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COGNITIVE FUNCTION AND THE DESCENDING PAIN MODULATORY SYSTEM: THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) IN FIBROMYALGIA

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FUNÇÃO COGNITIVA E SISTEMA MODULATÓRIO DESCENDENTE DA DOR: O EFEITO DA ESTIMULAÇÃO TRANSCRÂNIA DE CORRENTE CONTINUA (ETCC) NA FIBROMIALGIA

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I dedicate this work to my Parents and family, without you, I won´t be where I am, you are my strength and my motivation to keep going on.

I also dedicate it to the beloved memory of my cousin Roberto Suarez, to my uncles José, Oswaldo, Alonso, and to other relatives and friends that now rest in peace. And last but not least, to our beloved colleague, Vani dos Santos, who always helped us and took a smile out of us in any situation.

“Whatever the mind of man can conceive and believe, it can be achieve."(Napoleon Hill)

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Abstract

Fibromyalgia (FM) is a chronic primary pain condition characterized by generalized musculoskeletal pain, fatigue, and non-repairing sleep. Additionally, there is a significant cognitive impairment related to working memory (WM), associated with higher levels of pain, stiffness, and severe depression and anxiety symptoms. These complaints comprise the "FibroFog" syndrome, which includes forgetfulness, mental activity blurring, sensory overload, and diminished ability to think, process information, or follow conversations. The same cortical and subcortical brain networks that manage the cognitive functions mentioned above, also control the emotional - motivational process that convey directly with the descending pain modulatory system (DPMS), essential for the effective modulation of sensory input to the central nervous system and behavioral responses to pain. Growing evidence supports the concept that chronic pain is associated with dysregulation in DPMS. However, persist a gap in the research about the relationship between the severity of symptoms affecting Prefrontal Cortex (PFC) neural networks and the effectiveness of the descending pain inhibitory system (DPIS). Based on this, it is conceivable to hypothesize that the PFC, the internal DPMS, and the system controlling the neuroplasticity state are involved in the dysfunction of pain processing pathways and cognitive impairment. Moreover, to treat such hassle, besides pharmacological interventions, Transcranial Direct Current Stimulation (tDCS), a safe and cost-effective neuromodulation technique that modulates the membrane potential of neurons, has demonstrated clinical benefits for complex chronic pain conditions, including FM. This thesis has two main aims. The *first study* evaluated if working memory, verbal and semantic fluency, and sustained, and divided attention could be suitable to discriminate cognitive impairment in FM compared to Healthy Controls (HC). Additionally, it investigated, using a standardized paradigm, the link between cognitive ability and the function of the DPMS in responders and non-responders of the conditioned pain modulation test (CPM-test). We included 69 FM subjects and 21 HC women aged from 30 to 65 years old. For the Cross sectional study we used scores from the Digits subtest from Wechsler Adult Intelligence Scale (WAIS-III) (short-term and working memory), Controlled Oral Word Association Test (COWAT) (orthographic and semantic fluency), and Trail Making Test (TMT-B-A) (sustained and divided attention) as dependent variables. A generalized linear model (GLM) adjusted by educational level revealed significantly lower scores in FM than HC on the Span digits forward, COWAT-orthographic, and TMT-B-A. For FM patients, multilevel MANCOVA revealed that the cognitive performance of non-responders compared to responders to CPM-test

showed lower adjusted scores in Span digits forward (Partial-η2=0.358, P=0.001), Span digits backward (Partial-η2=0.358, P=0.001), COWAT-orthographic (Partial-η2=0.551, P=0.001), COWAT-semantic (Partial-η2=0.355, P=0.001), and TMT-B-A (Partial-η2=0.360, P=0.001). Serum brain-derived neurotrophic factor (BDNF) is a moderating factor in the relationship between the cognitive tests and DPMS. Besides, antidepressant use and pain pressure threshold were positively correlated with these cognitive tests. In contrast, the cognitive tests were conversely associated with the quality of life.

The *second study* evaluates the efficacy of twenty sessions of anodal-(a)-tDCS on the left-DLPFC and cathodal on the right-DLPFC over four weeks would be better than a sham-(s)-tDCS to increase the cognitive performance evaluated by the sustained and divided attention (primary outcome), WM, verbal fluency (secondary outcomes). Besides, we explored if the severity of dysfunction of the Descendant Pain Modulation System (DPMS) predicts the tDCS effect and if its effect is linked to changes in neuroplasticity as measured by the brain-derived neurotrophic factor (BDNF). In this randomized, double-blind, parallel, sham-controlled trial, we included 36 FM subject, assigned 2:1 to receive active (a)-tDCS (n=24) and sham (s)-tDCS (n=12). The intervention of home-based tDCS lasted 20-minute per daily session for four weeks (total 20 sessions), 2 mA anodal-left (F3) and cathodal-right (F4) prefrontal stimulation with 35 cm2 carbon electrodes. A GLM revealed a main effect for treatment Wald $\chi 2=6.176$; Df=1; P=0.03 in the TMT-B-A. The a-tDCS improved cognitive performance. The effect size estimated Cohen's d at treatment end in the TMT-B-A scores was large [-1.48, confidence interval (CI) 95%= -2.07 to -0.90]. Likewise, the a-tDCS effects compared to s-tDCS improved the performance in the WM, verbal and phonemic fluency, and improved scores on the quality-of-life scale. The impact of a-tDCS on the cognitive tests was positively correlated with the reduction in serum BDNF from baseline to treatment end. Besides, the reduction in the serum BDNF was positively correlated with the improvement in the quality of life due to FM symptoms.

In summ, these findings showed that HC performed substantially better on cognitive exams than FM did. They demonstrated a link between clinical complaints about attention and memory and decreased DPMS effectiveness. Additionally, they demonstrated that the BDNF is a moderating element in a potential relationship between the severity of cognitive impairment and DPMS dysfunction. And we also have found that daily treatment with a home-based tDCS device over l-DLPFC compared to sham stimulation improved the cognitive impairment in FM, being the a-tDCS at home stimulation well-tolerated, underlining its potential as an alternative

treatment for cognitive dysfunction. Besides, the a-tDCS effect is related to the severity of DPMS dysfunction and changes in neuroplasticity state.

Keywords: Fibromyalgia, fibroFog, chronic pain, cognitive impairment, working memory, tDCS, descendant pain modulation system.

Resumo

A fibromialgia (FM) é uma condição crônica de dor primária caracterizada por dor musculoesquelética generalizada, fadiga e sono não reparador. Além disso, há um comprometimento cognitivo significativo relacionado à memória de trabalho (WM), associado a níveis mais altos de dor, rigidez e sintomas graves de depressão e ansiedade. Essas queixas compreendem a síndrome "FibroFog", que inclui esquecimento, desfocagem da atividade mental, sobrecarga sensorial e diminuição da capacidade de pensar, processar informações ou acompanhar conversas. As mesmas redes cerebrais corticais e subcorticais que administram as funções cognitivas mencionadas acima, também controlam o processo emocional - motivacional que transmite diretamente com o sistema modulatório descendente da dor (DPMS), essencial para a modulação efetiva da entrada sensorial no sistema nervoso central e comportamental das respostas à dor. Evidências crescentes apoiam o conceito de que a dor crônica está associada à desregulação no DPMS. No entanto, persiste uma lacuna nas pesquisas sobre a relação entre a gravidade dos sintomas que afetam as redes neurais do córtex pré-frontal (PFC) e a eficácia do sistema descendente inibitório da dor (DPIS). Com base nisso, é concebível a hipótese de que o PFC, o DPMS interno e o sistema que controla o estado de neuroplasticidade estejam envolvidos na disfunção das vias de processamento da dor e no comprometimento cognitivo. Ademais, para tratar esse incômodo, além de intervenções farmacológicas, a Estimulação Transcraniana por Corrente Contínua (tDCS), uma técnica de neuromodulação segura e econômica que modula o potencial de membrana dos neurônios, demonstrou benefícios clínicos para condições complexas de dor crônica, incluindo FM. Esta tese tem dois objetivos principais. O primeiro estudo avaliou se a memória de trabalho, a fluência verbal e semântica e a atenção sustentada e dividida poderiam ser adequadas para discriminar o comprometimento cognitivo em FM em comparação com Controles Saudáveis (HC). Além disso, investigou, usando um paradigma padronizado, a ligação entre a capacidade cognitiva e a função do DPMS em respondedores e não respondedores do teste de modulação da dor condicionada (CPM-test). Para pacientes com FM, a MANCOVA multinível revelou que o desempenho cognitivo de não respondedores em comparação com respondedores ao teste CPM apresentou pontuações ajustadas mais baixas em dígitos Span para frente (Parcial-$\eta 2$ = 0,358, P = 0,001), dígitos Span para trás (Parcial-$\eta 2$ = 0,358, P=0,001), COWAT-ortográfico (Parcial-$\eta 2$=0,551, P=0,001), COWAT-semântico (Parcial-$\eta 2$=0,355, P=0,001) e TMT-B-A (Parcial-$\eta 2$=0,360, P= 0,001). O fator neurotrófico sérico derivado do cérebro (BDNF) é um fator moderador na relação entre os testes cognitivos e o DPMS. Além disso, o uso de

antidepressivos e o limiar de pressão de dor foram positivamente correlacionados com esses testes cognitivos. Em contraste, os testes cognitivos foram inversamente associados à qualidade de vida. O segundo estudo avalia a eficácia de vinte sessões de tDCS anodal-(a)-tDCS no DLPFC esquerdo e catódico no DLPFC direito ao longo de quatro semanas seria melhor do que um sham-(s)-tDCS para aumentar o desempenho cognitivo avaliado pela atenção sustentada e dividida (desfecho primário), WM, fluência verbal (desfechos secundários). Além disso, exploramos se a gravidade da disfunção do DPMS prediz o efeito do tDCS e se seu efeito está ligado a alterações na neuroplasticidade medida pelo BDNF. Neste estudo randomizado, duplo-cego, paralelo e controlado simuladamente, incluímos 36 indivíduos FM, designados 2:1 para receber (a)-tDCS ativo (n=24) e simulado (s)-tDCS (n=12). A intervenção de ETCC domiciliar durou 20 minutos por sessão diária por quatro semanas (total de 20 sessões), estimulação pré-frontal 2 mA anodal-esquerda (F3) e catódica-direita (F4) com eletrodos de carbono de 35 cm2. Um GLM revelou um efeito principal para o tratamento Wald $\chi 2=6,176$; Df=1; P=0,03 no TMT-B-A. O a-tDCS melhorou o desempenho cognitivo. O tamanho do efeito estimado de Cohen no final do tratamento nas pontuações TMT-B-A foi grande [-1,48, intervalo de confiança (IC) 95% = -2,07 a -0,90]. Da mesma forma, os efeitos a-tDCS comparados ao s-tDCS, melhoraram o desempenho na WM, fluência verbal e fonêmica e melhoraram os escores na escala de qualidade de vida. O impacto da a-tDCS nos testes cognitivos foi positivamente correlacionado com a redução do BDNF sérico desde o início até o final do tratamento. Além disso, a redução do BDNF sérico correlacionou-se positivamente com a melhora da qualidade de vida devido aos sintomas da FM.

Assim, esses achados mostraram que os sujeitos saudaveis tiveram um desempenho substancialmente melhor em exames cognitivos do que o FM. Eles demonstraram uma ligação entre queixas clínicas sobre atenção e memória e diminuição da eficácia do DPMS. Além disso, demonstraram que o BDNF é um elemento moderador em uma potencial relação entre a gravidade do comprometimento cognitivo e a disfunção do DPMS. E também descobrimos que o tratamento diário com um dispositivo tDCS domiciliar sobre o l-DLPFC comparado à estimulação simulada melhorou o comprometimento cognitivo na FM, sendo a estimulação domiciliar do a-tDCS bem tolerada, destacando seu potencial como tratamento alternativo para disfunção cognitiva. Além disso, o efeito do a-tDCS está relacionado com a gravidade da disfunção do DPMS e alterações no estado de neuroplasticidade.

Palavras-chave: Fibromialgia, fibroFog, dor crônica, comprometimento cognitivo, memória de trabalho, ETCC, sistema descendente de modulação da dor.

LIST OF THESIS FIGURES

LIST OF FIGURES ARTICLE 1

LIST OF FIGURES ARTICLE 2

LIST OF TABLES ARTICLE 1

LIST OF TABLES ARTICLE 2

LIST OF ABBREVIATIONS

ACC = Anterior Cingulate Cortex
ACR = American Society of Rheumatology
BDI–II = Beck Depression Inventory-II
BDNF = Brain-Derived Neurotrophic Factor
B-PCS = Brazilian - Pain Catastrophizing Scale
CID= International Classification of Diseases.
CNS = Central Nervous System
CONSORT = Consolidated Standards of Reporting Trial
COWAT = Controlled Oral and Word Association Test
CPM-test= Conditioned pain modulation test
CS = Central Sensitization
CSI-BP = Central Sensitization Inventory for Brazilian Population
DBS = Deep Brain Stimulation
DIPS = Descending Inhibitory Pain System
DLPFC = Dorsolateral Prefrontal Cortex
DNIC= Diffuse noxious inhibitory control
DPIS= Descending pain inhibitory system
DPMS= Descending pain modulatory system
DSM=Diagnostic and Statistical Manual of Mental Disorders.
EEG = Electroencephalogram
FIQ = Fibromyalgia Impact Questionnaire
FM = Fibromyalgia
fMRI= Functional magnetic resonance image
fNIRS = functional Near Infrared Spectroscopy
GLM=Generalized Linear Models.
HC= Healthy Controls
HCPA= Hospital de Clínicas de Porto Alegre
IASP= International association for the study of pain
ICD-11= International Classification of Diseases
LTD= Long Term Depression
LTP= Long Term Potentiation
LTM = Long-Term Memory
MEG = Magnetoencephalographic
NAc = Nucleus Accumbens
NIBS = Non-Invasive Brain Stimulation
NMDA = N-methyl-D-aspartate
NPS = Numerical Pain Scale score
PAG = Periaqueductal Gra
PFC = prefrontal cortex.
PPT=Pain pressure threshold.
PSQI =Pittsburgh Sleep Quality Index.
PPGCM = *Programa de Pós Graduação de Ciências Médicas*
QST=Quantitative sensory testing
rTMS = repetitive Transcranial Magnetic Stimulation
ROI = Region of Interest
RVM = Rostral Ventromedial Medulla
SD = Standard Deviation
STM = Short-Term Memory
STROBE= Strengthening the Reporting of Observational Studies in Epidemiology.
tES = low-intensity Electric Stimulation
TMT = Trail Making Test
tACS = Transcranial Alternating Current Stimulation
tDCS= Transcranial Direct Current Stimulation
TMS = Transcranial Magnetic Stimulation
WAIS-III = Wechsler Adult Intelligence Scale
WHO= World Health Organization
WIP = Widespread Pain Index
WM = Working Memory

INDEX

1 - INTRODUCTION

Fibromyalgia (FM) is a chronic primary pain condition, that comprises widespread pain, generalized musculoskeletal pain, fatigue, non-repairing sleep, and is accompanied by significant emotional distress or functional disability that interferes with daily life activities, that lingers or recurs for at least three months without any other condition that would explain the pain (Treede, Rolf-Detlef, 2015)(Dueñas et al., 2016). The severity scale of the symptoms includes pain, fatigue, sleep, cognitive impairment, and somatic symptoms, that leads to disability, and deteriorates their personal and social relationships, generating a high level of psychological suffering linked to depression, and anxiety that can affect pain perception and attention (Montoro et al., 2015). This may lead to a cognitive impairment related to a physiological pathway through which psychosocial and clinical factors can affect cognition due to a modification in cerebral blood flow responses during cognitive processing (Montoro et al., 2015). Seventy-five percent of FM patients state significant problems with concentration, multitasking, memory, attention, and executive functions, including inhibition, and reasoning among others (Bell et al., 2018). Therefore, pain may impair voluntary attentional systems and associated executive functions (Bell et al., 2018)(Eccleston & Crombez, 1999). This cognitive impairment hinders interaction with the environment and generates difficulties with working memory (WM), responsible for the temporary storage and manipulation of information necessary to perform complex tasks, such as language comprehension, learning, and reasoning (Miyake & Shah, 1999), which is a fundamental function that organizes our behavior, focusing on internal goals (Miller EK, 2018). The WM is essential to the adequate performance of complex behaviors. Hence, when it fails, so does the capacity to carry out daily living activities and the ability to elaborate on ain confrontation strategies (D'Esposito, M., & Postle, B. R. 2015). In FM, the core complaints related to cognitive impairment are mental confusion, concentration difficulties, and failing memory.

Frontal lobes, such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex, regulate executive functioning (Verdejo-García et al., 2009). It also was found that the DLPFC has an important role on mood regulation, cognitive functions, and maladaptive emotional functioning (Dixon et al., 2017). Based on the rationale that cognitive impairments are linked to maladaptive neuroplasticity processes, the therapeutic targets should be interventions that modulate pain transmission.

Consequently, patient tends to turn his attention to the pain they suffer (Diamond A, 2013). Moreover, the core symptoms of FM characterized by complaints of poor cognition, like

mental confusion, concentration difficulties, and failing memory referred as "FibroFog", understood as a perceived cognitive dysfunction characterized by subjective nay than objective cognitive impairment (Kravitz H. 2015, Kravitz H. & Katz R., 2015, Bell et al., 2018, Walitt et al., 2016). According to Kravitz H. 2015, cognitive symptoms are 2.5 times more prevalent in FM patients than other rheumatologic conditions like mental confusion, concentration difficulties, and failing memory (Kravitz H. & Katz R., 2015). Moreover, despite some studies indicating cognitive impairment in FM, only a few have investigated if the severity of cognitive symptoms is associated with pain and psychophysical measures. Therefore, pain may impair voluntary attentional systems and associated executive functions (Bell et al., 2018)(Eccleston & Crombez 1999). Likewise, the cognitive modulator of pain, the descending pain modulatory system (DPMS), has the function of modulating sensory input to the central nervous system and behavioral responses to pain. Besides inhibition, it can also facilitate the spinal transmission of nociceptive information. However, they might form the basis for how cognitive modulations amplify the pain experience. Recent evidence shows that the DPMS has a crucial role in a wide variety of adaptive and maladaptive modulations of the pain experience (Fields H, 2004, Tracey. I., 2007). The dysfunction of the DPMS is associated with hyperalgesia and allodynia (Caumo et al., 2016), which constitute one of the main symptoms of FM. The DPMS can be assessed by the conditioned pain modulation (CPM) paradigm by the CPM-test, which evaluates the diffuse noxious inhibitory control in humans (Yarnitsky D, 2015). The CPM-test proposes that pain at one site (conditioning stimulus) can modulate (facilitate or inhibit) the experience of pain at a second distant site (test stimulus) (Pud D, 2009). So, it may activate the descending inhibitory control (DNIC) mechanism, where the "pain-inhibits pain" phenomenon (Yarnitsky D, 2010; Le Bars D, 1979).

As an effort to improve the symptoms mentioned above, transcranial direct current stimulation (tDCS) arises as a safe, cost-effective technique that modulates the membrane potential, promising for the treatment of diverse conditions of chronic pain (Luedtke et al., 2015), including FM (Zhu et al., 2017). The evidence of tDCS is growing for refractory pain to pharmacological interventions without the systemic side effects of polypharmacy (Liu C., 2019). Studies have shown that tDCS can modulate cortical and subcortical neural networks, which are associated with the clinical effects mediated by the modulation of excitability of neuronal membrane potential, inducing a top-down effect. The study of Andrews et al., (2011), was the first to provide evidence supportive of an activity-selectivity like the effect of tDCS in healthy cohorts by demonstrating that anodal stimulation applied over the left DLPFC, a key brain region involved in WM (Barbey, Koenigs, & Grafman, 2013; Rottschy et al., 2012). It

was able to improve digit-span performance following stimulation, but only if stimulation was also paired with an online WM (n-back) task (Hill, Rogasch, Fitzgerald & Hoy, 2019). Also in a randomized clinical trial, we demonstrated that a single session of tDCS with 2mA, anodal stimulation applied to the left-DLPFC in FM patients, associated with a cognitive task, improved the function of neural networks involved in spatial and executive attention, as well as reduced the perception of pain (Silva et al., 2017). Adam et al. (2021) have also shown that when the target cortical area on a subject's head is stimulated with a direct current, it can enhance cortical excitability and function, reflecting on serum brain-derived neurotrophic factor (BDNF) levels. This protein is a neurotrophic factor, directly involved in neuronal and synaptic growth, and vital for cognitive performance and plasticity (brain morphology adaptations) (Neeper S.A., 1996). Studies conducted by our group have demonstrated that serum BDNF levels correlate positively with the severity of inhibitory dysfunction (Caumo et al., 2016) and are linked to the development of depression symptoms (Khera. T & Rangasamy. V., 2021), as well as the decrease of BDNF levels on the hippocampus is correlated positively to cognitive impairment and to the decline of WM (Etnier J et al., 2015). Despite the fact that the literature related to cognitive impairment in FM is growing, there is a lack of studies that investigate the impact of transcranial neuromodulation techniques on cognitive impairment, taking into account the neuroplasticity state evaluated by the neuroplasticity marker indexed by dysfunction of DPMS and the serum BDNF.

Considering the above-mentioned, this thesis has two main aims: (i) To evaluate if the tests used to assess working memory, verbal and semantic fluency, and sustained, and divided attention could be suitable to discriminate cognitive impairment in FM compared to Healthy Controls (HC) as well explore the relationship of the impairment in these cognitive tests according to the responders' spectrum of non-responders to the CPM-tes't. (ii) To evaluate if twenty sessions of anodal-(a)-tDCS on the left-DLPFC and cathodal on the right-DLPFC over four weeks would be better than a sham-(s)-tDCS to increase the cognitive performance evaluated by the sustained and divided attention (primary outcome), WM, verbal fluency (secondary outcomes). This study originated two papers; one accepted for publication in the *Frontiers in Behavioral Neuroscience* (impact factor 3,61; quartile 1) and *Frontiers of Human Neuroscience* (impact factor 3.47; quartile 2). It is presented according to the Postgraduate in Medical Science of Universidade Federal do Rio Grande do Sul.

2 - SYSTEMATIC SEARCH OF LITERATURE

2.1 Strategies for locating and selecting information

To identify relevant studies of Transcranial Direct Current Stimulation, tDCS, Working Memory, Descendant Pain Modulation System, DPMS and Fibromyalgia, Embase, MEDLINE (PubMed site), Scielo, and Cochrane search was made. The bibliography references of the articles identified were subsequently reviewed to find other articles not considered in the initial search. Textbooks were also used for the construction of theoretical rationale concepts, mechanisms, and processes.

Search Terms	Embase	Pubmed	Scielo	Cochrane
"Transcranial Direct Current Stimulation" OR "tDCS"	11,191	7,580	66	1018
"Working Memory"	60,521	37,253	616	34106
"Descending Pain Modulatory System" OR "DPMS"	359	259	0	260
"Fibromyalgia"	25,671	13,253	453	2371
("Transcranial Direct Current Stimulation" OR "tDCS") AND "Working Memory"	827	417	1	348
("Transcranial Direct Current Stimulation" OR "tDCS") AND Fibromyalgia	147	73	4	58
("Transcranial Direct Current Stimulation" OR "tDCS") AND ("Descending Pain Modulatory System" OR "DPMS")	6	6	0	32
"Working Memory" AND "Fibromyalgia"	101	45	1	352
"Working Memory" AND ("Descending Pain Modulatory System" OR "DPMS")	2	1	0	84
"Fibromyalgia" AND ("Descending Pain Modulatory System" OR "DPMS")	8	8	0	50
("Transcranial Direct Current Stimulation" OR "tDCS") AND "Working Memory" AND ("Descending Pain Modulatory System" OR "DPMS")	0	0	0	20
("Transcranial Direct Current Stimulation" OR "tDCS") AND "Fibromyalgia" AND ("Descending Pain Modulatory System"	0	0	0	12

OR “DPMS”)				
(“Transcranial Direct Current Stimulation” OR “tDCS”) AND “Working Memory” AND “Fibromyalgia” AND (“Descending Pain Modulatory System” OR “DPMS”)	0	0	0	11
“Working Memory” AND “Fibromyalgia” AND (“Descending Pain Modulatory System” OR “DPMS”)	0	0	0	21

2.2 Diagnostic criteria and epidemiology of fibromyalgia

FM is defined as chronic widespread pain that is associated with sleep disorders, cognitive dysfunction, and other somatic symptoms. Chronic widespread pain is associated with significant emotional distress and/or functional disability, and the pain is not directly attributable to a nociceptive process in the musculoskeletal system. There is no doubt that most patients with FM in clinical settings report high levels of somatic and psychological distress and limitations and daily functioning.

In 1990, the American College of Rheumatology (ACR) proposed the first official diagnostic criteria, which included a pain response to a pressure up to 4 kg/cm2 (performed with an algometer), was evaluated in 18 body bilateral points (Fig. 1); to make the diagnosis, it was required to elicit a painful response in 11 of these points (Wolfe L. et al., 1990). Furthermore, a history of generalized pain for at least 3 months was necessary in some regions of the axial skeleton and in at least three of the 4 body quadrants Galvez-Sánchez C. M., & Reyes Del Paso G. A. (2020). However, the ACR 2010 diagnostic criteria were based on interview and medical examination performed by a physician mainly on rheumatology patients, also considering that it was focused on self-reported painful symptoms mostly used on research than on clinical diagnose (Wolfe et al., 2016), which could generate a bias in the diagnosis. Currently, the diagnosis is based on Häuser W. et al., 2021 propose “Modified 2016 American College of Rheumatology Fibromyalgia Criteria…”, the widespread pain (WPI) 2016 criterion, which is satisfied when the presence of pain in 4 or 5 musculoskeletal body regions is noted (axial, left upper, right upper, left lower, right lower (jaw, chest, and abdominal pain are not included in the pain region assessment)). According to the ACR criteria reviewed in 2016, FM prevalence reached 5.4% of the total population (Jones et al., 2015). It is estimated that the total annual cost per patient in the United States reaches US$9573 (Lacasse A. et al., 2016), which represents an expenditure of more than 29 billion dollars per year. This scenario is a

consequence of health care expenditures and the fact that FM is associated with early retirement due to disability (Markkula, 2011). There is a higher prevalence in women than in men, 2.3 to 1 according to Jones et al., (2015). This condition also restricts daily activities related to work. Almost 50% of FM patients had lost their capacity to do their activities, 23% had obtained a disability pension for incapacity, and only 30% of them had work adaptations, (Dueñas et al., 2016). This was the cause of early retirement, (Markkula, 2011), which also harms social and personal relationships.

