Neuromodulação complementar à fisioterapia na fibromialgia e seus correlatos eletroencefalográficos: um protocolo para ensaio clínico randomizado

Neuromodulation complementary to physiotherapy in fibromyalgia and its electroencephalographic correlates: a randomized clinical trial protocol

Neuromodulación complementaria a la fisioterapia en la fibromialgia y sus correlatos electroencefalográficos: un protocolo para un ensayo clínico aleatorizado

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Resumo

O objetivo da presente pesquisa é apresentar um protocolo para um ensaio clínico randomizado, controlado por placebo, triplo-cego, que avaliará os efeitos da neuromodulação com a estimulação transcraniana por corrente direta (tDCS) associada ao tratamento fisioterapêutico na fibromyalgia e seus correlatos eletroencefalográficos. As voluntárias serão mulheres diagnosticadas com fibromialgia há pelo menos três meses, com idades entre 40 e 55 anos. As participantes serão divididas aleatoriamente em três grupos: Grupo 1, com

estimulação anódica no córtex motor esquerdo e estimulação catódica na região supraorbital direita; Grupo 2, com estimulação anódica no córtex prefrontal dorsolateral esquerdo e estimulação catódica na região supraorbital direita; e Grupo 3, com estimulação do tipo simulada (placebo). Todos os grupos serão acompanhados por tratamento fisioterapêutico. Os desfechos primários serão as variações nos níveis de dor, ansiedade e depressão, resultantes da neuromodulação, avaliadas pela Escala Visual Analógica e Inventários de Ansiedade e Depressão de Beck, respectivamente. O resultado secundário será a avaliação da atividade elétrica cortical registrada pelo eletroencefalograma de 32 canais. Na análise dos dados, será utilizada uma ANOVA mista, com 3 grupos de participantes versus 2 momentos de avaliação, com nível de significância de $p < 0,05$. Para comparações de pares, será utilizado o teste post hoc com correção de Bonferroni-Sidak. Considerando que a fibromialgia é uma doença multifatorial, pouco responsiva a medicamentos e outros tratamentos convencionais, é importante analisar o potencial efeito terapêutico da neuromodulação, além do tratamento fisioterapêutico, em indivíduos com fibromialgia.

Palavras-chave: Fibromialgia; Estimulação transcraniana por corrente direta; Terapia por exercício; Dor; Ansiedade; Depressão.

Abstract

The objective of the present research is to present a protocol for a randomized, placebo-controlled triple-blind clinical trial, which will evaluate the effects of neuromodulation with transcranial direct current stimulation (tDCS) associated with physiotherapy treatment in fibromyalgia and its electroencephalographic correlates. The volunteers will be women diagnosed with fibromyalgia for at least three months, aged between 40 and 55 years. Participants will be randomly assigned to three groups: Group 1, with anodic stimulation in the left motor cortex and cathodic stimulation in the right supraorbital region; Group 2, with anodic stimulation in the left dorsolateral prefrontal cortex and cathodic stimulation in the right supraorbital region; and Group 3, with simulated type stimulation (sham). All groups will be accompanied by physiotherapy treatment. The primary outcomes will be the variations in pain, anxiety and depression levels, resulting from neuromodulation, as assessed by the Visual Analogue Scale and Beck's Anxiety and Depression Inventories, respectively. The secondary outcome will be the evaluation of the cortical electrical activity as registered by a 32-channel electroencephalogram. In data analysis, a mixed ANOVA will be used, with 3 groups of participants versus 2 moments of evaluation, with a level of significance of $p < 0.05$. For pair comparisons, *post hoc* test with Bonferroni-Sidak correction will be used. Considering that fibromyalgia is a multifactorial disease, not very responsive to drugs and other conventional

treatments, it is important to analyze the potential therapeutic effect of neuromodulation, in addition to the physiotherapeutic treatment, in individuals with fibromyalgia.

Keywords: Fibromyalgia; Transcranial direct current stimulation; Exercise therapy; Pain; Anxiety; Depression.

