UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

IMPACTO DA ESTIMULAÇÃO TRANSCRANIANA DE CORRENTE CONTÍNUA DOMICILIAR NO COMPORTAMENTO ALIMENTAR DE MULHERES COM FIBROMIALGIA: UM ENSAIO CLÍNICO RANDOMIZADO FATORIAL

MANOELA NEVES DA JORNADA

Porto Alegre

2024

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Orientador: Prof. Dr. Wolnei Caumo
Coorientara: Profª. Drª Luciana da Conceição Antunes
Tese apresentada como requisito parcial para obtenção de título de Doutor em Medicina: Ciências Médicas, da Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Medicina: Ciências Médicas.

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"Dor, prazer e morte não são mais do
que um processo para a existência.
A luta revolucionária neste processo
é um portal aberto à inteligência."

Frida Kahlo

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RESUMO

A fibromialgia (FM) é uma condição de dor crônica primária, definida por dor musculoesquelética generalizada, distúrbios do sono, disfunções cognitivas e outros problemas autonômicos. Além disso, está associada a sofrimento psicológico, incluindo catastrofismo e sintomas depressivos, que podem agravar o prognóstico e a incapacidade. Atualmente, observa-se uma alta prevalência de excesso de peso em pacientes com fibromialgia, cerca de 70%, impactando negativamente no curso e prognóstico da doença, eleva os custos de saúde e compromete a qualidade de vida desses pacientes. Existem evidências que sugerem possíveis vias fisiopatológicas compartilhadas entre a FM e a obesidade, incluindo aspectos relacionados ao comportamento alimentar. Sabe-se que a neurotransmissão dopaminérgica está alterada em ambas as condições e, alguns polimorfismos dopaminérgicos podem influenciar a disponibilidade ou a funcionalidade dos produtos gênicos relacionados. Entre as opções não farmacológicas para o manejo da dor e do comportamento alimentar disfuncional, a estimulação cerebral não invasiva, como a estimulação transcraniana por corrente contínua (ETCC), desempenha um papel importante. Esta técnica aplicada em diferentes sítios de estimulação, como o córtex pré-frontal dorsolateral (DLPFC) e o córtex motor primário (M1) não apenas demonstrou eficácia na redução dos sintomas depressivos, mas também no controle dos sintomas da fibromialgia. Isso inclui a diminuição dos níveis de dor, melhoria da função cognitiva e aumento da capacidade funcional para atividades diárias. Além disso, estudos de pequena escala sugerem seu potencial efeito em aumentar a resistência a alimentos hiperpalatáveis, contribuintes para o excesso de peso. O polimorfismo Taq1A alelo A1 (rs1800497) no gene do receptor D2 da dopamina pode afetar os domínios do comportamento alimentar e hipotetizamos que possa desempenhar um papel na resposta individual à ETCC, devido ao seu papel no sistema dopaminérgico.

Portanto, este estudo visa investigar como a ETCC aplicada no córtex pré-frontal dorsolateral (DLPFC) e no córtex motor primário (M1) afeta aspectos homeostáticos e hedonistas do comportamento alimentar em mulheres com FM, considerando a influência desse polimorfismo. **Métodos:** O *estudo 1*, exploratório, incluiu 106 mulheres com diagnóstico de fibromialgia (30 a 65 anos), divididas em dois grupos

com base na presença do alelo A1 no polimorfismo Taq1A (rs1800497): A1+ (n = 42) e A1- (n = 64). O *food craving* foi avaliado através do State and Trait Food-Cravings Questionnaires (FCQ-estado e FCQ-traço), os domínios do comportamento alimentar por meio do Three Factor Eating Questionnaire (TFEQ-R21), a psicopatologia alimentar através do Eating disorder Examination (EDE-Q) e a percepção de saciedade foi avaliada em uma escala de 0 a 10. Também se avaliou medidas antropométricas (peso e circunferência abdominal), a presença do polimorfismo TaQ1A e níveis séricos de BDNF. O *estudo 2* incluiu 102 pacientes com fibromialgia com idades entre 30 e 65 anos, distribuídas randomicamente em um dos quatro grupos de ETCC usando uma proporção de 2:1:2:1. Os grupos incluíram e-DLPFC (a-ETCC, n=34) e (s-ETCC, n=17), ou ETCC no M1 (a-ETCC, n=34) ou (s-ETCC, n=17). As pacientes autoadministraram 20 sessões de ETCC, com 2mA por 20 minutos 5x/semana, sob supervisão remota após treinamento presencial. Os domínios do comportamento alimentar foram avaliados por meio do Three Factor Eating Questionnaire (TFEQ-R21) e o *food craving* através do State and Trait Food-Cravings Questionnaires (FCQ-S e FCQ-T) e de forma secundária avaliamos medidas antropométricas como peso e circunferência abdominal. **Resultados:** *Os* resultados do *estudo* 1 mostraram que os indivíduos portadores do alelo A1 (A1+) no polimorfismo Taq1A (rs1800497) apresentaram maior gravidade nos scores de *food craving* associados aos sintomas da fibromialgia, como sintomas depressivos, sensibilização central e incapacidade relacionada à dor, destacando a interação entre o *craving*, a alimentação disfuncional e a gravidade dos sintomas associados à FM. O estudo forneceu uma estrutura que integra sintomas da FM, neuroplasticidade e sinalização dopaminérgica para compreender a alta prevalência de excesso de peso nessa população. Os resultados do *estudo 2* comprovam a eficácia da ETCC domiciliar autoaplicada sobre o DLPFC esquerdo ou M1 na melhoria de vários domínios do comportamento alimentar, incluindo restrição cognitiva, descontrole alimentar e alimentação emocional. Além disso, considerando a influência dos sintomas da FM, apenas o grupo que recebeu estimulação em M1 apresentou melhora nos padrões de *Food Craving* após a intervenção, sugerindo que a eficácia da ETCC na redução do *Food Craving* está ligada à gravidade dos sintomas da fibromialgia.

Os achados dos estudos que fazem parte da presente tese abrem caminho para ensaios clínicos maiores que explorem os efeitos da ETCC domiciliar em diferentes sítios de estimulação e/ou em combinação com outras abordagens terapêuticas, incluindo terapia

de aconselhamento nutricional, terapia cognitivo-comportamental, programas de exercícios físicos e tratamentos farmacológicos no futuro. O *estudo 2* destaca o potencial terapêutico das intervenções destinadas a reequilibrar o sistema motivacional da dopamina e a melhora da sintomatologia associada à FM, através da indução de neuroplasticidade bem-adaptativa promovida pela ETCC domiciliar, visando tratar o ganho de peso e a obesidade comórbida à fibromialgia. Ainda, padronizamos o protocolo para o uso do equipamento de ETCC domiciliar (*estudo 3)*, estabelecendo diretrizes claras para segurança, educação do usuário, padronização e controle de qualidade. O protocolo inclui detalhes sobre as características do dispositivo, posições dos eletrodos, protocolos de estimulação, treinamento do usuário; e abordagens para monitorar o cumprimento do protocolo. Acreditamos que um protocolo estruturado de ETCC domiciliar pode contribuir significativamente para o avanço das práticas de neuromodulação.

Palavras-chave: Fibromialgia, *Food Craving*, DRD2 Taq1A, Estimulação Transcraniana por Corrente Contínua.

ABSTRACT

Fibromyalgia (FM) is a chronic pain condition defined by widespread musculoskeletal pain, sleep disturbances, cognitive dysfunction, and other autonomic problems. It is associated with psychological distress, including catastrophizing and depressive symptoms, which can worsen prognosis and disability. Currently, the prevalence of overweight in patients with FM is approximately 70%, which negatively impacts the course and prognosis of the disease, increases healthcare costs, and compromises the quality of life of these patients. Evidence suggests possible shared pathophysiological pathways between FM and obesity, including aspects related to eating behavior. Dopaminergic neurotransmission is altered in both conditions, and some dopaminergic polymorphisms may influence the availability or functionality of related gene products. Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), are key non-pharmacological options for managing pain and disordered eating behavior. tDCS can be applied to different stimulation sites, such as the dorsolateral prefrontal cortex (DLPFC) and the primary motor cortex (M1), and has demonstrated efficacy in reducing depressive symptoms and controlling the symptoms of fibromyalgia. Specifically, its effects include decreased pain levels, improved cognitive function, and increased functional capacity for daily activities. Furthermore, small-scale studies have suggested that tDCS can increase resistance to hyperpalatable foods, which contribute to excess weight. The Taq1A allele A1 polymorphism (rs1800497) in the dopamine D2 receptor gene may affect domains of eating behavior, and we hypothesized that it plays a role in the individual response to tDCS because of its role in the dopaminergic system.

Therefore, this study aimed to investigate how tDCS applied to the DLPFC and M1 impacts homeostatic and hedonic aspects of eating behavior in women with FM, considering the influence of this polymorphism. **Methods**: *Study 1* was an exploratory study that included 106 women (30 to 65 years old) diagnosed with fibromyalgia. The participants were divided into two groups according to the presence of the A1 allele in the Taq1A polymorphism (rs1800497): A1+ (n = 42) and A1− (n = 64). Food craving was assessed with the State and Trait Food Cravings Questionnaires (FCQ-state and FCQ-trait), the domains of eating behavior were assessed with the Three Factor Eating Questionnaire (TFEQ-R21), eating psychopathology was assessed with the Eating

Disorder Examination (EDE-Q), and perception of satiety was evaluated on a scale from 0 to 10. Anthropometric measurements (weight and waist circumference), the presence of the TaQ1A polymorphism, and serum brain-derived neurotrophic factor (BDNF) levels were also evaluated. *Study 2* included 102 fibromyalgia patients aged 30 to 65 years who were randomly assigned to one of four tDCS groups in a 2:1:2:1 ratio. The groups consisted of e-DLPFC (a-tDCS, n = 34 and s-tDCS, n = 17) and tDCS applied to M1 (a-tDCS, n = 34 or s-tDCS, n = 17). The patients self-administered 20 sessions of tDCS at 2 mA for 20 minutes 5 times per week under remote supervision after in-person training. The eating behavior domains were assessed with the TFEQ-R21, and food craving was assessed with the FCQ-S and FCQ-T; in addition we evaluate anthropometric measurements, such as weight and waist circumference. **Results:** The results of *Study 1* showed that individuals carrying the A1 allele (A1+) in the Taq1A polymorphism (rs1800497) presented greater severity in food craving scores associated with fibromyalgia symptoms, such as depressive symptoms, central sensitization, and pain-related disability, highlighting the interaction between craving, disordered eating, and the severity of symptoms associated with FM. The study provides a framework that integrates FM symptoms, neuroplasticity, and dopaminergic signaling to elucidate the high prevalence of overweight in this population. The results of *Study 2* indicate the effectiveness of self-applied home tDCS on the left DLPFC or M1 in improving several domains of eating behavior, including cognitive restriction, uncontrolled eating and emotional eating. Furthermore, considering the influence of FM symptoms, only the group that received stimulation in M1 showed an improvement in Food Craving patterns after the intervention, suggesting that the effectiveness of tDCS in reducing Food Craving is linked to the severity of fibromyalgia symptoms.

The findings of these studies pave the way for larger clinical trials that explore the effects of home-based tDCS at different stimulation sites and/or in combination with other therapeutic approaches, including nutritional counseling therapy, cognitive behavioral therapy, physical exercise programs, and pharmacological treatments, in the future. *Study 2* highlights the therapeutic potential of interventions aimed at rebalancing the dopamine motivational system and improving symptoms associated with FM through the induction of neuroplasticity promoted by home tDCS to treat weight gain and obesity comorbid with fibromyalgia. Furthermore, we standardized the protocol for the use of home tDCS equipment (*study 3*), establishing clear guidelines for safety, user education,

standardization and quality control. The protocol includes details on device characteristics, electrode positions, stimulation protocols, user training; and approaches to monitoring protocol compliance. We believe that a structured home tDCS protocol can significantly contribute to the advancement of neuromodulation practices.

Keywords: Fibromyalgia, food craving, DRD2 Taq1A, transcranial direct current stimulation.

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Table 5 - Factorial Generalized linear model: Treatment Effects (M-HB-a-tDCS or s-tDCS) by Stimulation Area (M1 or DLPFC) on the cognitive restraints (CR), emotional eating (EE), food craving state, the impact of fibromyalgia symptoms on quality of life and disability, waist circumference, and BMI (n = 102).