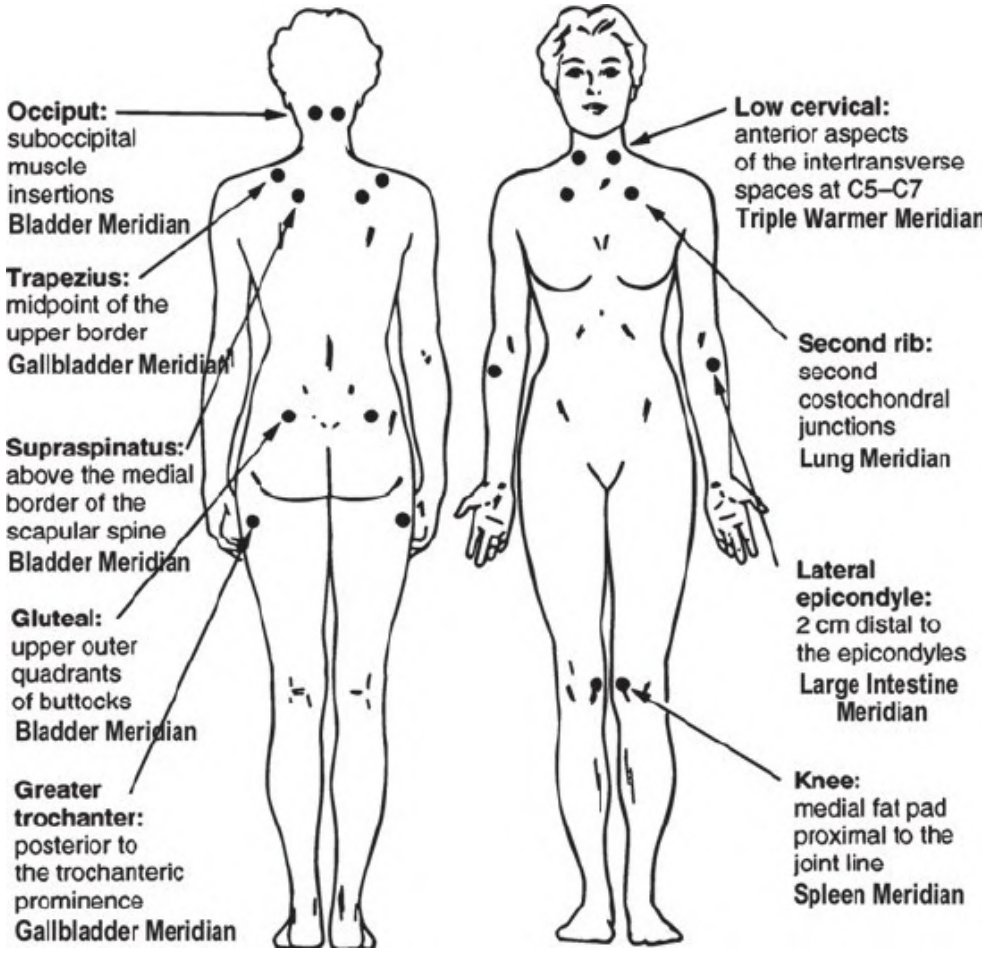

Figure 1. American College of Rheumatology (ACR) FM tender point map (Leskowitz, E., 2008)

2.3 Central Sensitization

The exacerbated response of the central nervous system to various stimuli, such as pressure, temperature and light, etc., is known as central sensitization (CS) (Nijs, et al., 2010; Staud, 2008). Defined by the International Association for the Study of Pain (IASP) as the "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (Loeser JD, Treede RD, 2008). It also involves symptoms like

sleep disorder, fatigue, memory, mood disturbances, and difficulty concentrating (Yunus, 2007). In addition to clinical symptoms, functional neuroimaging studies using functional magnetic resonance imaging (fMRI) and functional near infrared spectroscopy (fNIRS) have shown increased connectivity between neural networks in areas involved in pain processing as the right anterior insula that has a decrease in activity in FM (Harris et al., 2009), as well as a decreased connectivity in neural networks in areas involved in antinociceptive mechanisms (Harte SE et al., 2018). These changes in connectivity have been associated with changes in neurochemical processes involving the Gamma-Amino-Butyric (GABAergic) system, the main inhibitory system (Goudet et al., 2009). These shifts imply a synaptic reinforcement of certain neural networks at the expenses of debilitating others, known as CS (Häuser et al., 2015b). Studies with functional analysis at the peripheral level with FM patients compared to controls have shown a higher detection threshold for cold, heat and lower pressure pain threshold. These findings suggest involvement of peripheral fine nerve fibers characterized by sensory perceptions (i.e., burning pain, tingling sensation, and allodynia) (Kraychete DC, 2011). Symptoms such as allodynia (pain in stimuli that usually don't cause pain), hyperalgesia (increased pain to algogenic stimuli) and temporal summation (sensory summation that involves the decrease in the depolarization threshold of C-fiber neurons) are also part of peripheral sensitization (Meeus & Nijs, 2007). To better understand this sensitization process, it is important to consider that peripheral and central sensitization are related phenomena and that the symptoms are mostly due to the sensitization response as a single phenomenon (Fig. 2).

Afterwards the set of symptoms that cause alterations in perception and behavior, have been associated with the organization of sensory maps, with many of them viewed as maladaptive neuroplasticity, that range from tinnitus to focal dystonia and phantom limb pain (Makin TR, Flor H. Brain, 2020). Also, when there is damage to the peripheral nervous system, their perseverance appears to rely on maladaptive processes into the central nervous system (CNS) (Meacham K et al., 2017).

Additionally, a study conducted by our group found that FM patients have increased Short Intracortical Inhibition compared to healthy subjects which shows a cortical excitability dysfunction associated to CS (Cardinal, 2019).

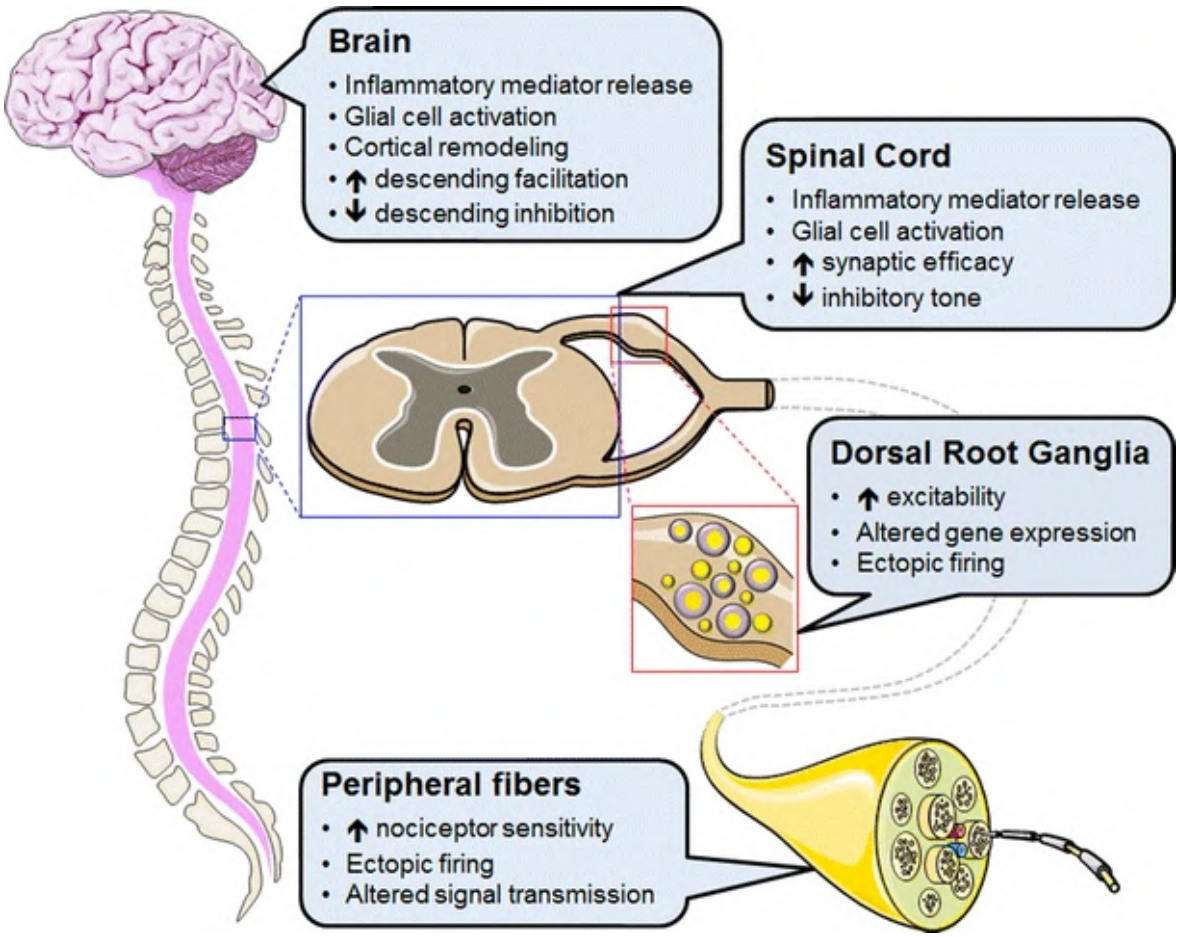

Figure 2: Overview of peripheral and central changes contributing to neuropathic pain (Extracted from: Meacham K, et al., 2017)

2.4 Descending pain modulatory system (DPMS)

The DPMS constitutes a network of widely distributed brain regions, including midbrain and medullary sites as the PAG, the rostral ventromedial medulla (RVM), and the ACC, whose integrated function is essential for effective modulation of sensory input to the CNS and behavioral responses to pain (Goksan S. et al., 2018). Studies have established that the activation of the sites mentioned above can exert bidirectional control over nociception. The PAG being capable of activating a powerful analgesic effect, and the RVM being able to facilitate or inhibit nociceptive inputs and acts as a final relay in the control of descending pain facilitation at receiving inputs from higher brain centers (Ossipov MH. et al., 2014). These structures supply a mechanism through which cortical and subcortical sites can influence nociception as showed on Figure 3, Based on Martyn JAJ et al., 2019 model.

DPMS could be either facilitatory or inhibitory and has an important role under different pain conditions (Tao ZY et al., 2019). Thus to confirm the clinical relevance of top-down pain

modulatory circuits, brain imaging techniques, deep brain stimulation, and the mechanisms of action of drugs have been used in the treatment of pain. Therefore, rising evidence supports the fact that the diminished descending inhibition due to the disruption of the balance of DPMS could be an important event which favors facilitation, and might promote and define whether pain may become chronic (Ossipov MH, 2014). Another consideration is related to the dynamic activity between facilitation and inhibition that could be altered by behavioral, pathological, and emotional states. Hence, a dysfunctional and imbalanced DPMS, that controls at multiple levels the pain circuitry, could increase and promote chronic pain favoring its facilitation (Ossipov M H. et al., 2014). As evidenced by preclinical and clinical studies, diseases like FM, whose pathophysiology is poorly understood, are linked to abnormal central pain processing, this abnormal central pain processing involves a number of mechanisms, including the enhancement of descending facilitatory pathways and the suppression of descending inhibitory pathways (Petersel DL, 2011), which leads to a dysfunctional pain processing system that worsens the DPMS's capacity to manage pain compromising the whole system.

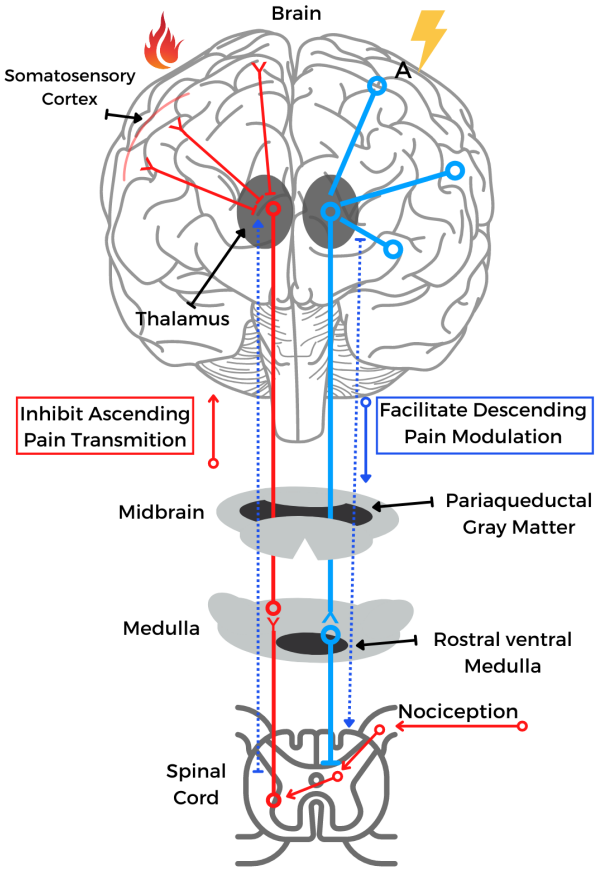

Figure 3: Descending pain modulatory system (DPMS), showing the Inhibit Ascending Pain Transmition in Red, and the Facilitatie Descending Pain Modulation in Blue. Based on Martyn JAJ et al., 2019 model.

2.5 Brain Derived Neutrophic Factor (BDNF)

BDNF is a neutrophin that has a high level of expression and potent effects on synapses, that is widely distributed in the central nervous system and is one of the several molecules that have been related to pain processing, it has been considered as a potential neuroplasticity marker (Zanette et al. 2014) and also as an important marker of neuronal plasticity related to N-methyl-D-aspartate (NMDA) receptors in ascending and descending nociceptive pathways (Brietzke et al. 2016). Furthermore, its neuroplastic effect is associated with balance in excitatory (glutamatergic) and inhibitory (GABAergic) synapses (Binder and Scharfman 2004). A study developed by our group evaluated the motor cortex excitability and BDNF levels present in chronic musculoskeletal pain and in FM, in which it was found that BDNF inversely correlates with intracortical inhibition and changes in NPS during the CPM-test, suggesting greater disinhibition in the motor cortex and descending inhibitory pain system (DIPS) in FM and myofascial pain syndrome than in patient with osteoarthritis and healthy subjects (Caumo et al. 2016). Besides, in FM patients, serum BDNF levels are increased (Haas et al. 2010) and inversely correlated with pressure pain thresholds (Zanette et al. 2014). Additionally, BDNF has a critical role on cognitive functions as WM, thus a decrease on BDNF serum levels has shown a decline of WM as well (Etnier J et al., 2015).

2.6. Fibromyalgia and Working Memory

Almost 50 years ago, the concept of WM was introduced as a cognitive domain to understand a specific cognitive process involving multiple areas and functions. The multicomponent WM model is undeniably one of the most prominent WM models that are widely cited in the literature (Baars and Franklin, 2003; Cowan, 2005; Chein et al., 2011; Ashkenazi et al., 2013; D'Esposito and Postle, 2015; Kim et al., 2015). The rigid and binary view of memory as either short-term memory (STM) or long-term memory (LTM) was revolutionized by the WM model proposed by Baddeley and Hitch in 1974. The WM model posited that, as opposed to the simplistic functions of STM in providing short-term information storage, WM is a multicomponent system that manipulates information storage for greater and more complex cognitive utility (Baddeley and Hitch, 1974; Baddeley, 1996, 2000). WM is made up of three subcomponents: the phonological loop, the visuospatial sketchpad, and the central executive, which includes the attentional control system (Baddeley and Hitch, 1974; Baddeley, 2000). In 2000, a fourth component known as the "episodic buffer" was added to this WM model as shown on Figure 4; it was viewed as a temporary storage system that modulates and integrates

various sensory information. Instead of seeing WM as merely an extension and a useful version of STM, it appears to be more closely related to activated LTM, as suggested by Cowan (2005, 2008), who emphasized the role of attention in WM; his conjectures were later supported by Baddeley (2010). Cowan's theoretical framework toward WM is consistent with Engle (2002)'s view, in which it is posited that WM capacity is comparable to directed or held attention information inhibition (Cowan, 1999, 2008).

This model similarly demonstrated that cognitive load and WM capacity that were so often discussed by WM researchers were mainly a product of attention that one receives to allocate to tasks at hand (Barrouillet et al., 2004, 2009; Barrouillet and Camos, 2007). Thus, WM in comparison with STM is not the same and differs from it, because it involves higher-order processing and executive cognitive controls that are not observed in STM. WM is closely linked to LTM, and its contents consist primarily of currently activated representations. However, it is worth highlighting that the roles of executive processes involved in WM are indisputable, irrespective of whether different components exist. Hence, the consensus regarding WM supports the idea that it is extensively involved in goal-directed behaviors in which information must be retained and manipulated to ensure successful task execution. (Chai et al., 2018)

Due to this complex system, attention could easily be drawn apart from our tasks. This occurs in pain, which is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." by the IASP (IASP, 2022). So, when we feel pain, we focus on it, and it demands almost all of our attention. The deviation of attention to unpleasant sensations impairs our WM. In FM, the widespread pain is not related to a specific stimulus but to dysfunctional, maladaptive neuroplasticity processes in the neuronal networks which are involved either in pain or WM. So, the pain may directly affect WM. Besides, people with FM show consistent difficulties in episodic/semantic memory and WM. (Cánovas et al., 2009). Other comorbidities, such as depression, are potential confounding factors given the strong evidence for neuropsychological impairment in depressed patients. Among the typical cognitive impairments in depression are deficits in attention, memory, psychomotor speed, processing speed, and executive function (Gelonch et al., 2018). However, in a clinical setting, one cannot isolate if the symptoms are related specifically to FM or depression or if it is a symptom that is shared for both diseases. Thus, based on literature studies, it is concluded that FM is associated with lower WM capacity compared to people without chronic pain; and also shows other relationships, such as attention bias, catastrophic

thoughts, rumination, depression, etc. Theoretically, it is predicted that the severity of the clinical FM symptoms will increase the degree of WM impairment.

Thus, by understanding the objective impact of FM on specific cognitive domains, clinicians may be able to predict and improve treatment outcomes for this population more accurately (Bell et al., 2018). WM also becomes affected by lack of attention due to pain and cognitive complications of the disease as it occurs in any illness; this function refers to multiple mental abilities, including learning, thinking, reasoning, remembering, and attention (Fisher GG et al., 2019). Some investigation has found cognitive impairment associated with FM patients compared with healthy people. They found that FM patients mainly exhibit problems related to WM and/or their attentional and executive domains, as well as processing speed (Gelonch et al., 2018). Besides, approximately 75% of FM patients report significant problems with concentration, memory, and multitasking (Donaldson et al., 1998; Leavitt F. et al., 2002). In addition, the self-reported cognitive difficulty is associated with higher levels of pain, poor sleep, and a diminished quality of life in FM (Leavitt F. et al., 2002; Wolfe et al., 2010). Overall, research has documented cognitive difficulties in several domains, including processing speed (Reyes del Paso et al., 2015), STM (Park, Glass, Minear & Crofford, 2001), LTM (Cánovas et al., 2009), and inhibitory control (Walitt et al., 2008). Specifically, some investigations have focused on WM difficulties in FM (Coppieters et al., 2015). Therefore, considering the negative impact of cognitive impairments caused by FM, it is important to understand the dysfunctional processes involving either pain or cognitive dysfunction to develop and study new treatments.

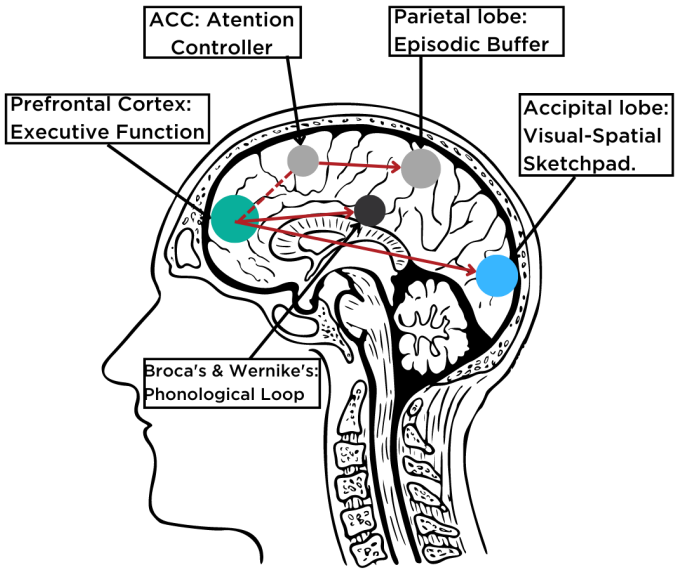

Figure 4: Simplified depiction, adapted from the multicomponent WM model by Baddeley, 2010. (Chai, W.J, 2018)

2.7 Non-Invasive Brain Stimulation (NIBS)

The development of Non-invasive brain stimulation (NIBS) presents a different outlook to understand the novelty of plasticity, physiology, and characteristics of cortical behavior. However, countless facts that are complex and difficult to control, such as the response to stimulation, technical details such as current, waveform, stimulation time, area of stimulation, and other facts such as psychological, emotional, or physiological, may influence the treatment. For more than one century, researchers are trying to find the mechanisms behind the functioning of the human brain through some techniques such as observing brain functioning or activity to have a better understanding of neurologic and psychiatric disorders (Vosskuhl J, et al., 2018). The NIBS offers a promising treatment for a variety of medical conditions, for interventional neurophysiology applications, which could modulate brain activity in a specific, distributed, cortico-subcortical network to inflect controlled behaviors, and for psychiatric disorders, such as depression, bipolar disorders, acute mania, etc.; neurologic diseases, such as tics, Parkinson's disease, tinnitus, epilepsy, and others; rehabilitation of aphasia or stroke; and pain syndromes, such as those caused by FM, migraine, neuropathies, and so on (Wagner T, et al., 2007) also known as Neuroenhancement, which "can be defined as any augmentation of core information processing systems in the brain apart from natural training, including the mechanisms underlying perception, attention, conceptualization, memory, reasoning, and motor performance" (Antal et al., 2022). Interventions, such as repetitive transcranial magnetic (rTMS) and low-intensity electric (tES) stimulation (Fig. 5), impact perception, cognition, mood, motor activities, and other brain functions, both in healthy humans and patients (Buch et al., 2017, Ekhtiari et al., 2019, Huang et al., 2009, Lefaucheur et al., 2017, Lefaucheur et al., 2020). There is active research on if NIBS has the potential to improve (or worsen) performance in competitive environments, school evaluations, athletic competitions up to the level of the Olympics, and in musicianś performance (Luber and Lisanby, 2014). Long-term effects of NIBS, when used in uncontrolled ways (e.g, at-home environments), have not been fully explored (Antal A et al.,2022).

Some earlier studies targeted some brain areas with the goal of reducing the activity in these pain processing regions with high-frequency stimulation in a protocol similar to deep brain stimulation (DBS) utilized for Parkinson's disease (Levy RM et al., 1987). In some instances, lower frequency direct stimulation has been attempted to activate the region of interest (ROI). These targets include the anterior cingulate cortex (ACC), DLPFC, motor cortex, sensory thalamus, periaqueductal gray (PAG), and nucleus accumbens (NAc). A number of studies

targeting these areas have shown a varying degree of success in pain relief, chiefly in the motor cortex and DLPFC (Liu C., 2019). This effect has been attributed to the induction of use-dependent neuroplasticity, which is related to "synaptic learning" and long-term changes (Nitsche et al., 2009; Nitsche & Paulus, 2001, Nitsche & Paulus, 2000).

A potentially significant moderator of the influence of tDCS on cerebral function is the activity state of underlying neuronal populations at the time of stimulation. Indeed, it is common for experimental protocols aiming to facilitate cognitive or motor learning to apply stimulation concurrently with task performance in an attempt to leverage a potential synergistic relationship between ongoing neural activity and tDCS-induced electric fields (Martin et al., 2014; Reis & Fritsch, 2011).

Furthermore, tDCS affects a number of physiological processes in both the central and peripheral nervous systems, which may be relevant to its effect on disease states. It is also feasible to modulate the activation of pain-associated regions in the primary somatosensory cortex (SI, SII), insula, and thalamus through the cognitive modulation of pain which is related to the activation of prefrontal brain areas like DLPFC and ACC (Apkarian, A.V, 2005; Bushnell, M.C., 2013; Leknes, S., 2008). The DLPFC is connected to the ACC, which, in turn, projects to the thalamus and the PAG, a core component of the descending pain modulatory system (DPMS). Different aspects of neuroenhancement, including possible long-term effects, placebo effects, self-applied and directed stimulation are discussed. Notwithstanding the rapid growth in interest and applications of these techniques, the mechanisms of action have not yet been fully explored, a reason why the research should continue to explore biomedical engineering approaches that could lead to more effective stimulation devices.

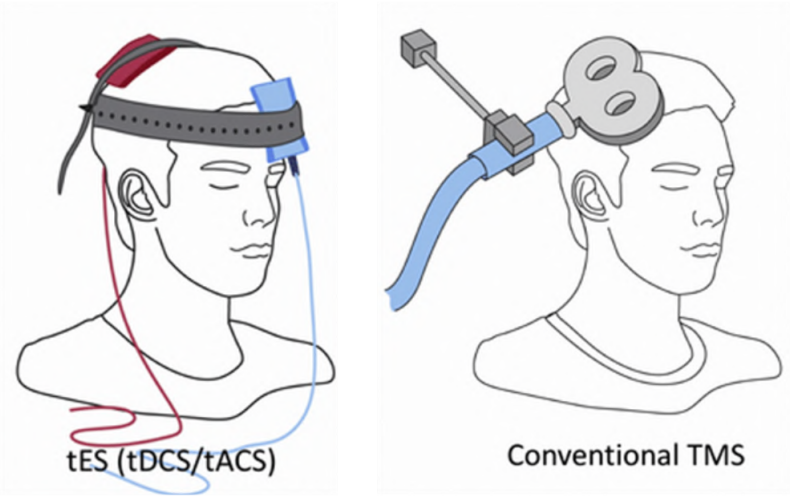

Figure 5: Two major non-invasive brain stimulation technologies. Transcranial Electrical Stimulation (tES) (Transcranial Direct Current Stimulation (tDCS) and Transcranial Alternating Current Stimulation (tACS)), and Transcranial Magnetic Stimulation (TMS) (Conventional) (Ekhtiari H et al., 2019).