Resumen

El objetivo de la presente investigación es presentar un protocolo para un ensayo clínico aleatorizado, triple ciego controlado con placebo, que evaluará los efectos de la neuromodulación con estimulación transcraneal de corriente continua (tDCS) asociada con el tratamiento de fisioterapia en la fibromialgia y sus correlatos electroencefalográficos. Las voluntarias serán mujeres diagnosticadas con fibromialgia durante al menos tres meses, con edades comprendidas entre 40 y 55 años. Los participantes se dividirán aleatoriamente en tres grupos: Grupo 1, con estimulación anódica en la corteza motora izquierda y estimulación catódica en la región supraorbital derecha; Grupo 2, con estimulación anódica en la corteza prefrontal dorsolateral izquierda y estimulación catódica en la región supraorbitaria derecha; y Grupo 3, con estimulación simulada (placebo). Todos los grupos estarán acompañados de un tratamiento de fisioterapia. Los resultados primarios serán variaciones en los niveles de dolor, ansiedad y depresión resultantes de la neuromodulación, evaluados por los Inventarios de Escala Visual Analógica y de Ansiedad y Depresión de Beck, respectivamente. El resultado secundario será la evaluación de la actividad eléctrica cortical registrada por el electroencefalograma de 32 canales. En el análisis de datos, se utilizará un ANOVA mixto, con 3 grupos de participantes versus 2 momentos de evaluación, con un nivel de significancia de p <0.05. Para las comparaciones entre pares, se utilizará la prueba post hoc con corrección de Bonferroni-Sidak. Teniendo en cuenta que la fibromialgia es una enfermedad multifactorial, que no responde muy bien a los medicamentos y otros tratamientos convencionales, es importante analizar el posible efecto terapéutico de la neuromodulación, además del tratamiento fisioterapéutico, en individuos con fibromialgia.

Palabras clave: Fibromialgia; Estimulación transcraneal de corriente continua; Terapia de ejercicio; Dolor; Ansiedad; Depresión.

1. Introduction

Fibromyalgia (FM) is a condition with the presence of generalized chronic pain, fatigue, sleep disorders, and psychological symptoms such as anxiety and depression, which can lead to work disability and decline in life quality. (González-Roldán, Cifre, Sitges, & Montoya, 2016).

The difficulty in identifying its etiology hinders the development of effective treatments for FM. In general, it is necessary to apply a multidisciplinary and individualized approach, combining pharmacological and non-pharmacological therapies, such as psychotherapy, health education and physical activity with physiotherapy (Goldenberg et al., 2008, Heymann et al., 2010, Helfenstein, Goldenfum, & Siena, 2012). Professionals involved in the care of FM patients should consider physiological and psychosocial aspects, family history, and the presence of psychological symptoms (Goldenberg et al., 2008).

Physiotherapy treatment should include exercises of low intensity (Dos Santos Sabbag et al., 2000), strength training (Häkkinen, Häkkinen, Hannonen, & Alen, 2001), aerobic exercise, muscle stretching, and overall relaxation. Drug treatment available for FM treatment provided only modest relief (Häuser & Fitzcharles, 2018). Besides, the high levels of anxiety and depression symptoms in FM (Goldenberg, 1999) must be considered in the therapeutic process.

In this scenario, transcranial direct current stimulation (tDCS) emerges as a possible technique to benefit individuals with FM through the stimulation of specific brain areas. Current evidence of tDCS is still very limited in relation to the ideal parameters, such as duration and frequency of the stimulation (Cruccu et al., 2016, Hou, Wang, & Kang, 2016). Also, divergent findings regarding the location of the brain stimulation in FM, whether in M1, to reduce pain (Mendonca et al., 2016, Cummiford et al., 2016, Zhu et al., 2016) or in CPFDL, to reduce pain associated with improved psychological symptoms (Silva et al., 2017) needs to be clarified by further investigations.

Studies that compare the effects of different stimulation sites, associated with a therapeutic exercise protocol, are still scarce and mainly focused on the assessment of behavioral responses (Fagerlund, Hansen, & Aslaksen, 2015, Foerster et al., 2015). Electrophysiological measurement of treatment response, such as cortical electrical activity, associated with behavioral assessment, would help to elucidate brain activity after tDCS. Therefore, the electroencephalogram (EEG) stands out as an important tool for monitoring response to treatment (González-Roldán, Cifre, Sitges, & Montoya, 2016).

The objective of the present research is to present a protocol for a randomized, placebo-controlled triple-blind clinical trial, to evaluate the effects of two tDCS protocols associated with a therapeutic exercise program in the treatment of FM as well as its electroencephalographic correlates. The results will contribute to define a complementary therapeutic alternative for FM, involving brain neuromodulation and physical exercises.

