Does anodal transcranial direct current stimulation over left motor cortex show body side pain-related difference in fibromyalgia?

A estimulação transcraniana por corrente contínua anódica sobre o córtex motor esquerdo apresenta diferença na dor entre os hemicorpos na fibromialgia?

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ABSTRACT

BACKGROUND AND OBJECTIVES: Fibromyalgia (FM) is a chronic widespread musculoskeletal pain resulting in central sensitization of nociceptive signaling. Transcranial direct current stimulation (tDCS) over the left motor cortex (M1) is a non-invasive neuromodulation technique indicated for a broad range of chronic pain disorders, including FM. Studies suggest that left and right M1 (contralateral and ipsilateral hemisphere of tDCS stimulation) are modulated. But it is necessary to clarify the differences in clinical pain perception comparing the right and left side of the body. This study aimed to evaluate the pain-related difference between right-left side of the body after five sessions of anodal tDCS in women with FM.

METHODS: A double-blinded, parallel, randomized, sham-controlled trial with 30 women with FM was performed. Five sessions of anodal C3 and cathodal supraorbital (Fp2) tDCS were conducted (2 mA for 20 min). Pain, impact of FM and anxiety were evaluated. No statistically significant three-way interaction between time, stimulation type and body side were found.

RESULTS: Active-tDCS showed significant improvement in pain, but impact of FM and anxiety did not show significant improvement.

CONCLUSION: Five sessions of anodal tDCS over the left M1 improves pain in women with FM, however there was no difference between right-left body sides.

Keywords: Chronic pain, Fibromyalgia, Motor cortex, Noninvasive brain stimulation, Transcranial direct current stimulation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A fibromialgia (FM) é uma dor musculoesquelética crônica generalizada que resulta na sensibilização central da sinalização nociceptiva. A estimulação transcraniana de corrente contínua (eTCC) sobre o córtex motor esquerdo (M1) é uma técnica de neuromodulação não invasiva indicada para uma ampla gama de distúrbios de dor crônica, incluindo a FM. Estudos sugerem a modulação do M1 esquerdo e direito (hemisfério contralateral e ipsilateral da eTCC). Mas é necessário esclarecer as diferenças na percepção clínica da dor comparando os lados direito e esquerdo do corpo. Este estudo teve como objetivo avaliar a diferença relacionada à dor entre o lado direito e esquerdo do corpo após cinco sessões de eTCC anodal em mulheres com FM.

MÉTODOS: Foi realizado um estudo duplo-cego, paralelo, randomizado e controlado por sham com 30 mulheres com FM. Foram realizadas cinco sessões de eTCC anodais C3 e supraorbitais catodais (Fp2) (2 mA por 20 min). Foram avaliados a dor, o impacto da FM e a ansiedade. Não foi encontrada nenhuma interação de três vias estatisticamente significativa entre tempo, tipo de estimulação e lado do corpo.

RESULTADOS: A eTCC-Ativa mostrou uma melhora significativa na dor, mas o impacto da FM e da ansiedade não mostrou uma melhora significativa.

CONCLUSÃO: Cinco sessões de eTCC anodal sobre o M1 esquerdo melhoram a dor nas mulheres com FM, entretanto não houve diferença entre os lados direito e esquerdo do corpo.

Descritores: Córtex motor, Dor crônica. Estimulação transcraniana por corrente contínua, Fibromialgia, Síndrome de fadiga crônica.

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INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome associated with maladaptive plasticity in neural central circuits characterized by the presence of diffuse pain throughout the body, sleep disturbance, mood dysfunction, musculoskeletal stiffness, and chronic fatigue[1,2]. Due to the central nervous system dysfunction, pain pathways seem to operate abnormally, resulting in central sensitization of pain signaling[3]. This mechanism leads to maladaptive plastic changes in cortical activity from brain areas, including pain neuromatrix[2]. Neuroimaging and electrophysiological approaches suggest that FM is a condition associated with brain dysfunction and rehabilitation programs should target the central nervous system[2].

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that has been used to modulate the excitability and the firing rate of individual neurons in a polarity-dependent fashion[4,5]. Several studies about FM and neuromodulation suggest promising results in pain relief[6-9]. Pain improvement has been demonstrated in other chronic pain syndromes such as traumatic spinal cord injury, cancer, migraine, and chronic post-stroke pain[6-9].