2.8 Transcranial Direct Current Stimulation (tDCS)

Transcranial Direct Current Stimulation (tDCS) tDCS is a safe, cost-effective technique that has shown promise in the treatment of a variety of chronic pain conditions, including FM (Zhu et al., 2017). Another aspect being considered is the low cost of neuromodulation with tDCS, easy application, and a great therapeutic potential to cross the barrier, which until then has limited its long-term use, which is that patients need to come to the centers repetitively on consecutive days. This technique allows the study and modulation of brain plasticity with the purpose of understanding neurobiological systems as well as seeking therapeutic alternatives for various pathologies such as chronic pain syndromes. It is a therapeutic method that modulates the membrane potential through the application of weak direct currents that circulate between two surface electrodes placed on the scalp (Nitsche et al., 2008), in which anodal stimuli induce cortical excitability and cathodal stimuli reduce it (Nitsche, Paulus, 2000).

This set of evidence demonstrates that tDCS modulates cortical and subcortical neural networks, which are associated with the clinical effects mediated by the modulation of excitability of neuronal membrane potential, inducing a top-down effect (Polanía R. et al., 2012b; Bai Y et al., 2017). tDCS affects a number of physiological processes in both the central and peripheral nervous systems, which may be relevant to its effect on disease states. In the treatment of pain, the largest contingent of accumulated evidence on the use of tDCS on the left dorsolateral prefrontal cortex (DLPFC), has been a promising proposal to improve cognitive information processes, with emphasis on attentional and depressive symptoms. The study by Brunoni et al., 2014, showed that a tDCS intervention modulated negative attentional bias in patients with depressive disorder. Another study by Andrews et al., 2011, was the first to provide evidence supportive of an activity-selectivity-like effect of tDCS in healthy cohorts by demonstrating that anodal stimulation applied over the left DLPFC, a key brain region involved in WM (Barbey et al., 2013; Owen et al., 2005; Rottschy et al., 2012), was able to improve digit-span performance following stimulation, but only if stimulation was also paired with an online WM (n-back) task. (Hill et al., 2019) In a randomized clinical trial we demonstrated that a single session of tDCS with 2 mA, applied to the DLPFC cortex in FM patients associated with a cognitive task, improved the function of neural networks involved in spatial and executive attention, as well as reduced the perception of pain (Fig. 6) (Silva et al., 2017). Furthermore, there is evidence of the effectiveness of tDCS in pain treatment for diverse conditions, including FM, neuropathic pain, phantom pain, etc. These phenomena can be explained by the increase in synaptic efficiency and also by direct effects on spontaneous

neuronal activity (Nitsche et al., 2008). However, it is known that the effect of tDCS depends on the region to be stimulated, the type of stimulus (anodic or cathodic), and the stimulation frequency. A potentially important moderator of the influence of tDCS on cerebral function is the activity state of underlying neuronal populations at the time of stimulation. These observations corroborate with a recently proposed 'activity-selectivity' model suggesting that tDCS might preferentially modulate active over inactive neural populations, leading to functionally specific effects across networks engaged in the specific task performed (Bikson & Rahman, 2013; Fertonani & Miniussi, 2017; Pisoni A. et al., 2017). The use of tDCS for prolonged periods is theoretically supported as described above.

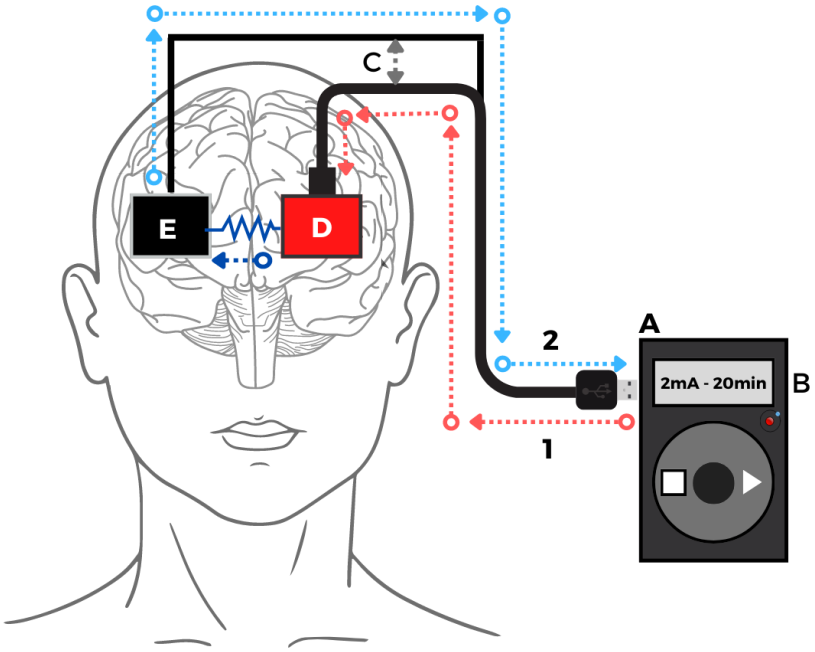

Figure 6. tDCS flow: Direction of current flow from device across the brain, **1)** Anodal current(+), **2)** Cathodal current flow(-). **A)** tDCS at Home device. **B)** Display with stimulation settings (2mA x 20min). **C)** Electrode cables **D)** Anode, positioned in the l-DLPFC (F3) **E)** Cathode, positioned at r-DLPFC (F4)

2.9 DLPFC and Working Memory

The DLPFC plays an important role in WM, goal-driven attention, planning, problem-solving, and task switching (Jones DT., Graff-Radford J., 2021). It is also associated with the executive components of WM, which coordinate the processing of information in associative and storage areas (D'esposito et al. 2000). Consequent to this, in studies where fMRI acquisition was performed to assess the impairment of WM performance in depressed patients, the converse pattern of reduced DLPFC activity is often seen (Smith J. et al., 2018). Neuroimaging studies also reinforce the association of DLPFC with WM, as they have shown that performance in

n-back tasks is strongly associated with activation of the prefrontal cortex (Owen et al., 2005), even though the left DLPFC activation correlates positively with n-back test accuracy and negatively with response time (Zhang et al., 2013). Another study shows that DLPFC activation is reduced in healthy subjects when task difficulty is low, and when the workload increases, cortical activation increases as well, until it reaches its maximum point, in which the increasing difficulty reduces DLPFC activation, resulting in a decrease in the accuracy of WM tests (Callicott et al., 1999).

Wager TD. & Smith EE., 2003, also found that anodal tDCS over left DLPFC has been shown to improve cortical excitability, which improves WM in healthy adults (Karthikeyan R. et al., 2021)(Fregni et al., 2005). Additionally, there is evidence that suggests that tDCS stimulation during cognitive training could enhance cognition and increase the learning process (Martin et al., 2014). The same was demonstrated by Andrews et al., 2011, in which the association of tDCS and cognitive training presented a better result in the performance of WM task performance. Finally, the effect of tDCS on WM depends on stimulation time (20min) and current intensity (2mA) (Teo et al., 2011).

2.10 tDCS and Cognition

Most of the previous research on tDCS has focused on its use in clinical application, such as treating or improving symptoms of neurological and psychiatric diseases like depression (Bennabi D. Haffen E., 2018) (Brunoni A.R. et al., 2016) (Shiozawa P. et al., 2014), Anxiety Disorder, Obsessive-Compulsive Disorder, improving stroke rehabilitation (Schlaug G. et al., 2008), and improving cognition and executive function in patients with mild cognitive impairments (Park J. et al., 2019). Also improving areas related to emotional and cognitive regulation can be linked to the severity, chronicity, and treatment responsiveness of the disease (Chi KF. et al., 2015; Dichter GS. et al., 2015). Besides the positive clinical outcomes of tDCS; other prior research has explored its effects on cognition. For instance, previous studies have found that tDCS can remediate cognitive decline in healthy, older adults (Indahlastari A. et al., 2021), and modulate episodic memory (Galli G. et al., 2019), and WM as shown in studies at our laboratory (Saldanha JS. et al., 2020) (Santos VSDSD. et al., 2018), it also improves attention and concentration in children with ADHD (Cosmo C. et al., 2020) as well as in adults as observed in the Leffa DT. et al., study (2022). Additionally, a Parkinson's disease study shows that both active and sham groups with mild cognitive impairment (Manenti et al., 2016) significantly positively improved cognition and static and dynamic balance for up to 3 months

(Schabrun et al., 2016) (Fregni et al., 2021), and the stimulation over the prefrontal cortex for a few weeks improved cognition in patients with Alzheimer's disease (Im JJ. et al., 2019).
TMS as well as tDCS have been shown to enable plastic reorganization processes on the brain, owing to this, they have been extensively used on healthy and clinical subjects to explore the modulation of various cognitive processes, for more than a decade (Nitsche et al., 2009; Berlim et al., 2013; Haraldsson et al., 2004)

2.11. Home-use tDCS and its Benefits

Therefore, the development of a safe and easy-to-handle device to maintain stimulation for longer periods at home motivated us to develop tDCS equipment with HCPA Biomedical Engineering (Fig. 7-8), whose objective is to overcome this barrier of centralizing treatment in dependence on the medic, and thus allow its use as a complementary therapy to control pain and related symptoms such as improved mood, cognition, fatigue and sleep quality. Considering the negative impact of chronic pain, having as a prototype in this project the FM, whose relevance to the individual and society is unquestionable, especially for aspects of law and humans, it is necessary to advance in the understanding of its pathophysiological mechanisms with a view to the therapeutic advancement. Considering the negative impact of chronic pain, having as a prototype in this project the FM, whose relevance to the individual and society is unquestionable, especially for aspects of human rights, it is necessary to advance in the understanding of its pathophysiological mechanisms with a view to the therapeutic advancement. In this scenario, the present study is inserted, which aims to introduce tDCS at the household level, transforming the use of a restricted therapeutic resource into a large-scale use modality, without underestimating safety. The relevance of this study transcends the objective of helping to improve symptoms and rehabilitation in FM for future use in the treatment of neuropsychiatric disorders such as depression. Also, understanding that FM is a disease that affects areas involved in cognitive and affective processes, tDCS is a technique that helps in the improvement of chronic pain and attention-related areas, objectively stimulating neuronal connectivity with the main objective of cognitive functions. Above all, the home tDCS proposed in this study will use national technology equipment, which is useful to the health care system and unique, with devices of superior quality to imported equipment, which is high-cost and with fewer safety features.

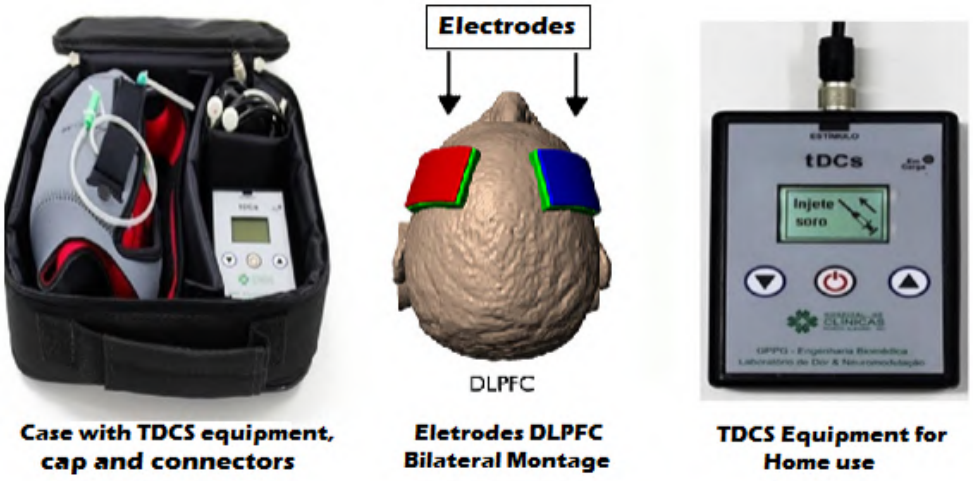

Figure 7. Case, customized cap for positioning electrodes in DLPFC and Home-tDCS equipment.

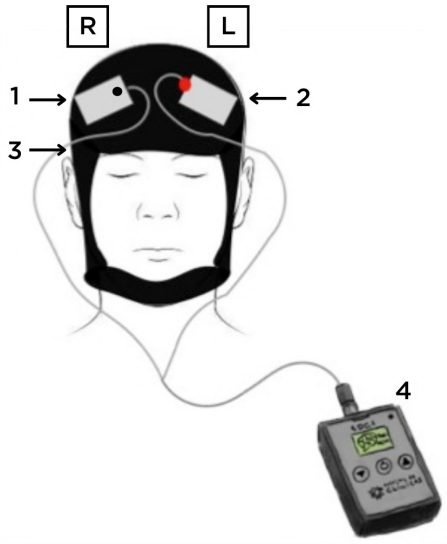

Figure 8. Positioning of electrodes. **1)** The cathode will be positioned at r-DLPFC (F4)(Black dot). **2)** The anode will be positioned in the l-DLPFC (F3) (Red dot). **3)** tDCS cap. **4)** tDCS at Home device.

3. CONCEPTUAL FRAMEWORK

FM is related to chronic generalized pain, as well as emotional and cognitive aspects that are related to changes in the CNS. Current treatments do not allow us to achieve high efficacy in improving the quality of life of patients with FM, therefore, it is important to develop new techniques that allow modulating specialized areas in the CNS, in order to reduce pain in these patients. The development of this will be possible from the assessment of cognitive

performance, the evaluation of the nociceptive system by the QST & CPM, changes in neuroplasticity measured by the BDNF, and pain perception through the NPS (Fig.9).

Therefore, evaluating this technique in FM subjects and verifying their relationship with cortical parameters and cognitive performance, would bring contributions to assist in a better treatment of the disease in the future.

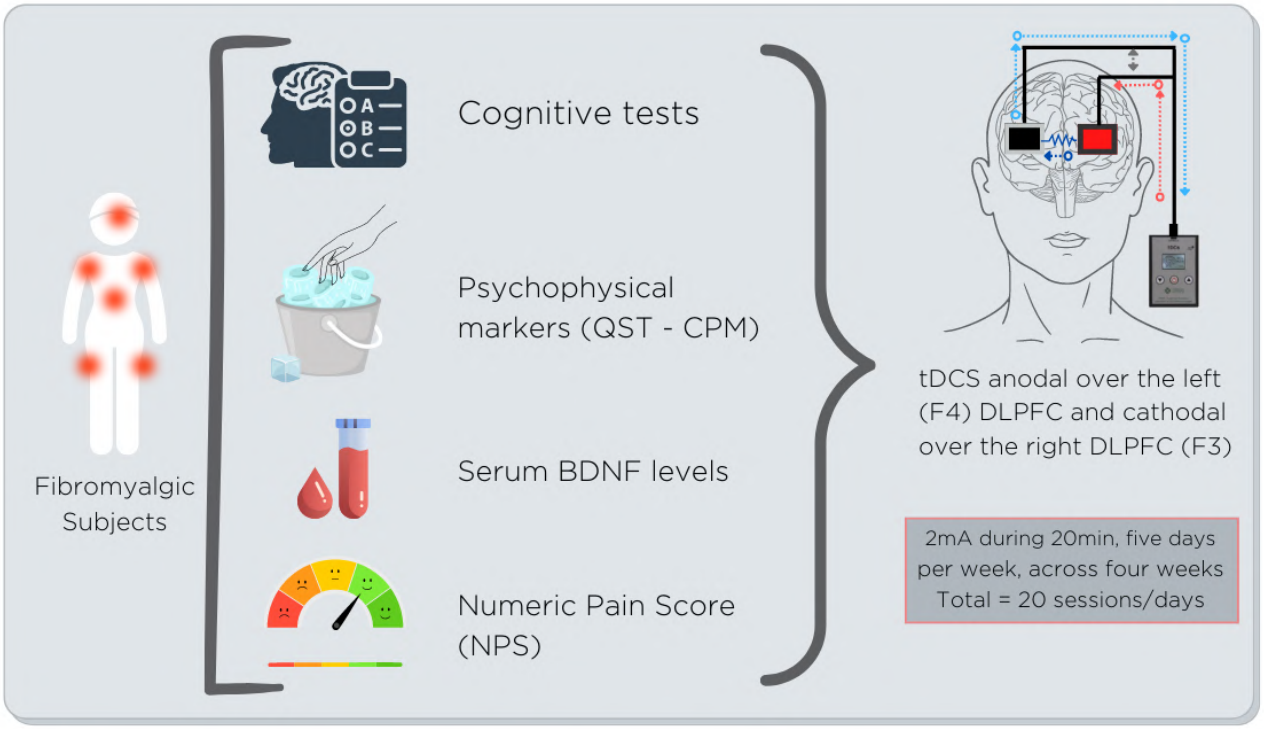

Figure 9. Framework

4. JUSTIFICATION

Although throughout history some diagnostic methods have been developed, the complexity of the etiology of FM does not allow there to be an effective guideline to diagnose or treat FM, due to the similarity with other diseases like arthritis, multiple sclerosis, myalgia, among others, which hinders a clear clinical picture. Additionally, it usually carries the psychological symptoms of depression, anxiety, catastrophizing, and low resilience, which could worsen the symptoms and cause an important cognitive impairment, being one of the main complaints of FM patients. A better understanding of the impact of this pain condition on specific cognitive domains may help provide a more comprehensive view of FibroFog and its impact on daily living and health. Thus, clinicians may be able to predict and improve treatment outcomes for this population more accurately.

Considering that the treatment lies in drugs and therapies such as physiotherapy, massages, acupuncture, psychotherapy, and other alternative therapies, neuromodulation is a technique that has gained popularity in the last years, which makes NIBS techniques famed. Within these novelty techniques, tDCS represents one of the most popular and safe treatment methodologies. The use of tDCS has become known due to its capability of neuromodulation and feasibility to treat chronic conditions as well as enhance cognition and some psychiatric disorders like depression and anxiety almost without any collateral symptoms.

The importance of this study is to find a way to carry out guided home treatments to avoid the patient's constant displacement and thus, reduce the discomfort. In addition, doing it at home means that the environment is comfortable, the patient's cognitive functions are different, are adapted, and related to a familiar environment, so it may be likely that the effective treatment varies by the simple fact of being at home and not at the hospital. If we could demonstrate that the use of tDCS decreases pain and improves cognitive functions like WM and attention in patients with FM, we could offer a new alternative treatment that may improve their life quality, treatment adherence, and negative health outcomes.

It also has a great potential for scientific innovation, since it proposes to study the effect and impact of tDCS over DLPFC to improve cognitive impairment, with the aim of understanding and guiding diagnostic and therapeutic studies applied to different contexts and interventions applicable to clinical neuroscience, especially in the study of pain and working memory.

5. OBJECTIVES

5.1 General Objective

Assess the cognitive impairment between FM Subjects and HC and test the effect of active a-tDCS compared to sham s-tDCS on executive attention, divided attention, working memory, and cognitive flexibility.

5.2 Specific objectives

- Compare the variation (Δ) of the working memory (*Digits subtest from Wechsler Adult Intelligence Scale (*WAIS-III)), verbal and semantic fluency (COWAT-FAS), and sustained and divided attention (TMTB-A) between FM subjects and HC (primary outcome) (**Cross-sectional study**)

- Compare the efficiency of DPMS according to the spectrum of responders and nonresponders to the CPM-test. (**Cross-sectional study**)

- Compare the variation (Δ) on executive function, defined as TMT Part B minus Part A between a-tDCS and s-tDCS (**Randomized CT**)
- Compare the variation (Δ) of working memory, assessed by Digits Span (*Digits subtest from Wechsler Adult Intelligence Scale (*WAIS-III)), verbal fluency (semantic and orthographic), assessed by Controlled Oral and Word Association Test (COWAT), and everyday dysfunction due to FM, assessed by Fibromyalgia Impact Questionnaire (FIQ) between a-tDCS and s-tDCS (**Randomized CT**)

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7. ARTICLES

ARTICLE 1

Association between descending pain modulatory system and cognitive impairment in fibromyalgia: A cross-sectional exploratory study

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Association between descending pain modulatory system and cognitive impairment in fibromyalgia: A cross-sectional exploratory study

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Background: The successful regulation of sensory input to the central nervous system depends on the descending pain modulatory system (DPMS). For the effective regulation of sensory input to the central nervous system and behavioral responses to pain, the DPMS is required. Its connection to fibromyalgia (FM)-related cognitive dysfunction has not yet been investigated. Therefore, this study tested whether measures of verbal fluency, sustained attention, and short-term and working memory could distinguish FM patients from healthy controls (HC). Additionally, it investigated, using a standardized paradigm, the link between cognitive ability and the function of the DPMS in responders and non-responders to the conditioned pain modulation test (CPM-test).

Materials and methods: We enrolled 21 HC women and 69 FM patients, all of whom ranged in age from 30 to 65. We employed scores from the Trail Making Test (TMTB-A) (sustained and divided attention), the Controlled Oral Word Association Test (COWAT) (orthographic and semantic fluency), and the Digits subtest of the Wechsler Adult Intelligence Scale (WAIS-III) as dependent variables.

Results: A generalized linear model (GLM) adjusted by educational level revealed significantly lower scores in FM than HC on the Span digits forward, COWAT-orthographic, and TMTB-A. For FM patients, multilevel MANCOVA

revealed that the cognitive performance of non-responders compared to responders to CPM-test showed lower adjusted scores in Span digits forward (Partial-η^2 = 0.358, P = 0.001), Span digits backward (Partial-η^2 = 0.358, P = 0.001), COWAT-orthographic (Partial-η^2 = 0.551, P = 0.001), COWAR-semantic (Partial-η^2 = 0.355, P = 0.001), and TMTB-A (Partial-η^2 = 0.360, P = 0.001). The association between the cognitive tests and the DPMS is moderated by the serum level of brain-derived neurotrophic factor (BDNF). Additionally, these cognitive assessments had a positive correlation with antidepressant use and pain threshold. The cognitive assessments, on the other hand, were conversely associated with a life of quality.

Conclusion: Based on these findings, it can be shown that HC performed substantially better on cognitive exams than FM did. They demonstrated a link between clinical complaints about attention and memory and decreased DPMS effectiveness. Additionally, they demonstrated that the BDNF is a moderating element in a potential relationship between the severity of cognitive impairment and DPMS dysfunction.

KEYWORDS

fibromyalgia, fibrofog, cognitive impairment, working memory, descendant pain modulation system

Introduction

Fibromyalgia (FM) is a chronic primary pain condition characterized by generalized musculoskeletal pain, fatigue, non-repairing sleep, cognitive alterations, and depressive symptoms (Duruturk et al., 2015; Treede et al., 2015). Around the world, 2–5 percent of people are affected by it (De Souza and Perissinotti, 2018). Only 30% had job modifications, 23% had received disability compensation for incapacity, and over 50% had lost the ability to do their everyday duties (Duenas et al., 2016). In 50% of the FM population, significant cognitive deficits have been found (Katz et al., 2004). These issues comprise the "FibroFog" syndrome, which includes amnesia, mental activity blurring, sensory overload, and a decreased capacity for thought, information processing, or conversational following (Kravitz and Katz, 2015).

Abbreviations: ACC, anterior cingulate cortex; ACR, American College of Rheumatology; BDI, Beck Depression Inventory; BDNF, Brain-derived neurotrophic factor; Br-PCS, Brazilian Portuguese Pain Catastrophizing Scale; ICD, International Classification of Diseases; COWAT, Controlled Oral Word Association Test; CPM-test, conditioned pain modulation test; CSI-BP, Central Sensitization Inventory for Brazilian Population; DLPFC, dorsolateral prefrontal cortex; DNIC, diffuse noxious inhibitory control; DPIS, descending pain inhibitory system; DPMS, descending pain modulatory system; DSM, Diagnostic and Statistical Manual of Mental Disorders; FIQ, fibromyalgia impact questionnaire; FM, fibromyalgia; GLM, generalized linear models; HC, healthy controls; mPFC, medial prefrontal cortex; NPS, Numerical Pain Scale; PAG, periaqueductal gray; PFC, prefrontal cortex; PPT, pain pressure threshold; PSQI, Pittsburgh Sleep Quality Index; QST, Quantitative sensory testing; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale; WM, working memory.

Despite the subjective burden of cognitive symptoms associated with FM, several studies assessing cognitive performance by standard neuropsychological tests demonstrated that their performance was comparable to that of healthy controls (HC). They observed these findings on tests of verbal memory (Leavitt and Katz, 2009; Kim et al., 2012), visual memory (Grace et al., 1999), short-term memory storage (Landro et al., 1997), attention (Landro et al., 1997), and visual memory (Grace et al., 1999; Miro et al., 2011). A previous study looked at how effort, pain, exhaustion, and sadness affected the cognitive impairment in FM. However, they had an impact on the ratings for attention and information processing speed (Bar-On Kalfon et al., 2016). On the other hand, according to further research, FM had cognitive impairment that was evident in their performance on measures of executive functioning, attention, processing speed, and memory (Santos et al., 2018; Wu et al., 2018). The mental tiredness brought on by exerting more effort to perform well on a particular test might be a variable contributing to the variety of results. This idea is at least somewhat supported by neuroimaging findings, which show that FM sufferers require more brain resources to complete the same task than healthy people (Bar-On Kalfon et al., 2016). Additionally, psychological comorbidities, including depression, anxiety, and insomnia, may exacerbate the negative effects of pain on cognition (Austin et al., 2001; Airaksinen et al., 2005; Castaneda et al., 2008). Additionally, they take analgesics, especially opioids, which may contribute to cognitive deficits (Ersek et al., 2004). Despite conflicting findings, the American College of Rheumatology (ACR), which included

them in the current diagnostic criteria for FM, acknowledged the significance of cognitive function for FM (Wolfe et al., 2016). Nevertheless, there isn't a standardized battery of neuropsychological tests for evaluating cognitive function in chronic pain. Hence, it has been suggested in the literature that the cognitive assessment of FM include tests to gauge executive functioning, complex psychomotor speed, attention, and working memory (WM) (Kravitz and Katz, 2015).

Although there is a growing corpus of knowledge about cognitive failure in FM, it is still not apparent what brain pathways underlie its pathogenesis. Brain areas implicated in affective responses to pain, including the rostral anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), and amygdala, have been discovered to have altered neural activation patterns (Yarns et al., 2022). These regions, which include the anterior cingulate gyrus, prefrontal cortex (PFC), nucleus accumbens, and hypothalamus, input the descending inhibitory networks and contribute to emotional and cognitive aspects of pain (Mercer Lindsay et al., 2021). Through ascending and descending projections, the periaqueductal gray (PAG) is a crucial component in the regulation and propagation of pain. Notably, abnormal cortical control may contribute to the maladaptation of the descending pain modulatory system (DPMS), and this mechanism may be relevant to chronic pain in general. This agrees with further studies that found altered functional connectivity between the mPFC and PAG in patients with musculoskeletal, neuropathic, and inflammatory chronic (Drake et al., 2021). The PAG propagates nociceptive and analgesic inputs in a bidirectional manner and can reduce or increase pain perception (Benarroch, 2008). Additionally, as descending pathways may prevent or promote the transfer of nociceptive information from the spinal cord, the PAG plays a significant role in both adaptive and maladaptive modulations of the pain experience (Tracey and Mantyh, 2007). The PFC, striatum, and hippocampus are related to the lateral and dorsolateral subregions of the PAG, which have been linked to executive function (Coulombe et al., 2016).