2. Methodology

The present research is exploratory, descriptive, and transversal. It is a field research, in which data collection will be through questionnaires and equipment. The approach is quantitative, in which numerical data are collected and analyzed using mathematical techniques (Pereira et al., 2018).

2.1 Ethical Aspects

The project was approved by the Research Ethics Committee of the Federal University of Paraíba under the CAAE: 64247317.6.0000.5188. The participants will sign the Informed Consent Form to take part in the study. The autonomy and anonymity of the participants will be respected, according to the National Health Council Resolution 466/2012. The ethical principles expressed in the Declaration of Helsinki will be respected, and this clinical trial was registered on the Brazilian Clinical Trial Registry (ReBEC) platform (www.ensaiosclinicos.gov.br), under the code RBR-6W2VTP.

2.2 Study design

This is a protocol for a placebo-controlled, randomized, triple-blind clinical trial, following the *Consolidated Standards of Reporting Trials* (CONSORT) guidelines for clinical trials.

2.3 Sample size calculation

The sample size calculation was performed using the G*Power (version 3.1.9.7) (Erdfelder, Faul, & Buchner, 1996), based on data of the research of Valle et al. (2009), which pain in FM was assessed through EVA, before and after the tDCS application. The means of improvement obtained in the initial and final evaluation were: active group (n = 14; -2.07; ± 2.1) and placebo group (n = 14; -0.567; ± 2.4). Considering an effect size of 0.334 for the ANOVA test, with an $\alpha = 0.05$ and $\beta = 0.7$, we obtained a sample size of 75 participants. Participants will be recruited through the information means, such as posters in clinic-schools and hospitals, and *websites*, in the city of João Pessoa - PB.

2.4 Eligibility criteria

The volunteers will be included in the study following the inclusion criteria: (1) have been diagnosed with FM according to the American College of Rheumatology criteria; (2) have been diagnosed at least three months ago; (3) be female; (4) age varying between 40 to 55 years old; (5) have a pain level greater than or equal to four in VAS; and (6) sign the Free and Informed Consent Term (TCLE). The exclusion criteria will be: (1) score below 24 in the Mini Mental State Exam (MEEM); (2) illiterate; (3) metallic implants located in the head, cochlear implants and cardiac pacemaker; (4) pregnant; and (5) history of seizure.

2.5 Study Groups

The volunteers will be randomly assigned to 03 groups: Group 1 (GM1), with anodic stimulation on the left M1 and cathodic stimulation on the right supraorbital region; Group 2 (GCPFDL), with anodic stimulation on the left CPFDL and cathodic stimulation on the right supraorbital region; and Group 3 (GSham), with simulated type stimulation, following the placement of the GM1 electrodes. All groups will be accompanied by physiotherapy.

2.6 Randomization and Blinding

Participants will be randomly distributed, with a 1:1:1 block exchange rate using the online randomization program (www.random.org). The design of the groups is illustrated in Figure 1. The generated codes will be placed in sequentially numbered, opaque and sealed envelopes in order to hide the allocation. These envelopes will be delivered to the researcher responsible for the neuro-stimulation one day before the beginning of the sessions.

The flow chart should show the number of participants evaluated for the eligibility criteria, the quantity that was randomly allocated to the three treatment groups, possible sample losses, and how many participants were statistically analyzed. The evaluators of the outcomes, the patients, and the researcher responsible for the statistical analysis, will be blinded regarding the type of stimulation applied. In addition, the person responsible for the neurostimulation will be blinded regarding the performance achieved by the participants in the evaluations. In the reevaluation, the volunteers will be asked if they received the active current or sham in order to verify the power of blinding. Blinding will only be broken in case of a reported worsening of a volunteer's clinical condition, in order to investigate the possible

causes of this decline, thus maintaining the integrity of the individual's health conditions.