Table 6 - Side effects presented as percentage (%), and the incidence or severity of side effects classified as mild, moderate, and severe (n=102)

LISTA DE ABREVIATURAS E SIGLAS

ACR	American College of Rheumatology
AC	Adenilato Ciclase
ACC	Córtex Cingulado Anterior
AMY	Amígdala
AMPAr	Receptor Permeável ao Cálcio
AMPc	Adenosina Monofosfato Cíclico
BDNF	Fator Neurotrófico Derivado do Cérebro
Ca^{2+}	Cálcio
COMT	Catecol-O-Metiltransferase
CID-11	International Classification of Diseases-11
DA	Dopamina
DCNT	Doenças Crônicas Não Transmissíveis
DHSC	Corno Dorsal da Medula Espinhal
DLPFC	Córtex Pré-Frontal Dorsolateral
DRD2	Receptor D2 da Dopamina
DS	Estriado Dorsal
ECT	Eletroconvulsoterapia
EMT	Estimulação Magnética Transcraniana
ETCC	Estimulação Transcraniana por Corrente Contínua
FM	Fibromialgia
GABA	Ácido Gama-Aminobutírico
GCs	Glicocorticóides
GRD	Gânglios da Raiz Dorsal
HPA	Hipotálamo-Hipófise-Adrenal
IASP	Associação Internacional do Estudo da Dor

LTD	Depressão a Longo Prazo
LTD	Potenciação a Longo Prazo
IMC	Índice De Massa Corporal
M1	Córtex Motor Primário
MAOA	Monoamina Oxidase A
NAc	Núcleo Accumbens
NIBS	Estimulação Cerebral Não Invasiva
NMDA	Receptor N-Metil-D-Aspartato
NPY	Neuropeptídeo Y
NRM	Núcleo da Rafe Magnus
OFC	Córtex Orbitofrontal
OMS	Organização Mundial de Saúde
PAG	Substância Cinzenta Periaquedutal
PET	Tomografia por Emissão de Pósitrons
PKA	Proteína Quinase A
PFC	Córtex Pré-Frontal
PVN	Núcleo Paraventricular do Hipotálamo
SIG	Giro Cingulado
SNA	Sistema Nervoso Autônomo
SNC	Sistema Nervoso Central
TENS	Estimulação Nervosa Elétrica Transcutânea
TLR4	Toll Like Receptor
TNFα	Fator de Necrose Tumoral Alfa
TCA	Transtorno de Compulsão Alimentar
VTA	Área Tegmentar Ventral
VS	Estriado Ventral

SUMÁRIO

APRESENTAÇÃO

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1. INTRODUÇÃO

O excesso de peso tem um impacto negativo na progressão e no prognóstico de pacientes com dor crônica, acarretando custos adicionais para o sistema de saúde e comprometendo a qualidade de vida (Neumann, Lerner e Glazer, 2008). Pesquisas recentes exploram a ligação entre fibromialgia e obesidade, identificando possíveis vias fisiopatológicas compartilhadas e influências no comportamento alimentar (ELKFURY *et al.*, 2021; OKIFUJI; HARE, 2015; SOMINSKY; SPENCER, 2014; WRIGHT *et al.*, 2010; YUNUS; ARSLAN; ALDAG, 2002). O comportamento alimentar é controlado por mecanismos homeostáticos e hedônicos. O primeiro é regulado pelo hipotálamo, monitorando o metabolismo, a fome e a saciedade, enquanto o segundo, governado pelo sistema de recompensa, envolve estruturas cerebrais que influenciam a motivação relacionada à recompensa. A via mesocorticolímbica, por meio da regulação dopaminérgica, desempenha um papel motivacional no comportamento alimentar. A dopamina é essencial para os efeitos gratificantes da recompensa (VOLKOW; WANG; BALER, 2011), uma vez que as vias dopaminérgicas mesolímbicas são cruciais nos processos de recompensa e reforço (VOLKOW; WISE; BALER, 2017).

Recentemente foi demonstrado que alimentos hiperpalatáveis desencadeiam esses mecanismos de forma mais intensa (EDWIN THANARAJAH *et al.*, 2023) comparado a outros alimentos, e que o intenso desejo por esses alimentos, chamado "*food craving*", está associado à obesidade (YEH *et al.*, 2016). Estudos anteriores propuseram não apenas o envolvimento da ansiedade e da catastrofização ao mediar a relação entre dor crônica e alimentação emocional (EMAMI *et al.*, 2016; JANKE *et al.*, 2016), mas também a utilização, com maior frequência, deste domínio do comportamento alimentar disfuncional como estratégia mal-adaptativa de enfrentamento à dor e ao estresse crônico (GROESZ *et al.*, 2012; JANKE *et al.*, 2016; O'LOUGHLIN; NEWTON-JOHN, 2019). Também se observam alterações na neurotransmissão

dopaminérgica na fibromialgia, incluindo possíveis aumentos na sensibilidade ou densidade dos receptores D2 de dopamina (DRD2) (MALT *et al.*, 2003). Os polimorfismos genéticos, como o Taq1A (rs1800497) no gene do DRD2, estão associados a maior ingestão calórica e podem influenciar o reforço alimentar (EPSTEIN *et al.*, 2004). Ainda, indivíduos portadores do alelo A1 desta variante genética possuem menor disponibilidade de DRD2 e podem apresentar maior consumo de alimentos hiperpalatáveis (ARIZA *et al.*, 2012; COLLINS; FRANK, 2014; STICE *et al.*, 2008).

Em alternativa a anormalidades na sinalização dopaminérgica, técnicas neuromodulatórias, como a estimulação transcraniana por corrente contínua (ETCC), têm se destacado no tratamento do comportamento alimentar disfuncional. A ETCC pode reduzir o desejo por alimentos hiperpalatáveis, diminuir a ingestão calórica e aumentar a saciedade imediatamente após a atividade física em pessoas com sobrepeso (FREGNI; PASCUAL-LEONE, 2007; GOLDMAN *et al.*, 2011). Em indivíduos com fibromialgia, a ETCC sob o córtex motor primário (M1) possui eficácia clínica no tratamento da dor (Pacheco-Barrios, 2020; Caumo, 2023), enquanto sua aplicação no córtex pré-frontal dorsolateral (DLPFC) esquerdo está associada a melhora dos processos cognitivos (BRUNONI *et al.*, 2013; SERRANO *et al.*, 2022), sintomas depressivos, capacidade funcional e na diminuição do uso de medicação analgésica (BRIETZKE *et al.*, 2020; MORENO *et al.*, 2015; NEJATI; MAJIDINEZHAD; NITSCHE, 2022; TEIXEIRA *et al.*, 2023).

Uma vez que protocolos de ETCC mais longos possuem uma eficácia clínica maior, para transpassar uma barreira que é o fato de os pacientes precisarem ir consecutivamente aos centros especializados, uma técnica a ser considerada é a ETCC domiciliar, que possui baixo custo, fácil aplicação e um grande potencial terapêutico. Seu uso, por períodos prolongados, encontra sustentação teórica e uma série de vantagens, como prover o fornecimento do número de sessões necessárias para uma eficácia clínica, reduzir o tempo e o custo com transporte,

facilitar o acesso aos pacientes com restrição de mobilidade e possibilitar autonomia para realização das sessões conforme a rotina.

As alterações mal-adaptativas no sistema de recompensa, envolvendo disfunções dopaminérgicas e desregulação emocional, parecem ter um papel bidirecional na psicopatologia da fibromialgia e da obesidade. Mudanças no comportamento alimentar ocorrem em ambas as condições e incluem características fisiopatológicas comuns, como uma maior suscetibilidade ao comportamento alimentar disfuncional e uma alterada percepção da dor, sintomas depressivos e de ansiedade.

Considerando o exposto, mais pesquisas que possibilitem o desenvolvimento de intervenções terapêuticas para promover o equilíbrio do sistema motivacional dopaminérgico e/ou a melhora da sintomatologia associada à FM, se fazem necessárias para possibilitar uma melhora global no comportamento alimentar desses pacientes, prevenindo ou tratando o ganho de peso e a obesidade. Com esta perspectiva, este estudo visa esclarecer como os polimorfismos genéticos afetam a resposta da ETCC no comportamento alimentar e nos sintomas da fibromialgia, oferecendo uma visão mais ampla das relações entre genética, neuromodulação e saúde em pacientes com fibromialgia. Dessa forma, esta tese teve como objetivo compreender o processo fisiopatológico, inteirando aspectos genéticos relacionados ao comer disfuncional, estado de neuroplasticidade e o efeito da ETCC domiciliar aplicada ao M1 e DLPFC esquerdo no comportamento alimentar e nos sintomas da FM.

A tese está estruturada conforme as normas do Programa de Pós-Graduação em Medicina: Ciências Médicas da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul e deu origem a três artigos. O estudo exploratório foi sunbetido no periódico *Nutritional Neuroscience*, o ensaio clinico foi publicado no periódico *Brain Stimulation* e o protocolo para o uso do equipamento de ETCC domiciliar foi submetido no periódico *MethodsX*.

2. REVISÃO SISTEMATIZADA DA LITERATURA

2.1 Estratégias de busca bibliográfica

Na revisão da literatura, para estruturar o delineamento deste projeto, buscou-se suporte em artigos de revisão, estudos experimentais, observacionais e ensaios clínicos randomizados. Para localizá-los, foi adotada a estratégia de busca nas bases de dados PubMed, SciELO e EMBASE. Os descritores chave utilizados para a busca foram: 1*) Fibromyalgia (Fibromialgia), 2) Eating Behavior (Comportamento alimentar) 3) Estimulação Transcraniana por Corrente Contínua (Transcranial Direct Current Stimulation) 4) Polimorfismo Taq1A* (*polymorphism Taq1A), bem* como as suas combinações.

A tabela 1 sumariza a estratégia de busca das referências bibliográficas sobre as bases que fundamentam os objetivos do estudo:

PALAVRAS-CHAVE

Tabela 1. Estratégia de busca de referências bibliográficas.

Descritor	Pubmed	Embase	SciELO
(*Fibromyalgia**)* **AND (***Transcranial Direct Current Stimulation)*	**89**	**43**	**2**
(*Fibromyalgia**)* **AND (***Eating Behavior**)*	**36**	**28**	**1**
(*Fibromyalgia**)* **AND** (*Transcranial Direct Current Stimulation)* **AND (***polymorphism Taq1A**)*	**0**	**0**	**0**

Da busca pelos termos selecionados e suas combinações selecionou-se 224 artigos, incluindo metanálises, revisões e ensaios clínicos, os quais foram utilizados para compilar a revisão da literatura desta tese.

2.2 *Fibromialgia (FM)*

2.2.1 Aspectos epidemiológicos

A dor crônica faz parte das doenças crônicas não transmissíveis (DCNT), definidas pela Organização Mundial de Saúde (OMS) como enfermidades com longa latência, progressão lenta, etiologia parcialmente compreendida, lesões irreversíveis e complicações que podem levar a diferentes graus de incapacidade ou óbito (NEUMANN; LERNER; GLAZER, 2008). No Brasil, as DCNT têm um impacto significativo devido ao rápido crescimento, atribuído à transição demográfica, ao aumento da longevidade e ao envelhecimento da população. Nesse contexto, este estudo está alinhado com os objetivos do Ministério da Saúde, que lançou o "Plano de Ações Estratégicas para o Enfrentamento das DCNT no período de 2011–2022", visando combater e reduzir as DCNT.

A fibromialgia (FM) é uma condição que afeta mais de 5 milhões de pessoas anualmente nos EUA (LAWRENCE *et al.*, 2008). A prevalência estimada da fibromialgia varia de 1,7% a 5,4%, conforme os critérios da Sociedade Americana de Reumatologia, que foram sendo modificados ao longo do tempo. Os critérios vigentes foram revisados em 2016 (DI CESARE *et al.*, 2016). Isso resulta em custos significativos, estimados em mais de 29 bilhões de dólares anualmente, devido ao tratamento médico e à aposentadoria precoce por incapacidade (MARKKULA; KALSO; KAPRIO, 2016; WALITT *et al.*, 2015). Na população brasileira, a prevalência de FM varia em torno de 2%, com proporção entre os gêneros de 1 homem para cada 5,5 mulheres (SENNA, 2013; SOUZA, 2018).

Além do ônus da dor e da limitação funcional, a FM também foi associada a um maior risco de acidente vascular cerebral, de acordo com um estudo de coorte realizado em Taiwan, que incluiu 47.279 pacientes com FM (SU *et al.*, 2015). Para os pacientes fibromiálgicos sem

outras comorbidades, o risco de acidente vascular cerebral ajustado foi de 1,44 em comparação aos controles (intervalo de confiança de 95% de 1,35-1,53). Outra comorbidade aliada à fibromialgia, que destaca-se em estudos da última década, tem sido a obesidade (NEUMANN; LERNER; GLAZER, 2008; OKIFUJI *et al.*, 2010; SENNA; AHMAD; FATHI, 2013; WRIGHT *et al.*, 2010).

Com base nos dados de uma metanálise recente, a prevalência global de obesidade na FM situa-se em torno de 35,7%, sendo que números mais elevados foram reportados nos Estados Unidos (D'ONGHIA *et al.*, 2021). Nos Estados Unidos, BENNETT *et al*., (2007), encontraram uma elevada prevalência de sobrepeso (70%) e obesidade (43%) em seu estudo com 2.569 indivíduos diagnosticados com FM e OKIFUJI *et al*., (2010) observaram uma prevalência de 30% de sobrepeso e uma taxa ainda mais alta de obesidade (47%) em uma amostra de 215 pacientes com FM. Esses achados foram corroborados por NEUMANN *et al*., (2008) que identificaram uma prevalência de 45% de sobrepeso e 28% de obesidade em uma amostra de 100 mulheres com diagnóstico de FM em Israel.

No contexto das mulheres brasileiras com FM, a prevalência de obesidade é semelhante, situando-se em cerca de 41% (DE ARAÚJO *et al.,* 2015). Vale ressaltar que esses índices de sobrepeso e obesidade na FM ultrapassam as taxas encontradas na população mundial, que estima a obesidade em 14,9% entre mulheres (DI CESARE *et al.*, 2016). Adicionalmente, é importante considerar que o tempo de doença e a idade contribuem para uma maior prevalência de obesidade comórbida (SENNA *et al.,* 2013).

De fato, a dor crônica é mais prevalente em indivíduos com obesidade, e a obesidade é altamente prevalente em diferentes tipos de dor crônica, incluindo a FM (ALLEN *et al*., 2016; WILSON *et al*., 2010). A literatura sugere que essas duas condições são comorbidades significativas, impactando-se negativamente uma na outra (OKIFUJI *et al*., 2015). Um estudo de base populacional (WRIGHT *et al.*, 2010) relatou que a obesidade foi associada a vários

diagnósticos de dor, incluindo dor lombar, dores de cabeça e fibromialgia. A dor crônica é uma das principais razões apontadas pelos pacientes obesos como contribuinte para o ganho de peso (FRANSEN *et al.*, 2002).