Studies in both clinical and pre-clinical settings have shown that cognitive dysfunction and pain intensity are associated (Van der Leeuw et al., 2016). However, a network of cortical regions, limbic system components, and the spine-bulbospinal loop control the mechanisms underlying the link between chronic pain and cognitive impairment. It is necessary to examine the relationship between psychophysical, neurochemical, and cognitive functions considering this complex interaction. The spinal-bulbar-spinal loop, which is triggered by ascending nociceptive inputs, is a component of the endogenous pain inhibitory system examined by the conditioned pain modulation test (CPM-test). In several musculoskeletal chronic pain diseases, such as myofascial pain syndrome, FM, and osteoarthritis, the intensity of descending pain inhibitory system (DPIS) dysfunction is connected to pain severity (Botelho et al., 2016; Caumo et al., 2016). Additionally, serum brain-derived neurotrophic factor (BDNF) levels have a positive correlation with the degree of DPMS dysfunction (Soldatelli et al., 2021). According to Ong et al. (2019), this neurotrophic factor is highly expressed in the PFC in chronic pain and is a crucial marker of neuroplasticity linked to structural changes in various cortical regions responsible for learning, memory, fear, and emotional responses (such as the hippocampus and amygdala) (Mazza et al., 2018).

This body of data shows a gap in the research about the relationship between the severity of symptoms affecting PFC neural networks and the effectiveness of the DPIS. Based on this, it is conceivable to hypothesize that the PFC, the internal descending pain modulation system, and the system controlling the neuroplasticity state are involved in the dysfunction of pain processing pathways and cognitive impairment. We, therefore, postulate that the cognitive performance involving PFC-related neural networks is comparable to the effectiveness of the DPIS and that the tests of working memory, executive function, divided attention, and cognitive flexibility (TMTB-A), as well as the Digits subtest of the Wechsler Adult Intelligence Scale (WAIS-III), are indicators of the severity of cognitive impairment. Therefore, this cross-sectional study sought to respond to two inquiries: (i) To determine whether the assessments of working memory, verbal and semantic fluency, sustained attention, and divided attention can be used to distinguish between cognitive impairment in FM and HC. (ii) To explore in a multivariate hierarchical model the relationship of the impairment in these cognitive tests according to the spectrum of responders and non-responders to the CPM-test, considering the patterns of the severity of symptoms across FM and serum markers of neuroplasticity, nominally the BDNF.

Materials and methods

Procedure, study design, and setting

We performed an exploratory cross-sectional study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. This study has been registered and approved by the Certificate of Presentation of Ethical Appreciation (36995020.3.0000.5327 CAAE registry) and Hospital de Clínicas de Porto Alegre (HCPA) Research Ethical Committee registration number 2017-0330. We performed the research following the Helsinki Declaration. We obtained written informed consent from all participants before taking part in the study. The study enrollment period ranged from May 2018 to December 2021. De-identified data relating to intervention and primary outcomes will be made available on request to WC (wcaumo@hcpa.edu.br) with no

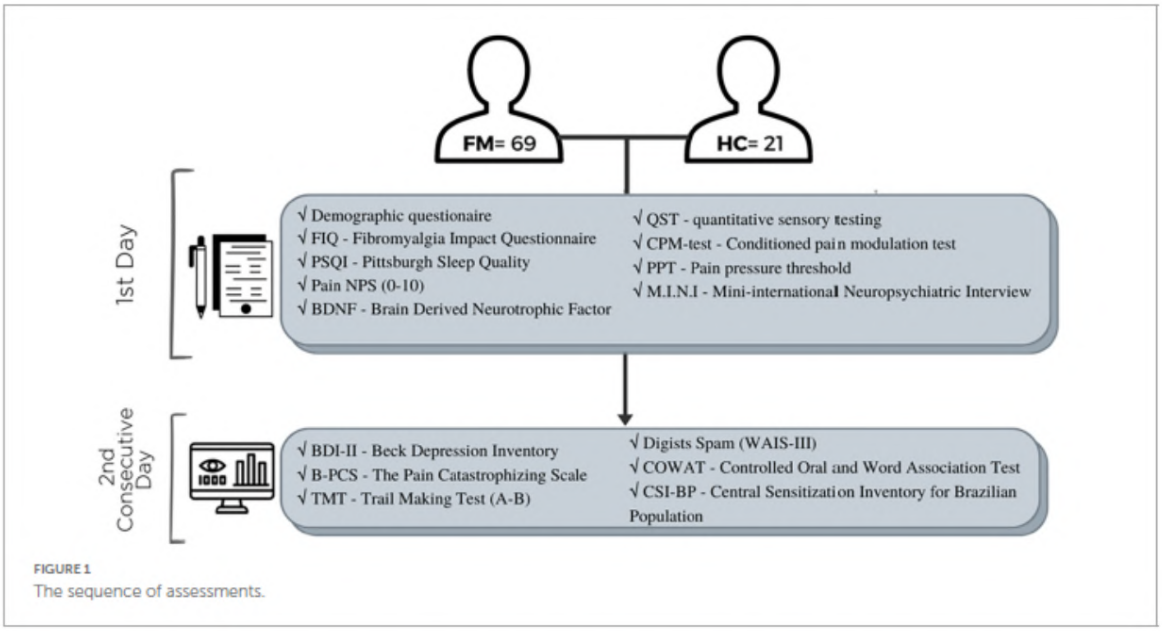

FIGURE 1
The sequence of assessments.

time restriction. The sequence of assessments is presented in Figure 1.

Recruitment, inclusion, and exclusion criteria

Fibromyalgia patients

A convenience sample of literate females between the ages of 30 and 65 who had been diagnosed with FM in accordance with the American College of Rheumatology's 2016 guidelines (Wolfe et al., 2016) was included. They had to report pain scores on the Numerical Pain Scale (NPS) of six or more on most days over the previous 3 months to be considered. They were recruited at the Hospital de Clínicas de Porto Alegre's (HCPA) Basic Health Unit from the outpatient chronic pain wards, Brazil, and social media. For the initial screening, telephone calls were made to every patient. They were invited for a medical evaluation, medical history taking, a thorough description of their symptoms, and confirmation of the diagnosis if they met the inclusion criteria. Physicians with more than 10 years of expertise in pain management applied the ACR score evaluation. Pregnancy, past alcohol or drug misuse, history of decompensated systemic disorders or any chronic inflammatory condition (such as lupus, rheumatoid arthritis, or Reiter's syndrome), as well as a personal history of cancer now being treated or in the past 6 months were all exclusion criteria.

We screened 142 eligible participants, 62 were excluded for diverse reasons such as restrictions by pandemic conditions (i.e., infection, fear of contact, difficulty with public transportation, etc.). They did not meet the diagnostic criteria for FM or presented pain levels lower than 6 (NPS 0–10) on most days in the last 3 months. To have another uncompensated clinical disease (rheumatoid arthritis, lupus, hypothyroidism, etc.). We selected 80 participants, remaining a total of 69 subjects. Eleven patients were excluded from the analysis by loss of data, the most part by incomplete cognitive tests because of isolation by the pandemic of SARCS-Cov2.

Healthy controls

The group of healthy subjects was chosen from local volunteers. We included literate, healthy women between the ages of 30 and 65. They had a thorough phone screening to make sure they had no serious health problems, were free of any acute or chronic illnesses and were not currently on any medications.

We also screened 22 healthy subjects, and one was excluded for showing a score higher than 13 on the Beck Depression Inventory (BDI-II). However, the final sample comprises 21 individuals.

Demographic characteristics, depressive symptoms, and cognitive performance are presented in Table 1. The analysis showed that FM patients (n = 69) are older and have a lower formal education level compared to controls (n = 21).

Instruments and assessment of outcomes

Dependent and independent variables of primary interest

The dependent variables were sustained and divided attention (TMTB-A), verbal and semantic fluency [Controlled

TABLE 1 Demographic characteristics and cognitive performance of FM and HC (total $n = 90$).

	Healthy controls ($n = 21$)		Fibromyalgia ($n = 69$)		P
	Mean (SD)	Median (IQ_{25-75})	Mean (SD)	Median (IQR_{25-75})	
Age (year) €	45.67 (10.79)	–	49.04 (9.39)	–	0.16
Years of formal education €	16.04 (4.65)	–	12.78 (4.65)	–	0.01
Span digits forward ¥	8 (1.65)	8 (6, 11)	7.33 (2.32)	7 (3, 140)	0.15
Span digits for backward ¥	5.70 (2.02)	6 (2, 9)	5.05 (1.66)	6 (2, 9)	0.16
COWAT-orthographic ¥	33.26 (8.82)	34 (17, 57)	40.95 (9.66)	43 (20, 55)	0.00
COWAT-semantic ¥	16.28 (4.22)	16 (9, 28)	18.30 (3.88)	18 (11, 26)	0.02
Trail Making Test (TMT-A) ¥	29.86 (11.56)	27.60 (14.40, 65.40)	38.99 (15.91)	35.38 (17.67, 122)	0.00
Trail Making Test (TMT-B) ¥	63.05 (23.29)	56.82 (30.20, 125.90)	82.74 (40.340)	72.51 (17.23, 235)	0.02
Trail Making Test (TMTA-B) ¥	80.96 (36.19)	72.38 (17.23;,186.81)	64.32 (23.12)	57.46 (30.20, 125.90)	0.17

€ = Comparisons using t-test for independent sample.
¥ Comparison by Kruskal–Wallis test. 25th to 75th interquartile range [IQR].

Oral Word Association Test (COWAT)-FAS], and working memory (Digits subtest from WAIS-III). Divided attention (TMTB-A) was the primary outcome, and the WAIS-III and COWAT-FAS were the secondary outcomes used to compare cognitive performance between FM and HC. The main factor of interest was the efficiency of DPMS as determined by the range of respondents and non-responders to the CPM-test.

Evaluation of characteristics that are reliant on cognitive performance

To assess distinct aspects of cognitive performance and executive processes, we chose a battery of neuropsychological tests. All tools have been verified for use by Brazilians. Instruments and their properties to identify different dominions of cognitive performance are described below.

(a) The Digits subtest of the WAIS-III consists of eight series of digits that are read aloud to the subject and asked to repeat in the same order (forward) and seven sequences that are asked to repeat in the opposite direction (reverse) (Nascimento, 2004; Wechsler, 2004). The Digits test evaluates working and short-term memory.

(b) The Controlled Oral Word Association Exam (COWAT), known as the verbal fluency test, measures both linguistic and executive processes, such as cognitive flexibility, strategy use, interference suppression, and response inhibition (Perret, 1974; Troyer et al., 1997; Abwender et al., 2001; Hedden and Yoon, 2006; Schinka et al., 2010). Participants in the Orthographic subtest (COWAT-Ort) are asked to list as many words as they can that start with the letters F, A, and S. There is a time limit of 60 s for each letter. Once the root word has been revealed, people cannot use proper names, numbers, or words with multiple tenses or endings (Lezak et al., 2004). The Semantic task (COWAT-Sem) test demands the participant to list the most animals in a certain category as they can. There is a 60-s time limit for this (Lezak et al., 2004).

(c) The Trail Making Test (TMTA-B): This quick, two-part test measures processing speed, split attention, and cognitive flexibility. The subject is directed to trace a line connecting the circled numbers in Part A, which has sequential numbers 1 through 25, to measure sustained attention (Reitan and Wolfson, 1993; Campanholo et al., 2014). The participant is instructed to trace a line connecting circled numbers and circled letters in consecutive order while alternating between numbers and letters (1 to A, A to 2, 2 to B, B to 3, 3 to C, and so on) in Part B, which contrasts with Part A's alternately mixed numbers and letters (1 to A, A to 2, 2 to B), and it evaluates attention set-shifting (Campanholo et al., 2014). TMTA-B evaluates working memory, executive motor attention, and split attention (Corrigan and Hinkeldey, 1987; Gaudino et al., 1995; Lezak et al., 2004). The amount of time needed to finish the job and the number of mistakes affect how well you score.

Evaluation of the independent variables

Psychological-physical tests

(d) Quantitative sensory testing (QST) was used to evaluate the heat pain threshold. The thermode was first affixed to the skin of the mid-ventral forearm's region. The system comprises a Peltier-based thermode (30 × 30 mm) digital device connected to a desktop computer that gauges a person's tolerance for heat pain using the method of limitations (Schestatsky et al., 2011). The initial temperature was set at 30°C, and it rose by 1°C/s until it reached a high of 52°C. Participants were told to press the button as soon as the stimulation started to be painful. The position of the thermode was

gently changed between assessments to prevent nociceptors from becoming sensitized and to prevent the summation effect. With a 40-s interstimulus interval, we conducted three assessments (Schestatsky et al., 2011). For the analysis, we determined the three assessments' average temperature.

(e) The CPM-test was assessed using the following steps: First, we used the thermode described above in the thermo-test in the non-dominant forearm's ventral forearm to determine the average of three temperatures measured by the QST for patients' report scores of 6/10 (NPS, 0–10). Second, after 3 mi, they were instructed to submerge their dominant hand up to the wrist in water that was 0–1°C for 1 min. After 30 s, the QST was introduced to measure the pain score on the NPS (0–10) in the thermo-test area (QST + CPM-test). Third, the difference between the NPS 0–10 at the start of the test (T0) and the pain score on the NPS (0–10) during the cold-water immersion (QST + CPM-test) at the temperature set at 6/10 during T1 was used to determine the CPM-test score. Responders would have values lower than zero whereas non-responders would have a difference in the count on NPS (T1 T0) equal to zero or higher (Botelho et al., 2016; Soldatelli et al., 2021).

(f) Pain pressure threshold (PPT): To conduct the test, we employed an electronic algometer from J-Tech Medical Industries in Midvale, Utah, United States. Patients were advised to distinguish between pressure and pain before the assessment began. Patients were told to verbally communicate their pain when it started. At 3- to 5-min intervals, we took three measures in succession (da Graca-Tarragó et al., 2019).

Psychological symptoms, psychoactive drugs, and psychiatric diagnoses

(g) Using the Mini-International Neuropsychiatric Interview (MINI), the psychiatric diagnoses were established (Amorim, 2000). The Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R/IV and International Classification of Diseases (ICD) 10 criteria are compatible with the MINI, a quick (15–30 min) standardized diagnostic interview that is used in clinical practice and research in primary care and psychiatry. It was certified to identify psychiatric problems in the Brazilian population (Amorim, 2000).

(h) Beck Depression Inventory: This tool was used to evaluate the severity of depressive symptoms (Wang and Gorenstein, 2013).

(i) Brazilian Portuguese Pain Catastrophizing Scale (Br-PCS) was used to assess pain catastrophizing, which is a maladaptive response to pain and is one of the factors that contribute to the chronicity of some pain syndromes (Sehn et al., 2012).

Clinical and sociodemographic traits, pain measurements, central sensitization, sleep quality, and overall quality of life

(j) Using a standardized questionnaire, demographic information and medical comorbidities were evaluated. They were asked for their age, gender, number of years of schooling, socioeconomic status, self-reported diagnoses and health difficulties, medication use, medical procedures, and pain-related problems.

(k) A NPS (NPS 0–10) was used to measure the intensity of the pain, zero, no pain, and 10 maximum pain. Patients answered the following question: How severe was your worst pain over the past week?

(l) Central Sensitization Inventory for Brazilian Population (CSI-BP) was utilized to evaluate the central sensitization symptoms. Higher ratings reflect more severe symptoms. Part B of the CSI-BP also evaluates the existence of neurological conditions linked to central sensitization and mental diagnoses (Caumo et al., 2017).

(m) The fibromyalgia impact questionnaire (FIQ) was used to evaluate the quality of life in FM patients. We used the validated version for usage in Brazil (Paiva et al., 2013). There are 10 domains, which comprehend items that evaluate the capacity for doing everyday activities as well as their level of weariness, stiffness in the morning, mood, anxiety, and sadness. The scoring ranges from 0 to 100.

(n) The Pittsburgh Sleep Quality Index (PSQI) was used to rate the sleep quality of the previous month. The PSQI score ranges from 0 to 21. The score with the highest rating represents more severe sleep disturbance.

Brain-derived neurotrophic factor evaluation

(o) Dosage of BDNF serum levels: Blood samples were centrifuged and divided into 0.5 ml aliquots for additional examination. According to the manufacturer's instructions, sandwich ELISA was used to measure the serum levels of BDNF using monoclonal antibodies that are specific for this neurotrophic factor (R&D Systems, Minneapolis, MN, United States). To evaluate the inter-assay variation, two plates per kit were utilized over two distinct days of the same week. The manufacturer's instructions are followed by protocols. To ascertain serum BDNF, the Enzyme-linked Immunosorbent was employed. The kit's BDNF lower detection limit is 7.8 pg/ml. Use the ChemiKine BDNF Sandwich ELISA kit, CYT306 (Chemicon/Millipore, Billerica, MA, United States) for the assay (ELISA). GloMax®-Multi Microplate Reader from Promega or the Bio-Plex®-200 device from Bio-Rad was used to assess optical density for multiplexing assay readings. Using the Bradford method, which uses bovine serum albumin as a standard, we measured the total protein using the standard. The information was presented as pg/mg of protein.

Actions to address potential bias sources

Two trained psychologists applied the cognitive tests. Each examiner was given a specific training program that included the following steps: (i) Reading and studying each test's manual; (ii) watching an experienced examiner administer the test; (iii) practicing administering the test on volunteers in role-playing sessions; (iv) if necessary, discussing issues and questions with regional experts. (v) The examiners gave patients accurate instructions for the exam, and all assessments were conducted without interruptions in a quiet, private setting.

The study sample size

We determined the sample size to equal 39 patients to compare the cognitive performance of FM with HC. The estimation compared the cognitive performance in the Making Test (TMTB-A) based on a prior study. For a Cohen's d of 0.5, an alpha of 0.05, and a power of 0.80. In this estimation, the averages and standard deviations (SD) for FM and HC were 44.1 (SD, 35.8) and 22.2 (6.5), respectively (Vucurovic et al., 2019). To compare the cognitive performance of respondents and non-responders to the CPM-test, a sample size of 62 subjects was estimated. This estimation was based on a MANCOVA with three levels, five dependent variables, an effect size (f2) of 0.25, an alpha of 0.05, and a power of 0.80 (Soper, 2020). We increased the sample size by 15%, bringing the total to 69 cases. This was done to guarantee the study's power and prevent the attrition rate from unforeseen events.

Statistical analysis

Descriptive statistics were presented as mean (standard deviation) or frequency. Age and formal education years were compared between groups using independent sample *t*-tests. The Shapiro–Wilk test evaluates a variable's normality. The cognitive tests did not meet the criteria for parametric analysis. Thus, we used the generalized linear models (GLMs) to compare the results of cognitive tests (digit span forward and backward, COWAT-semantic and orthographic, TMTB-A) adjusted for years of formal education between groups of FM and HC. We adjusted these cognitive tests by age and education level by using multiple regression models by the stepwise forward method for the exploratory analysis involving the FM subjects, considering this and the consistent evidence that age and years of formal education may influence the performance in cognitive tests (Lenehan et al., 2015).

The adjusted average of digits spans forward, and backward, COWAT-semantic and orthographic, and TMTB-A were included as dependent variables in the hierarchical multilevel multivariate analysis of covariance (MANCOVA). This model was based on an analytic framework defined *a priori*, which integrates the severity of symptoms related to FM according to the spectrum of the responders and non-responders to the CPM-test (Soldatelli et al., 2021). A *p*-value of less than 0.05 on the bivariate analysis presented in Table 4 was required for a factor to be included in the hierarchical multilevel regression model. Another criterion was the biological plausibility that such factors might influence the relationship between DPMS and cognitive performance. The following variables were included in the models based on the biological plausibility despite the *p*-value related to the efficiency of DPMS or cognitive impairment: depressive symptoms, sleep quality, scores on the quality of life due to FM in the FIQ, and the PPT (Silva et al., 2016; Caumo et al., 2017; Soldatelli et al., 2021). Variables were retained in each model level if they had a *p*-value less than 0.05. The first hierarchical level included pain scores, diagnosis of depressive disorders, central sensitization scores, sleep quality, and antidepressant dual and tricyclic. These variables could directly or indirectly determine the effect of all the variables analyzed in the additional analysis hierarchical levels. The second level included pain catastrophizing and depressive symptoms. Finally, the third level had the impact of FM symptoms on quality of life, PPT, and serum BDNF (log). The variables included in the third level are close to the cognitive performance and could have been affected by all the variables studied in the previous hierarchical levels. Following this rationale, we examined the interaction of BDNF with the DPMS function according to responders and non-responders to the CPM-test. The regression coefficients (β) values in Table 5 are derived from the full model with all variables since we do not know the explanatory power of many of these factors across the hierarchy. We used Bonferroni's Multiple Comparison Test to identify the source of significant differences and adjust for multiple comparisons. For all analyses, we considered a two-sided *p*-value less than 0.05. Data were analyzed using SPSS software version 22.0 (SPSS, Chicago, IL, United States).

Results

Evaluation of cognitive function in fibromyalgia and healthy control

Table 2 showed GLM to evaluate the performance in cognitive tests according to groups of FM and HC. The GLM models revealed a statistically significant difference between FM and HC in the Span digits forward (short-term memory), COWAT-orthographic (executive functions related to verbal fluency), and marginally non-significant in the TMTB-A (sustained and alternate attention, and WM). The interaction analysis showed that the lower performing cognitive

TABLE 2 Primary outcomes–generalized linear model analyses to compare cognitive performance in FM and HC (n = 90).

Cognitive tests	Beta	SEM	CI 95%	Wald χ^2	df	P
Span digits forward						
(Intercept)	7.534	1.4389	4.71 to 10.35	27.418	1	0.000
Fibromyalgia (N = 69)	−3.572	1.5441	−6.59 to −0.54	5.353	1	0.021
Healthy controls (n = 21)	$0^{reference}$					
Formal education (years)	0.029	0.0873	−0.14 to 0.20	0.113	1	0.737
Interaction group × Years of formal education						
Fibromyalgia	0.253	0.0977	0.06 to 0.44	6.696	1	0.010
Healthy subjects	$0^{reference}$					
Span digits backward						
(Intercept)	5.929	1.3158	3.35 to 8.50	20.302	1	0.000
Fibromyalgia (n = 69)	−2.465	1.4124	−5.23 to 0.30	3.046	1	0.081
Healthy controls (n = 21)	$0^{reference}$					
Formal education (years)	−0.014	0.0798	−0.17 to 0.14	0.033	1	0.856
Interaction group × Years of formal education						
Fibromyalgia	0.147	0.0894	−0.03 to 0.32	2.724	1	0.099
Healthy subjects	$0^{reference}$					
COWAT-orthographic						
(Intercept)	35.663	6.6631	22.60 to 48.72	28.648	1	0.000
Fibromyalgia (n = 69)	−16.451	7.1441	−30.45 to −2.44	5.303	1	0.021
Healthy controls (n = 21)	$0^{reference}$					
Formal education (years)	0.279	0.4037	−0.51 to 1.07	0.477	1	0.490
Interaction group × Years of formal education						
Fibromyalgia	0.927	0.4511	0.04 to 1.81	4.223	1	0.040
Healthy subjects	$0^{reference}$					
COWAT-semantic						
(Intercept)	15.834	3.1312	9.69 to 21.97	25.572	1	0.000
Fibromyalgia (n = 69)	−5.412	3.3572	−11.99 to 1.67	2.599	1	0.107
Healthy controls (n = 21)	$0^{reference}$					
Formal education (years)	0.163	0.1897	−0.20 to 0.54	0.740	1	0.390
Interaction group × Years of formal education						
Fibromyalgia	0.333	0.2120	−0.08 to 0.75	2.464	1	0.116
Healthy subjects	$0^{reference}$					
Trail Making Test (TMT-A)						
(Intercept)	51.714	11.143	29.87 to 73.55	21.535	1	0.000
Fibromyalgia (n = 69)	4.481	11.970	−18.98 to 27.94	0.140	1	0.708
Healthy controls (n = 21)	$0^{reference}$					
Formal education (years)	−1.374	0.6751	−2.69 to −0.5	4.141	1	0.042
Interaction group × Years of formal education						
Fibromyalgia	−0.083	0.7587	−1.57 to 1.40	0.012	1	0.913
Healthy subjects	$0^{reference}$					
Trail Making Test (TMT-B)						
(Intercept)	50.150	19.622	11.69 to 88.60	6.532	1	0.011
Fibromyalgia (n = 69)	40.324	21.087	−1.00 to 81.66	3.657	1	0.056
Healthy controls (n = 21)	$0^{reference}$					
Formal education (years)	−1.067	1.1887	−3.39 to 1.26	0.805	1	0.370
Interaction group × Years of formal education						
Fibromyalgia	−2.986	1.7043	−6.32 to 0.36	3.069	1	0.080
Healthy subjects	$0^{reference}$					

(Continued)

TABLE 2 (Continued)

Cognitive tests	Beta	SEM	CI 95%	Wald χ^2	df	*P*
Trail Making Test (TMTB-A)						
(Intercept)	50.150	19.622	11.69 to 88.60	6.532	1	0.011
Fibromyalgia ($n = 69$)	40.324	21.087	−1.00 to 81.66	3.657	1	0.056
Healthy controls ($n = 21$)	$0^{reference}$					
Formal education (years)	−1.067	1.1887	−3.39 to 1.26	0.805	1	0.370
Interaction group × Years of formal education						
Fibromyalgia	−2.904	1.3384	−5.52 to −0.28	4.708	1	0.030
Healthy subjects	$0^{reference}$					

performance persisted in the FM group despite the years of formal education.

Exploratory analysis of cognitive performance in fibromyalgia subjects

Adjustment of cognitive tests performance by years of formal education and age

We adjusted each cognitive test for years of education level and age using linear regression analyses following the stepwise method. The variables age and education level were retained in the regression models only when they correlated with cognitive tests with a statistically significant difference ($P < 0.05$). We found that education level was positively correlated with performance in all cognitive tests. In contrast, the attention and cognitive flexibility tests were negatively correlated with age. However, one needs to realize that the TMTA-B scores assess the time required to complete the task and the number of errors. In this way, higher values indicate the worst performance in the test. So, this result is aligned with the results of other cognitive tests. Table 3 displays the adjusted mean of cognitive tests by age and years of education. We observed that higher prevalence of depressive illnesses in non-responders compared to responders. Additionally, they displayed higher pain scores and a greater degree of pain catastrophizing.

