition, increased high-frequency oscillatory activities in DLPFC were associated with higher affective pain scores in FM patients. These results show that FM patients have increased low- and high-frequency oscillatory activity in brain areas related to cognitive and emotional modulation of pain. Increased low- and high-frequency activity in the prefrontal cortex may contribute to persistent

Table 6. *Results of the application of the statistical model used, t test for related samples, at alpha frequency (8-12 Hz) for different areas of the brain with a 95% CI.*

| Brain Structure | FM Patients | FC Patients |
|---|---|---|
| | ***P* value** | ***P* value** |
| Left DLPFC | 0.03* | 0.84 |
| Right DLPFC | 0.11 | 0.39 |
| Right Cingulum | 0.06 | 0.17 |
| Left Cingulum | 0.09 | 0.06 |
| Right Insula | 0.25 | 0.52 |
| Left Insula | 0.54 | 0.86 |

Abbreviations: FM, patient group; FC, control group; DLPFC, dorsolateral prefrontal cortex; CI, confidence interval.

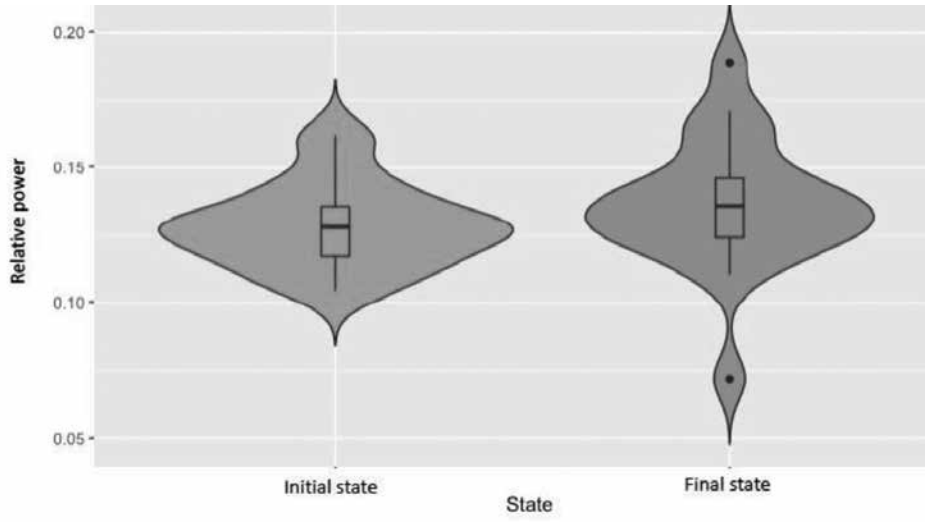


Fig. 5. *Violin plot of the relative power in the alpha frequency band in the left DLPFC. The final state (after finishing LITMS) and the initial state (before starting LITMS) in the group of patients with FM could be shown. Significant differences are found between the 2 states (P = 0.03).* DLPFC, dorsolateral prefrontal cortex; LITMS, low intensity transcranial magnetic stimulation; FM, fibromyalgia.

pain perception in FM. The same authors argue that a therapeutic intervention based on manipulation of neural oscillation to restore normal rhythmicity may be beneficial for pain relief in FM.

The results obtained are very encouraging and are consistent with the starting hypothesis that the application of LITMS produces positive changes in brain activity, restoring adaptive modulation to pain. In our work, we observed differences in the activity of the DLPFC before and after treatment, with an increase in activity at alpha frequencies, most likely due to the stimulation applied holocranially, and at a frequency close to 8 Hz (16). It could be that the very low stimulation frequency could correct the modulation and response to pain and, in turn, this correct modulation corrected the brain oscillations.

The improvement in symptomatology is supported by the results of the FIQ questionnaire with patients showing a better general state of health at the end of the 5 treatment sessions than at the beginning of the sessions. Most of them show similar levels of FM impact as controls, which overall represents an improvement in their quality of life.

This study has several limitations; they include the difference in age range between patients and controls. This was due to the fact that the controls were healthy volunteers from the CTB, where age is more concentrated in that range. It would be desirable to know the results in a larger group of patients and controls, as well as to describe whether these results are maintained in the long term.

## Conclusions

Functional changes are observed at the level of the left cerebral DLPFC (in alpha frequency), before and after treatment with LITMS, as observed by MEG in the patients. Furthermore, between-patient differences show a tendency to modulate relative power in the left and right DLPFC after treatment. In turn, LITMS treatment has been effective in reducing symptoms associated with FM.

Very low intensity magnetic stimulation may be effective in the treatment of pain and other symptoms associated with FM, and this improvement may be associated with changes in modular frequencies in areas of the central nervous system related to this disease.

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