Anodal tDCS over the motor cortex (M1) is a promising intervention to relieve pain and improve general quality of life in FM[9]. Most studies used the anodal electrode over M1 or left dorsolateral prefrontal cortex (DLPFC), and the cathode over the contralateral supraorbital region[6,10,11]. In this sense, it has been suggested that M1 anode stimulation may reduce pain by activating neural circuits present in the precentral gyrus[10]. These connected structures are involved in the sensory and emotional component of pain processing, facilitating descending pain inhibitory control[10].

In most studies, anodal stimulation was applied over M1 in the contralateral hemisphere of pain (in case of focal or lateralized pain) or the dominant hemisphere (in case of widespread pain)[10]. A study demonstrated that tDCS applied over M1 was able to induce neuromodulatory effects on the corticospinal and cortical excitability indexes by measuring a single or left and right hemisphere through transcranial magnetic stimulation (TMS)[12]. Authors found that both anodal and cathodal tDCS induced an overall excitability increase compared to the baseline in the contralateral hemisphere of stimulation[12]. Anodal stimulation increased cortical response in both stimulated cortex and contralateral homotopic areas[12].

Moreover, another neuroimage study shows that tDCS not only modulates activity in the brain region directly underlying the stimulating electrode but also in a network of brain regions that are functionally related to the stimulated area[13]. This result supports a possible coupling of neural activity between motor regions[13]. However, for protocols involving specific pain syndromes such as migraine, phantom limb pain, and orofacial pain, the anodal stimulation was applied over M1 or DLPFC of the hemisphere contralateral to pain[6,10].

Following this assumption, the aim was to clarify the differences in clinical pain perception comparing the right and left side of the body after a short-term effect of bilateral bipolar-non balanced tDCS (C3/Fp2, 10/20 International EEG System™). The hypothesis is a global pain improvement with no pain-related difference between right-left side of the body. The primary objective of the current study was to evaluate the left-right body pain-related difference using algometry threshold after five days of anodal tDCS over M1 in women with FM. The secondary outcomes were to assess pain, impact of FM and anxiety.

METHODS

This study was a single-center, double-blinded, parallel, randomized, sham-controlled trial that followed the recommendations of the CONSORT/2010[14] and TIDier[15] checklist. This study complied with ethical standards based on Declaration of Helsinki and was approved by the local institutional ethics committee at Federal University of Rio Grande do Norte under registration number 2.932.953. The study was registered in clinicaltrials.gov with identifier NCT03084094. Data were collected in a Pesq-Clin Lab at Federal University of Rio Grande do Norte from October 2016 to March 2017 and the recruitment was performed during the entire period since interventions were carried out. All patients were selected from a specialized outpatient service and evaluated by a rheumatologist before the trial.

Participants were eligible to enter the study if they fulfilled the following inclusion criteria: women with FM according to the American College of Rheumatology (ACR, 2010)[16], pain score of at least 4 on the Numeric Rating Scale (NRS) in the two weeks preceding the clinical trial, and age between 18 and 70 years. Participants were excluded if they had another associated rheumatic disease, such as lupus and rheumatoid arthritis, pregnancy or lactating, history of convulsive crises or intracranial implants. Patients who were receiving drugs for pain were not excluded and no changes in the medication were permitted throughout the trial.

The G*Power (V._3.1.9.4™, Kiel, Germany) was used to calculate sample size. Sample size was based on previous studies that investigated the effect of tDCS on FM[6,11]. A significance of 0.05 and power of 0.80 was assumed. Authors suggested in previous studies that a mean reduction of 3 points in the visual analogue scale (VAS) for the group under active stimulation was expected in contrast to no improvement in the sham group[17]. According to this method, the sample size resulted in two groups of 12 participants each. Three more patients were added in each group to prevent any reduction of power in case of patient dropout.

Initially, 36 women were enrolled in the study (Figure 1). Six women were excluded for not meeting the inclusion criteria (n=2) or rejecting to participate (n=4). Patients were considered dropouts if they missed one day of treatment. Patients were randomized (1:1) and divided into two groups (M1 and Sham). All participants were blinded to the intervention allocation group.