Features of fibromyalgia subjects according to responders and non-responders to the conditioned pain modulation-test

Table 4 is presented data FM according to responders and non-responders to the CPM-test. This analysis included 69 patients. However, we found missing data related to the CPM-test in one subject, so the analysis was run with a sample of 68. We observed that non-responders are older and have lower years of formal education. Non-responders compared to responders showed a higher prevalence of depressive disorders. Also, they showed higher scores on pain and a higher level of pain catastrophizing.

Cognitive performance in fibromyalgia according to the spectrum of responders and non-responders to conditioned pain modulation-test

The multilevel MANCOVA was conducted to determine independent factors associated with cognitive tests according to responders and non-responders to CPM-test. Data are presented in Table 5. The MANCOVA model using Bonferroni's Multiple Comparison Test revealed a significant relationship between the responders and non-responders to CPM-test and cognitive performance (Hotelling's Trace = 0.29, $F = (3.30)$, $P < 0.01$). The variables included in the first hierarchical level were pain scores in the VAS, diagnosis of depressive disorders, central sensitization scores, sleep quality, and antidepressant dual and tricyclic use. The second level included pain catastrophizing and depressive symptoms. Finally, the third level included the impact of FM symptoms on quality of life, PPT, and serum BDNF (log). The regression coefficients (β) values (Table 5) are derived from the full model with all variables. The variables retained in the multilevel model comprise the use of antidepressant dual and tricyclic, the impact of FM symptoms on quality of life, PPT, and serum BDNF (log).

The performance in the Span Digits (forward and backward) and COWAT (orthographic and semantic) are positively correlated with using antidepressant dual and tricyclic and higher PPT. In contrast, serum BDNF and the negative impact of FM symptoms on the quality of life are negatively correlated with cognitive performance, while serum BDNF was positively associated with the TMTB-A. However, the interaction analysis presented in Table 5 indicates that the BDNF is a moderating factor in the relationship between the cognitive measurement and the dysfunction of DPMS. The beta coefficient of the interaction analysis between BDNF and the spectrum of responders and non-responders to the CPM-test changed the direction of its relationship with cognitive tests. So, these results indicate that the increase in BDNF is positively correlated to more severe cognitive impairment in non-responders.

Figure 2A displays results for responders and non-responders to the CPM-test on the TMTB-A (primary

TABLE 3 Linear regression analyses to adjust the cognitive performance for years of formal education and age in FM patients.

	B[£]	Std. Error	Beta[¥]	*t*	*P*	CI 95%	Crude mean (SD)	Adjusted mean (SD)
Dependent Variable: Span digits forward							7.48 (2.10)	7.30 (1.14)
Formal education (years)	0.341	0.055	0.595	6.152	0.000	(0.23 to 0.45)		
Dependent Variable: Span digits backward							5.19 (1.72)	5.04 (0.49)
Formal education (years)	0.108	0.035	0.296	3.130	0.002	(0.04 to 0.18)		
Dependent Variable: COWAT-orthographic							34.98 (9.79)	33.56 (4.76)
Formal education (years)	1.082	0.175	0.514	6.176	0.000	(0.74 to 1.43)		
Dependent Variable: COWAT-semantic							16.78 (4.39)	16.34 (2.11)
Formal education (years)	0.439	0.081	0.466	5.419	0.000	(0.28 to 0.60)		
Dependent Variable: Trail Making Test (TMT-A)							37.82 (5.37)	39.90 (6.43)
Constant	31.40	11.31		2.774	0.007	8.87 to 53.93		
Formal education (years)	−1.13	0.38	−0.31	−2.92	0.004	−1.90 to −0.36		
Age	0.431	0.17	0.256	2.41	0.018	0.076 to 0.79		
Dependent Variable: Trail Making Test (TMT-B)							78.77 (38.26)	82.49 (23.83)
Constant	70.65	24.89		2.838	0.006	21.08 to 120.22		
Formal education (years)	−4.41	0.85	−0.47	−5.14	0.000	−6.12 to −2.71		
Age	1.307	0.39	0.307	3.33	0.001	0.52 to 2.09		
Dependent Variable: Trail Making Test (TMTB-A)							42.44 (29.050)	43.49 (17.43)
Constant	39.314	19.75		1.99	0.050	−0.016 to 78.64		
Formal education (years)	−3.29	0.682	−0.46	−4.82	0.000	−4.64 to −1.93		
Age	0.876	0.311	0.270	2.82	0.006	0.25 to 1.49		

Data presented the mean (SD) non-adjusted and adjusted mean by formal education and age ($n = 69$). B[£], Unstandardized coefficients; Beta[¥], Standardized coefficients.

outcome). Figures 2B,C showed scores on the secondary outcomes measures according to a spectrum of responders and non-responders to the CPM-test. Working memory tests (DS-forward and DS-backward) were displayed in Figure 2B. Figure 2C presents the scores on executive functions (COWAT-orthographical and COWAT-semantic). The multilevel MANCOVA and Bonferroni's Multiple Comparison Test were used to compare the means. Table 5 displays the results of the multivariate model. Non-responders need more time to complete the test that measures complex psychomotor-related processing speed, such as divided attention and cognitive flexibility. Non-respondents to the CPM-test compared to responders had lower working memory and executive function scores.

Discussion

These findings showed that the FM group scored considerably lower on the Span digits forward, COWAT-orthographic, and TMTB-A tests than the HC. The lower performance in cognitive domains, including working memory, attention, and executive function, is related to the deficiency of the inhibitory mechanism of DPMS. We found that BDNF is a moderating factor in the relationship between the severity of cognitive impairment and the dysfunction of DPMS. Antidepressant use and PPT were positively correlated with these cognitive tests. In contrast, the impact of FM symptoms on quality of life was associated with lower cognitive performance.

This study showed that FM has a lower cognitive performance than HC in WM and attention, executive functioning, and information processing speed. Despite the difference between groups in age and education, all analyses were adjusted by these factors, so it is improbable that the confounding effect of these variables explains our results. As previously mentioned, these results converge with studies over the past decade on cognitive impairment in FM, with a special focus on the effects of pain on the key cognitive parameters examined, including attention, learning, memory, sustained concentration, processing speed, psychomotor ability, and executive function (Nadar et al., 2016; Khera and Rangasamy, 2021). Also, they are allied to the results of numerous controlled studies in FM that found impairment in cognitive performance related to attention and memory (Galvez-Sánchez et al., 2018). These findings contradict studies that revealed similar cognitive performance in FM patients and HC, which support the hypothesis that these symptoms are disruptive and disturbing for patients who may report feeling more functionally handicapped by cognitive dysfunction than by pain (Landro et al., 1997; Grace et al., 1999; Leavitt and Katz, 2009; Miro et al., 2011; Walitt et al., 2011; Walteros et al., 2011; Kim et al., 2012; Bar-On Kalfon et al., 2016). The discrepancy among findings may be explained by variation in cognition assessment, involving different neuropsychological

TABLE 4 Demographic and clinical characteristics of the study sample of FM patients.

Characteristics	Responders ($n = 42$)	Non-responders ($n = 26$)	P
Age (years)	47.38 (8.82)	52.73 (8.72)	0.01
Education (years)	13.17 (4.85)	10.67 (4.21)	0.00
American College of Rheumatology (ACR) diagnosis criteria score	22.70 (3.34)	23.24 (4.45)	0.54
Smoking (Yes)	8	14	0.48
Alcohol (Yes)	11	25	0.39
Clinical comorbidity (Yes)	20	46	0.24
Ischemic cardiac (Yes)	1	1	
Hypertension (Yes)	6	24	
Diabetes (Yes)	3	6	
Hypothyroidism (Yes)	7	9	
Asthma (Yes)	2	2	
Other (Yes)	1	4	
Psychiatric disorder according to the MINI (Yes/No)†			
Maniac-depressive disorder (Yes)	25 (56.8%)	23 (88.5%)	0.00
Generalized anxiety disorder (Yes)	21 (47.7%)	12 (42.2%)	0.59
Pain, sleep quality and psychological measures			
Visual Analogue Scale£	8.17 (1.18)	8.85 (1.31)	0.01
Beck Depression Inventory II (BDI-II)£	25.29 (11.02)	27.38 (10.84)	0.31
Brazilian Portuguese Pain Catastrophizing Scale£	34.82 (10.65)	39.19 (8.84)	0.03
Pittsburg Seep Quality Index (PSQI)£	12.75 (3.59)	13.42 (93.39)	0.41
Heat Pain Threshold to produce 6/10 on NPS (°C)£	37.74 (2.63)	37.32 (3.04)	0.50
Fibromyalgia Impact Questionnaire (FIQ)£	68.15 (17.68)	71.11 (16.05)	0.40
Central Sensitization Inventory£	63.48 (14.88)	66.59 (14.24)	0.32
Pain pressure threshold (kg/cm^2/second)Σ	1.69 (1.49)	1.66 (0.80)	0.24
Change on Numerical Pain Scale during CPM-testΣ	−2.24 (1.32)	1 (1.19)	0.00
Opioid medication user (Yes)‡	12	16	0.17
Acetaminophen (Yes)	12	17	
Dipyrone (Yes)	8	12	
Dorflex (Yes)	16	23	
Opioid medication user (Yes)‡	12	16	0.17
Codeine	6	3	
Methadone	0	2	
Buprenorphine	1	0	
Tramadol	5	13	
Active central nervous system medication‡	25	42	0.27
Antidepressant tricyclic or dual (Yes)	23	48	0.39
Antidepressant dual (Yes)	18	37	0.26
Antidepressants selective serotonin reuptake inhibitors (Yes)	21	43	0.43
Pregabalin (Yes)	23	43	0.50
Brain-derived neurotrophic factor (BDNF) (ng/ml)	40.58 (27.16)	47.29 (34.10)	0.36
Cognitive assessments			
Span digits forward	7.40 (1.10)	6.85 (1.11)	0.05
Span digits backward	5.07 (0.47)	4.84 (0.046)	0.06
COWAT-orthographic	33.88 (4.60)	31.64 (4.64)	0.04
COWAT-semantic	16.48 (2.04)	15.48 (2.03)	0.05
Trail Making Test (TMTB-A)	41.64 (14.76)	50.11 (12.84)	0.03

Values are given as the mean (SD) or number of subjects ($n = 68$).
‡Non-opioid analgesics, opioid analgesics; active central nervous system medications and psychiatric disorder patients could have none or more than one of them.
ΣComparison using Wilcoxon Mann–Whitney.
£Comparisons using t-test for independent sample.
†represents one or more than one psychiatric disorder.

TABLE 5 Multilevel MANCOVA to assess the relationship between cognitive performance tests in responders and no responders according to change in NPS (0–10) during the CPM-test and related factors (n = 68).

Dependent variable	Type III sum of squares	df	Mean square	F	P	Partial eta squared
Corrected model						
Span digits forward	30.011[a]	6	5.002	5.675	0.000	0.358
Span digits backward	5.468[b]	6	0.911	5.676	0.000	0.358
COWAT-orthographic	512.134[c]	6	85.356	5.509	0.000	0.351
COWAT-semantic	101.039[d]	6	16.840	5.602	0.000	0.355
Trail Making Test (TMTB-A)	6977.627[e]	6	1162.938	5.710	0.000	0.360
Regression coefficient						
	B	Std. Error	t	P	CI 95%	
Span digits forward						
Intercept	10.028	1.040	9.642	0.000	(7.94 to 12.10)	
Responders to CPM-test	−2.007	1.198	−1.675	0.099	(−4.40 to 0.39)	
Non-responders to CPM-test	$0^{reference}$					
Use antidepressant dual or tricyclic (Yes)	0.821	0.233	3.525	0.001	(0.36 to 1.29)	
Fibromyalgia Impact Questionnaire (FIQ) scores	−0.015	0.006	−2.334	0.023	(−0.03 to −0.002)	
Pain pressure threshold (kg/cm^2/second)	0.204	0.091	2.231	0.029	(0.02 to 0.39)	
Brain derived neurotrophic factor (BDNF log) ng/ml	−0.818	0.272	−3.012	0.004	(−1.36 to −0.28)	
Interaction changes on NPS (0–10) during CPM-test vs. serum BDNF (log) ng/ml						
Responders to CPM-test	0.723	0.334	2.168	0.034	(0.06 to 1.39)	
Non-responders to CPM-test	$0^{reference}$					
Span digits backward						
Intercept	6.197	0.444	13.961	0.000	(5.30 to 7.08)	
Responders to CPM-test	−0.896	0.511	−1.753	0.085	(−1.92 to 0.13)	
Non-responders to CPM-test	$0^{reference}$					
Use antidepressant dual or tricyclic (Yes)	0.361	0.099	3.633	0.001	(0.16 to 0.56)	
Fibromyalgia Impact Questionnaire (FIQ) scores	−0.006	0.003	−2.171	0.034	(−0.03 to −0.001)	
Pain pressure threshold (kg/cm^2/second)	0.085	0.039	2.175	0.034	(0.007 to 0.16)	
Brain derived neurotrophic factor (BDNF log) ng/ml	−0.358	0.116	−3.086	0.003	(−0.59 to −0.13)	
Interaction changes on NPS (0–10) during CPM-test vs. serum BDNF (log) ng/ml						
Responders to CPM-test	0.320	0.142	2.245	0.028	(0.04 to 0.60)	
Non-responders to CPM-test	$0^{reference}$					
COWAT-orthographic						
Intercept	44.860	4.360	10.288	0.000	(36.14 to 53.58)	
Responders to CPM-test	−8.837	5.024	−1.759	0.084	(−18.88 to 1.21)	
Non-responders to CPM-test	$0^{reference}$					
Use antidepressant dual or tricyclic (Yes)	3.421	0.977	3.501	0.001	(1.47 to 5.37)	
Fibromyalgia Impact Questionnaire (FIQ) scores	−0.060	0.027	−2.264	0.027	(−0.11 to −0.007)	
Pain pressure threshold (kg/cm^2/second)	0.838	0.383	2.190	0.032	(0.07 to 1.60)	
Brain derived neurotrophic factor (BDNF log) ng/ml	−3.431	1.139	−3.013	0.004	(−5.70 to −1.15)	
Interaction analysis: Changes on NPS (0–10) during CPM-test vs. serum BDNF (log) ng/ml						
Responders to CPM-test	3.138	1.399	2.243	0.029	(0.34 to 5.94)	
Non-responders to CPM-test	$0^{reference}$					
COWAT-semantic						
Intercept	21.348	1.921	11.115	0.000	(17.50 to 25.19)	
Responders to CPM-test	−3.967	2.213	−1.793	0.078	(−8.39 to 0.46)	
Non-responders to CPM-test	$0^{reference}$					
Use antidepressant dual or tricyclic (Yes)	1.511	0.430	3.512	0.001	(0.65 to 2.37)	

(Continued)

TABLE 5 (Continued)

Dependent variable	Type III sum of squares	df	Mean square	F	P	Partial eta squared
Fibromyalgia Impact Questionnaire (FIQ) scores	−0.026	0.012	−2.198	0.032		(−0.05 to −0.02)
Pain pressure threshold	0.381	0.169	2.259	0.027		(0.04 to 0.72)
Brain derived neurotrophic factor (BDNF log) ng/ml	−1.545	0.502	−3.079	0.003		(−2.54 to −0.54)
Interaction analysis: Changes on NPS (0–10) during CPM-test vs. serum BDNF (log) ng/ml						
Responders to CPM-test	1.408	0.616	2.285	0.026		(0.18 to 2.64)
Non-responders to CPM-test	0[reference]					
Trail Making Test (TMTB-A)						
Intercept	2.024	15.808	0.128	0.899		(−29.59 to 33.64)
Responders to CPM-test	31.928	18.216	1.753	0.085		(−4.49 to 68.35)
Non-responders to CPM-test	0[reference]					
Use antidepressant dual or tricyclic (Yes)	−12.919	3.542	−3.647	0.001		(−20.00 to −5.84)
Fibromyalgia Impact Questionnaire (FIQ) scores	0.219	0.096	2.271	0.027		(0.03 to 0.41)
Pain pressure threshold	−2.930	1.387	−2.113	0.039		(−5.70 to −0.16)
Brain derived neurotrophic factor (BDNF log) ng/ml	12.497	4.129	3.027	0.004		(4.24 to 20.75)
Interaction analysis: Changes on NPS (0–10) during CPM-test vs. serum BDNF (log) ng/ml						
Responders to CPM-test	−11.456	5.072	−2.259	0.027		(−21.56 to −1.32)
Non-responders to CPM-test	0[reference]					

[a]R Squared = 0.358 (Adjusted R Squared = 0.295)[a].
[b]R Squared = 0.358 (Adjusted R Squared = 0.295)$_b$.
[c]R Squared = 0.351 (Adjusted R Squared = 0.288)[c].
[d]R Squared = 0.355 (Adjusted R Squared = 0.292)[d].
[e]R Squared = 0.360 (Adjusted R Squared = 0.297)[e].

tests and distinct methods of applying them. For instance, some studies use computerized experimental tasks, while others use traditional pencil-and-paper neuropsychological examinations (Duenas et al., 2016). The sample size, the severity of the disease, the mental weariness caused by extended cognitive testing, and studies with lower statistical power play a role in this gap. The inability of numerous studies to record psychological symptoms including anxiety, catastrophizing, and self-efficacy may have an impact on cognitive function and chronic pain. Additional factors, such as sleep disruption and psychotropic medications, such as antidepressants, anticonvulsants, opioids, etc., might interact with chronic pain and cognitive function (Menefee et al., 2000).

This study is significant because it is the first to show a connection between cognitive decline and DPMS dysfunction. Given the exploratory nature of our study, we were unable to establish a cause-and-effect relationship between cognitive symptoms related to the PFC neural networks with deficiencies in the DPMS pathways due to the exploratory nature of our study. It is also possible that both processes are effects of distinct phenomena. The current research, however, showed that this integrative pattern evaluates changes that might affect cognitive function and aberrant pain pathway activities. They emphasize how BDNF secretion, the primary indicator of neuroplasticity, changes along with the interaction between the neural network comprising cortical areas and the spine-bulbospinal loop. This modification thus supports the idea that the DPMS and the brain networks involved in cognitive processing have similar neurobiological underpinnings. Given that FM is a condition of nociplastic pain, central sensitization is its primary underlying mechanism (Kosek et al., 2021). Therefore, a characteristic of the clinical picture known as central sensitization syndrome may be the degree of cognitive impairment (Caumo et al., 2017). Altered activity in brain-orchestrated nociceptive facilitatory pathways is one of the mechanisms underlying these various dysfunctions of the central nervous system (Staud et al., 2008; Bosma et al., 2016). It includes the dysfunction of the DPMS and brain areas involved in processing sensory and cognitive information, such as the insula, ACC, and PFC (Nijs et al., 2021). Because of this, these findings provide a neurobiological substrate to link the clinical symptoms that make up the "FibroFog" with the variation in the dysfunction spectrum of DPMS, even though the underlying mechanisms are not fully understood. Responders and responders to the CPM-test presumably differ regarding an imbalance between systems involved in excitability and inhibition in pain pathways. Pre-clinical studies indicate that this imbalance is biologically plausible because peripheral inflammation dynamically upregulates both BDNF in the PAG and its receptor TrkB in the rostral ventromedial medulla (RVM), which plays a central role in initiating and maintaining neuronal hyperexcitability. This may help explain how the BDNF may be crucial for initiating and maintaining the maladaptive neuroplasticity that underlies persistent pain and its relationship to DPMS dysfunction and cognitive decline (Guo et al., 2006).

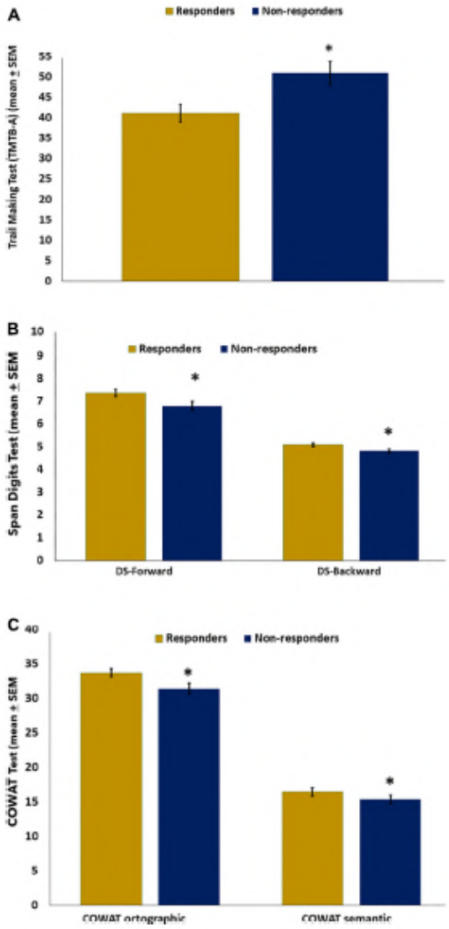

FIGURE 2
Mean of cognitive performance in FM (n = 68) according to responders and non-responders to CPM-test on the Trail Making Test (TMTB-A) **(A)**, **(B)** DS, Digits Spam (Forward–Backward), and **(C)** COWAT-orthographic; COWAT-semantic. The error bars indicate the standard error of the mean (SEM). Asterisks (*) positioned above the bars indicate significant differences ($P < 0.05$). All comparisons were performed by a hierarchical multilevel multivariate analysis of covariance (MANCOVA), followed by the Bonferroni correction for *post hoc* multiple comparisons.

Brain-derived neurotrophic factor is a moderating factor in the relationship between cognitive measurements and the dysfunction of DPMS. In non-responders, the rise in BDNF is positively correlated with more severe cognitive impairment. Although the design of this study leaves it unclear whether alterations in serum BDNF were caused by the disease or occurred before cognitive dysfunction in FM, these findings help to strengthen the case that BDNF functions as a moderator in this association. Even though they are pertinent to understanding in a functional framework the mechanism that connects functions involving PFC neural networks with the DPMS, we cannot confidently say whether the clinical outcome is related to changes in this neurotrophic factor in a particular neural network. This integrative view gives support to understanding the effects of interventions that can improve pain and enhance cognitive performance [i.e., antidepressant duals and tricycle, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS)] (Nir et al., 2012; Nahman-Averbuch et al., 2016). However, we are unable to determine if these changes are related to persisting chronic pain conditions, such as mirroring pain-related stress, inactivity, depression, and inadequate sleep quality (Bäckryd et al., 2017) or if these neuroplasticity marker increases are linked to the severity of clinical symptoms, including the dysfunction of DPMS (Botelho et al., 2016; Soldatelli et al., 2021). Even though there is growing literature about BDNF as a marker of the severity of clinical symptoms of FM (Alves et al., 2020), serum levels are an indirect measure of the BDNF of the brain since it contributes to 70–80% of circulating BDNF (Poduslo and Curran, 1996; Pan et al., 1998; Laske and Eschweiler, 2006). So, longitudinal studies are required to conclude if the generation of BDNF is a compensatory mechanism related to maladaptive neuroplasticity due to the severity of central sensitization or if it is a driving force underlying neuroplasticity involved in neural repair, or both.

Additionally, our results show that FM patients who take dual antidepressants performed better on cognitive tasks that measured cognitive flexibility, speed, and divided attention assessed by the TMTB-A test. In this situation, the advantages of antidepressant dual may be linked to improvement in the DPMS, improvement of depressive symptoms, or both. This hypothesis found support in an earlier study that dual antidepressants might improve the efficiency of DPMS (Marks et al., 2009; Bidari et al., 2019). The fact that FM is a complex syndrome with additional confounding factors that cannot be controlled entirely must be considered. Polypharmacy is just one of the many contributing factors that FM patients typically experience throughout their lifetimes of chronic suffering. Despite the drawbacks of an exploratory study, these findings represent the clinical profile of FM patients and add to the neurobiological foundation for the connections between the DPMS and cortical areas involved in cognitive processing.

Pain pressure threshold and cognitive function have a positive relationship aligned with the idea that allodynia and hyperalgesia are reflected in pain responses to low pain thresholds. Since pain is an attention-demanding condition that lowers the brain resources available for cognition, this result may be read as an interference impact of pain on attention and cognitive functioning. According to research (del Paso et al., 2012), there is some overlap between the brain networks that control attention, memory, and executive functions and those that control how pain is processed (de Guevara et al., 2018). Although we lack a clear explanation for the positive link between PPT and cognitive ability, we must remember that the groups we are comparing have varying degrees of DPMS dysfunction. As a result, it is conceivable that fewer

cognitive resources were available during experimental pressure stimulation due to increased demands on central nervous system resources (Duschek et al., 2012; Montoro et al., 2015). According to PPT, the severity of cognitive dysfunction related to pain interferes with the standard performance of several activities, including movement, leisure activities, sleep, self-care, housework, job, and psychological functioning. The converse relationship between cognitive performance and the worst quality of life is also in line with this perspective (Silva et al., 2016).

We addressed some points concerning study design that should be considered. First, because the cognitive impairments (such as concentration, multitasking, memory, attention, executive function, etc.) are either the same or different in other chronic pain illnesses, a related drawback involves the unsure representativeness of the present sample. Therefore, this must be used to interpret these results. Second, we believe this sample size is appropriate to confirm the clinical significance of the reported results. However, due to the exploratory nature of the correlation study and the considerable number of computed correlations, which increases the likelihood of alpha mistakes, care must be used when interpreting the findings. Third, we only included females since there are sex differences in how pain is processed, involving physiological and psychological factors, including the excitability in the corticospinal pathway, the capacity to withstand pain, pain expectation, etc. (Wiesenfeld-Hallin, 2005; Gasparin et al., 2020). Fourth, psychiatric illnesses are an uncontrollable potential confounding factor in cognitive function in chronic pain. It's also important to note that our control sample was, on average, younger and had a higher level of formal education. Because of this, we run all analyses using the adjusted mean for education level to avoid the impact of these confounding factors.

These findings showed that HC performed substantially better on cognitive exams than FM did. They demonstrated a link between clinical complaints about attention and memory and decreased DPMS effectiveness. Additionally, they showed that BDNF is a moderating element in the relationship between the severity of cognitive impairment and DPMS dysfunction.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Hospital de Clínicas de Porto Alegre (HCPA) Research Ethical Committee registration number 2017-0330. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PS, RA, and GB participated in the sequence alignment, participated in the design of the study, drafted the manuscript, and approved the final version to be published. MZ participated in the sequence alignment, participated in the design of the study, and approved the final version to be published. CD and AM participated in the sequence alignment and approved the final version to be published. IT and FF drafted the manuscript and approved the final version to be published. WC conceived the study, performed the statistical analysis, participated in the design of the study, drafted the manuscript, and approved the final version to be published.