2.2.2 Aspectos conceituais e critérios diagnósticos

A fibromialgia (FM) é uma condição de dor crônica primária que impõe uma carga substancial de sofrimento ao paciente, sua família e ao sistema de saúde. Caracteriza-se por dor musculoesquelética generalizada, fadiga, alterações de sono, disfunções cognitivas, sintomas depressivos e outros problemas autonômicos, como síndrome do cólon irritável e tenesmo vesical (DURUTURK *et al.*, 2015). Além disso, está associada a sofrimento psicológico, incluindo catastrofismo e sintomas depressivos, que podem agravar o prognóstico e a incapacidade mais do que em outras condições de dor crônica (VERBUNT *et al.,* 2008). A FM é uma síndrome que envolve disfunções no sistema nervoso central e periférico (CLAUW, 2014).

Segundo a Associação para o Estudo da Dor (IASP), a FM pertence ao grupo das dores crônicas primárias, conforme sua inclusão no *International Classification of Diseases* (CID-11). Sua inclusão neste grupo deve-se ao fato de a dor acometer uma ou mais regiões anatômicas, estar associada com significativo estresse emocional, apresentar importante incapacidade funcional para atividades da vida diária e sociais, sem existir outra explicação. Na verdade, trata-se de uma síndrome de dor crônica difusa, cujo mecanismo fisiopatológico não está completamente esclarecido (TSENG *et al.*, 2016). Possivelmente, uma das razões pelas quais existe certa dificuldade para classificá-la num grupo específico, quando o agrupamento se baseia no mecanismo fisiopatológico. No entanto, os sinais e sintomas da dor na FM permitem

classificá-la como dor mista por envolver os sistemas neuro-imune-endócrinos e apresentar mecanismos centrais e periféricos.

Conforme os critérios da *American College of Rheumatology* (ACR), Sociedade Americana de Reumatologia, a FM é uma condição de dor crônica cujos sintomas correlatos são desproporcionais à evidência da lesão tecidual ou dano anatômico, mas não por isso menos relevante. E tais características reforçam a teoria de que se trata de uma condição cujo mecanismo envolve disfunção central, com um nível de complexidade que transcende uma patologia da musculatura esquelética (WOLFE *et al.*, 2016).

Os mecanismos pelos quais a dor crônica afeta o comportamento alimentar e o peso corporal ainda não estão completamente elucidados. Uma vez que a FM e a obesidade são frequentemente comórbidas e devido à relevância da FM para os indivíduos e a sociedade, avançar na compreensão de seus mecanismos fisiopatológicos compartilhados possui um importante significado clínico, a fim de desenvolver tratamentos mais eficazes.

2.2.3 Fisiopatologia da FM

Com base em estudos recentes, a fibromialgia (FM) está associada a disfunções nos sistemas modulares descendentes da dor e a uma redução na inibição intracortical, medida por meio da estimulação magnética transcraniana (EMT) (CAUMO *et al.*, 2016, 2017). Essa inibição intracortical parece ser mais prejudicada na FM em comparação com outras condições de dor crônica, como a osteoartrite (TARRAGÓ et al., 2016). Apesar de sinais de "neuropatia de pequenas fibras" terem sido observados na FM, a relação entre essas descobertas e a presença ou gravidade da dor é complexa, pois a nocicepção periférica pode modular o sistema nervoso central (SNC), sendo crucial na determinação da dor crônica (CLAUW, 2014).

A FM é caracterizada por uma ampla gama de sintomas multifacetados, que vão além da dor, incluindo fadiga, alterações no padrão de sono, problemas cognitivos e sintomas

depressivos (CAGNIE *et al.*, 2014). Isso sugere uma disfunção central (sensibilização central) como componente-chave da FM, associada à perda da capacidade da via inibitória descendente da dor (ABELES *et al.*, 2007).

O modelo fisiopatológico mais estabelecido na fibromialgia é o aumento do processamento de vias relacionadas à dor. Manifestações como reduzidos limiares de dor, hiperalgesia, alodinia e sensibilidade difusa, não apenas à dor, mas também a outros estímulos sensoriais, são consideradas indicadores clínicos do fenômeno de sensibilização central (KRAYCHETE; SAKATA, 2011; SCHMIDT-WILCKE; CLAUW, 2011; STAUD, 2002). Evidências de estudos exploratórios (CAUMO *et al.*, 2016) e clínicos (CAUMO *et al.*, 2023) sugerem que essas anormalidades no processamento sensorial ocorrem globalmente na FM, não se limitando especificamente à dor. Os principais mecanismos fisiopatológicos da FM, incluindo vias nociceptivas, sensibilização central e processos de plasticidade mal-adaptativa, estão representados na Figura 1.

Figura 1. *Vias nociceptivas, sensibilização central e principais processos de plasticidade mal-adaptativa.*

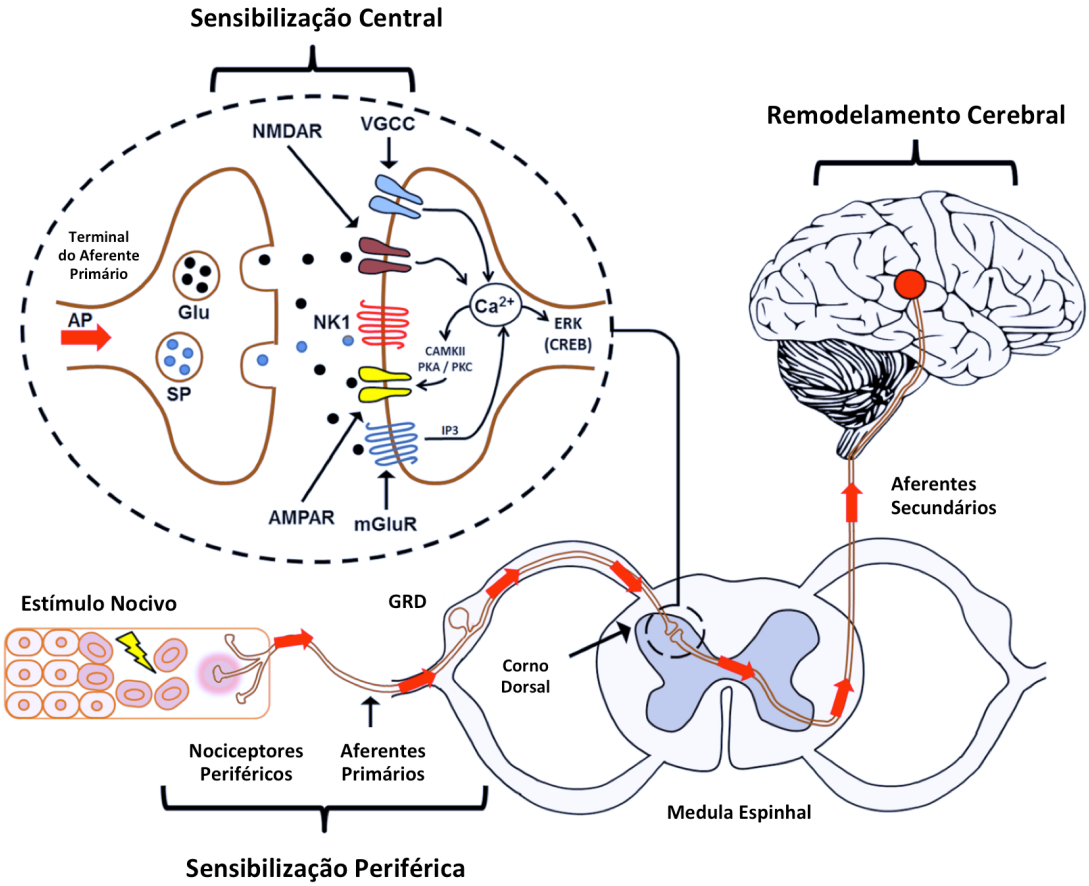

Figura 1. *A liberação constante de glutamato, substância P e peptídeo relacionado ao gene da calcitonina por nociceptores desloca o íon de magnésio do poro do receptor NMDA, permitindo o influxo de Ca^{2+} no neurônio. O receptor NMDA, com sua característica de manutenção do tempo de estímulo, prolonga o estímulo doloroso. As fibras C aferentes dos gânglios da raiz dorsal (GRD) e dos gânglios trigeminais fazem sinapse com neurônios do corno dorsal da medula e do tronco encefálico, resultando na "segunda dor" e promovendo a somação temporal lenta, intensificando a percepção da dor. Glutamato e substância P podem modular respostas pós-sinápticas, transmitindo sinais para locais supraespinhais (tálamo, córtex cingulado anterior, córtex insular e córtex somatossensorial) através das vias ascendentes. Neurônios de terceira ordem partem do tálamo para diversas regiões corticais e subcorticais, codificando aspectos da dor: i) sensório-discriminativos (córtex somatossensorial), ii) afetivo-motivacionais (córtex cingulado anterior, amígdala, córtex insular e sistema límbico), e iii) cognitivo-avaliativos (córtex pré-frontal). A atividade intensa e prolongada dessas vias, causada por estimulação nociva repetida ou sustentada, pode levar ao aumento da capacidade de resposta neuronal (LTP), resultando em plasticidade mal-adaptativa. AP, Potencial de ação, AMPAR, receptor de ácido 3-hidroxi-5-metil-4-isoxazol propiônico, GRD, gânglio da raiz dorsal, Glu, glutamato, mGluR, receptor metabotrópico de glutamato, NK1, receptor de neurocinina, NMDAR, receptor N-metil-D-aspartato, PKA/PKC proteína quinase A/C, SP, substância P, VGCC, canal de cálcio dependente de voltagem. Figura adaptada de Bazzari et al., 2022.*

Paralelamente às alterações corticais, ocorre uma diminuição na capacidade do SNC em estimular o sistema modulatório descendente da dor (SMDD). Por meio de neurotransmissores como GABA, opioides, serotonina, adenosina, noradrenalina e canabinoides, este sistema comunica o SNC com o sistema nervoso periférico (SNP), facilitando ou inibindo os sinais nociceptivos (CLAUW, 2014; HARTE *et al.*, 2016; ZANETTE *et al.*, 2014). Esses processos induzem um desequilíbrio entre os mecanismos pró-nocicepção e antinocicepção em pacientes com FM, resultando na diminuição da função das vias inibitórias da dor e hiperalgesia secundária. Isso leva a uma percepção dolorosa acima do esperado, e à manutenção da Síndrome de Sensibilização Central (SSC) (CAUMO *et al.*, 2016, 2017).

2.3 Estimulação Transcraniana de Corrente Contínua (ETCC) no tratamento da FM

Entre as opções não-farmacológicas para o tratamento da FM, incluindo seus sintomas e comorbidades, como dor, sintomas depressivos e ansiosos, destacam-se as técnicas neuromodulatórias, com ênfase na estimulação cerebral não invasiva (CAUMO *et al.*, 2023; FREGNI *et al.*, 2021; NITSCHE *et al.*, 2008; PACHECO-BARRIOS *et al.*, 2020), como a Estimulação Transcraniana por Corrente Contínua (ETCC) para uso domiciliar (BRIETZKE *et al.*, 2020; CAUMO *et al.*, 2023). Revisões sistemáticas e meta-análises atuais apresentam evidências da eficácia clínica da ETCC no tratamento desses pacientes (CAUMO *et al.*, 2022; LLOYD *et al.*, 2020; MOLERO-CHAMIZO *et al.*, 2023) ainda que com grande variabilidade no tamanho de efeito encontrado em diferentes ensaios clínicos (TEIXEIRA *et al.*, 2023).

2.3.1 Estimulação Transcraniana por Corrente Contínua — ETCC

A ETCC é uma técnica neuromodulatória segura, custo-efetiva e promissora para o tratamento de várias condições de dor crônica (WOODS *et al.*, 2016), incluindo a fibromialgia (PAN *et al.*, 2017), bem como para a redução do desejo e do consumo em indivíduos com dependência química, obesidade e *food craving* (SONG *et al.*, 2022). Trata-se de um método terapêutico que modula o potencial de membrana através da aplicação de correntes elétricas baixas (1-2 mA) diretamente no escalpo. Utilizam-se dois eletrodos, os quais afetam a excitabilidade cortical de regiões próximas à área da estimulação, podendo atingir redes neurais distantes que possuem conexão com estas (efeito default) (NITSCHE *et al.*, 2008).

2.3.2 Aspectos históricos

A descoberta dos efeitos biológicos da corrente contínua, através da sua eficácia na modulação do disparo neuronal espontâneo, deu início à história da eletrofisiologia. Na época do Império Romano (43–48 AC), Scribonius Largus observou que colocar um peixe-torpedo vivo, entregando uma forte corrente elétrica direta, sobre o couro cabeludo de um paciente com cefaleia provocava um estupor repentino e transitório com alívio da dor. Descobertas semelhantes também foram relatadas pelo médico grego Claudius Galen (131–401 AC) ao observar que o choque elétrico causado por um peixe torpedo aliviou a dor da gota. No entanto, seu estudo sistemático com métodos científicos modernos foi iniciado por Walsh (1773) e seguido pelo trabalho de Galvani (1791) que estabeleceu uma relação entre a contração elétrica do músculo da rã, correlacionando a eletricidade e a resposta muscular,

dando início à ciência da eletrofisiologia. Muitos outros pesquisadores nos últimos dois séculos fizeram uso extensivo da corrente galvânica para o tratamento de transtornos mentais, com resultados variáveis (PRIORI, 2003).