Interventions

Direct current was administered by a trained physical therapist using a continuous electric stimulator, with three energy batteries (9 V) connected in parallel. The maximum energy output was

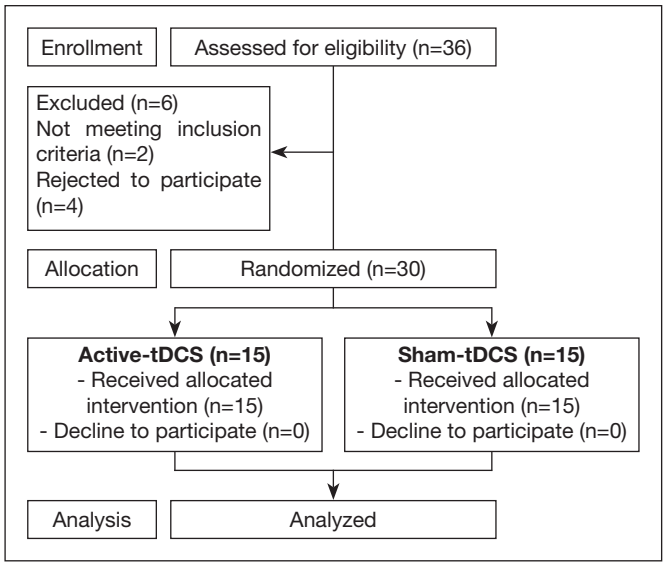

Figure 1. Flowchart

10 mA and was controlled by a professional digital multimeter (DT832, WeiHua Electronic Co.™, Zhangzhou, Fujian, China) with a standard error of ±1.5%. Patients received five consecutive sessions (Monday-Friday) of either sham or anodal stimulation over left M1. The anode electrode was placed over C3 and the cathode was placed over the contralateral supraorbital area (Fp2) according to the 10–20 EEG system. Electrodes were placed into a 35 cm^2 (5 cm x 7 cm) square sponge soaked in saline solution (150 mMols of NaCl diluted in Milli-Q water). Rubber bandages were used to hold the electrodes in place for the duration of stimulation. For the active tDCS, a constant current of 2 mA was applied for 20 min/day. For sham-tDCS, electrodes were placed at the same position as for the active tDCS, but the current was turned off after 30 seconds of stimulation, according to the methods of clinical studies in the brain stimulation[10,18]. Previous studies described this method of blinding as reliable[11,19]. Subjects felt the initial itching sensation but received no current for the rest of the stimulation period.

Outcome measures

Sociodemographic data were assessed to characterize the sample. Measures of pressure pain threshold (PPT) and NRS were collected one week before the first session (baseline), after the first stimulation (day 1) and after the last stimulation (day 5). For impact of FM and anxiety, data were assessed at baseline and on day 5.

Primary outcome

PPT was quantified in kg/cm^2 and measured by a digital pressure algometer through a 1-cm diameter rubber tip, (FDX™, Wagner Instruments, Greenwich, Connecticut, USA) on the 18 tender points recommended by the ACR/1990 (left and right low cervical, second rib, lateral epicondyle, knee, occiput, trapezius, supraspinatus, gluteal and greater trochanter)[20]. The measurement was performed positioning the algometer perpendicularly to the skin, with an interval of 20 to 30 seconds between applications. The examiner positioned the rubber tip above the area to be examined and gradually increased the pressure by 1 kg/cm^2 per second. PPT was identified when the participant reported the beginning of an unpleasant sensation by stating "it started".

This method of evaluation records the initial pain sensation informed by participants in 18 different points throughout the body (9 points on the left and 9 on the right side). A mean of total tender points of each side of the body was used to statistical analysis. Furthermore, each pair of tender points (ipsilateral *vs* contralateral to stimulation) were compared. A second analysis was done with the mean of total pain threshold (mean of 18 tender points) of each time of evaluation.

Secondary outcomes

NRS was used to assess the intensity of pain. This straight 10-cm scale is numbered from 0 to 10, in which 0 represents no pain and 10 the most pain. Subjects were instructed to mark the number that best reflected the symptoms of pain at that moment. Baseline NRS was assessed one week before intervention for three consecutive days. For statistical analyses, a mean of these three days before the intervention was adopted. This method was used to measure the most real pain feeling before the intervention.