Figure 1. Flowchart of CONSORT showing the outline of the study groups and the respective sample losses.
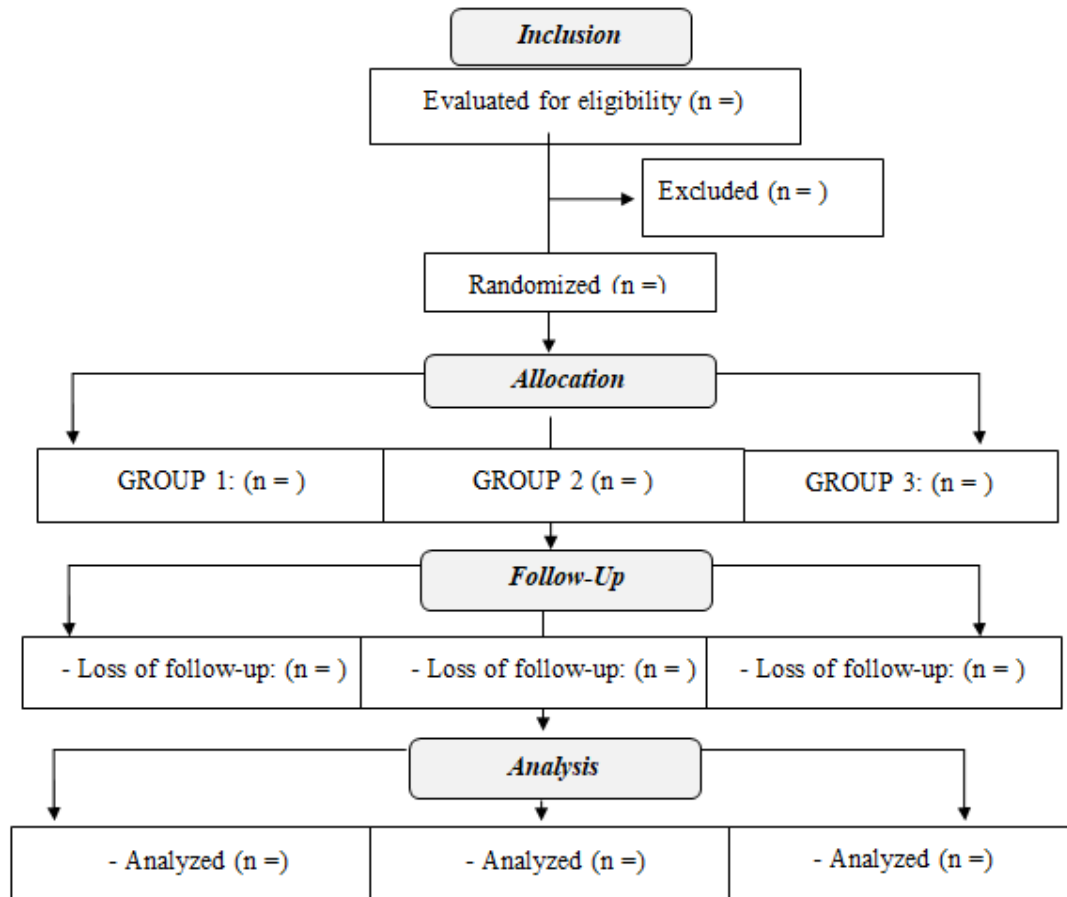
Source: Research data, (2020).

2.7 Friction and adhesion

As friction, we will consider the missing in two sessions or a single missing without replacement. To facilitate the adherence of the participants to the study, an initial meeting will be held with the participants in order to explain the importance of compliance with the attendance protocol. A follow-up form will be delivered to the participants so that they can verify the existence or not of a missing to be reschedule. In addition, the absence will be allowed in one day of attendance, and will be replaced at the end of the sessions, in addition to periodic calls, in order to maintain contact and avoid the study evasion.

2.8 Instrumentation

The instruments will be used to collect data: the Sociodemographic and Clinical Questionnaire, to characterize the sample; the Cumulative Disease Classification Scale – CIRS (Linn, Linn, & Gurel, 1968); the Visual Analog Scale - EVA (Kopf & Patel 2010, Schumann et. al, 2003); the Mini Mental State Exam - MMSE (Folstein, Folstein, & McHugh, 1975); the Beck Anxiety Inventory - BAI (Beck, Epstein, Brown, & Steer 1988); the Beck Depression Inventory - BDI (Beck, Steer, & Carbin 1988; the Epworth Sleepiness Scale (Johns, 1991); and an 32-channel electroencephalogram (EEG), with silver chloride electrodes. The amplifier will be an ActiChamp, developed by *Brain Products Inc*., with a 500Hz sampling rate. The right and left mastoid region electrodes will be used as reference electrodes at the time of data collection.

2.9 Phases of the study

The primary outcomes will be the variations in pain, anxiety and depression levels, resulting from the application of tDCS, evaluated through EVA, BAI and BDI, respectively. The secondary outcomes will be the changes in cortical electric activity, evaluated by EEG. The phases of the study are presented in Table 1. The primary and secondary outcomes will be evaluated before (- t1) and after the treatment (t3).