Os primeiros experimentos modernos sobre estimulação cerebral, realizados em cães por Fritz e Hitzig e em primatas por Ferrier, mostraram que a estimulação elétrica no córtex motor produzia movimentos no lado oposto do corpo. No cérebro humano, Roberts Bartholow (1874) estimulou o córtex no cérebro exposto de pacientes conscientes, o que produziu movimentos e sensações no lado oposto do corpo (ROTHWELL, 2018).

Na década de 1940, a eletroconvulsoterapia (ECT), mostrou-se eficaz no tratamento da depressão grave (KELLNER *et al.*, 2012). Outra técnica que se destacou neste mesmo século foi a estimulação nervosa elétrica transcutânea (TENS), para indução de analgesia (TEOLI; AN, 2023).

Em 1985, ao conectar uma bobina a uma fonte de corrente elétrica no escalpo subjacente ao córtex motor, Barker et al. destacou o importante papel da estimulação magnética transcraniana (EMT) em ativar axônios e fazer com que disparassem potenciais de ação. Os efeitos da EMT podem alterar o equilíbrio entre a atividade neural inibitória em relação à excitatória (DAYAN *et al.*, 2013; HUERTA; VOLPE, 2009; PERINI *et al.*, 2012). Uma década depois, a EMT do córtex motor mostrou-se eficaz para produzir analgesia (MIGITA *et al.*, 1995).

No início dos anos 2000, a estimulação transcraniana por corrente contínua (ETCC) foi introduzida como uma técnica de estimulação cerebral não invasiva (NIBS) aplicável em humanos, (NITSCHE; PAULUS, 2000; PRIORI, 2003) com efeitos clínicos obtidos por meio da modulação sublimiar dos potenciais de membrana neuronal, que altera a excitabilidade e a atividade cortical dependendo da direção do fluxo da corrente através dos neurônios-alvo (CAUMO *et al.*, 2023; MOFFA *et al.*, 2020; PURPURA; MCMURTRY, 1965). O acumulado

número de evidências quanto aos efeitos clínicos e segurança de uso nas últimas décadas fez a estimulação cerebral não invasiva se destacar como alternativa e/ou complemento a intervenções farmacológicas, as quais geralmente apresentam maiores efeitos colaterais, potencial aditivo e/ou de tolerância, bem como um maior custo.

2.3.3 Efeito da ETCC nos Processos Neurobiológicos

A ETCC excitatória (anódica) induz redução local do GABA (ácido gama aminobutírico), enquanto a estimulação inibitória (catódica) causa redução da atividade neuronal glutamatérgica com uma redução altamente correlacionada no GABA, presumivelmente devido à estreita relação bioquímica entre os dois neurotransmissores (NITSCHE *et al.*, 2008; STAGG *et al.*, 2009). A ETCC modula redes neurais corticais e subcorticais, as quais estão associados os efeitos clínicos mediados pela modulação da excitabilidade sublimiar do potencial de membrana neuronal, induzindo um efeito do tipo *top down*. Este efeito atribui-se a indução de neuroplasticidade uso-dependente, que se relaciona ao "aprendizado sináptico" e mudanças de longo prazo (LTP e LTD) das sinapses glutamatérgicas (NITSCHE *et al.*, 2003; NITSCHE; PAULUS, 2001). Esses fenômenos podem ser explicados pelo incremento da eficiência sináptica e, também, por efeitos diretos sobre a atividade neuronal espontânea (LANG *et al.*, 2005; NITSCHE *et al.*, 2008). No entanto, sabe-se que o efeito da ETCC depende do sítio a ser estimulado, do tipo de estímulo (anódico ou catódico) e que o efeito é aditivo à repetição dos cursos de estimulação. O efeito duradouro da ETCC deve-se ao aumento do *input* pré-sináptico e a *up-regulation* do tônus sináptico, mediado pelo receptor NMDA. Este efeito é dependente da síntese proteica, das modificações na concentração de AMPc intracelular e do influxo da corrente de cálcio intracelular, os principais mecanismos da ETCC são apresentados na Figura 2.

Figura 2. Principais mecanismos da ETCC

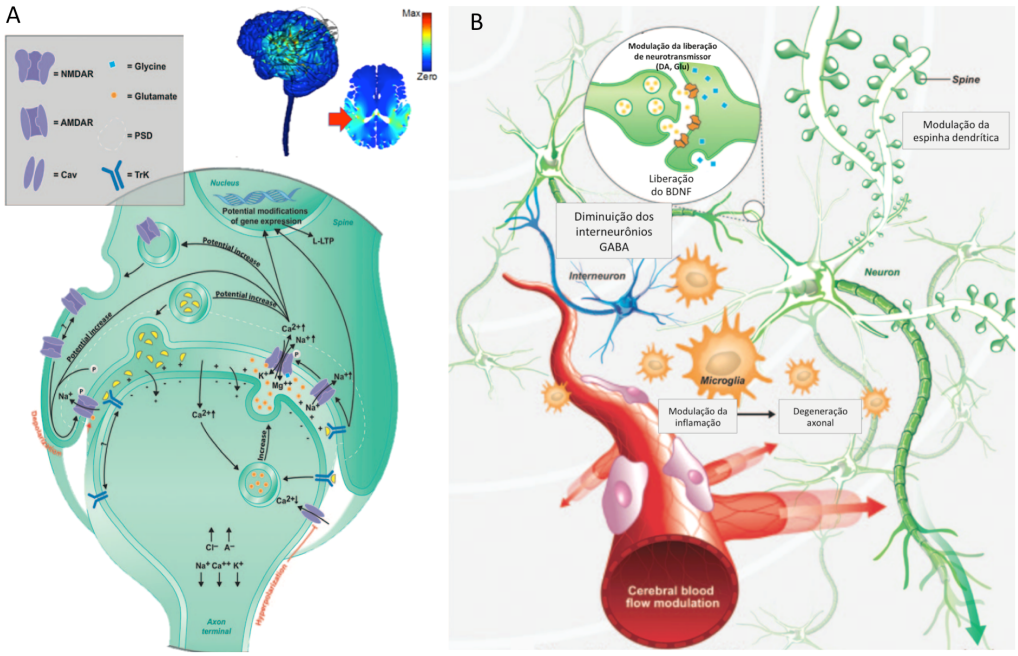

Figura 2. (A) *A ETCC anódica hiperpolariza a membrana, e há maior liberação do neurotransmissor, um efeito causado por um aumento no Ca^{2+} intracelular, enquanto uma diminuição do Ca^{2+} leva a menor liberação do neurotransmissor. A ativação da quinase do receptor de Tropomiosina (Trk) sugere um papel para BDNF na ETCC anódica, seu efeito aumenta ainda mais a probabilidade de acoplamento de vesículas sinápticas e a liberação de neurotransmissor. Em geral, com respostas de potencialização a longo prazo (LTP), existe uma regulação positiva da liberação de neurotransmissores que facilita a abertura de canais do tipo AMPA e indiretamente a de canais de NMDA. O oposto é verdadeiro para a depressão a longo prazo (LTD). O influxo de Ca^{2+} aumenta a fosforilação de AMPA e a sua incorporação à membrana. O aumento do Ca^{2+} aumenta ainda mais a liberação do fator neurotrófico para a fenda sináptica, enquanto na ausência do Ca^{2+}, a diminui. Uma vez ativado, o receptor de Trk pós-sináptico induz a LTP de fase tardia (L-LTP) e favorece a abertura de canais do NMDA, o que também promove L-LTP, enquanto ocorre o oposto na ETCC catódica, que promove a LTD. Tanto a L-LTP como a L-LTD dependem de modificações da expressão gênica.* ***(B)*** *A ETCC anódica está envolvida no remodelamento dendrítico, juntamente com um aumento na densidade dendrítica, um mecanismo sugerido para suas propriedades neuroprotetoras e neuro-reparadoras. Em modelos animais de dor crônica induzida por estresse, o fator de necrose tumoral-α (TNF-α) também foi down regulado pela ETCC anódica. Foi observado também, aumento da angiogênese e dos níveis de fator de crescimento endotelial vascular (VEGF) em tecidos periféricos. A ETCC afeta uma série de processos fisiológicos tanto no sistema nervoso central quanto ao nível periférico, os quais podem ser relevantes para os seus efeitos nos estados patológicos. AP, potencial de ação; BDNF, fator neurotrófico derivado do cérebro; DA, dopamina; Glu, glutamato. Figura adaptada de Pelletier and Cicchetti, 2015; Bikson, 2014.*

A ETCC não deflagra diretamente potenciais de ação, mas altera o ambiente da rede neuronal, diminuindo ou aumentando a suscetibilidade de disparo do neurônio, ou sua resposta diante de impulsos sinápticos aferentes (BRUNONI, *et al*., 2012; CREUTZFELDT *et al*.,

1962).

Conforme apresentado, a ETCC infere efeitos químicos e não químicos integrados: *i)* aumento de produção de proteínas, *ii)* aumento do nível intracelular de cálcio e *iii)* expressão gênica precoce durante e após a estimulação (ARDOLINO *et al.*, 2005; LIEBETANZ, 2002; NITSCHE *et al.*, 2003; STAGG *et al.*, 2009; STAGG; NITSCHE, 2011).

Os resultados mais robustos e com efeitos prolongados da ETCC, apontam para o número de sessões consecutivas (FREGNI *et al.*, 2021; NITSCHE *et al.*, 2008; SONG *et al.*, 2022). No entanto, há um limite, se extrapolado, pode ocorrer uma inversão (inibição) ou resultar na redução dos efeitos pós-estimulação, que são essenciais na indução da plasticidade (FREGNI *et al.*, 2021; NITSCHE *et al.*, 2008).

No entanto, é sempre um desafio manter a adesão quando uma pesquisa envolve sessões consecutivas, pois os pacientes que participam desses estudos geralmente apresentam dor, dificuldade de locomoção, sofrem de transtornos psiquiátricos, entre outras condições que dificultam o acesso aos grandes centros repetitivamente e em dias consecutivos. Uma metanálise atual evidencia que a maioria dos protocolos de ETCC contam com menos de 20 sessões consecutivas, administradas em hospitais e centros especializados (MOFFA *et al.*, 2020). Sendo o número de sessões consecutivas durante períodos prolongados o componente chave na resposta clínica da ETCC (FREGNI *et al.*, 2021; NITSCHE *et al.*, 2008; SONG *et al.*, 2022), para transpassar uma barreira, que até então limita o seu uso a longo prazo, sendo o fato de os pacientes precisarem ir aos centros, uma técnica a ser considerada é a ETCC domiciliar.

2.3.4 ETCC para uso Domiciliar

A ETCC domiciliar possui baixo custo, fácil aplicação e um grande potencial terapêutico. Seu uso por períodos prolongados encontra sustentação teórica (BRIETZKE *et al.*,

2020; CARVALHO *et al.*, 2018; CAUMO *et al.*, 2023) e uma série de vantagens, como prover o fornecimento do número de sessões necessárias para uma eficácia clínica, reduzir o tempo e o custo com transporte, facilitar o acesso aos pacientes com restrição de mobilidade, possibilitar autonomia para realização das sessões conforme a rotina, entre outras vantagens, como, por exemplo, o tratamento continuado durante a pandemia de COVID-19. Entretanto, pesquisas são necessárias para melhor entender sobre a eficácia e benefícios em relação à ETCC domiciliar (CAUMO *et al.*, 2023; CHARVET *et al.*, 2023).

Ao utilizar a técnica de ETCC domiciliar, é fundamental prover um treinamento quanto ao uso adequado do aparelho e da realização das sessões, das visitas programadas ao centro aplicador para avaliações (no início, no decorrer do protocolo e no final), bem como da assistência remota rápida para esclarecer dúvidas e resolver problemas que possam surgir. O aparelho precisa ser validado e contar com dispositivos de controle programáveis, com sistemas de bloqueio para evitar uso indevido, registrando o horário e a qualidade das sessões realizadas. A avaliação dos possíveis efeitos adversos da técnica também é imprescindível.

2.3.5 ETCC sobre o córtex pré-frontal dorsolateral (DLPFC) na FM

ETCC aplicada sobre o DLPFC esquerdo tem sido uma proposta promissora para melhorar os processos cognitivos de informação, com destaque aos atencionais (BRUNONI; VANDERHASSELT, 2014; MORENO *et al.*, 2015; SERRANO *et al.*, 2022), sintomas depressivos, capacidade funcional e diminuição do uso de medicação analgésica (CAUMO *et al.*, 2022; MOFFA *et al.*, 2020; NEJATI; MAJIDINEZHAD; NITSCHE, 2022).

O aumento da ativação bilateral do córtex pré-frontal (PFC), particularmente do DLPFC

esquerdo, tem sido correlacionada com a inibição da dor (LORENZ et al., 2003), enquanto o controle percebido da dor foi associado à ativação do DLPFC direito (Allen, 2012). Estudos de neuroimagem relacionam a catastrofização da dor a uma maior atividade no DLPFC (GALAMBOS *et al.*, 2019), enquanto em transtornos depressivos parece ocorrer um desbalanceamento do PFC, com uma hipoativação mais pronunciada no lado esquerdo (GRIMM *et al.*, 2008).