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Conflict of interest

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

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ARTICLE 2

The effect of home-based transcranial direct current stimulation in cognitive performance in fibromyalgia: A randomized, double-blind sham-controlled trial

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The effect of home-based transcranial direct current stimulation in cognitive performance in fibromyalgia: A randomized, double-blind sham-controlled trial

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Short title: Home-based tDCS effect in cognitive performance.

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Declaration of conflict of interest:
All authors declare other relationships that might lead to conflicts of interest to any of the following arrangements: employees of a company, financial relationship to the work; stockholders of the company; members of a speaker's bureau, or any other form of financial compensation.

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

Abstract

Background: Transcranial Direct Current Stimulation (tDCS) is a promising approach to improving fibromyalgia (FM) symptoms, including cognitive impairment that hinders interaction with the environment and prejudice working memory (WM), responsible for the temporary storage and manipulation of information necessary to perform complex tasks, such as language comprehension, learning, and reasoning. So, we evaluated the efficacy and safety of home-based tDCS in treating cognitive impairment. Besides, we explored if the severity of dysfunction of the Descendant Pain Modulation System (DPMS) predicts the tDCS effect and if its effect is linked to changes in neuroplasticity as measured by the brain-derived neurotrophic factor (BDNF).

Methods: This randomized, double-blind, parallel, sham-controlled clinical trial, single-center, included 36 women with FM, aged from 30 to 65 years old, assigned 2:1 to receive a-tDCS (n=24) and s-tDCS (n=12). The primary outcome was the Trail Making Test's assessment of executive attention, divided attention, WM, and cognitive flexibility (TMT-B-A). The secondary outcomes were the Controlled Oral Word Association Test (COWAT), the WM by Digits subtest from the Wechsler Adult Intelligence Scale (WAIS-III), and quality of life. Twenty-minute daily sessions of home-based tDCS for four weeks (total of 20 sessions), 2mA anodal-left (F3) and cathodal-right (F4) prefrontal stimulation with 35 cm2 carbon electrodes.

Results: GLM showed a main effect for treatment in the TMT-B-A [Wald $\chi 2$=6.176; Df=1; P=0.03]. The a-tDCS improved cognitive performance. The effect size estimated by Cohen's d at treatment end in the TMT-B-A scores was large [-1.48, confidence interval (CI) 95% =-2.07 to-0.90]. Likewise, the a-tDCS effects compared to s-tDCS improved performance in the WM, verbal and phonemic fluency, and quality-of-life scale. The impact of a-tDCS on the cognitive tests was positively correlated with the reduction in serum BDNF from baseline to treatment end. Besides, the decrease in the serum BDNF was positively associated with the improvement in the quality of life due to FM symptoms.

Conclusion: These findings revealed that daily treatment with a home-based tDCS device over l-DLPFC compared to sham stimulation over four weeks improved the cognitive impairment in FM. The a-tDCS at home was well-tolerated, underlining its potential as an alternative treatment for cognitive dysfunction. Besides, the a-tDCS effect is related to the severity of DPMS dysfunction and changes in neuroplasticity state.

Keywords: Fibromyalgia, pain, cognition, working memory, tDCS.

Trial registration: NCT03843203

1. Introduction

Fibromyalgia (FM) comprises widespread chronic pain and concurs with significant emotional distress associated with functional disability for daily activities. The symptoms linger or recur for at least three months without other conditions explaining the pain (Treede, R-D, 2019) (Dueñas et al., 2016). The symptoms' severity scale of the American College of Rheumatology (ACR – 2016) diagnosis criteria included cognitive impairment as an element of core symptoms of FM (Montoro et al., 2015). Attention, perception, memory, motor skills, executive functioning, and linguistic and language abilities are essential components of cognition (Gellman and Rick Turner, 2013). The processing of cognitive components includes active decision-making, learning, and memory of past events (Hansen and Streltzer, 2005; Moriarty et al., 2011). This complex processing involves extensive cortical and subcortical neural circuitry responsible for perception, localization, processing, relaying, and pain modulation, thus, the pain experience is modulated by an affective-motivational and cognitive-evaluative components rather than being a purely sensory phenomenon (Tyng et al., 2017). Chronic pain syndromes, such as FM, have been linked to cognitive processing disturbance (Khera T, 2021).

There is evidence that pain and neurocognition have anatomical, biochemical, and molecular associations (Khera T, 2021). The frontal lobes control executive functions, particularly the orbitofrontal cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex (DLPC) (Verdejo-García et al., 2006). The somatosensory cortex distinguishes between painful and non-painful sensations, whereas the medial thalamus and anterior cingulate cortex (ACC) record the stimuli as painful. The emotional component of pain perception and memory formation are both impacted by this encoding process, which is also linked to improved functional connectivity between the thalamus and the mPFC (Tseng et al., 2017). There is an overlap of brain structures involved in executive function and pain perception, and either cognitive impairment or chronic pain involves maladaptive neuroplasticity processes (Khera T, Rangasamy V, 2021). Higher executive functioning requires the ability to make emotional decisions (Tyng et al., 2017). They include executive function, learning, memory, sustained focus, processing speed, and psychomotor ability (Khera T, 2021). The cognitive impairment hinders interaction with the environment and generates difficulties with working memory (WM) (Miller EK, 2018). The WM is responsible for the temporary storage and manipulation of information necessary to perform complex tasks, such as language comprehension, learning, and reasoning (Cowan N.2014). It is essential to the adequate performance of complex behaviors. Hence, when it fails, so does the capacity to carry out daily living activities and the ability to elaborate pain confrontation strategies (D'Esposito, M., & Postle, B. R. 2015). In FM, the core complaints related to cognitive impairment are mental confusion, concentration difficulties, and failing memory. This set of symptoms is often called "FibroFog" (Kravitz. H & Katz. R, 2015, Bell et al., 2018, Walitt et al., 2016). According to a recent study, FM patients performed less accurately on activities requiring split attention and attentional switching (Moore et al., 2019). Regardless of chronic pain impact on cognitive impairment in FM, it does not seem to correlate with other musculoskeletal or neuropathic pain (Grisart and Van der Linden, 2001; Verdejo-García et al., 2009).

Clinical and preclinical studies indicate a bidirectional link between cognition and chronic pain. However, the targets of treatment of chronic pain comprise modulation of the central sensory processing either pain transmission (i.e., opioids and tricyclic antidepressants (TCAs) or neural excitability should be the therapeutic targets (i.e., opioids, anticonvulsants). However, multiple medicines are needed to treat FM symptoms; some might worsen cognitive impairment (i.e., opioids) (Ngian. GS, Guymer EK, Littlejohn GO., 2011). Despite the modulation of the central sensory pain processing to be a treatment target, the pharmacological approaches might be ineffective in many patients (Schiltenwolf M et al., 2014), and some of them can worsen cognitive performance, so the interest in non-pharmacological interventions. Among these interventions, transcranial direct current stimulation (tDCS) has demonstrated clinical benefits for complex chronic pain conditions, such as FM (Zortea et al. 2020). The main target to apply the anodal(a)-tDCS for pain is the primary motor cortex (M1), based on the rationale that it enhances the excitability of the sensory-discriminative networks (Zortea et al., 2020). Another potential target area to apply the a-tDCS is over DLPFC since it has been found to have beneficial effects on mood regulation, cognitive functions, and maladaptive emotional functioning (Dixon et al., 2017). Regarding the a-tDCS impact on FM, its use on the left-(l)-DLPFC revealed benefits on cognitive performance (Santos et al., 2018), and its use at home was effective in improving pain (Brietzke, 2020) and pain catastrophizing (Caumo, 2021).

The a-tDCS can modulate cortical and subcortical neural networks, inducing a top-down effect. Its effect on healthy controls (HC) demonstrates that a-tDCS over the l-DLPFC improved digit-span performance (Barbey, Koenigs, & Grafman, 2013; Rottschy et al., 2012). However, other studies found that it enhanced digit-span performance only if the stimulus had been paired with an online WM (n-back) task (Hill, Rogasch, Fitzgerald & Hoy, 2019). Additionally, we showed that the alertness, orienting, and executive control attentional networks are all modulated by a single session of a-tDCS with 2mA administered to the l-DLPFC in combination with a Go/No-go test (Silva AF, 2017). Besides, studies found that tDCS's impact on pain and cognitive function is neuroplasticity state-dependent, as indexed by the brain-derived-neurotrophic factor (BDNF) (Tarrago, 2019, Brietzke, 2019; Santos, 2018). In the same perspective, earlier studies found that serum BDNF is associated positively with the descending pain modulatory system malfunction (DPMS) (Soldatelli, 2021, Caumo et al., 2016) and that the BDNF likely interplay the a-tDCS effect in the improvement of DPMS (Tarrago, 2019; Beltran, 2020). Hence, substantial evidence supports the critical role of BDNF in synaptic plasticity, learning, and memory (Kowianski, P, 2018), and a decrease of this neurotrophic factor in the hippocampus is related to the worst cognitive performance on memory tasks (Etnier J et al., 2015). In this setting, it is reasonable to consider the BDNF as a neural plasticity marker involved in the tDCS effects either on pain processing or cognitive functions (Cocco, Brietzke, 2019; Santos, 2018). Within this frame, more in-depth analyses of tDCS action are of pivotal importance to comprehending the molecular and neurophysiological mechanisms subtending tDCS effects on cognitive processes and the dysfunction of DPMS (Soldatelli, 2021). So, comprehension of its impact on the neuroplasticity processes, with the perspective to link them with clinical effectiveness, might help with better use of this technique.

Thus, we determine whether 20 sessions of a-tDCS on the left (l)-DLPFC and cathodal on the right (r)-DLPFC over four weeks self-applied at home would be superior to a sham-(s)-tDCS in improving the executive attention, divided attention, working memory, and cognitive flexibility assessed by the Trail Making Test (TMT-B-A) (primary outcome). Additionally, we evaluated its impacts on executive functioning (Controlled Oral Word Association Test; COWAT); the WM (Digits subtest from Wechsler Adult Intelligence Scale; WAIS-III); and quality of life (secondary outcomes). We investigated if the tDCS effects were related to the severity of dysfunction in the DPMS at the start of the treatment and with neuroplasticity changes evaluated by the percent change in the BDNF from pre- to treatment end. We hypothesized that a-tDCS could improve cognitive performance more effectively than s-tDCS. Besides, we investigated whether these effects were correlated with the degree of pain processing pathway malfunction as measured by baseline DPMS deficit. As well, we investigated if the tDCS effects are mediated by changes in the neuroplasticity state, as indexed by serum BDNF.

2. Materials and methods

2.1. Study design and eligibility

The trial's protocol was approved by the research ethics committee at the Hospital de Clinicas de Porto Alegre (HCPA), Brazil. Institutional Review Board IRB (36995020.3.0000.5327 CAAE registry) and Research Ethical Committee registration number 2017-0330. Each patient gave their verbal and written consent to take part in this randomized, double-blind, sham-controlled trial. No compensation was given to participants in exchange for their participation.

2.2. Inclusion and exclusion criteria

We included adult females ages 30 to 65 right-handed if they met the diagnostic criteria of fibromyalgia according to the American College of Rheumatology (ACR - 2016). Patients were assessed in accordance with the eligibility requirements by a board-certified pain specialist from Brazil. They were recruited through newspaper advertisements and recruitment from the outpatient pain clinic at HCPA. Phone calls were made to volunteers inviting them to a medical evaluation to confirm the diagnosis. If a subject was able to read and report a score of at least six on most days during the previous three months on the Numerical Pain Scale (NPS 0-10), they were included in the study. Additionally, they should have consented to continue taking their medication during the study at the same doses used during the previous month before starting the study.

They were excluded if presented they had any conditions that made them eligible for using the tDCS according to guidelines, such as a history of brain surgery, a tumor, a stroke, or the implantation of intracranial metal. Additionally, individuals were excluded if they had used illicit drugs during the previous six months or had an uncompensated clinical illness (i.e,ischemic heart disease, renal disease, hepatic disease,

diabetes mellitus, hypertension, etc.). Rheumatoid arthritis, lupus, autoimmune disease, neurologic, oncologic disease, or any Covid symptoms were additional exclusion criteria.

2.3. Sample size justification

Sample size estimation was based on a previous study that tested ten sessions of a-tDCS over the l-DLPFC in non-demented, ambulatory older adult patients on the Trail Making Test (TMT- B-A) (Brad Manor, 2018). Our estimation was established using a 2-tailed test for a ratio of 2:1 (a-tDCS vs. s-tDCS on the DLPFC), a type I error of 5%, and a power of 80%. The standard deviation (SD) from the s-tDCS group was used as a reference to estimate the effect size (Brad Manor, 2018). For an ES of large magnitude [(*f*) equal to 1.02, considering a pooled standard deviation (SD) at treatment end equal to 34)], the estimated sample size was 30 patients. We included an additional 20% of subjects to account for possible dropouts. Thus, the final sample size was 36 patients (24 in the a-tDCS vs. 12 in the s-tDCS group)

2.4. Randomization

Thirty-six patients were randomized at an allocation of 2:1 to groups a-tDCS or s-tDCS, using random numbers created with the proper software. We employed randomization in three blocks of twelve patients to prevent predicting the following patient. Two investigators who were not involved in the patient assessments conducted the randomization prior to the recruitment stage. The envelopes containing the randomization number were prepared and according to the exterior numerical order, these envelopes were sealed and numbered in order. Research partners not involved in the trial, neither in the contact with subjects, or evaluations, opened the envelopes and programmed the devices.

2.5. Blinding

Participants were uninformed of their therapy throughout the entire program (active or sham). Additionally, the allocation was unknown to the research team, the investigators who assisted with patient care, and the people who used the scales. The s-tDCS group's device was set up to provide 30 seconds of stimulation throughout the course of 20 minutes at the beginning, after 10 minutes, and at the conclusion of the stimulation. At each of these times, the device was set up to automatically switch on and off. By employing this strategy, we were able to conceal the intervention from the participants.

2.6. Intervention

The anode was placed on the l-DLPFC (F3) and the cathode at the r-DLPFC (F4) in accordance with the 10-20 system for EEG). The treatment was administered for five consecutive days over the course of four weeks with a total of 20 sessions.

Participants received the programmed device to use at home. For the active a-tDCS, the current applied was 2mA for 20 minutes (Brietzke AP et al., 2020) (Carvalho F et al., 2018). For sham s-tDCS conditions, the montage was the same as active tDCS. A 30-second ramp-up in intensity from zero to 2mA was used for a-tDCS and s-tDCS stimulation, as well as a ramp-down for about the same duration, as explained in the blinding session. Using two silicone cannulas attached to 35cm2 (5 x 7cm) electrodes coated in sponges wet with saline solution, the current was supplied. The gadget was programmed by a single biomedical engineer to provide a set number of stimulation sessions, with a minimum gap of 16 hours between each successive session. Details about the protocol can be seen in complementary material and in a paper by Caumo et al (2021).

Treatment protocol with tDCS at home was established according to the standardized protocol described below: (1) Visit the facility, (2) Cap size and electrode placement, (3) Training, (4) Compliance with the protocol, proper application, and adverse effects.

i) Volunteer who visited the lab as part of the methodology

First Visit: Upon arriving at the laboratory, they provided their written, formal consent, confirmed the diagnosis, completed the sociodemographic questionnaire, underwent the cognitive test, and completed other baseline assessment procedures. They were also provided with information regarding the protocol they will follow.

Second visit: The first 20 minutes of the treatment session were administered, which also included a training session on how to use the device at home.

Third Visit: The patient returned the device to the lab after completing the assessment at the end of the treatment, which took place after four weeks of tDCS at home.

ii) Size of the cap and electrodes' position, training session, protocol compliance, and adherence

a). *Procedures to choose the size of the cap and electrodes' position:* Following the measurement of the head circumference, the researcher selected the size of the cap from small (38 cm x 55 cm), medium (39 cm x 57.5 cm), and large (40 cm x 59 cm). The researcher then localized the electrode positions using the 10-20 system for EEG and placed electrodes in the F3 and F4 positions to deliver current to the scalp. The user cannot move the electrodes once they are inside the sponges, so an exact location of the electrode to provide the electric current during stimulation is assured.

b) Training session and instructions on how to self-apply the tDCS: After guiding the participants with the information from the tDCS use at the home manual and answering any questions, we conducted a face-to-face training session in the clinical research facility at HCPA in Porto Alegre, Brazil.

- Patients might access the step-by-step procedure for self-administration of tDCS at the following link (youtube: https://youtu.be/3Wtji4esOGE).

c) Protocol compliance, appropriate use, and record of adverse effects, during the sessions of tDCS at home:

- Participants received instructions to pick a peaceful during the day to administer the therapy session.

- One research team member supervised the first session remotely at home (the second overall). If the participant had questions or issues about the device, they could contact the team via WhatsApp anytime.

-The researcher in charge of getting in touch with patients did so once a week.

-The tDCS device software recorded every session.

- Additionally, participants were oriented to note any adverse effects in their diary immediately after the session.

d) Control of the adherence: An engineer who was not involved in the patients' treatment oversaw downloading the data stored in the software during the treatment to maintain the study team's blinding. Such data include records of hour use, time of use, impedance, resistance, and the number of sessions. The timeline of the study is presented in figure 1.

----------Insert figure 1----------

2.7. Instruments and Assessments

Pain scales, psychological assessments, and psychophysical measurements were all performed by two evaluators unaware of the group assignment. The cognitive assessments were conducted by two trained psychologists. The tests were administered with auditory or paper stimuli and oral responses. All evaluators received a specific train, which followed a sequence of steps: ***(i)*** read and study manuals of each test; ***(ii)*** observe the administration of tests by an experienced examiner; ***(iii)*** practice it on volunteers in role-playing sessions, and (***iv***) discuss problems and questions with local experts if was needed. All assessments were performed in a quiet and private area without interruptions after patients received correct and clear instructions for the test in a slow speaking voice.

Outcomes

The primary outcome was executive function, defined as TMT Part B minus Part A. The secondary outcomes were working memory, assessed by Digits Span (*Digits subtest from Wechsler Adult Intelligence Scale (*WAIS-III)), verbal fluency (semantic and orthographic), assessed by Controlled Oral and Word Association Test (COWAT), and everyday dysfunction due to FM, assessed by Fibromyalgia Impact Questionnaire (FIQ).

Outcome assessments

a. ***TMT - Trail Making Test (TMT A-B)****:* TMT A-B measures working memory, executive attention, cognitive flexibility, split attention, and processing speed (Reitan and Wolfson 1993; Lezak et al., 2004). The amount of time needed to finish the job and the number of mistakes affect how well you score. Lower performance is indicated by higher scores.

b. Digits subtest from Wechsler Adult Intelligence Scale (WAIS-III)*:* The Digit's subtest consists of eight series of digits presented aloud to the subject and asked to repeat in the same order (forward), and seven sequences that should be repeated in inverse order (backward), each series with a gradual increase in the number of digits (Wechsler, 2004) (Nascimento, 2004). The Digits test assesses working memory. Higher scores indicate better performance.

c. Controlled Oral Word Association Test (COWAT): It is the verbal fluency exam that evaluates both linguistic and executive skills, including cognitive flexibility, strategy use, interference suppression, and reaction inhibition (Schinka et al., 2010). (Hedden and Yoon, 2006). Better performance is indicated by higher scores.

d. Fibromyalgia Impact Questionnaire (FIQ) was proposed by Burckhardt et al., 1991 to assess the quality of life in FM patients. We used the version adapted for use in Brazil. (Paiva et al., 2013) The FIQ consists of 10 domains. The items evaluate the patient's capacity for doing everyday activities as well as their level of weariness, stiffness in the morning, mood, anxiety, and sadness. The scoring cap is 100. Higher scores indicate the worse quality of life due to FM symptoms.

Psychophysical measurements, depressive symptoms, sleep quality, and serum BDNF

e. The following sequence of procedures evaluated the conditioned pain modulation test (CPM-test): ***First***, we employed the thermo-test placed in the non-dominant forearm on the ventral forearm to define the temperature to produce a score of 6/10 (NPS, 0-10) by an average of three successive measures (T0). ***Second***, patients submerge their dominant hand for one minute in water at a temperature of 0 to 1 °C. Thirty seconds after they dipped their non-dominant hand in cold water, the non-dominant forearm underwent the QST's thermo-test. The pain intensity in the thermode region was measured using a scale of 0 to 10 (QST+CPM-test) (T1). ***Third,*** we calculate the CPM–test score by the difference between the change in NPS 0–10 at the temperature set at 6/10 in the region of thermos-test minus 6 (reference value) (Botelho et al., 2016) (Soldatelli et al., 2021). For the analysis, we used CPM-test score as a continuous variable. So higher values indicate lower efficiency of DPMS.

f. Pain pressure threshold (PPT): To conduct the test, we employed an electronic algometer made by J-Tech Medical Industries in Midvale, Utah, USA. Patients were advised to distinguish between pressure and pain before the assessment began. Patients were told to verbally communicate their pain when it started. At 3–5-minute intervals, we took three measurements in succession (da Graca-Tarragó et al., 2019)

g. Beck Depression Inventory-II (BDI–II): It is a self-applied used to evaluate the severity of depressive symptoms (Gomes-Oliveira MH et al., 2012).

h. The Pain Catastrophizing Scale (B-PCS): It is a self-administered questionnaire with 13 items to measure pain-related catastrophizing (Sehn et al., 2012).

i. Pittsburgh Sleep Quality Index (PSQI) evaluates the quality of sleep over the previous month. The score with the highest rating represents the poorest sleep.

j. Dosage of BDNF serum levels: The blood was collected in serum separator activator tubes provided with wall blasted clot activator coagulant type, used to obtain blood serum. After centrifuging blood samples, the serum was divided into 0.5 ml aliquots for additional examination. According to the manufacturer's instructions, sandwich ELISA was used to measure the serum levels of BDNF using monoclonal antibodies that are specific for the neurotrophin (R&D Systems, Minneapolis, United States). To evaluate the inter-assay variation, two plates per kit were utilized over two distinct days of the same week. The manufacturer's instructions are followed by protocols. To ascertain serum BDNF, the Enzyme-linked Immunosorbent was employed. The kit's BDNF lower detection limit is 7.8 pg/ml. Use the ChemiKine BDNF Sandwich ELISA kit, CYT306 (Chemicon/Millipore, Billerica, MA, USA) for the assay (ELISA). GloMax®-Multi Microplate Reader from Promega or the Bio-Plex®-200 device from Bio-Rad was used to assess optical density for multiplexing assay readings. Using the Bradford method, which uses bovine serum albumin as a standard, we measured the total protein using the standard. The information was presented as pg/mg of protein.

Clinical measurements: CSS symptoms, pains score, and analgesic use

k. A standardized questionnaire was used to evaluate demographic information and medical comorbidities. They self-reported diagnoses, medication use, medical procedures, and pain-related problems.

l. The Numerical Pain Scale was used to measure the level of pain (NPS). The NPS scores range from zero (no pain) to maximum agony (10). Patients provided the response for the following question: How severe was your worst pain over the past week?

m. The symptoms of central sensitization were evaluated using the Central Sensitization Inventory for Brazilian Population (CSI-BP). Its 25 items (total score 0-100) examine urological symptoms, headache/jaw symptoms, mental distress, and physical problems. Higher ratings reflect more severe symptoms. Part B of the CSI-BP also evaluates the existence of neurological conditions linked to central sensitization and mental diagnoses (Caumo et al., 2017).

n. If an extra analgesic medication (such as acetaminophen, ibuprofen, or tramadol) was required to treat their pain, they could do so. As rescue analgesia, they may take 500 mg of acetaminophen up to four times per day (QID) at the most. They could take Dorflex® (Sanofi Aventis, So Paulo, Brazil; 35 mg orphenadrine citrate coupled with 300 mg dipyrone and 50 mg caffeine) up to three times daily (TID) if their discomfort continued. Patients could utilize tramadol at their highest tolerated daily dose if their discomfort continued.

2.8. Statistical Analysis

Continuous and categorical variables were compared using Fisher's exact test, the chi-square test, and the t-test for independent samples. We utilized the Shapiro-Wilk normality test to determine if the continuous variables displayed a normal distribution.

We utilized the Mann-Whitney U-Wilcoxon test for comparisons between groups and the Wilcoxon test for comparisons within groups. Furthermore, we used a linear regression model to examine the impact of the treatment. The treatment group was factored into the models (a-tDCS or s-tDCS) and the dependent variables were evaluated by percent change in average [((value post-intervention minus value pre-intervention)/value pre-intervention) *100]. The primary outcome was assessed by the Trail Making Test (TMT-B-A)]. The secondary outcomes were the following: working memory, verbal fluency (semantic and orthographic), phonemic fluency, and the impact of FM symptoms on quality of life. Since it is known that cognitive measures exhibit substantial individual variability on the same test, and they do not have a reference value to define the severity of cognitive impairment, they utilized the percent change in the average from pre-to treatment end. We restrict the intention-to-treat analysis (ITT) to subjects who had received at least 50% of the total protocol sessions, in the case of 10 sessions. We used a single imputation approach for missing data, replacing missing values with the mean for the outcome variables (Dziura JD, 2013). We used the pool of baseline standard deviation (SD) to calculate the ES using the standardized difference mean (SDM) (mean difference a-tDCS vs. s-tDCS). The ES was considered minor if it ranged (from 0.20 to 0.49), moderate if it ranged (from 0.5 to 0.79), and large if it was equal to 0.8 or over (Kazis LE, 1989). Spearman's correlation analysis was used to test the correlation between the average percent change (pre-intervention to treatment end) of TMT-B-A, QIF, and serum BDNF according to a-tDCS and s-tDCS groups. All analyses used two-tailed tests with a significance threshold of 5% and were adjusted for multiple comparisons using Bonferroni's test. SPSS was used to examine the data, version 22.0 (SPSS, Chicago, IL).

3. Results

3.1. Demographic and clinical characteristics of the subjects

We screened 63 patients, and 27 patients didn't fit the criteria for inclusion. The flow presents the exclusion criteria (figure 2). This study included 36 patients who were randomly assigned to receive either a-tDCS (n = 24) or s-tDCS (n = 12). Three patients discontinued therapy—two in the s-tDCS and one in the a-tDCS—one owing to a covid infection that prevented her from applying the stimulation session, one because she did not feel the effects of the treatment quickly enough, and one because she did not have enough time to apply the treatment. We conducted an ITT analysis including all of them (n = 36) since all had completed at least 10 sessions of tDCS.