The impact of FM was evaluated by using the Brazilian version of the Fibromyalgia Impact Questionnaire (FIQ), which is a self-administered questionnaire that measures patients' functional aspects[21]. FIQ contains three Likert-scale-type questions (levels of response) and seven visual analog questions. All scales vary from 1 to 10 and a high score indicates a negative impact and more severe symptoms. The total FIQ score is graded from 1 to 100 points. Higher scores are related to greater impact of the disease on patients' functionality and a reduction in their quality of life[21].

The severity of anxiety symptoms was measured by using the Brazilian version of Hamilton Anxiety Scale (HAS). HAS was administered by an interviewer who asked a series of semi-structured questions related to symptoms of anxiety[22]. The interviewer rated the individuals on a five-point scale for each of the 14 items. Seven items specifically address psychic anxiety and the remaining seven, somatic anxieties. The values on the scale range from zero to four: zero means that there is no anxiety, one indicates mild anxiety, two indicates moderate anxiety, three indicates severe anxiety, and four indicates very severe or grossly disabling anxiety. The total anxiety score ranges from 0 to 56[22].

Statistical analysis

Derived data supporting the findings of this study are available from the corresponding author. Analyses were performed using Graph Pad Prism 5 and SPSS software (V.19.0™, Chicago, Illinois, USA). Data were expressed as means and standard deviations. Shapiro-Wilk's and Levene's tests were applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity was used to validate the correlation of the repeated measures and if the assumption of sphericity was violated. The Greenhouse-Geisser correction was applied. Differences in sociodemographic data were calculated using the unpaired t-test or Chi-square test.

Table 1. Sociodemographic and pain characteristics

Clinical and demographic data	Active-tDCS (mean ± SD)	Sham-tDCS (mean ± SD)	P-value
Age (years)	49.40 ± 11.89	51.73 ± 12.44	0.60
FIQ	70.3 ± 13.34	63.02 ± 15.47	0.17
NRS	6.24 ± 1,63	6.69 ± 1.94	0.50
Threshold right side*	1.4 ± 0.57	1.78 ± 0.73	0.12
Threshold left side*	1.92 ± 0.79	1.92 ± 0.65	0.09
Anxiety (HAS)	31.07 ± 7.46	34.73 ± 10.12	0.26
Income** (%)			0.17
1 minimum wage	6.7	29.4	
2 to 3 minimum wage	53.3	41.2	
4 minimum wage or more	33.3	11.8	
Unreported	6.7	17.6	
Marital status (%)			0.73
Married	60	41.2	
Never married	26.7	41.2	
Widowed	6.7	5.9	
Divorced	6.7	11.8	
Schooling (%)			0.56
Elementary (incomplete)	0	5.9	
Elementary	26.7	23.5	
Secondary	26.7	41.2	
University	46.7	29,4	

SD = Standard Deviation; FIQ = Fibromyalgia Impact Questionnaire; NRS = Numeric Rating Scale; HAS = Hamilton Anxiety Scale. Numeric data were calculated using unpaired t test. Categorical data were calculated using Chi-square test. Threshold and tolerance were calculated with the mean of the 9 tender points on left side of the body and 9 points on right side of the body according to ACR. *Values in kg/cm^2 **Brazilian National Minimum Wage, US$ 257.56 per month.

Three-way analysis of variance (ANOVA) for repeated measures were used to assess the effect of tDCS intervention on PPT. This analysis compared the time (factor 1, "time": baseline, 1st day of treatment and 5th day of treatment), sham and active tDCS conditions (factor 2: "type of stimulation") and body side (factor 3: right side of the body = contralateral to the tDCS; left side of the body = ipsilateral) as within-subjects factors. ANOVA was used to compare the effects of tDCS on the total threshold and NRS. To compare FIQ and HAS before and after treatment, a one-way ANOVA was used to determine whether the treatments/interventions have a different effect. Partial η^2 were calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η^2 was used to calculate the effect size, where $\eta^2 = 0.01$ was considered small, $\eta^2 = 0.06$ moderate and $\eta^2 = 0.14$ large effect. Alpha levels were set to ≤ 0.05.

RESULTS

Thirty women (mean age of 50.57±12.01 years) were randomized to either M1 or sham groups. There were no dropouts in this trial. There was no significant baseline difference in demographic and clinical characteristics (Table 1). Patients tolerated the tDCS and evaluations well. Adverse effects were minor and uncommon, such as skin redness and tingling.