A ativação e inibição de circuitos neurais no PFC podem estar relacionadas a processos nociceptivos mal-adaptativos, onde os neurônios GABAérgicos modulam a atividade neuronal (CAUMO *et al.*, 2022). Esses circuitos também estão envolvidos nos componentes sensoriais, cognitivos e afetivos da dor. Eles participam no ajuste fino do equilíbrio entre facilitação e inibição da via descendente da dor (KUNER et al., 2021; SEMINOWICZ et al., 2017). Acredita-se, portanto, que a ETCC aplicada sobre o DLPFC, especialmente o esquerdo, ofereça uma vantagem potencial para modular redes neurais na interface entre o processamento cognitivo e afetivo de regulação da dor (CAUMO *et al.*, 2022).

Em revisão sistemática e metanálise, Brunoni *et al.* 2014 destacam o papel da ETCC anodal sob DLPFC esquerdo na melhora do desempenho de operações relacionadas à memória de trabalho, especialmente em medidas de tempo de resposta. Um ensaio clínico randomizado recente mostrou que em mulheres com FM o efeito de 4 semanas de ETCC anódica sobre DLPFC esquerdo exerceu efeitos positivos no déficit cognitivo em comparação com a estimulação simulada (SERRANO *et al.*, 2022). Brietzke *et al.,* 2020, mostraram que 60 sessões de ETCC domiciliar com a mesma montagem, melhorou a dor generalizada e a incapacidade relacionada à dor, o que reduziu a chance de uso de analgésicos em 55% em uma amostra de mulheres com FM, quando comparada à estimulação simulada. Corroborando esses achados, outro ensaio clínico também em mulheres com FM utilizou um protocolo de 20 sessões de ETCC domiciliar anódica sobre o DLPFC esquerdo e apresentou resultados positivos na incapacidade para atividades diárias devido aos sintomas da fibromialgia, na

diminuição da catastrofização da dor (ruminação e magnificação), na melhora dos sintomas depressivos, qualidade do sono e tolerância à dor pelo calor (CAUMO *et al.*, 2022).

2.3.6 ETCC sobre o córtex motor primário (M1) na FM

Enquanto a ETCC anódica aplicada sobre o DLPFC esquerdo parece modular conexões em redes cognitivas e afetivas, envolvendo o PFC, acredita-se que a estimulação anódica sobre o córtex motor primário (M1) module a excitabilidade das redes sensório-discriminativas envolvidas no processamento da sensibilidade à dor, devido à sua influência sobre o sistema somatossensorial e sobre o sistema inibitório descendente da dor (CAUMO *et al.*, 2023; PACHECO-BARRIOS *et al.*, 2020). A ETCC anodal sobre o M1 exerce uma regulação do tipo *top-down*, enviando sinais para as conexões tálamo-corticais, pré-frontais, para o giro cingulado e substância cinzenta periaquedutal (LANG *et al.*, 2005; YOON *et al.*, 2014).

A plasticidade mal-adaptativa no M1 é um achado comum em pacientes com dor crônica e estudos em modelos animais e em humanos mostraram que a modulação da atividade desta área induz efeitos analgésicos importantes (SAAVEDRA et al., 2014). Evidências em pacientes com fibromialgia mostraram que as características basais do M1 estão alteradas nestes indivíduos (MHALLA *et al.*, 2010; SALERNO *et al.*, 2000), apresentando um padrão de atividade anormalmente aumentado em resposta à dor induzida experimentalmente quando comparado a controles saudáveis, refletindo uma ativação contralateral aumentada (PUJOL *et al.*, 2009).

Na última década, estudos utilizando protocolos de ETCC anodal sobre o M1 mostraram que a modulação desta região reduz a dor na FM (CAUMO *et al.*, 2023; FREGNI *et al.*, 2006; VILLAMAR *et al.*, 2013).

Um estudo pioneiro mostrou que em mulheres com fibromialgia, cinco sessões consecutivas de ETCC anódica sobre M1 mostraram-se superiores na melhora da dor, em comparação às estimulações sobre o DLPFC e simulada. Também foi observado um impacto positivo na qualidade de vida entre as pacientes que receberam estimulação anódica em M1 (FREGNI *et al.*, 2006). Outro estudo maior, com metodologia semelhante, ressaltou que tais efeitos permaneceram por 30 dias (FAGERLUND; HANSEN; ASLAKSEN, 2015). KHEDR et al., 2017, observaram que 10 sessões, no entanto, de maior densidade de corrente, reduziram a dor em mais de 40% ao longo de 2 semanas. Ensaios posteriores encontraram benefícios na combinação da ETCC anódica em M1 com reabilitação ou atividade física (MENDONCA *et al.*, 2016; RIBERTO, 2011).

Diretrizes Baseadas em Evidências propõe recomendação de nível B (eficácia provável) do uso de ETCC anódica em M1 na fibromialgia (FREGNI *et al.*, 2021; LEFAUCHEUR *et al.*, 2017).

2.3.7 Estimulação Transcraniana de Corrente Contínua (ETCC) no Comportamento Alimentar Disfuncional

Uma recente revisão sistemática e metanálise avaliou estudos em indivíduos com descontrole alimentar e transtorno por uso de substância e destacou o potencial da ETCC para modular comportamentos alimentares disfuncionais, reduzir a ingesta alimentar e o peso corporal. ETCC sob DLPFC reduziu o *craving* e o consumo alimentar nesses indivíduos e seus efeitos foram percebidos por até 12 meses (SONG *et al.*, 2022).

Para contextualizar o efeito da ETCC nos comportamentos alimentares disfuncionais e a relação destes com a fibromialgia, alguns conceitos serão abordados antes de explorarmos as evidências do uso da ETCC nessa área, bem como seu mecanismo de ação.

2.3.7.1 Comportamento Alimentar e FM

A elevada prevalência de excesso de peso e obesidade comórbida à FM, mencionada anteriormente, impulsionou uma gama de estudos buscando elucidar possíveis vias fisiopatológicas compartilhadas pela FM e obesidade (NEUMANN; LERNER; GLAZER, 2008; OKIFUJI; HARE, 2015; SOMINSKY; SPENCER, 2014; YUNUS; ARSLAN; ALDAG, 2002). O excesso de peso na FM, parece ter uma etiologia multifatorial, potencializando o desafio do manejo terapêutico destas comorbidades, bem como a total compreensão dos mecanismos fisiopatológicos. Dentre estes fatores etiológicos, destacam-se sedentarismo, sintomas depressivos, ansiedade, catastrofismo, distúrbios do sono, anormalidades tanto no eixo hipotálamo-hipófise-adrenal (HPA) quanto na sinalização dopaminérgica (HORSTMANN, 2017; MITSI; ZACHARIOU, 2016; OKIFUJI; HARE, 2015; URSINI; NATY; GREMBIALE, 2011). Na FM, o desbalanceamento no sistema nervoso autonômico, também parece comprometer a resposta a outros estressores e evidências relacionam esta condição à síndrome metabólica, uma vez que o aumento da atividade simpática sabidamente a prediz (LICHT; DE GEUS; PENNINX, 2013; MARTINEZ-LAVIN, 2007).

A exposição crônica ao estresse no curso inicial da FM, pode levar à hiper-reatividade do eixo HPA, sustentando níveis mais altos de secreção de cortisol (RIVA *et al.*, 2010). O organismo visa alcançar estabilidade e adaptação fisiológica por meio da alostase, um processo que apoia a homeostase, enquanto os ambientes e/ou estágios da vida mudam e em resposta aos eventos estressores. Como mediadores primários da alostase, destacam-se os hormônios do eixo HPA, outras catecolaminas e citocinas (MCEWEN; WINGFIELD, 2003). Se o desequilíbrio

perdurar, aparecem sintomas de sobrecarga alostática. Quando a exposição ao estresse torna-se contínua/crônica, como na FM, essas adaptações passam a não executar seu papel adequadamente, seja devido ao custo acumulado de mantê-las (carga alostática) ou devido a disfunções nos mecanismos de moderação (CAUMO; SEGABINAZI; STEFANI, 2017). Consequente à sobrecarga alostática, a secreção de cortisol passa a não aumentar adequadamente em resposta ao estresse e, como mecanismo contra-regulatório, acontece a elevada liberação de citocinas inflamatórias (MCEWEN; WINGFIELD, 2003).

A hiperativação do eixo HPA repercute em alterações metabólicas, como adipogênese, resistência insulínica e alterações em hormônios e adipocinas com papel na regulação da fome e saciedade tanto em níveis centrais quanto periféricos, o que pode induzir a ingestão alimentar (GROESZ *et al.*, 2012; LO SAURO *et al.*, 2008; RUTTERS; FLEUR; LEMMENS, 2012; SINHA; JASTREBOFF, 2013; SOMINSKY; SPENCER, 2014). Somado a isso, cerca de 50% das pessoas aumentam o seu consumo alimentar quando expostos a situações estressoras (ADAM; EPEL, 2007; EPEL *et al.*, 2004).

Em nível de neurocircuito, o estresse parece afetar o sistema dopaminérgico mesolímbico, bem como áreas subjacentes no sistema de recompensa. Um estudo investigou a exposição ao estresse agudo durante a tomografia por emissão de pósitrons (PET) e revelou que tanto o estresse quanto a liberação de cortisol aumentaram a secreção de dopamina do núcleo accumbens (NAc) (Wand GS, 2007). Outro estudo utilizando a mesma técnica revelou que indivíduos com maior reatividade ao cortisol liberam mais dopamina no estriado ventral, sugerindo uma forte interconectividade entre os dois (PRUESSNER *et al.*, 2004). Paralelamente, reguladores homeostáticos periféricos do balanço energético, como leptina, grelina, insulina e orexina (associados ao eixo HPA), também podem modular aspectos hedonistas do comportamento alimentar, interagindo com o sistema de recompensa por meio de receptores cognatos nos neurônios dopaminérgicos da área tegmentar ventral (VTA), exercendo um efeito potencializador da sensibilidade à recompensa, preferência e do desejo alimentar

(*food craving*), bem como da busca por alimentos hiperpalatáveis (VOLKOW; WANG; BALER, 2011). Sabe-se que tanto as dietas ricas em alimentos hiperpalatáveis quanto o uso de substâncias de abuso alteram a produção e secreção do fator de liberação de corticotrofina e dos glicocorticoides e a atividade noradrenérgica, aumentando a sensibilização das vias de recompensa (VTA, NAc, estriado dorsal e mPFC), o que, por sua vez, influencia a preferência por substâncias e por alimentos hiperpalatáveis, aumentando o desejo e o consumo bidirecional (YAU; POTENZA, 2013). Ainda, alterações nos padrões de sono, outra condição estressora frequente em indivíduos com FM, igualmente associam-se ao aumento do consumo calórico, bem como à preferência por alimentos ricos em carboidratos e gorduras (GROESZ *et al.*, 2012; YAU; POTENZA, 2013).

2.3.7.2 Dor Crônica, Sensibilização Central e Excesso de Peso

A dor é um estressor comum e um provável fator de risco para obesidade (Stone & Broderick, 2012). Indivíduos com sobrepeso demonstraram maiores escores percebidos de estresse e de fome, bem como nos níveis séricos de cortisol e grelina após medidas de dor pressora ao frio (GELIEBTER; CARNELL; GLUCK, 2013), e descobertas semelhantes foram demonstradas em pessoas com obesidade (GLUCK; GELIEBTER; LORENCE, 2004). Estudos anteriores propuseram não apenas o envolvimento da ansiedade e da catastrofização ao mediar a relação entre dor crônica e comportamento alimentar emocional (EMAMI *et al.*, 2016; JANKE *et al.*, 2016), mas também a utilização do comportamento alimentar disfuncional como estratégia mal-adaptativa de enfrentamento (AMY; KOZAK, 2012; O'LOUGHLIN; NEWTON-JOHN, 2019).

O comportamento alimentar e as vias de processamento da dor compartilham anormalidades em áreas cerebrais envolvidas na regulação emocional e afetiva no sistema

mesolímbico dopaminérgico, incluindo neurônios do núcleo accumbens, amígdala e hipocampo (HORSTMANN, 2017; MITSI; ZACHARIOU, 2016), e também no sistema opioidérgico (MALDONADO; BAÑOS; CABAÑERO, 2018), ambos fundamentais no processamento da recompensa alimentar.

Um estudo recente (ELKFURY *et al.*, 2021) propôs o envolvimento de vias hedonistas na associação entre FM e obesidade. O envolvimento em comportamentos alimentares emocionais mostrou-se 30% maior em mulheres com FM em comparação a voluntárias saudáveis. Este estudo também encontrou uma associação negativa entre o BDNF sérico, um importante marcador de neuroplasticidade, e medidas de fome autorrelatadas. De fato, o papel do BDNF investiga-se tanto na FM (CAUMO *et al.*, 2016) quanto na obesidade (CORDEIRA *et al.*, 2010) e alterações estruturais associam-se a alterações específicas nos circuitos de recompensa e de estresse, relacionados ao controle da motivação (IKEMOTO; BONCI, 2014; KOOB; VOLKOW, 2016). Na FM ocorre uma secreção aumentada de BDNF, em comparação a indivíduos saudáveis (CAUMO *et al.*, 2016), enquanto indivíduos com obesidade tendem a apresentar níveis mais baixos de BDNF sérico em comparação àqueles com peso saudável (GOLDEN *et al.*, 2010; MCALLAN *et al.*, 2018). Além disso, sabe-se que as variantes genéticas do BDNF com perda de função, como o polimorfismo BDNF Val66Met, podem alterar a vulnerabilidade ao estresse, a reatividade do eixo HPA e do sistema de recompensa (MIAO; WANG; SUN, 2020; NOTARAS; VAN DEN BUUSE, 2020), ambos envolvidos na fisiopatologia da obesidade e da FM, representando uma possível integração entre essas patologias.