----------Insert figure 2----------

Table 1 displays the demographic and clinical traits of the patients. There are balanced baseline features between treatment groups

---------- Insert table 1----------

3.2. Univariate analysis: Interventions Effects within groups on primary and secondary outcomes

The within-group treatment effect in the outcomes: primary [sustained and divided attention assessed through the Trail Making Test (TMT-B-A)] and secondary outcomes [working memory, verbal fluency (semantic and orthographic), phonemic fluency, and impact of fibromyalgia symptoms on quality of life] are presented in Table 2. We showed the mean (standard deviation), median (interquartile 25-75) at baseline, and treatment end, as well as the effect size (ES) according to groups (s-tDCS and a-tDCS).

----------Insert able 2----------

3.3. Primary outcome: Impact of tDCS in the executive attention, divided attention, and working memory by TMT-B-A

The GLM revealed a main effect for treatment assessed through the Trail Making Test (TMT-B-A) (Wald $\chi 2=6.17$; Df=1, P=0.013). The TMT-B-A score was adjusted by the multivariate analysis presented in table 3 revealed that the a-tDCS reduced the total score in the Trail Making Test (TMT-B-A) to -29.53 (8.89) compared to an increase in the scores in the s-tDCS 23.09 (16.32). The ES based on the SDM of a-tDCS vs. s-tDCS was large [-1.48, confidence interval (CI) 95%= -2.07 to -0.90]. It is important to realize that a reduction in the scores of the TMT-B-A indicates better cognitive performance.

According to the analysis presented in table 3, the effect of a-tDCS on TMT-B-A was positively correlated with the severity of dysfunction in the DPMS at baseline. For the study of the DPMS function, we used the NPS (0-10) as a continuous variable. Thus, higher scores indicate a lower efficiency of the DPMS. Also, the performance in the TMT-B-A was positively associated with more significant decreases in the serum BDNF from pre-intervention to treatment end. In other words, more considerable reductions in the TMT-B-A in the a-tDCS are associated with a more remarkable decrease in the BDNF at the treatment end.

---------- Insert table 3----------

---------- Insert figure 3 ----------

3.4. Secondary outcomes: Impact of tDCS on Working memory (Digits subtest from WAIS-III), cognitive flexibility (COWAT) and quality of life

The GLM revealed a main effect for treatment of the a-tDCS effects compared to s-tDCS to improve the performance in the working memory, verbal fluency (semantic and orthographic), phonemic fluency, and impact of fibromyalgia symptoms on quality of life. Data are presented in Table 4.

3.5. *Secondary outcomes' analysis: Trail Making Test (TMT-B-A) serum BDNF, and quality of life after treatment ends*

In the a-tDCS, there is a moderate and positive correlation between the TMT-B-A at treatment end with changes in serum BDNF [(Rho=0.57, confidence interval (CI) 95%=0.28 to 0.76; P=0.01]. In contrast, in s-tDCS the correlation between these two variables was not significant [(Rho=0.25, confidence interval (CI) 95%= -0.1 to 0.55, P=0.70]. In the a-tDCS, the TMT-B-A scores at the treatment end showed a positive and moderate correlation with the scores related to FM symptoms on quality-of-life [(Rho=0.66, confidence interval (CI) 95%=0.4 to 0.82; P=0.001]. In contrast, in s-tDCS the correlation between these two variables was not significant [(Rho=0.20, confidence interval (CI) 95%= -0.15 to 0.51; P=0.60]. Such non-parametric correlations showed that patients who received a-tDCS showed a remarkable cognitive performance improvement. In the same way, they presented a more considerable reduction in serum BDNF, which was moderate and positively correlated with improved cognitive performance and improvement of symptoms that impact the quality of life.

3.6. Assessment of Adverse Events and Safety

The adverse effects comprise headache, tingling, burning, redness, and itching were not significantly different between a-tDCS and s-tDCS (see Table 5). Both groups experienced comparable mild side effects (a-tDCS or s-tDCS). Many side effects were rated as light, and no patients discontinued therapy because of uncomfortable side effects.

----------Insert table 5----------

To determine protocol compliance and adherence, we verified the co number of valid sessions by the software's records. The mean number of sessions administered in the a-tDCS group the mean (SD) was 17.35 (3.57); median 19; IQ 25-75=(10; 20) and in the s-tDCS the mean (SD) was 17.30 (2.54) , median 17.5; IQ 25-75=(14; 20). There would be 440 sessions in the group that received a-tDCD (n=22), but we logged 370 valid sessions (84.09%). There were 220 legitimate sessions in the group that received s-tDCS (n=11), while there would have been 178 sessions (80.09%). We recorded 548 valid sessions out of 660 scheduled sessions in all samples, considering a-tDCS and s-tDCS.

4. Discussion

This trial demonstrated that the current protocol of home-based a-tDCS compared to sham for four weeks of stimulation over the l-DLPFC improved the cognitive functions assessed by TMT-B-A (executive attention, divided attention, W.M., and cognitive flexibility). Additionally, they provide evidence of the a-tDCS benefits to improving secondary outcomes, including W.M., verbal semantic fluency, phonemic fluency, and the impact of F.M. symptoms on quality of life. The a-tDCS effects on the cognitive tests were positively correlated with the percent changes in averages from pre-treatment to treatment end of the BDNF. Also, the severity of dysfunction of DPMS

at baseline predicted more remarkable a-tDCS effects in the cognitive impairment. Besides, we found that the reduction in the BDNF related to the a-tDCS is related to improving symptoms due to F.M. The study had a dropout rate of 10%, mainly due to restrictions on circulation in the streets instituted during the COVID-19 pandemic. Mild to moderate adverse events were more common in the active tDCS group, particularly skin tingling, burning, and itching, and the global adherence was 83.03%.

This trial has key methodological differences compared to previous studies on tDCS to improve the cognitive impairment in F.M. We used a home-based tDCS device that enabled a considerably higher number of sessions. Hence, until we can be known, this is the study that evaluated the highest number of sessions used to improve cognitive performance at home. This is particularly relevant since preliminary evidence points to the increased efficacy of tDCS with more extended periods of treatment (Castillo-Saavedra L, 2016; Brunoni AR, 2016, Brietzke, 2020). Additionally, the need for daily visits to clinics or hospitals has always been a significant challenge for using tDCS in the clinical context (Charvet LE, 2020; Salehinejad MA, 2021). Thus, the home-based device opens a new window of opportunity, especially for subjects with physical or cognitive disabilities that hinder their access to the clinical center. So, these results corroborate other previous studies which found that the a-tDCS on the DLPFC might activate regions associated with pain processing, such as the anterior cingulate cortex (ACC) cortex, the primary somatosensory cortex (S.I., SII), insula, and thalamus (Apkarian, A.V, 2005; Bushnell, M.C., 2013; Leknes, S., 2008). The fact that pain, as well as attention, share the same cognitive network results in a hindrance to having an efficient cognitive system. Therefore, pain may impair voluntary attentional systems and associated executive functions (Bell et al., 2018) (Eccleston & Crombez, 1999). A-tDCS can alter the electrical activity of specific brain regions, encourage cortical plasticity, and enhance functional connections in the area that is being treated, improving pain modulation and quality of life. So, the a-tDCS's effect modulates neuronal membrane potential on cortical and subcortical neural networks involved in cognitive functions and pain processing. This effect corroborates the results of an earlier trial in a single session of tDCS with 2mA, applied to the DLPFC cortex in F.M., which found improvements in the function of neural networks involved in spatial and executive attention, as well as a reduced perception of pain (Silva et al., 2017). Another trial also observed the benefit of eight tDCS sessions paired with cognitive training on working memory, verbal fluency, and immediate and delayed memory (Santos et al., 2018). Besides, the current findings are aligned with previous studies in patients with a depression diagnosis, which found that a-tDCS over the DLPFC reduced depressive symptoms and other symptoms linked to inappropriate emotional functioning (Brunoni AR, 2017). As well, it reduced pain catastrophizing (Caumo, 2021) and improved cognitive functions (e.g., decision-making) (Dixon ML, 2017). According to the literature, this effect can be related to top-down control that up-regulates reactions to positive emotional stimuli (Grimm S, 2007, Goldin PR, 2009). The ability of a-tDCS on the l-DLPFC to alleviate cognitive abnormalities, notably hypoactivity in the l-DLPFC and hyperactivity in the r-DLPFC, may be one of the potential mechanisms behind these processes and related to its impact on the on cognitive impairment. This hypothesis is supported in a study that assessed how inter-hemispheric connectivity conservation could have cognitive implications (Krupnik R, Yovel Y, Assaf Y., 2021). So, the current result might contribute to a greater understanding of the tDCS effect on brain function.

According to the CPM-test, the severity of DPMS inhibitory dysfunction predicts a remarkable a-tDCS effect compared to s-tDCS on improving cognitive function. This finding suggests that the a-tDCS impact on the outcomes has been more evident in more severe diseases. These findings demonstrate that there is an interaction between the spine-bulbospinal loop and the neural network of cortical areas from an integrative approach. They support the notion that the DPMS and the brain networks involved in cognitive processing have similar neurobiological workings. According to the research, the DLPFC is, therefore, a crucial brain area for modulating the experience of pain. The benefits of using the l-DLPFC as a target area to modulate pain corroborate meta-analysis data that showed the a-tDCS on pain with a moderate E.S. (0.54) (Zortea, 2019). Besides, the DPLCF as a target area for improving cognitive performance finds support in data that links prefrontal cortex function with a decline in cognitive abilities (Wen et al., 2011; Wiseman et al., 2018), as well as with the impact of a-tDCS on the l-DLPFC in W.M. (Santos, 2018). Thus, it is plausible that the cognitive impairment in chronic pain encompasses dysfunctions in neural networks in brain areas with a central role, either in pain (Staud, R, 2008; Bosma, R.L, 2016) or in cognition, such as the insula, ACC, and PFC (Nijs, J, 2021). Other studies showed the benefits of a-tDCS on l-DLPFC are supported by improvement in the W.M. and clinical and experimental pain either by repetitive transcranial magnetic stimulation (r-TMS) (Graff-Guerrero et al., 2005; Borckardt et al., 2007) or a-tDCS (Santos, 2018). This information reveals that the downstream regulating circuits, including the anterior insula, hypothalamus, periaqueductal gray substance, nucleus accumbens, and rostroventral medulla, are involved in the processes encompassing the effects of a-tDCS on the l-DLPFC (Wager 2013).

The effect of repetitive sessions of a-tDCS has been attributed to the induction of use-dependent neuroplasticity, which is related to "synaptic learning" and long-term changes, which resemble glutamatergic synapses' long-term potentiation (LTP) or long-term depression (LTD) (Nitsche et al., 2003; Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). The activity level of underlying neuronal populations at stimulation time is a potentially important mediator of the effect of tDCS on brain function. This is further corroborated by the fact that the impact of tDCS to improve cognitive performance is positively correlated with the neuroplasticity state, according to the percent change in serum BDNF from pre- to treatment end. This discovery aids in understanding how a-tDCS affects faulty neuroplasticity since it can alter mechanisms that include strengthening glutamatergic synapses while weakening GABAergic synapses (Coull JA, 2005). The relationship of serum BDNF to predict the a-tDCS was found in our previous studies with F.M. with a-tDCS applied to the DLPFC in work memory (Santos, 2018). In a study with a similar montage, the baseline BDNF predicted the tDCS effect on daily pain scores after sixty sessions of tDCS self-applied at home (Brietzke, 2020). Besides, in the postoperative recovery of the hallux valgus surgery, the liquor BDNF after two a-tDCS sessions was associated with lower pain scores and disability due to pain seven days after surgery (Ribeiro H, 2017). We should interpret this result sparingly because the BDNF can be a marker to probe dysfunctional neuroplasticity; it is an indirect measure of the neuroplasticity phenomenon. According to the cumulative evidence in FM, higher serum BDNF has been found compared to other chronic pain and healthy subjects (Luciana Cadore Stefani, 2019). So, the positive correlation between the improvement of cognitive performance and the decrease of

serum BDNF in a-tDCS compared to sham suggests that the intervention counter-regulated the dysfunctional neuroplasticity associated with FM. Nevertheless, these findings open a new line of inquiry into how much the maladaptive neuroplasticity state can change the impact of this type of therapy.

Our findings should be viewed considering some limitations. *First*, although patients received comprehensive training in using the device, no remote monitoring of sessions was performed. Therefore, there should be caution in direct comparison with studies with supervised electrode placement and exposure supervision. *Second*, given that women are more likely to experience adverse emotional reactions (such as dread and anxiety), these results may be generalized to women to remove potential bias due to sex (Rothwell PM, 2006. *Third,* our findings are consistent with past research that supported this method of self-application for prolonged tDCS use at home. We also see similar outcomes to studies in which the therapy was administered under close observation (Santos, 2018). *Fourth*, the tDCS system used in the current study provides an effective technical solution that enables medical engineers who were not involved in the patients' care to program the tDCS system by the randomization sequence to ensure that all members of the research team and patients are blinded. *Fifth*, in this study, high adherence was observed by the records of devices in use, like those obtained in real-life environments. *Sixth,* despite the randomization processes permit to have balanced groups of a-tDCS and s-tDCS on cognitive performance may be confounded by other variables, such as psychiatric comorbidities (i.e., depression, anxiety, and sleep disturbance) (Airaksinen E, 2005; Austin MP., 2001; Castaneda AE, 2008), or medication use, particularly opioids, which may lead to cognitive side effects that cannot be controlled entirely (Ersek M, 2004). *Seventh*, there is no standard battery of neuropsychological tests for cognitive function assessment in chronic pain. So, the literature has recommended that the cognitive assessment in FM. should include tests to evaluate attention and W.M., complex psychomotor speed, and executive functioning (Kravitz. H.M., 2014). *Eight,* we decide by the allocation 2:1 based on the rational that fibromyalgia has important suffering. Based on the argument that fibromyalgia causes significant long-term discomfort, we allocate 2:1, since, if a lower number of participants in the sham group, we may treat more individuals actively, leading to increased adherence. Additionally, the higher sample size in the active group increases the ability to identify side effects (Dumville JC, 2006; Spencer P Hey, 2014). Finally, with an adherence rate of more than 85% to sessions in both a-tDCS and s-sham tDCS, we adopted a strict and reproducible technique to demonstrate the efficacy and viability of t-DCS at home. However, further studies must explore if neurophysiological measures, such as EEG records, might help to shed light on the specific modulated cognitive processes by the intervention. Another aspect is to allow a more focal target area of the stimulation using multichannel tDCS montages.

These findings revealed that daily treatment with a home-based tDCS device over l-DLPFC compared to sham stimulation over four weeks improved the cognitive impairment in F.M. The a-tDCS at home was well-tolerated, underlining its potential as an alternative treatment for cognitive dysfunction. Besides, the a-tDCS effect is related to the severity of DPMS dysfunction and changes in neuroplasticity state.

Author Contributions

W.C., R.L., P.V., F.F. had substantial contributions to the conception or design of the work. CFSA, L.R., PRS, DPS, ILST, F.F. and W.C. drafted the work or revised it critically for important intellectual content. All the authors agree and approve the final version of this work.

W.C., F.F. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Legends of Figures

Figure 1. Figure 1: Timeline of the study. **A**) Home tDCS device; **B)** Position of electrodes on the DLPFC (dorsolateral prefrontal cortex); **C)** Typical curves of current intensity versus contact impedance during a tDCS session.

Figure 2: Flowchart showing randomization, allocation, and progress through the study.

Figure 3. Mean of percent changes of averages from the pre-intervention period to treatment end period of the total score in the Trail Making Test (TMT-B-A). Error bars indicate the standard error of the mean (SEM). Asterisks (*) positioned above symbols indicate significant differences ($p<0.05$) between groups (a-tDCS and s-tDCS).

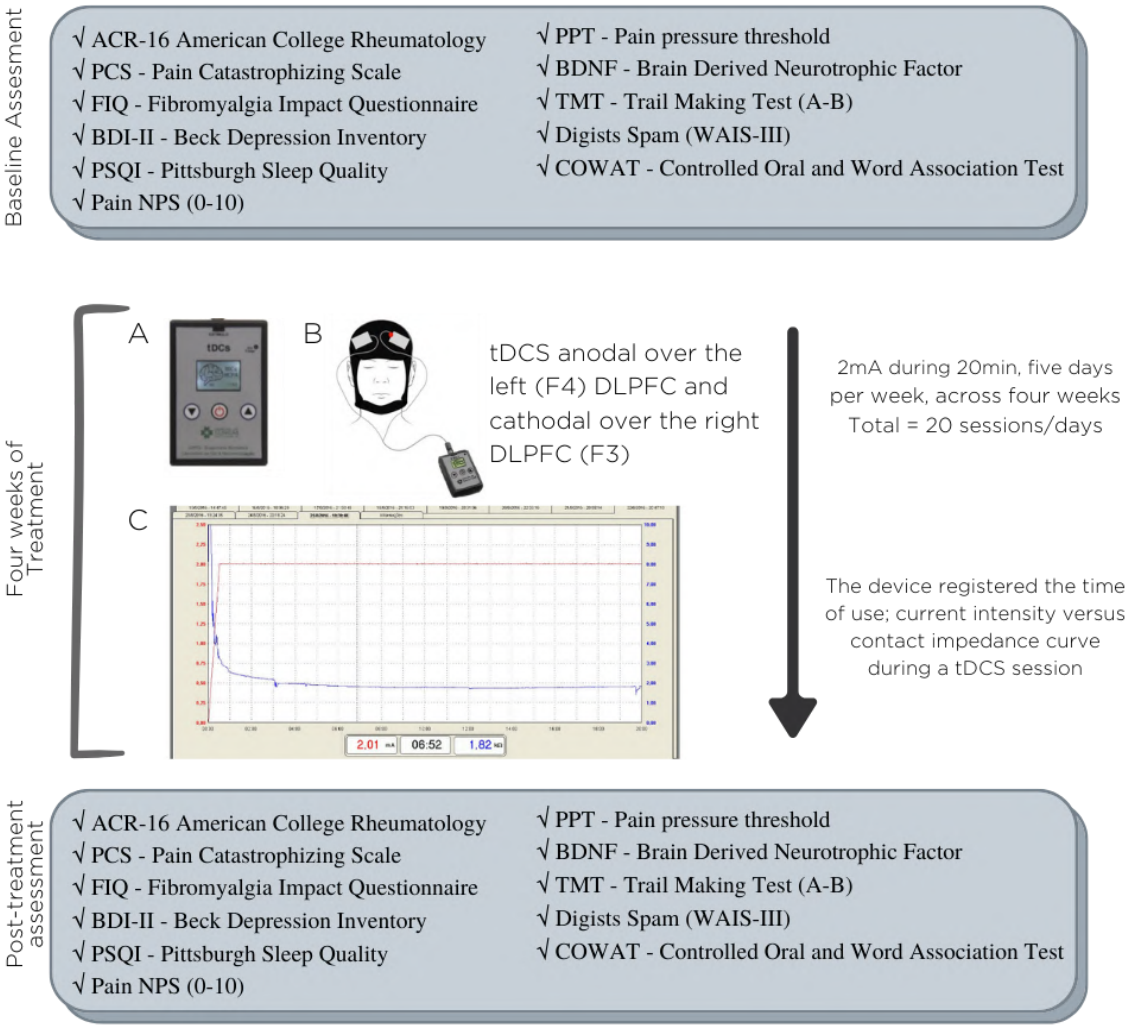
Baseline Assesment
√ ACR-16 American College Rheumatology
√ PCS - Pain Catastrophizing Scale
√ FIQ - Fibromyalgia Impact Questionnaire
√ BDI-II - Beck Depression Inventory
√ PSQI - Pittsburgh Sleep Quality
√ Pain NPS (0-10)
√ PPT - Pain pressure threshold
√ BDNF - Brain Derived Neurotrophic Factor
√ TMT - Trail Making Test (A-B)
√ Digists Spam (WAIS-III)
√ COWAT - Controlled Oral and Word Association Test
Four weeks of Treatment
A
B
C
tDCS anodal over the left (F4) DLPFC and cathodal over the right DLPFC (F3)
2mA during 20min, five days per week, across four weeks
Total = 20 sessions/days
The device registered the time of use; current intensity versus contact impedance curve during a tDCS session
2,01
06:52
1,82
Post-treatment assessment
√ ACR-16 American College Rheumatology
√ PCS - Pain Catastrophizing Scale
√ FIQ - Fibromyalgia Impact Questionnaire
√ BDI-II - Beck Depression Inventory
√ PSQI - Pittsburgh Sleep Quality
√ Pain NPS (0-10)
√ PPT - Pain pressure threshold
√ BDNF - Brain Derived Neurotrophic Factor
√ TMT - Trail Making Test (A-B)
√ Digists Spam (WAIS-III)
√ COWAT - Controlled Oral and Word Association Test

Figure 1.

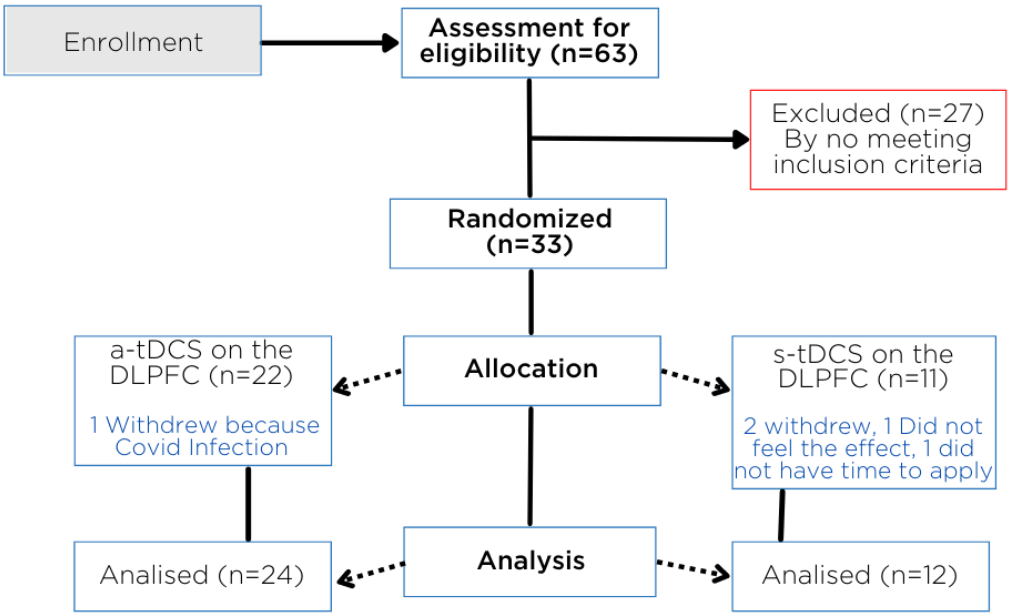

Figure 2.

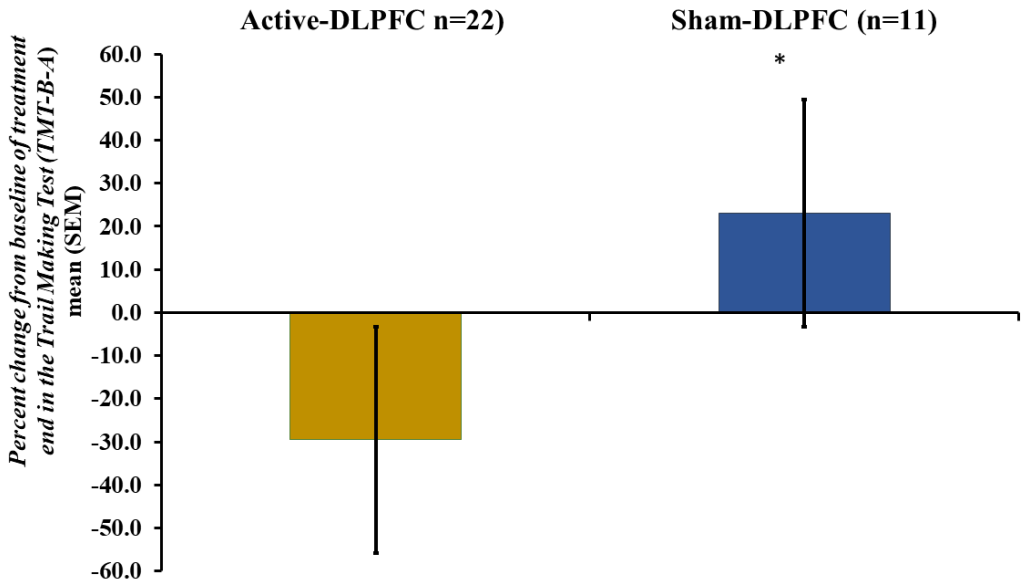

Figure 3.

Table 1. Epidemiological and clinical characteristics at baseline, according to the treatment group, values are given as the mean (SD) or frequency (n=36).

Characteristics	**s-tDCS (n=12)**	**a-tDCS (n= 24)**	**P**
Age (years)	46.09(11.34)	49.18(8.63)	.392
Education (years)	12.64(5.07)	10.23(3.75)	.134
American College of Rheumatology (ACR) diagnosis criteria score	22.82(4.36)	23.00(3.94)	.901
Smoking (*Yes*)	3	7	.785
Alcohol (*Yes*)	7	10	.320
Clinical Comorbidity (*Yes*)	50%	70%	0.251
Ischemic cardiac *(Yes)*	0	0	
Hypertension *(Yes)*	0	0	
Diabetes *(Yes)*	1	2	
Hypothyroidism *(Yes)*	2	4	
Asthma *(Yes)*	1	5	
Other *(Yes)*	6	16	
Psychiatric disorder according to the MINI (Yes/No) †			
Maniac-depressive disorder *(Yes)*	75%	70%	0.541
Generalized anxiety disorder *(Yes)*	45%	40%	0.552
Pain, sleep quality and psychological measures			
Visual Analogue Scale£	8.12(1.12)	8.65(1.36)	.711
Beck Depression Inventory II (BDI-II) £	24.18(10.05)	27.91(11.36)	.445
Brazilian Portuguese Pain Catastrophizing Scale£	34.36(10.83)	36.48(10.94)	.727
Pittsburgh Seep Quality Index (PSQI) £	11.27(4.08)	13.45(4.01)	.713
Heat Pain Threshold to produce 6/10 on NPS (oC) £	40.68(3.31)	40.98(3.16)	.793
Change on Numerical Pain Scale during CPM-testΣ	-1.20 (1.87)	-0.85 (1.89)	.940
Central Sensitization Inventory £	58.27(9.51)	68.59(13.95)	.066
Pain pressure threshold (kg/cm2 /second) Σ	1.36(0.74)	1.49(1.16)	.490
Opioid medication user (Yes) ‡			
Acetaminophen *(Yes)*	1	7	.151
Dipyrone *(Yes)*	3	5	.774
Dorflex *(Yes)*	6	9	.458
Opioid medication user (Yes) ‡			
Codeine	2	7	.407
Methadone	1	0	.333
Tramadol $	3	4	.661
Active central nervous system medication ‡			
Antidepressant tricyclic or dual *(Yes)*	2	6	.566
Antidepressant dual *(Yes)*	6	10	.622

Antidepressants selective serotonin reuptake inhibitors *(Yes)*	2	4	.853
Pregabalin (Yes)	1	5	.338
Change on Numerical Pain Scale during CPM-test pre-treatment $^{\Sigma}$	-1.20 (1.87)	-.85 (1.89)	0.691
Brain-derived neurotrophic factor (BDNF) (ng/ml) before treatment $^{\Sigma}$	33.85 (22.17)	49.53 (36.33)	0.192
Brain-derived neurotrophic factor (BDNF) (ng/ml) at treatment end $^{\Sigma}$	58.53 (48.61)	31.39 (18.32)	0.140
Percent change serum BDNF from pre-intervention to treatment end $^{\Sigma}$	52.63 (67.82)	-14.48 (60.15)	0.031

‡Non-opioid analgesics, opioid analgesics; active central nervous system medications and psychiatric disorder patients could have none or more than one of them.