Table 1. Demonstrative schedule of the study phases - CONSORT 2010.

	Recruitment	Allocation	Post-allocation step Services	Conclusion
Time	$-t_1$	0	t_1	t_3
Recruitment:				
Screening selection	X			
Informed consent	X			
Allocation		X		
Interventions:				
Groups 1,2 e 3.			X	
Assessments	X			
Revaluations				X

Source: Research data, (2020).

Table 1 shows the study sentences, starting with the recruitment of participants (-t1), at that time the volunteers will be evaluated. Those who meet the eligibility criteria will be allocated to one of the treatment groups (0) and then start the care phase (t1). In the last phase,

of closure, re-evaluations will be carried out after the completion of care (t3).

2.10 Data Collection

The data will be collected in an individual session at the Audiology Clinic, UFPB. Initially, the participants will be instructed about the research procedures and invited to sign the TCLE. Afterwards, they will respond to the evaluation instruments. Then, the process of data collection with the EEG will begin. Participants will sit comfortably in a chair and will be instructed to avoid excessive body and eye movements, in addition to relaxing the mandibular muscles and avoiding muscle contractions in the face region during data acquisition to reduce the presence of artifacts. Data will be collected at rest, 6 minutes with the participant's eyes open and 6 minutes with the eyes closed (Hargrove et al., 2010). In order to avoid drowsiness during the acquisition, they will be subdivided into 2-minute times, repeating this procedure three times, ending the data acquisition in 12 minutes (Hassan, Fraser, Conway, Allan & Vuckovic, 2015), and keeping the impedance below 20kΩ (Tiemann et al., 2012). Data output of the amplifiers will be directed to a portable computer, 15 inches, with the BrainVision Pycorder, software for recording.

After the evaluation, participants will begin attending the tDCS, in an individual session, at the Laboratory of Studies in Aging and Neurosciences (LABEN) of the UFPB. They will be invited to sit comfortably on a chair and then the head will be measured in order to identify the appropriate sites for stimulation (M1 and left CPFDL). Finally, the stimulation parameters will be configured to start the application of the technique.

At the end of the 12 sessions, the participants' reevaluations will be carried out, following the same steps taken during the initial evaluation. All volunteers will be reevaluated within seven days after the completion of the services to ensure the measurement of the effects resulting from the application of the current.

Prior to the beginning of the examinations, a training will be carried out with the examiners, with direct observation of the application of the technique, followed by practical applications with supervision and discussion of the main difficulties encountered, to minimize random errors and among researchers. The training will be completed after the standardization of the process is ensured.

2.11 Analysis of EEG data

The analysis will be performed with EEGLAB, in the MATLAB environment. The pre- processing of the signal will be performed, with the filtering of the data, using the high pass filter of 8 Hz and low pass filter of 12 Hz, in order to evaluate the alpha frequency band. The noise inherent to the measurement of brain activity will be removed through the Multiple Artifact Rejection Algorithm - MARA (Winkler, Haufe, & Tangermann, 2011).

In the data processing phase, analyses of the power spectra of the alpha frequency band for the frontal, parietal, temporal and occipital regions will be performed, comparing them before and after the treatment. Thus, we intend to verify the average spectral power for each region of each cerebral hemisphere and then compare the activity of each lobe for the right and left cerebral hemispheres in order to verify the consistency of cortical activity in the cerebral lobes. Finally, the comparisons before and after the application of tDCS will be performed.

2.12 Statistical analysis

The statistical analyses will be performed through the *Statistical Package for the Social Sciences* (SPSS) *software* version 22.0 for Windows. First, the descriptive analyses will be made, through measures of central tendency and dispersion, in order to characterize the sample. For the inferential analyses, initially the Shapiro-Wilk test will be used, in order to observe if the sample has normal distribution. The chi-square test will be used to compare the groups in relation to the practical variables of physical activity, psychotherapy and medication use. The ANOVA *one way* will be used to check the group homogeneity before the treatment. For pre and post-treatment evaluation, an ANOVA with mixed design will be used, with the model: three groups (Group 1, Group 2 and Sham) x two times (pre and post-treatment). The level of significance considered will be $p < 0.05$. For comparison by pairs, the Bonferroni-Sidak *post hoc* test will be used.