É concebível que a alimentação excessiva associada a alimentos hiperpalatáveis (ricos em açúcar e gordura) desencadeie vias hedônicas e possa contribuir para a redução da dor por meio não apenas da analgesia induzida por endocanabinoides endógenos, mas também através da alimentação disfuncional como estratégia neuroplástica mal-adaptativa de enfrentamento à

dor. Esse padrão pode levar ao equilíbrio energético positivo e, em última análise, ao ganho de peso e à obesidade.

No entanto, até o presente, poucos estudos exploram as alterações fisiopatológicas encontradas na fibromialgia com mecanismos hedonistas do comportamento alimentar, a composição nutricional da dieta tem sido o principal foco da maior parte das publicações (ARRANZ; CANELA; RAFECAS, 2012; BATISTA *et al.*, 2016; HOLTON, 2016; ROSSI *et al.*, 2015), enquanto permanecem lacunas substanciais acerca da compreensão do comportamento alimentar na FM, o que possivelmente agrava o curso e o prognóstico desses pacientes que, expressivamente, apresentem obesidade como comorbidade. Frente a isso, a presente tese foi estruturada para abordar as principais alterações neurobiológicas envolvidas no comportamento alimentar e sua possível associação com a fisiopatologia da FM.

2.3.7.3 Neurobiologia do Comportamento Alimentar

Aspectos homeostáticos e hedônicos interagem para formar o comportamento alimentar humano. O primeiro, controlado pelo hipotálamo, regula o metabolismo, a fome e a saciedade, integrando sinais circulantes da periferia. O segundo, governado pelo sistema de recompensa, envolve vias e estruturas mesocorticolímbicas e nigroestriatais, responsáveis por modular a cognição relacionada à recompensa, incluindo o desejo de consumir alimentos por prazer, mesmo na ausência de fome. A conectividade entre essas estruturas é promovida por neurotransmissores como dopamina (DA), opioides e canabinoides (BECETTI *et al.*, 2023; MARQUÉS-ITURRIA *et al.*, 2015; TREASURE; CARDI; KAN, 2012).

Os processos de recompensa e reforço alimentar envolvem inúmeros componentes que culminam em uma sequência: *i) 'Liking'*, gostar hedônico, *ii) 'Wanting'*, elemento

motivacional, saliência de incentivo e *iii) 'Learning'*, aprendizagem associativa. As recompensas são "gostadas" e "desejadas", e essas duas palavras parecem quase sinônimos, no entanto, os circuitos cerebrais que medeiam o processo de "querer" (*Wanting*) uma determinada recompensa são dissociáveis dos circuitos que medeiam o grau em que ela é "gostada" (*Liking*). A saliência de incentivo ou "*Wanting*", uma forma de motivação, é gerada por sistemas neurais grandes e robustos que incluem a dopamina mesolímbica, enquanto o "*Liking*", ou o impacto prazeroso real do consumo de recompensas, é mediado por sistemas neurais menores e mais frágeis, que não dependem da dopamina (BERRIDGE; KRINGELBACH, 2015; BERRIDGE; ROBINSON, [*s. d.*]; RIBEIRO; SANTOS, 2013).

O sistema de recompensa inclui estruturas como a área tegmentar ventral (VTA), núcleo accumbens (NAc), amígdala (AMY), hipocampo, córtex pré-frontal (PFC), giro cingulado (SIG) e córtex orbitofrontal (OFC), desempenhando papéis específicos na volição, indução e perpetuação do comportamento alimentar. Os neurônios dopaminérgicos da VTA fazem sinapses com o NAc, processo crucial para a saliência e motivação. AMY e hipocampo processam e condicionam as memórias referentes ao estímulo e a recompensa, enquanto OFC é responsável pela tomada de decisão. O córtex pré-frontal dorsolateral (DLPFC) e o SIG, ativados por eventos motivacionais relevantes, exercem o controle inibitório, ponderam e definem a intensidade da resposta comportamental (LEE *et al.*, 2012; VOLKOW; WISE; BALER, 2017).

A dopamina é fundamental nos efeitos gratificantes da recompensa (VOLKOW *et al.,* 2012), e as vias dopaminérgicas nigroestriatal, mesolímbica e mesocortical (Figura 1) desempenham papel crucial nos processos de recompensa e reforço (WISE, 2002).

Figura 3. *Estruturas e vias envolvidas no controle do comportamento alimentar.*

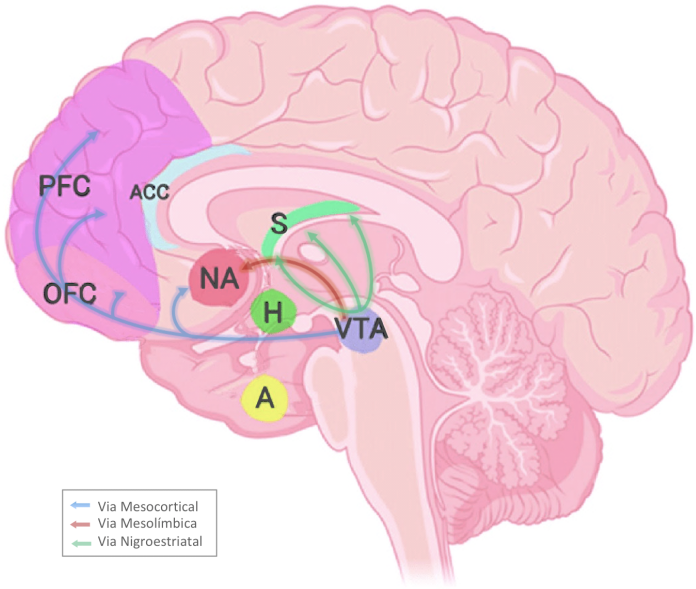

Figura 3. *Figura adaptada de (Stogios et. al., 2020). Legenda: VTA (Área Tegmentar Ventral), NA (Núcleo Accumbens), H (Hipotálamo), A (Amígdala), S (Corpo Estriado), OFC (Córtex Orbitofrontal), PFC (Córtex Pré-Frontal), ACC (Córtex Cingulado Anterior).*

Alimentos hiperpalatáveis desencadeiam de maneira mais pronunciada os mecanismos associados ao sistema de recompensa (EDWIN THANARAJAH *et al.*, 2023). O desejo intenso por esses alimentos, conhecido como *food craving*, tem sido correlacionado com a obesidade (YEH *et al.*, 2016).

O *food craving*, ou "fissura alimentar", refere-se a um estado motivacional subjetivo de "querer" (*Wanting*) que impulsiona comportamentos de busca e ingestão alimentar específicos, frequentemente relacionados a alimentos hiperpalatáveis. Esse fenômeno está associado à alimentação disfuncional, observada em condições como obesidade, transtorno de compulsão alimentar e bulimia nervosa (CEPEDA-BENITO *et al.*, 2000; GENDALL *et al.*, 1998; GREENO; WING; SHIFFMAN, 2000; WATERS; HILL; WALLER, 2001; WEINGARTEN; ELSTON, 1990). No entanto, é importante ressaltar que o desejo alimentar não é

necessariamente patológico ou mal-adaptativo, sendo um fenômeno onipresente, mesmo que frequentemente observado em estados patológicos (FRANKEN; MURIS, 2005).

A administração repetida de reforçadores, como alimentos hiperpalatáveis, regula negativamente os receptores D2 de dopamina (DRD2) no corpo estriado, associado à redução da atividade em regiões pré-frontais, facilitando respostas impulsivas e compulsivas a estímulos alimentares. Essa adaptação disfuncional da dopamina pode perpetuar a ingestão aumentada desses alimentos como forma de compensação pela diminuição da ativação desses circuitos (RIBEIRO; SANTOS, 2013; RICHARD, 2015). A resposta comportamental é representada pela necessidade de aumentar a ingestão para se obter o mesmo grau de recompensa, clinicamente caracterizada como tolerância. Sem a ingestão adicional, surgem os desejos alimentares intensos (*food cravings*) e sintomas de abstinência (BENTON; YOUNG, 2017). Indivíduos com obesidade e transtorno de compulsão alimentar frequentemente apresentam uma deficiência na sinalização dopaminérgica, evidenciada por menor disponibilidade de DRD2 quando comparados a indivíduos normoponderais e atenuada sinalização da dopamina estriatal em resposta à ingestão de alimentos hiperpalatáveis (EDWIN THANARAJAH *et al.*, 2023; STICE *et al.*, 2008; WISE; ROBBLE, 2020). Ao mesmo tempo, é observada uma aumentada sinalização da dopamina frente a imagens de alimentos em indivíduos com obesidade, sugerindo déficits na obtenção da recompensa alimentar e aumentada susceptibilidade às pistas alimentares (RIBEIRO; SANTOS, 2013; RICHARD, 2015). Ou seja, uma redução do *'liking'* e uma amplificação do *'wanting'*. A magnitude da resposta aos estímulos alimentares prevê ganho de peso futuro e resultados subótimos após intervenções de perda e manutenção de peso (BECETTI *et al.*, 2023; BURGER; STICE, 2014).

O padrão de consumo excessivo seguido por dieta restritiva e recidiva é comparável ao ciclo de intoxicação por drogas, abstinência e recaída observado em comportamentos aditivos (VOLKOW; WISE; BALER, 2017).

2.3.7.4 Sistema Dopaminérgico

A atividade no nível sináptico natural da dopamina é controlada pela densidade de receptores, quantidade de neurotransmissor liberado e pela reabsorção por transportadores específicos (Sikora et al., 2016). A dopamina é um neurotransmissor monoaminérgico, pertencente às famílias das catecolaminas e das feniletilaminas. Sua síntese e liberação são realizadas por neurônios dopaminérgicos do mesencéfalo, a partir do aminoácido tirosina, convertido em dopa e, posteriormente, em dopamina. Os receptores de dopamina são subdivididos em D1, D2, D3, D4 e D5, de acordo com sua localização e função (YU; MILLER; GROTH, 2022). Os receptores DRD1 e DRD5 (D1-*like*) estão presentes em estruturas relacionadas ao processamento e controle do comportamento alimentar, como o NAc, putâmen, núcleo caudado, substância negra, amígdala e córtex frontal; enquanto DRD2, DRD3 e DRD4 (D2-*like*) são encontrados na VTA, NAc, amígdala, hipocampo, globo pálido, hipotálamo e córtex (KLEIN *et al.*, 2019; SIKORA *et al.*, 2016).

No nível celular e de circuito, o impulso motivacional depende da concentração de dopamina extrassináptica em áreas específicas do cérebro, como o corpo estriado. As pistas que predizem um estímulo reforçador também modulam as concentrações extrassinápticas de dopamina, energizando a motivação (VOLKOW; WISE; BALER, 2017). A ativação dos substratos dopaminérgicos mesocorticolímbicos é fundamental para o desenvolvimento dos mecanismos motivacionais associados ao consumo alimentar excessivo (SOBIK; HUTCHISON; CRAIGHEAD, 2005; WANG *et al.*, 2001).

A atividade dos neurônios dopaminérgicos é influenciada por projeções de várias áreas cerebrais, tanto pré-sinápticas quanto pós-sinápticas. Seu disparo requer estimulação glutamatérgica nos receptores NMDA e AMPA, potencializando ou inibindo por meio do acoplamento às proteínas G, estimulando a produção de Adenosina Monofosfato Cíclico (AMPc) ou Adenilato Ciclase (AC) e Proteína Quinase A (PKA) (VOLKOW; WISE; BALER,

2017). A dopamina é um neuromodulador chave da neuroplasticidade e um importante substrato neuronal de aprendizagem e formação de memória, que envolve criticamente os receptores NMDA. A dopamina modula a atividade do receptor NMDA através dos subtipos de receptores D1-*like* e D2-*like*. Hipotetiza-se que a dopamina se concentra na plasticidade semelhante à potenciação de longo prazo (LTP), ou seja, reduz a disseminação difusa, mas aumenta a plasticidade restrita localmente por meio de uma redução da atividade do receptor NMDA dependente do DRD2 (GHANAVATI *et al.*, 2022).

O fortalecimento na estimulação das projeções dopaminérgicas da VTA para o estriado ventral (via mesolímbica) pode aumentar a saliência de incentivo e o *craving*. A energização das sinapses na via mesocortical (aferências da VTA para o estriado ventral e DLPFC) está associada ao controle inibitório e à memória de trabalho, enquanto a formação do hábito ocorre como consequência do reforço da via nigroestriatal (YU; MILLER; GROTH, 2022).

Modelos de compulsividade destacam a importância do tônus dopaminérgico nas alças ventrais que conectam o córtex cingulado anterior (ACC) e o estriado ventral (VS)/ NAc na regulação de comportamentos de recompensa e reforço, incluindo comportamento alimentar (FINEBERG *et al.*, 2010; WISE; JORDAN, 2021).

Estudos de neuroimagem demonstraram que pacientes com FM apresentam níveis reduzidos de atividade da dopa-descarboxilase, uma enzima envolvida no metabolismo da dopamina, em várias regiões, incluindo a área tegmentar ventral (WOOD *et al.*, 2007). Esses pacientes também apresentam respostas cerebrais dopaminérgicas reduzidas à dor evocada, enquanto os estudos de neuroimagem em saudáveis demonstram um papel regulador da dopamina na nocicepção durante a dor experimentalmente evocada (ALBRECHT *et al.*, 2016). É digno de nota que estudos de neuroimagem em humanos associaram um maior potencial de ligação nos receptores dopaminérgicos D2/D3, indicativo de níveis mais baixos de liberação endógena de dopamina, a maior sensibilidade à dor em adultos saudáveis, bem como em pacientes com FM (SCOTT *et al.*, 2006; WOOD *et al.*, 2007). Estudos neuroendócrinos

também mostraram uma neurotransmissão dopaminérgica alterada na FM, sugerindo um aumento da sensibilidade ou densidade dos DRD2 nessa população (MALT *et al.*, 2003).