$^{\Sigma}$ *comparison using Wilcoxon Mann-Whitney*

Table 2. Univariate analysis: Interventions effects within and between groups on primary and secondary outcomes (n=33)

	s-tDCS (n= 12)				a-tDCS (n=24)			
	Mean (SD)	**Median (IQR_{25-75})**	**ES**	**P**	**Mean (SD)**	**Median (IQR_{25-75})**	**ES**	**P**
Primary outcome								
Trail Making Test (TMT-A)								
Baseline	33.37 (7.94)	26 (9.07 ; 66.75)	0.36	0.20¥	38.23 (14.69)	38.58 (17.57; 133)	0.74	0.01¥
Treatment end	30.91 (10.17)	30.44 (15.19; 50.50)			30.91 (10.17)	29.55 (18.52; 69.90)		
Difference mean (%)	-8.81 (22.08)				-12.55 (23.31)		---	0.64€
Trail Making Test (TMT-B)								
Baseline	60.30 (22.76)	61 (30.62; 103.68)	0.31	0.26¥	87.45(33.44)	73.18 (52.81; 176)	0.5	0.00¥
Treatment end	72.49 (27.85)	66.38 (24.60 ; 139.5)			74.16 (44.11)	58 (41.04; 110)		
Difference mean (%)	11.73 (37.66)				-15.44 (17.40)		0.72	0.03€
Trail Making Test (TMT-B-A)								
Baseline	27.24 (17.61)	30.44 (15.19; 50.50)	0.4	0.32¥	47.72 (30.25)	29.55 (18.52 ; 69.90)	0.29	0.04¥
Treatment end	37.00 (24.40)	35.34 (8.23 ; 56.56)			40.01(26.15)	32.51 (10 ; 85)		
Difference mean (%)	57.20 (45.92)				-18.21 (24.90)		1.06	0.01€
Secondary outcomes								
Span digits forward								
Baseline	7.45 (1.74)	7 (4; 8)	0.46	0.00¥	7.18(1,32)	6 (4 ; 10)	0.35	0.15¥
Treatment end	6.60 (1.85)	6 (4; 10)			8.11(2.62)	7 (5 ;14)		
Difference mean (%)	-12.12 (15.02)		0.16		16.99 (31.43)			0.00€
Span digits for backward								
Baseline	5.23 (1.45)	4 (3; 8)	0.28	0.07¥	5.64 (1.43)	6 (3 ; 12)	0.14	0.38¥
Treatment end	4.80 (1.54)	4 (3; 8)			6.00 (2.65)	6 (3 ; 12)		
Difference mean (%)	-7.85 (23.83)		----		11.90 (36.80)			0.20€
COWAT orthographic								
Baseline	32.73 (7.86)	34 (17; 49)	0.23	0.08¥	33.36 (7.45)	34 (21 ; 43)	0.34	0.01¥
Treatment end	34.60 (8.07)	35 (19; 51)			36.67 (9.67)	36 (24 ; 52)		

Difference mean (%)	8.78 (16.26)		---		12.97 (10.01)			0.45€
COWAT semantic								
Baseline	17.91 (4.28)	16 (12 ; 27)	0.02	0.95¥	15.10 (3.68)	15 (10; 26)	0.68	0.01¥
Treatment end	17.78(5.83)	17 (11 : 28)			17.59 (3.86)	18.50 (10; 24)		
Difference mean (%)	4.39 (29.83)				13.93 (24.29)		0.31	0.04€
Fibromyalgia Impact Questionnaire (FIQ)								
Baseline	71.89 (7.55)	72.44 (55.87 ; 82.02)	0.65	0.02¥	76.99 (9.80)	76.13 (61.93; 98.73)	1.15	0.00¥
Treatment end	64.73 (10.94)	67.02 (47.72 ; 81.93)			58.42 (15.53)	62.19 (26.10; 83.23)		
Difference mean (%)	-10.30 (9.78)				-24.76 (15.71)		3.58	0.01€

¥ Comparisons within group by Wilcoxon test . € comparisons between groups by Mann-Whitney U-Wilcoxon.

*Difference mean average percent change [((value post-intervention minus value pre-intervention)/value pre-intervention) *100]*

Effect size (ES) (Mean difference a-tDCS vs. s-tDCS)/Pooled standard deviation]. The ES was defined as small if lower than 0.20 to 0.49; moderate if between 0.50–0.79; and large if larger than 0.80.

Table 3. Effect of treatment on TMT-B-A (primary outcome). Data present the comparisons between groups on the percent changes from pre-intervention to treatment end (n = 36).

Cognitive tests	Beta	SEM	CI 95%	Wald $\chi 2$	df	P
Trail Making Test (TMT-B-A)						
(Intercept)	25.836	17.992	(-9.42 to 61.10)	2.062	1	.151
Active-tDCS (n=24)	-48.391	19.472	(-86.55 to -10.22)	6.176	1	.013
Sham-tDCS (n=12)	$0^{reference}$					
Scores on NPS (0-10) during CPM-test at baseline	7.190	3.4483	(.43 to 13.94)	4.347	1	.037
Change on BDNF pre- to post-treatment (%)	.501	.1969	(.11 to 0.89)	6.483	1	.011

** Represents a difference significant from a P-value < 0.05. CPM-test , conditioned pain modulation;*

NPS, numerical pain scale; BDNF , brain-derivate neurotrophic factor.

Table 4. Effect of treatment on sustained attention, working memory, verbal fluency, phonemic fluency, and quality of life. Data present the comparisons between groups on the percent changes from pre-intervention to treatment end (n = 36).

Cognitive tests	Beta	SEM	CI 95%	Wald χ2	df	P
Span digits forward						
(Intercept)	6.956	8.20	-9.12 to 23.04	.71	1	.397
Active-tDCS (n=24)	22.19	8.85	4.84 to 39.54	6.28	1	.012*
Sham-tDCS (n=12)	$0^{reference}$					
Change on BDNF pre- to post-treatment (%)	.045	.04	-.02 to .11	1.67	1	.196
Responders vs. non-responders to CPM-test	12.41	7.60	-2.49 to 27.31	2.66	1	.103
Span digits backward						
(Intercept)	10.42	11.27	-11.66 to 32.53	.85	1	.355
Active-tDCS (n=24)	16.65	12.51	7.87 to 41.18	1.77	1	.183
Sham-tDCS (n=12)	$0^{reference}$					
Change on BDNF pre- to post-treatment (%)	.024	.085	-.14 to 0.19	.083	1	.773
Change on NPS (0-10) during CPM-test at baseline	.423	10.80	-20.75 to 21.60	.002	1	.969
COWAT orthographic						
(Intercept)	8.24	5.71	-2.98 to 19.44	2.07	1	.150
Active-tDCS (n=24)	.31	6.13	-11.72 to 12.34	.003	1	.959
Sham-tDCS (n=12)	$0^{reference}$					
Change on BDNF pre- to post-treatment (%)	.034	.02	-.01 to 0.08	1.93	1	.164
Change on NPS (0-10) during CPM-test at baseline	3.04	5.51	-7.76 to 13.85	.30	1	.581
COWAT semantic						
(Intercept)	7.52	10.38	-12.82 to 27.87	.53	1	.468
Active-tDCS (n=24)	23.44	11.20	1.49 to 45.40	4.38	1	.036*
Sham-tDCS (n=12)	$0^{reference}$					
Change on BDNF pre- to post-treatment (%)	-.05	.044	-.13 to 0.04	1.12	1	.290
Change on NPS (0-10) during CPM-test at baseline	3.49	9.621	-15.36 to 22.35	.13	1	.716
Fibromyalgia Impact Questionnaire (FIQ)						
(Intercept)	-13.34	5.51	-24.14 to -2.55	5.86	1	.015
Active-tDCS (n=24)	-13.96	5.88	-25.50 to -2.42	5.62	1	.018*
Sham-tDCS (n=12)	$0^{reference}$					
Change on BDNF pre- to post-treatment (%)	-.014	.0233	-.06 to 0.03	.37	1	.539
Change on NPS (0-10) during CPM-test at baseline	10.06	5.27	-.27 to 20.39	3.64	1	.056

** Represents a difference significant from a P-value < 0.05. CPM-test , conditioned pain modulation;*

NPS, numerical pain scale; BDNF , brain-derivate neurotrophic factor.

Table 5. Side effects are presented as percentage (%), and the incidence or severity of side effects classified as absent, mild, moderate, and severe (n=36).

		Severity of symptoms (%)				
	Group	Absent	Mild	Moderate	Severe	P-value
Headache	a-tDCS=24	45%	15%	35%	5%	0.26
	s-tDCS=12	40%	30%	10%	20%	
Tingling	a-tDCS=24	45%	25%	20%	10%	0.57
	s-tDCS=12	50%	20%	30%	0%	
Burning	a-tDCS=24	35%	25%	25%	15%	0.50
	s-tDCS=12	60%	10%	20%	0%	
Redness	a-tDCS=24	80%	10%	10%	0%	0.16
	s-tDCS=12	100%	10%	0%	0%	
Itching	a-tDCS=24	45%	20%	25%	10%	0.61
	s-tDCS=12	50%	20%	30%	0%	

8. FINAL CONSIDERATIONS

This doctoral thesis discloses the importance of strengthening the line of research that studies how cognition interacts with mechanisms of maladaptive neuroplasticity capable of worsening pain perception related to the deficiency of the inhibitory mechanism of DPMS and how neuromodulation processes could assist in the improvement of cognition as well as the quality of life of FM patients.

Our target is to have a better understanding of diseases not well understood, how we could improve diagnosis and integrate neuromodulation techniques to enhance the treatment and generate knowledge to support new care and training policies in managing chronic pain.

Further studies may promote the research and treatment with neuromodulation in FM subjects, especially focusing on the use of tDCS on DLPFC and its association with cognitive processes.

Finally, it is worth emphasizing that this study is the first to show a connection between cognitive decline and DPMS dysfunction, revealing also that BDNF is a moderating element in a relationship between the severity of cognitive impairment and DPMS dysfunction as well.

9. FUTURE PERSPECTIVES

As a future outlook, we hope to be able to study different tDCS montages and protocols such as the combination of the stimulation of the primary motor cortex and bilateral DLPFC stimulation, as well as the application of WM training online with transcranial stimulation to assess the response on pain, memory, attention, and quality of life variables.

In addition, we could increase the number of fibromyalgic patients to improve our results and gain more accuracy. We also think that we could make a pre and post assessment with electroencephalography (EEG), to have a better understanding of the neurosignature of electrophysiological signal process, and Near Infrared Spectroscopy (NIRS) to have a better comprehension of brain function through blood oxygen level dependant (BOLD) signal in patients with fibromyalgia, that could be useful for a better diagnostic method as well as to enhance the treatment efficiency.

Additionally, it would be interesting to try the same stimulation montages but with Transcranial Alternating Current Stimulation (tACS) with different frequencies of stimulation and Transcranial Magnetic Stimulation (TMS).

10. APPENDIX

10.1 APPENDIX 1 - STROBE - Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7-8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7-8-9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	---
		(c) Consider use of a flow diagram	---
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	---
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11

		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	---
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13 -14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

10.2 APPENDIX 2 - CONSORT

CONSORT 2010 checklist of information to include when reporting a randomized trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	---
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	---
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to assessing outcomes) and how	---
	11b	If relevant, description of the similarity of interventions	10-11
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	---
	14b	Why the trial ended or was stopped	---
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	11
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	13
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	---
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	---
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	---
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

10.3 APPENDIX 3

FREE AND CLARIFIED CONSENT TERM (In Portuguese)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Número do protocolo:_____

Você está sendo convidada a participar de uma pesquisa no Laboratório e Dor &Neuromodulação, cujo título é **Efeito da estimulação transcraniana de corrente contínua (ETCC) em nível domiciliar na dor e capacidade funcional na fibromialgia: um ensaio clínico randomizado, explanatório.** O objetivo deste estudo é avaliar o uso domiciliar a longo prazo e o efeito deste tratamento na melhora dos sintomas da fibromialgia.

1. EXPLICAÇÃO DOS PROCEDIMENTOS

Qual é o tratamento?

Neste estudo, a senhora poderá receber dois tipos de tratamentos: um tratamento para alívio da dor e melhora do quadro clínico e outro simulado, que pode ser benéfico, mas não é esperado que o seja. Apenas uma pessoa, que não está envolvida no estudo, saberá qual tipo de tratamento você recebeu. Os avaliadores, profissionais e alunos, não saberão qual o tratamento e, portanto, você não será informada sobre isto durante o estudo, apenas ao final. O tratamento consiste na Estimulação Transcraniana de Corrente Contínua, chamada ETCC, em duas fases. Na primeira, você usará a ETCC na sua casa, 5 dias por semana durante 4 semanas seguidas, de segunda a sexta-feira (menos aos finais de semana). Na segunda fase, 10 dias depois da primeira, você deverá vir 4 vezes no hospital, uma a cada 15 dias, para realizar uma sessão de ETCC por vez (veja Figura 1).

A ETCC consiste no uso de eletrodos de borracha que ficam dentro de esponjas vegetais que são umedecidas com soro fisiológico, e que ficam dentro de uma touca de neoprene, através dos quais vai passar uma corrente elétrica fraca que pode no máximo causar uma leve coceira ou sensação de queimação. Neste estudo será utilizado ETCC de 2mA, cada sessão terá 20 minutos. Tudo isto será programado no aparelho que você receberá para levar para casa. Durante o tratamento, a senhora terá um acompanhamento por *whatsapp* para observarmos possíveis efeitos adversos, dificuldades no uso e problemas no equipamento.

A senhora deverá continuar a tomar todas as suas medicações normalmente. Além disso, não deve interromper nenhum tipo de tratamento que realiza. Se for extremamente necessário iniciar o uso de alguma outra medicação, o pesquisador deve ser avisado imediatamente. Demais instruções serão dadas durante o estudo. Antes de iniciar, a senhora virá até o hospital para realizar diversas avaliações e receber o material, fazer o tratamento com acompanhamento do pesquisador e receber as informações sobre o tratamento e o material que a senhora levará para casa.

Quais são as avaliações?

Se você aceitar participar do estudo, será necessário que você venha até o hospital para realizar avaliações antes, durante e depois do tratamento, contabilizando o total de 10 encontros ao longo de 6 meses. Estas avaliações envolvem responder a questionários e escalas com perguntas sobre sua doença, seus sintomas físicos, psicológicos e emocionais e o impacto da doença no cotidiano. Alguns participantes serão selecionados para realizar exames de mapeamento cerebral, como a ressonância magnética funcional, em que você deitará em uma cama e permanecerá com a cabeça em um tubo vazado (o tubo não é fechado em nenhum lado e possui ventilação normal) por 30 minutos, imóvel (veja Figura 2). O exame é indolor. Outro exame será a estimulação magnética transcraniana, em que você receberá pulsos magnéticos indolores na cabeça, enquanto verifica-se o movimento da sua mão. O aparelho não gera lesão ou modifica o cérebro, apenas avalia seu funcionamento (veja Figura 3).

Figura 1. ETCC
Fonte: ttps://www.youtube.com/watch?v=3Wtji4esOGE

Figura 2. Ressonância Magnética
Fonte: http://www.kbdentalconsulting.com/philips-ingenia-1.5t-cx-mri-scanner.html

Figura 3. Estimulação magnética transcraniana
Fonte: https://www.aimedical.com.au/neurosoft

Será necessário coletar duas amostras de sangue e de urina. O volume de sangue será de 20 ml a cada coleta, o equivalente a duas colheres de sopa. Você também fará coleta de urina em casa, recebendo frascos para isto. A senhora será avaliada também com testes de pressão, calor e frio no braço. Estes testes são bastante simples, e geram leve sensação de dor, porém em níveis seguros, não havendo lesão ou persistência da dor depois do teste. O teste de pressão consiste em um aparelho que possui uma borracha que pressionamos num pequeno ponto do seu antebraço para verificar a dor em relação à pressão. Para o teste de calor e frio, será usado um equipamento validado do colocado no seu braço um estimulador que gera calor lentamente e você dirá quando começar a sentir calor, começar a sentir dor e o quanto de dor tolera. Algumas medidas serão realizadas enquanto você permanece com a mão do outro braço em um balde de água com gelo. Ao final, você mergulhará a mão na água com gelo, deixando lá o quanto aguentar. Por fim, você também realizará uma caminhada de 6 minutos no hospital, enquanto medimos pressão e frequência cardíaca e respiratória para testar seu condicionamento físico.

2. POSSÍVEIS RISCOS E DESCONFORTOS

Um desconforto previsto é a dor nos testes de dor, que é parte do próprio teste. Outros possíveis desconfortos poderão ser sentidos na coleta de sangue e durante a aplicação da ETCC, podendo ocorrer vermelhidão, sensação de coceira e leve formigamento no local onde serão colocados os eletrodos na cabeça. Todos estes efeitos são leves e passageiros. Além disso, você deverá vir ao hospital durante as avaliações e as sessões de tratamento da segunda fase.

3. POSSÍVEIS BENEFÍCIOS DESTES ESTUDOS

O tratamento ativo com ETCC prevê uma série de melhorias, como redução da dor, melhora da capacidade em realizar atividades do dia a dia e diminuição do impacto que a dor gera na sua vida. Se você receber este tratamento, poderá ter este benefícios. O uso domiciliar tem benefício sobre outros tratamentos que ocorrem somente no hospital. Participando da pesquisa, você estará contribuindo para uma melhor compreensão da dor crônica e de como melhorar seu diagnóstico e tratamento. Algumas avaliações e orientações fornecidas pela equipe lhe possibilitarão entender melhor seus problemas e seus sintomas e, ao final da pesquisa, espera-se que isto melhore sua qualidade de vida.

4. EXCLUSÃO DO ESTUDO

O investigador responsável poderá ao longo do estudo considerar o seu afastamento caso você não esteja se beneficiando da participação.

5. DIREITO DE DESISTÊNCIA

Sua participação é completamente voluntária e você pode desistir de participar a qualquer momento da pesquisa. Sua decisão de não participar ou de deixar a pesquisa depois de iniciada não prejudicará de nenhuma forma a atenção recebida no HCPA.

6. PRIVACIDADE

Todas as informações obtidas deste estudo poderão ser publicadas com finalidade científica, porém sem haver identificação sua ou de qualquer participante.

7. CONTATO DOS PESQUISADORES

Caso você tenha alguma dúvida poderá entrar em contato com o pesquisador responsável por este estudo: Profº Dr. **Wolnei Caumo,** através do telefone 3359-6377, ou no Laboratório de Dor &Neuromodulação, Centro de Pesquisa Clínica (CPC), 6º andar, sala 21608 do HCPA. Além disso, poderá contatar o Comitê de Ética e Pesquisa do Hospital de Clínicas de Porto Alegre, que está localizado no 2°andar do HCPA sala 2227, com funcionamento de segunda à sexta- feira, das 8hs às 17hs – telefone 3359-7640.

8. RESSARCIMENTO DE DESPESAS

Você não terá despesas com a sua participação na pesquisa, além de transporte e alimentação. Não haverá ressarcimento destes gastos.

9. CONSENTIMENTO

Declaro ter lido – ou me foi lido – as informações acima antes de assinar este Termo. Foi-me dada ampla oportunidade de fazer perguntas, esclarecendo plenamente minhas dúvidas. Por este instrumento, torno-me parte, voluntariamente, do presente estudo (este termo de Consentimento Livre e Esclarecido será assinado em duas vias, uma para você e uma via será arquivada pelo pesquisador).

Nome do participante: _____ Nome do pesquisador: _____

Assinatura do participante: _____ Assinatura do pesquisador: _____

Porto Alegre, ___de_____ de 20__.

10.4 APPENDIX 4

PRODUCTION DURING THE DOCTORATE PERIOD

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Universidade Federal do Rio Grande do Sul
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CERTIFICADO

Conferimos a **PAUL CORNELIO VICUNA SERRANO**, de acordo com o Regimento Geral da Universidade Federal do Rio Grande do Sul, o presente Certificado de Conclusão do Curso de Pós-Graduação *Lato Sensu*: Especialização em

TRATAMENTO DA DOR E MEDICINA PALIATIVA

promovido pelo Departamento de Cirurgia da Faculdade de Medicina, no período de 7 de março de 2019 a 6 de setembro de 2020, em Porto Alegre (RS), num total de 975 (novecentos e setenta e cinco) horas.

Porto Alegre, 17 de novembro de 2021.

Ione Borcelli Gonçalves
Vice-Pró-Reitora de Pós-Graduação

Lucia Maria Kliemann
Diretora da Unidade

Titulado

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The McGill Quality of Life Questionnaire-Revised (MQOL-R). Psychometric properties and validation of a Brazilian version on palliative care patients: a cross-sectional study

Paul Vicuña Serrano, Gerardo Beltran Serrano, Iraci L. S. Torres, Roberta Rossi Graudner & Wolnei Caumo

Health and Quality of Life Outcomes **18**, Article number: 368 (2020) | Cite this article

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Observational Study > Sci Rep. 2021 Nov 22;11(1):22716. doi: 10.1038/s41598-021-01982-0.

Spectral Power Density analysis of the resting-state as a marker of the central effects of opioid use in fibromyalgia

Maxciel Zortea [1], Gerardo Beltran [1 2 3 4], Rael Lopes Alves [1 2], Paul Vicuña [1 2], Iraci L S Torres [2 5 6 7], Felipe Fregni [8 9 10 11], Wolnei Caumo [12 13 14 15]

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PMID: 34811404 PMCID: PMC8608932 DOI: 10.1038/s41598-021-01982-0

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Published: November 30, 2021 • https://doi.org/10.1371/journal.pone.0259397

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Wolnei Caumo, Rael Lopes Alves, Paul Vicuña, Camila Fernanda da Silveira Alves, Leticia Ramalho, Paulo R S Sanches, Danton P Silva, Iraci Lucena da Silva Torres, Felipe Fregni

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Hyper-connectivity between the left motor cortex and prefrontal cortex is associated with the severity of dysfunction of the descending pain modulatory system in fibromyalgia

Álvaro de Oliveira Franco, Camila Fernanda da Silveira Alves, Paul Vicuña, Janete Bandeira, Maria Adelia de Aratanha, Iraci L. S. Torres, Felipe Fregni, Wolnei Caumo

Published: May 27, 2022 • https://doi.org/10.1371/journal.pone.0247629

40ª SEMANA CIENTÍFICA DO HOSPITAL DE CLÍNICAS DE PORTO ALEGRE

3301
ASSOCIAÇÃO ENTRE O USO CRÔNICO DE OPIOIDES, A INCAPACIDADE FUNCIONAL DEVIDO À DOR E O PROCESSAMENTO DISFUNCIONAL DA VIA MODULATÓRIA DESCENDENTE DA DOR NA FIBROMIALGIA.
RAEL LOPES ALVES; SAMUEL LOPES SOUZA; PAUL VICUÑA; PAULO ROBERTO SANCHES; DANTON PEREIRA; IRACI LUCENA DA S. TORRES ; FELIPE FREGNI; WOLNEI CAUMO
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Paul Vicuña Serrano

pela participação no curso de capacitação **Multiplicando o Conhecimento para Salvar Vidas: Programa de Capacitação para Equipes Multidisciplinares em Atenção Primária e Terciária**, promovido pelo **Instituto do Câncer Infantil** em parceria com o **PRONON** (Programa Nacional de Apoio à Atenção Oncológica), sobre o câncer infantojuvenil, tendo como objetivo Capacitar as equipes multidisciplinares dos centros oncológicos e das UBS de Porto Alegre, realizado no período de abril a julho de 2022, em formato presencial e online com carga horária total de 45 horas.

Dr. Algemir Lunardi Brunetto
Médico Oncologista Pediatra
Fundador e Superintendente ICI

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ORIGINAL RESEARCH article

Front. Public Health, 14 October 2022
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https://doi.org/10.3389/fpubh.2022.1009838

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Psychometric properties of the Chinese version of the sugar-sweetened beverages media literacy scale for undergraduates

Chen Long[1,2] and Myeong Sook Yoon[2*]

[1] Health Services Management Department, Guizhou Medical University, Guiyang, China
[2] Department of Social Welfare, Jeonbuk National University, Jeonju, South Korea

Specific domains of the Sugar-Sweetened Media Literacy Scale (SSM-ML) have been shown to significantly assess sugar-sweetened beverage (SSB) calorie intake in the US population. This study aimed to describe the psychometric properties of the revised Chinese version of the SSB-ML (C-SSB-ML) and evaluate its validity and reliability. Results from 975 undergraduates at two of the largest universities in a province in southwest China showed that Cronbach's alphas for the overall scale, the three dimensions, and two-halves analysis were satisfactory (0.71–0.92). The criterion-related validity of the C-SSB-ML was positively associated with the e Health literacy scale (eHEALS). Confirmatory factor analysis showed that the three-factor model of the C-SSB-ML had adequate fit indices χ^2 (153) = 4349.93, $p < 0.001$; Comparative fit index (CFI), Tucker-Lewis index (TLI), Incremental fit index (IFI) >0.90; Standardized Root Mean Square Residual (SRMR) <0.07; and Root Mean Square Error of Approximation (RMSEA) <0.08. Our findings provide evidence for a valid and reliable tool that can be used to assess sugar-sweetened media literacy in Chinese undergraduates and will help organizations leverage media literacy in strategy formulation to ensure SSB intake is controlled as much as possible through effective efforts on all fronts.

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Profª. Nadine Oliveira Clausell
Diretora-Presidente do Hospital de Clínicas

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