The size of the effect will be calculated from the partial squared *eta* for each variable within each of the three groups and d from Cohen for pairwise comparisons. Afterwards, Pearson's correlation test will be carried out in order to verify the existence of correlation between data from EEG, EVA, BDI and BAI before and after tDCS. The level of significance considered will be $p<0.05$. If the data do not have normal distribution, the corresponding non-parametric statistical tests will be used, in this case, the Friedman test and the Spearman

correlation test.

2.13 Neuromodulation Protocol

The protocol will be 20 minutes of stimulation per day for 12 alternate days (Monday, Wednesday and Friday). Electrodes wrapped in 5 x 7 cm sponges moistened with saline solution (NaCl 0.9%) will be used. The current applied will be 2mA, in which the current density is equivalent to 0.5 A/m2. The protocol for sham stimulation will be identical, but the device will be turned off after 30 seconds from the beginning of stimulation and no clinical effects will be induced. The equipment used for stimulation will be the stimulator tDCS (1ch) from *TCT Research Limited,* Hong Kong.

The participants will be asked, at the end of each stimulation, whether they experienced any adverse effects such as tingling, burning, headache, drowsiness and others, and then asked how intense this sensation was (1 - none, 2 - mild, 3 - moderate, 4 - strong), and whether this effect was related to stimulation, on a Likert scale varying from 1 (no relation) to 5 (strongly related) (Poreisz, Boros, Antal, & Paulus, 2007).

2.14 Physiotherapy Protocol

The participants will receive, in addition to the tDCS service, physiotherapeutic follow- up through activities developed collectively. The protocol consists of group dynamics, stretching, warming, and kinesiotherapy exercises, to improved joint mobility, relaxation, general well-being, in addition to the interaction between participants through the dynamics of the activities. All participants, including those who will receive placebo-type stimulation, will participate in the physiotherapeutic group. Thus, the intention is to verify the potential additional effect of the tDCS in those individuals already under conventional treatment for FM.

3. Expected Results and Discussion

The treatment of FM is a challenge due to the absence of effective medication to the clinical condition. Thus, these patients consume high financial resources in treatment and diagnostic investigation (Helfenstein, Goldenfum, & Siena, 2012). Considering that the

pharmacological therapies available for chronic pain have reduced efficacy (Da Silva et al., 2011), the tDCS may complement the conjoint of techniques used in the treatment of FM.

Due to the greater effectiveness of M1 stimulation in reducing pain (Zhu et al., 2016), pain levels in the M1 stimulation group are expected to be lower than in the other groups after the end of the protocol. Given that stimulation in the left CPFDL acts by modulating the cognitive and emotional aspects of pain (Duquette et al., 2007), we expect to find that the CPFDL stimulation group will have lower levels of anxiety and depression after the tDCS when compared to the other groups.

A previous study associating the application of tDCS and physical exercises in individuals with FM reported that neuromodulation would act in conjunction with physical activity promoting long-term brain changes (Mendonca et al., 2016). Individuals with FM have changes in different brain waves, analyzed by EEG at rest. Given the ability of tDCS to promote modulation of neuronal activity (Cruccu et al., 2016), it is expected that this technique will be able to modulate cortical electrical activity and increase the synchronization of this activity, reflecting in greater spectral power in the alpha frequency range (Boonstra et al., 2016, Song, Shin, & Yun, 2014). Considering that alpha frequency range activity is related to the state of relaxation, the increase in its average spectral power is expected to be associated with clinical improvement in FM (Bell et al., 2004).

In this sense, we hope to see benefits of tDCS associated with physiotherapy, improving symptoms of pain, anxiety and depression in fibromyalgia. In addition, these benefits are expected in conjunction with the change in cortical electrical activity because tDCS acts modulating brain activity. These data can be observed through the analysis of the electroencephalogram.

4. Final Considerations

The program of therapeutic exercises is one of the inherent resources used by physiotherapists, who are part of a multidisciplinary approach for the treatment of FM. The conventional treatment with medicines and other therapies available for this clinical condition are not completely effective.

Thus, a complementary treatment that help to reduce the symptoms, such as pain, anxiety and depression, would improve the quality of life of the individuals with FM. We suggest that further studies may evaluate the effectiveness of tDCS associated with conventional treatments, such as physiotherapy, to verify whether this technique is capable of

reducing the FM symptoms and promotes changes in the cortical brain activity.

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