Assim, a neurotransmissão dopaminérgica alterada se mostra, ao menos em parte, como um fator subjacente para a hiperalgesia observada em pacientes com FM (DESMEULES *et al.*, 2003; GRANGES; LITTLEJOHN, 1993; LOGGIA *et al.*, 2014; PETZKE *et al.*, 2003), bem como, considerando os conceitos abordados anteriormente nesta tese, servir de base para um racional envolvendo o controle do comportamento alimentar hedônico nestes pacientes.

2.3.7.5 Função Executiva

Como consequência das alterações na sinalização dopaminérgica em regiões corticofrontais, como OFC, DLPFC e SIG, ocorrem prejuízos na função executiva (WISE; ROBBLE, 2020). A função executiva é um domínio da função cognitiva, definida como processos cognitivos superiores que permitem a previsão e a ação direcionada a objetivos, subdividindo-se em *i)* Controle inibitório: capacidade de suprimir impulsos e respostas comportamentais automáticas para selecionar uma resposta mais apropriada; *ii)* Memória de trabalho: habilidade de monitorar a relevância dos estímulos e atualizar informações relevantes na memória; e *iii)* Flexibilidade cognitiva: capacidade de mudar a atenção, conjuntos ou regras mentais quando apropriado à situação, considerando alternativas diferentes (BANICH, 2009; DIAMOND, 2013; MIYAKE; FRIEDMAN, 2012; YANG *et al.*, 2018).

Em estudos de neuroimagem, adolescentes obesos, em comparação com adolescentes normoponderais, mostraram menor ativação das regiões pré-frontais (DLPFC, vlPFC) ao tentar inibir respostas a imagens de alimentos hiperpalatáveis e apresentaram evidências comportamentais de controle inibitório reduzido (BATTERINK; YOKUM; STICE, 2010). Estudos em adultos mostram que os indivíduos que apresentavam maior ativação do DLPFC

quando instruídos a “resistir ao desejo” enquanto visualizavam imagens de alimentos obtiveram melhor sucesso na perda de peso após cirurgia bariátrica (GOLDMAN *et al.*, 2013). Outro estudo revelou que os participantes que mostraram menos recrutamento de regiões de controle inibitório (giros frontais inferior, médio e superior) durante escolhas difíceis em comparação a fáceis, em uma tarefa de desconto de atraso, apresentaram ganho de peso futuro elevado (KISHINEVSKY *et al.*, 2012).

Prejuízos na função executiva, especialmente aqueles relacionados ao controle inibitório, podem desencadear e manter padrões alimentares disfuncionais, reduzindo a capacidade de resistir aos alimentos hiperpalatáveis, o que, por sua vez, promove o acúmulo de gordura corporal resultante do consumo calórico excessivo. Esse ciclo pode induzir a mais alterações estruturais e funcionais nas áreas corticofrontais responsáveis pelo controle executivo, configurando um mecanismo bidirecional e complexo (MEREDITH WEISS; LACONI; MARSHALL, 2020).

2.3.7.6 Alterações Estruturais

Estudos de neuroimagem evidenciam reduções de volume da substância cinzenta no giro frontal inferior, córtex orbitofrontal e córtex cingulado anterior/médio em indivíduos com obesidade quando comparados a indivíduos eutróficos. Em indivíduos que apresentam episódios de compulsão alimentar, este prejuízo mostra-se ainda maior (GARCÍA-GARCÍA *et al.*, 2019). Além disso, um maior IMC foi associado a uma menor espessura cortical, sendo as associações mais robustas com o IMC observadas no córtex pré-frontal de crianças (LAURENT *et al.*, 2020). Essas regiões estão associadas à função executiva, incluindo controle inibitório, e tais alterações podem causar uma ruptura na habilidade de exercer propriamente o controle sobre o consumo alimentar. A investigação de mecanismos neurais subjacentes à obesidade, particularmente no DLPFC, suporta a relação entre obesidade e a imparidade do funcionamento

executivo, como demonstrado tanto por estudos de neuroimagem quanto pela neurociência cognitiva (FORCANO et al., 2020; ICETA et al., 2021).

A neuromodulação mal-adaptativa no sistema de recompensa, resultante de modificações estruturais e na neurotransmissão dopaminérgica, pode aumentar a suscetibilidade dos indivíduos com FM a um comportamento alimentar disfuncional, a percepção e sensibilidade à dor e a sintomas depressivos e ansiosos. O sofrimento psicológico e os déficits no funcionamento executivo são provavelmente barreiras importantes para a perda e manutenção eficaz de peso nesses indivíduos. Tendo em vista isso, a investigação de possíveis alterações de componentes hedônicos da alimentação em pessoas com FM pode permitir novos avanços tanto na compreensão fisiopatológica quanto para o adequado direcionamento de modalidades terapêuticas, de modo a viabilizar resultados mais promissores e estratégias preventivas eficazes.

2.3.7.7 Evidências do uso da ETCC na Modulação do Comportamento Alimentar

A área alvo dos estudos em neuromodulação do comportamento alimentar é o DLPFC, uma região cerebral complexa relacionada às funções executivas que apoia o controle cognitivo da ingestão de alimentos. No geral, a hipótese subjacente é de que o aumento da atividade do DLPFC pode alterar o equilíbrio recompensa-cognição no sentido da facilitação do controle cognitivo e possivelmente da supressão de mecanismos relacionados à recompensa que impulsionam o desejo alimentar e a ingestão excessiva (VAL-LAILLET *et al.*, 2015). Acredita-se que o DLPFC possa ter um papel na inibição do desejo por alimentos hiperpalatáveis, exercendo uma modulação sobre regiões sensíveis à recompensa, como o mPFC e OFC (HARE; MALMAUD; RANGEL, 2011; HUTCHERSON *et al.*, 2012; UHER *et al.*, 2005). As

possibilidades incluem mudanças nos mecanismos de controle cognitivo requeridos para avaliação de recompensas (BAJBOUJ *et al.*, 2018; CAMUS *et al.*, 2009), vieses atencionais (FREGNI *et al.*, 2008) e controle inibitório (BAJBOUJ *et al.*, 2018; LAPENTA *et al.*, 2014).

A atividade reduzida do DLPFC direito na obesidade pode levar à alimentação excessiva e representa um possível envolvimento no controle inibitório (ALONSO-ALONSO; PASCUAL-LEONE, 2007). No entanto, o papel exato da ativação do DLPFC direito permanece controverso, uma vez que indivíduos com obesidade que resistem com sucesso aos desejos alimentares (*food cravings*) apresentam uma maior ativação no DLPFC esquerdo (GOLDMAN *et al.*, 2013). Ainda, estudos de neuroimagem sugerem que a normalização da atividade do DLPFC esquerdo pode ocorrer após a perda de peso, uma vez que indivíduos eutróficos e ex-obesos não apresentam diferenças na atividade cerebral (HIGUERA-HERNÁNDEZ *et al.*, 2018; LE *et al.*, 2007). No entanto, os processos cognitivos específicos dependentes do DLPFC afetados pela ETCC, que medeiam os efeitos comportamentais observados, ainda não estão completamente estabelecidos.

Não encontramos até o presente, estudos com protocolos de estimulação sobre o M1, ou em outros sítios, visando modular comportamentos alimentares disfuncionais. No entanto, hipotetizamos que a melhora da dor e dos sintomas relacionados a FM, tanto nestes indivíduos quanto em pessoas com excesso de peso ou obesidade, que apresentam dor crônica como comorbidade, possa impactar de maneira positiva no controle do *food craving* e dos domínios do comportamento alimentar, através da redução da dor, do estresse e consequente melhora da qualidade de vida. Ainda, acreditamos que a melhora no comportamento alimentar, possa levar à diminuição da adiposidade, exercendo efeitos positivos na dor e nos outros sintomas da FM.

Um estudo pioneiro que explorou os efeitos da ETCC no *craving* por alimentos hiperpalatáveis mostrou que uma única sessão de ETCC anódica em DLPFC direito induziu uma diminuição significativa no desejo por alimentos visualizados quando comparada à

estimulação anódica em DLPFC esquerdo. Após a estimulação simulada este desejo foi significativamente aumentado, enquanto após a ETCC em DLPFC esquerdo, os níveis de desejo não mudaram. Estes resultados sugerem que ambas as condições ativas de ETCC tiveram um efeito na redução do desejo alimentar que tais efeitos podem estar relacionados a uma modulação dos circuitos neurais associados à recompensa e tomada de decisão (FREGNI *et al.*, 2008). Posteriormente, outros estudos que utilizaram o mesmo método, observaram um aumento temporário na capacidade de resistir a alimentos hiperpalatáveis, redução do desejo por alimentos doces e da ingesta calórica (GOLDMAN *et al.*, 2011; KEKIC *et al.*, 2014; LAPENTA *et al.*, 2014). Com base nos achados de um ensaio clínico com mulheres saudáveis que apresentavam frequentes desejos por alimentos hiperpalatáveis, Lapenta et al. 2014 sugerem que ETCC em DLPFC direito é capaz de adequar a ingestão alimentar através da modulação do circuito de controle inibitório, demonstrado pelos potenciais evocados registrados por avaliações eletroencefalográficas em uma tarefa Go/No-Go que apresentava um estímulo visual alimentar e de controle. Em indivíduos com sobrepeso, uma sessão de ETCC em DLPFC esquerdo, combinada com exercícios, diminuiu a fome e aumentou a saciedade imediatamente após o exercício e diminuiu o apetite 30 minutos depois (MONTENEGRO *et al.*, 2012).

Ainda não há consenso sobre protocolos terapêuticos de neuroestimulação específicos para modulação de comportamento alimentar disfuncional e obesidade, no entanto, estimulação em DLPFC bilateral possui maiores evidências científicas (FORCANO *et al.*, 2020; SONG *et al.*, 2022). A literatura apresenta achados positivos tanto para estimulação anodal sobre DLPFC esquerdo quanto para o direito.

Os protocolos de sessões múltiplas de ETCC mostraram-se superiores aos de sessão única na redução do *craving* em indivíduos com transtornos alimentares, obesidade e transtorno por uso de substância em metanálise recente (SONG *et al.*, 2022). Em indivíduos com

sobrepeso, JAUCH-CHARA et al., 2014 demonstraram que uma semana de ETCC diária, anódica em DLPFC direito, reduziu a ingestão calórica total e escores de apetite autorreferidos. Corroborando com esses achados e utilizando a mesma técnica, Ljubisavljevic *et al.* 2016 observaram que a duração destes efeitos podem estar presentes 30 dias após a estimulação.

Revisões sistemáticas (DALTON *et al.*, 2018; GOUVEIA *et al.*, 2021) mostram haver uma literatura crescente sobre o uso de procedimentos de neuroestimulação para o tratamento da obesidade, transtornos alimentares e comportamentos alimentares relacionados (*food cravings*), o que é encorajador. No entanto, até ao momento, a maioria destes estudos, devido ao seu desenho, fornecem apenas evidências preliminares que sugerem que a neuroestimulação tem potencial para alterar comportamentos alimentares disfuncionais, consumo alimentar e peso corporal.

A grande maioria das evidências quanto ao uso da ETCC na neuromodulação do comportamento alimentar e da obesidade, concentram-se nos resultados sob a atenuação do *craving* e na diminuição do consumo calórico e/ou de alimentos hiperpalatáveis (GOUVEIA *et al.*, 2021), enquanto os resultados desta técnica permanecem superficialmente explorados em aspectos relativos a pensamentos e comportamentos alimentares restritivos, uso da alimentação em resposta a emoções negativas e estados de humor e em traços como descontrole e/ou compulsividade alimentar. Ainda, a maioria dos estudos conta com protocolos de menos de 5 sessões de ETCC e não possuem dados sobre acompanhamento. Mais ensaios clínicos são necessários para definir o número adequado de sessões, bem como explorar outros sítios de estimulação. A tabela 2 reúne os principais estudos envolvendo o uso da ETCC visando promover a modulação do comportamento alimentar disfuncional.

Tabela 2. Principais estudos envolvendo o uso da ETCC visando promover a modulação do comportamento alimentar disfuncional.