Three-way repeated measures ANOVA was normally distributed. PPT showed no statistically significant three-way interaction between time, stimulation type and body side, $F(2, 28) = 1.533$, $p = 0.23$, $\eta^2 = 0.09$ (Table 2). PPT showed no statistical significance for two-way "type of stimulation" and "body side" interaction, $F(2, 22) = 0.009$, $p < 0.92$, $\eta^2 = 0.001$; two-way "type of stimulation" and "time", $F(2, 22) = 2.118$, $p < 0.13$, $\eta^2 = 0.13$; and two-way "body side" and "time", $F(2, 22) = 0.23$, $p < 0.79$, $\eta^2 = 0.01$ (Table 2). When comparing each pair of tender points, no difference was found for three-way analysis (Table 2).

Table 2. Three-way repeated measures ANOVA comparing the effects of anodal and sham tDCS over contralateral and ipsilateral body side

Tender points comparations	ANOVA Factor													
	(1) Time		(2) Group		(3) Body side		Interaction 1 by 2		Interaction 1 by 3		Interaction 2 by 3		Interaction 1 by 2 by 3	
	f-value	p-value	f-value	p-value	f-value	p-value	f-value	p-value	f-value	p-value	f-value	p-value	f-value	p-value
1x2	0.51	0.65	2.37	0.14	4.43	0.05	2.33	0.11	1.22	0.31	1.24	0.28	1.22	0.31
3x4	0.53	0.59	1.53	0.23	2.09	0.17	0.62	0.54	0.76	0.47	2.22	0.15	1.54	0.23
5x6	1.33	0.28	3.46	0.08	1.55	0.23	0.38	0.68	0.00	0.99	0.06	0.79	2.11	0.14
7x8	1.16	0.32	1.21	0.28	1.58	0.22	1.72	0.19	0.79	0.46	0.001	0.96	1.2	0.29
9x10	4.39	0.02*	0.49	0.49	4.75	0.04*	1.23	0.30	1.75	0.19	0.01	0.89	0.26	0.77
11x12	3.27	0.05*	2.57	0.13	0.72	0.40	0.42	0.65	1.73	0.19	0.01	0.89	0.11	0.34
13x14	0.98	0.38	1.63	0.22	21.15	0.0001*	2.54	0.09	0.06	0.93	1.41	0.25	1.94	0.16
15x16	1.69	0.2	0.69	0.41	0.7	0.41	4.25	0.04*	0.35	0.7	2.15	0.16	0.85	0.43
12x18	0.45	0.64	0.02	0.88	6.28	0.25	0.51	0.54	0.82	0.45	2.92	0.1	0.5	0.61

*Denote significance.

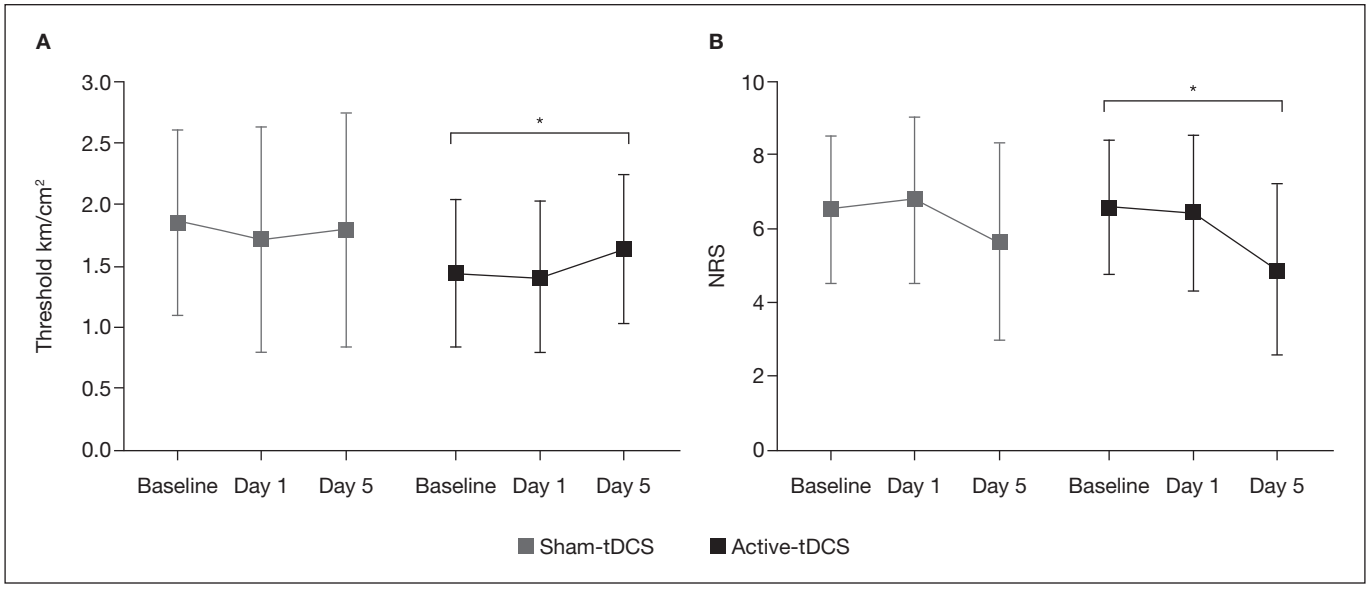

Figure 2. (A) ANOVA comparing the threshold means across the time. Active-tDCS showed significance increase in pain threshold (Sham: p=0.89 and Active: p=0.02). (B) Numeric Rating Scale (NRS). Active-tDCS showed a significant decrease in pain (Sham: p=0.31 and Active: p = 0.02).
*Statistical significance.

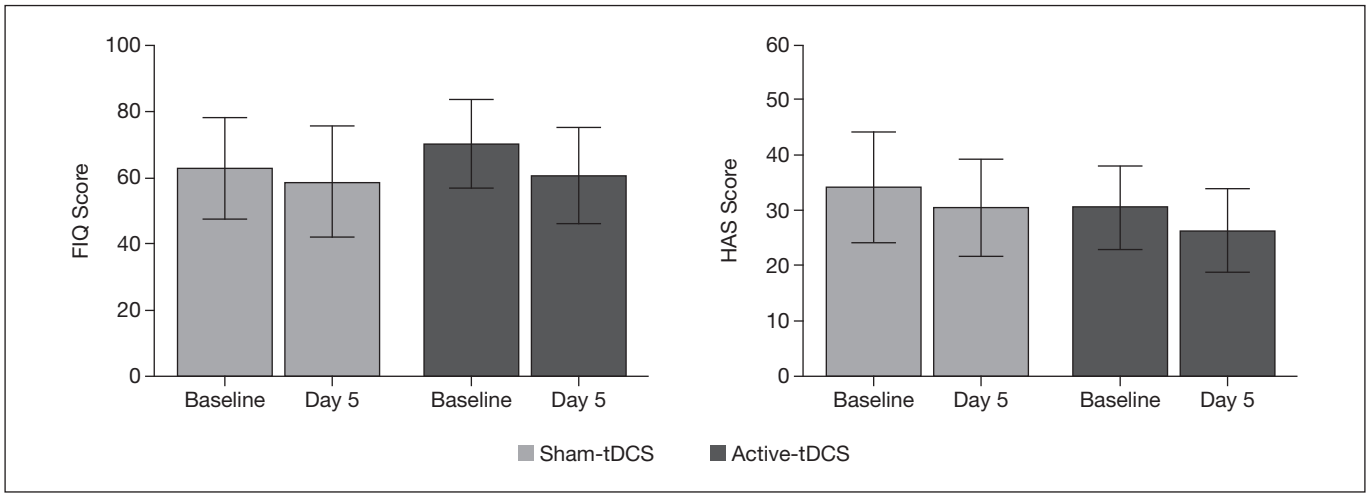

Figure 3. FIQ: Fibromyalgia Impact Questionnaire assessed to measure functionality and the impact of FM on daily activity. HAS: Hamilton Anxiety Scale was assessed at baseline and after the 5th session of tDCS.

ANOVA was used to compare baseline, 1st and 5th day. Active--tDCS showed significant increase in PPT (Sham: p=0.89 and Active: p=0.02) and improvement in NRS (Sham: p=0.31 and Active: p=0.02) (Figure 2).
There was a reduction on FIQ, although not significant (p=0.70; baseline: 69.6±13.5; day 5: 59.4±14.1). HAS showed a decrease in both groups but no significant results were found (p=0.42; mean difference: 1.75) (Figure 3).

DISCUSSION

tDCS over left M1 showed significant improvement in pain after 5 consecutive days of stimulation with no significant difference between ipsilateral and contralateral body pain perceptions. For three-way and two-way analysis no significant interaction was found for pain level and body side. The significant improvement in NRS for active-tDCS group suggests a global improvement in pain perception. There was no significant improvement for the impact of FM and anxiety. Additionally, there were no adverse effects during the study protocol.
Pain is an important outcome that influences mood and functionality in FM[24]. The primary target of FM nonpharmacological or pharmacological approaches is pain improvement[3,23,24]. Guidelines recommend that patients should be encouraged to monitor pain, particularly in the early stages of management[24]. Anodal tDCS stimulation of the M1 promotes low to moderate improvement on pain intensity with level A recommendation for FM[25].
The mechanisms of M1 stimulation and the reduction of pain are not yet entirely clear[26]. Studies suggested that anodal

tDCS over M1 has widespread effects on multiple cortical and subcortical areas, including cingulate, frontal areas, thalamus and striatum[12,26]. Moreover, after anodal stimulation over M1, studies observed an increase in the cortical response not only over the stimulated cortex but also over the contralateral homotopic areas[12]. This finding supports a possible coupling of neuroactivity of brain regions that are functionally related to the stimulated area[13]. Therefore, tDCS promotes a diffuse analgesic effect that could be used for diffuse pain syndromes such as FM[27]. For this reason, it is expected that M1 stimulation decreases pain in both sides of the body. Repetitive transcranial magnetic stimulation (rTMS) seems to be analogous to pain reduction for FM and both neuromodulation modalities presented fewer side effects compared with pharmacological approach[28].

Some authors suggest FM as a centralized pain state and that the central nervous system could amplify nociceptive input, even after a peripheral nociceptive input[2]. Brain networks involving pain perception seem to be altered in FM[2]. Patients exhibit multifocal pain in both sides with many cases of sensory hyperresponsiveness[2]. The impact of FM leads to a significant decrease in functional capacity and quality of life[16,29].

This study did not find significant differences in FIQ between groups. This may reflect the limited number of sessions and/or that the short period for participants' evaluation was insufficient to induce changes in daily activities. Authors suggest that tDCS could be used with adjuvant therapy and multimodal treatment, including aerobic or strength exercises, which need to be encouraged[27]. Authors have shown better effects on pain with combined aerobic exercise and tDCS in FM[1]. On the other hand, associated therapy including tDCS with functional exercises did not enhance the effects of physical exercise on pain, functionality and quality of life[30]. Further trials with multimodal therapy involving tDCS are necessary to clarify the effects for FM patients[30].

A complete understanding of FM requires a comprehensive assessment of pain, function and psychosocial context and the strategy of management should have a multidisciplinary approach[2]. The present results provide evidence that five sessions of anodal tDCS over M1 reduce pain with no body side difference in women with FM. No improvement was found for the impact of FM and anxiety.

Methodological limitations could be appointed. First, the menstrual cycle of participants was not evaluated and tDCS was performed not at the same menstrual period. Secondly, no long-term effect was assessed and further clinical trials with two or three weeks of follow-up is encouraged. Future studies should include DLPFC stimulation to investigate effects of tDCS on body side pain perception.

CONCLUSION

The use of five sessions of anodal tDCS over the left M1 improve pain with no body side difference in women with FM.

AUTHORS' CONTRIBUTIONS

Monayane Grazielly Leite Matias
Data Collection, Project Management
Antônio Felipe Lopes Cavalcante
Writing - Review and Editing
Karime Andrade Mescouto
Data Collection, Conceptualization, Visualization
Edson Meneses Silva-Filho
Statistical analysis, Writing - Preparation of the original
Abrahão Fontes Baptista
Writing - Review and Editing
Alexandre Hideki Okano
Conceptualization, Supervision
Rodrigo Pegado
Statistical analysis, Data Collection, Conceptualization, Writing - Preparation of the original

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