Referência	**Desenho**	**Variáveis**	**Intervenção**	**N**	**nostra**	**Achados/Conclusões**
Fregni *et al* 2008	Ensaio Clínico Randomizado	Desejo por alimentos hiperpalatáveis (*Food craving*) Consumo alimentar	ETCC ativa e simulada (ânodo esquerdo/cátodo direito e ânodo direito/cátodo esquerdo) do DLPFC.	23	Adultos saudáveis	ETCC em DLPFC direito induziu uma diminuição significativa no *food craving* quando comparada ao DLPFC esquerdo e ambas as condições ativas apresentaram um efeito quando comparadas à estimulação simulada.
Goldman *et al.* 2011	Ensaio Clínico Randomizado	Desejo por alimentos hiperpalatáveis (*Food craving*) Consumo alimentar	ETCC ativa e simulada (ânodo sobre DLPFC direito e cátodo sobre o DLPFC esquerdo)	19	Adultos saudáveis com desejos alimentares frequentes	ETCC ativa em DLPFC direito aumentou temporariamente a capacidade de resistir a alimentos hiperpalatáveis e reduziu o desejo por alimentos doces, quando comparada à estimulação simulada. Não foram observadas diferenças significativas no consumo.
Lapenta *et al*. 2014	Ensaio Clínico Randomizado	Desejo por alimentos hiperpalatáveis (Food craving), consumo alimentar e seus mecanismos subjacentes	ETCC ativa e simulada (ânodo sobre DLPFC direito e cátodo sobre o DLPFC esquerdo)	9	Mulheres adultas saudáveis com desejos alimentares frequentes	A ETCC ativa em DLPFC, comparada à simulada, reduziu o consumo alimentar e os efeitos foram duradouros. Esses achados sugerem que a ETCC é capaz de modular a ingestão alimentar através da modulação do circuito de controle inibitório, conforme indexado pelos ERPs N2 e P3a em respostas aos estímulos No-go.
Kekic *et al.* 2014	Ensaio Clínico Randomizado	Desejo por alimentos hiperpalatáveis (*Food craving*) Desconto temporal (medida de impulsividade)	ETCC ativa e simulada (ânodo sobre DLPFC direito e cátodo sobre o DLPFC esquerdo)	17	Mulheres adultas saudáveis com desejos alimentares frequentes	O desejo por alimentos doces, mas não salgados, foi reduzido após ETCC ativa em DLPFC direito. Os participantes que exibiram um comportamento de escolha mais reflexivo foram mais suscetíveis aos efeitos *anti-craving* da ETCC do que aqueles que exibiram um comportamento de escolha mais impulsivo (efeito moderador).
Montenegro *et al*. 2012	Ensaio Clínico Randomizado	Sobrepeso Desejo por alimentos hiperpalatáveis (Food craving) Níveis de fome e saciedade	ETCC ativa e simulada (ânodo sobre DLPFC esquerdo e cátodo sobre o DLPFC direito) isolada ou combinada com exercício aeróbico	9	Adultos com sobrepeso	A ETCC associada ao exercício teve maior efeito supressor do *food craving* em comparação à ETCC ou ao exercício isolado. Além disso, a ETCC associada ao exercício diminuiu a fome e aumentou a saciedade imediatamente após o exercício.

Forcano *et al.*, 2020	Ensaio Clínico Randomizado	Consumo de alimentos hiperpalatáveis Cognição Perda de peso futura	ETCC ativa e simulada (ânodo sobre DLPFC direito e cátodo sobre o DLPFC esquerdo) combinada com treinamento cognitivo (TC)	18	Adultos com obesidade mórbida	ETCC ativa + TC reverteu a assimetria frontal dominante esquerda e aumentou a coerência frontal aferida por EEG após a intervenção. A força deste último previu a redução do IMC. Neste grupo também houve redução da ingestão alimentar no acompanhamento.
Song *et al*., 2019	Metanálise	*Craving* e Consumo por drogas ou alimentos hiperpalatáveis	Estudos com ETCC em DLPFC sessão única versus multisessão	48	Indivíduos com dependência química, transtornos alimentares ou obesidade	ETCC em DLPFC reduz o desejo e os níveis de consumo, com efeitos maiores em intervenções de sessões múltiplas em comparação às de sessão única.
Jauch-Chara *et al.,* 2014	Ensaio Clínico Randomizado	Desejo por alimentos hiperpalatáveis (*Food craving*) Consumo alimentar	ETCC ativa e simulada (ânodo sobre DLPFC direito e cátodo sobre o DLPFC esquerdo)	14	Homens jovens saudáveis	Sessões diárias de ETCC em DLPFC direito por 8 dias reduziu a ingestão calórica total e escores de apetite autorreferidos.
Ljubisavljevic *et al*., 2016	Ensaio Clínico Randomizado	Desejo por alimentos hiperpalatáveis (*Food craving*) Consumo alimentar	ETCC ativa e simulada (ânodo sobre DLPFC direito e cátodo sobre o DLPFC esquerdo)	30	Adultos saudáveis com desejos alimentares frequentes	5 Sessões de ETCC no DLPFC direito têm efeitos na redução do *Food craving*, e a duração destes efeitos esteve presente 30 dias após a estimulação.

2.3.8 - Associações Genéticas e Bioquímicas

Muitos polimorfismos nos genes da dopamina afetam fenótipos cognitivos, de imagem ou clínicos, podendo impactar a disponibilidade ou a funcionalidade do produto gênico codificado (TUNBRIDGE *et al.*, 2019). Em revisão sistemática recente, Tunbridge *et al*. 2019, avaliou polimorfismos funcionais em genes relacionados à dopamina, destacando efeitos robustos e de médio a grande em quatro genes: DRD2 (polimorfismo Taq1A - rs1800497 e rs1076560), influenciando a ligação do receptor de dopamina D2 e o *splicing* de DRD2, COMT (polimorfismo Val158Met), que afeta a atividade enzimática e a estabilidade de proteínas e está relacionado à maior sensibilidade à dor e ao *craving*; DBH (polimorfismos rs1611115 e

rs2519152, além do polimorfismo DBH-STR), associado à atividade da dopamina b-hidroxilase e MAOA (polimorfismo 50 VNTR), relacionado à atividade da monoamina oxidase A.

Conforme exposto anteriormente, sabe-se que na FM ocorre uma secreção aumentada de BDNF (CAUMO *et al.*, 2016), enquanto indivíduos com obesidade tendem a apresentar níveis mais baixos de BDNF sérico (GOLDEN *et al.*, 2010; MCALLAN *et al.*, 2018). O polimorfismo BDNF-Val66Met (rs6265), uma variante genética do BDNF com perda de função, possui três genótipos possíveis (Val/Val, Val/Met ou Met/Met). Esse polimorfismo parece alterar a vulnerabilidade ao estresse, a reatividade do eixo HPA e do sistema de recompensa, ambos envolvidos na fisiopatologia da obesidade e da FM, representando uma possível integração entre essas patologias (MIAO; WANG; SUN, 2020; NOTARAS; VAN DEN BUUSE, 2020). Mulheres com FM apresentaram uma associação do polimorfismo Val66Met (rs6265) do BDNF com a catastrofização da dor. Os homozigotos Val/Val mostraram-se um potencial fator de risco genético associado à magnificação e ruminação dos domínios da catastrofização da dor na FM em comparação com controles saudáveis (DA SILVEIRA ALVES *et al.*, 2020). Ainda, os portadores do alelo Met apresentaram redução de volume no hipocampo e DLPFC (FERRIS; WILLIAMS; SHEN, 2007; PEZAWAS *et al.*, 2004), com risco aumentado de traços de ansiedade (ARIAS *et al.*, 2012), comportamento suicida (GONZÁLEZ-CASTRO *et al.*, 2017)e dependência de álcool (MATSUSHITA *et al.*, 2005), enquanto o alelo Val foi associado ao uso abusivo de heroína (CHENG *et al.*, 2005).

2.3.8.1 - Polimorfismo DRD2 Taq 1A (rs1800497)

A associação entre o genótipo do receptor dopaminérgico D2 e a obesidade em humanos tem sido investigada (BAIK, 2013; TUNBRIDGE *et al.*, 2019), e a maioria dos estudos

genéticos de fMRI que investigam a recompensa alimentar consideraram um polimorfismo comum, conhecido como Taq1A (rs1800497), cujo alelo A1 foi positivamente associado ao IMC em vários estudos genéticos iniciais (NOBLE *et al.*, 1994; SAVITZ *et al.*, 2013; SOUTHON *et al.*, 2003). Este polimorfismo está localizado a 10 kb abaixo da região codificadora do gene, na região codificadora da proteína de um gene vizinho de repetição de anquirina e domínio quinase 1 (ANKK1) (NEVILLE; JOHNSTONE; WALTON, 2004). O Taq1A (rs1800497) possui três variantes alélicas: (A1/A1), (A1/A2) e (A2/A2). Estudos post mortem e PET sugerem que indivíduos com uma ou duas cópias do alelo A1 apresentam 30–40% menos receptores D2 em comparação com aqueles sem o alelo A1 (BAIK, 2013).

O genótipo DRD2 está associado a uma maior ingestão calórica/energética, bem como a uma possível relação com o reforço alimentar (EPSTEIN *et al.*, 2004). Em homens, foi observada uma associação entre o genótipo DRD2 e uma maior ingestão de alimentos considerados "não-saudáveis" e ricos em calorias (COLLINS; FRANK, 2014). Além disso, o alelo A1 parece ser mais prevalente entre os indivíduos com diabete tipo 2 (BARNARD *et al.*, 2009).

Estudos genéticos de fMRI demonstraram que os portadores do alelo A1 (A1/A1 e A1/A2) apresentam respostas diminuídas em regiões ricas em dopamina no cérebro (estriado dorsal, mesencéfalo, tálamo, OFC) ao consumir milkshake em comparação a uma solução insípida, quando comparados aos indivíduos com genótipos A2/A2 (FELSTED *et al.*, 2010; STICE *et al.*, 2008). É importante ressaltar que essas respostas diminuídas às pistas e ao consumo de recompensa alimentar previram o ganho de peso futuro nos portadores do alelo A1 (Stice et al., 2008; Stice et al., 2010). Esses achados corroboram a ideia apresentada anteriormente de que a dopamina modula a resposta atenuada à recompensa alimentar e estímulos salientes na obesidade e em alguns transtornos alimentares (BECETTI *et al.*, 2023; BURGER; STICE, 2014). Ou seja, esses indivíduos podem recorrer ao consumo alimentar

excessivo para compensar a hipofuncionalidade desse sistema, especialmente aqueles com polimorfismos genéticos que parecem atenuar a sinalização da dopamina nessas regiões (MARQUÉS-ITURRIA *et al.*, 2015; STICE *et al.*, 2008).

2.3.8.2 - Associação entre o Polimorfismo Taq 1A (rs1800497) e o BDNF

Alguns estudos exploraram a possível associação entre o alelo A1 do polimorfismo Taq1A (rs1800497) e níveis de BDNF (GROVES, 2007; NONINO *et al.*, 2022), um fator de crescimento que desempenha um papel importante na plasticidade cerebral, desenvolvimento neuronal e regulação do humor (CAUMO *et al.*, 2016; FRIELINGSDORF *et al.*, 2010), abrindo novos caminhos para compreender a interação entre as características genéticas e os mecanismos de neuroplasticidade subjacentes à FM.

A presença do alelo A1 no polimorfismo Taq1A (rs1800497) no gene do receptor D2 da dopamina e o polimorfismo Val66Met (rs6265) no gene BDNF, isolados e/ou combinados, parecem um fator de risco adicional para o desenvolvimento de transtorno de compulsão alimentar em pacientes com obesidade, especialmente no contexto de reganho de peso (NONINO *et al.*, 2022). Uma interação epistática entre os polimorfismos Taq1A (rs1800497) e BDNF Val66Met (rs6265) foi observada em alguns traços de personalidade (Alexitimia, Busca de Novidades e Esquiva de Danos) (MONTAG *et al.*, 2010; WALTER *et al.*, 2011) e na gravidade dos sintomas do transtorno de estresse pós-traumático (HEMMINGS *et al.*, 2013). O racional mais bem aceito por trás da interação dos polimorfismos do BDNF (rs6265) e do DRD2 (rs1800497) pode ser o fato de o BDNF estar envolvido na modulação, manutenção e

funcionamento normal da neurotransmissão dopaminérgica mesolímbica (BERTON *et al.*, 2006; BUSTOS *et al.*, 2004; HÜNNERKOPF *et al.*, 2007). No entanto, mais estudos são necessários para se alcançar um completo entendimento dessa associação.

2.3.8.3 - Preditores Genéticos de Resposta à ETCC

Pesquisas examinam como diferentes genótipos podem modular a resposta à ETCC e algumas investigações sugerem que variações genéticas podem influenciar a resposta individual ao tratamento. Esses achados contribuem para estratificar melhor os participantes em ensaios clínicos e auxiliam na individualização de protocolos para proporcionar um tratamento mais efetivo. Tanto os níveis séricos quanto o polimorfismo Val66Met (rs6265) do BDNF têm sido apontados como um fator que influencia o efeito neuromodulador de terapias farmacológicas e não farmacológicas no tratamento da dor crônica, incluindo a ETCC (ZORTEA *et al.*, 2019). O polimorfismo Val66Met (rs6265) afeta a secreção de BDNF (EGAN *et al.*, 2003), impactando nos processos de plasticidade exercidos por este, anteriormente mencionados (Frielingsdorf, 2010). Na FM, o BDNF parece um intermediário entre a disfunção do sistema modulatório descendente da dor e os fenótipos emergentes caracterizados por sensibilização central e dor crônica, possivelmente subjacente ao padrão funcional entre áreas corticais para processamento e percepção da dor (DE OLIVEIRA FRANCO *et al.*, 2022). Outro sistema envolvido no processamento da dor, no *food craving* e provavelmente no efeito do tratamento é o sistema monoaminérgico, no qual a enzima COMT desempenha um papel crítico na degradação de catecolaminas, como a dopamina. O polimorfismo COMT Val158Met, que afeta a atividade dessa enzima e a estabilidade das proteínas, parece moldar os efeitos da ETCC aplicada ao DLPFC nas funções executivas (TUNBRIDGE *et al.*, 2019; ZORTEA *et al.*, 2019). Seguindo

esse racional, o polimorfismo Taq1A (rs1800497) no gene do receptor D2 da dopamina, que conforme exposto anteriormente, atenua a resposta dopaminérgica, também poderia predizer a resposta individual à ETCC, especialmente em pacientes com FM e comportamento alimentar disfuncional, onde a presença do alelo A1 exacerba os sintomas e está associado a piores respostas a outros tratamentos. No entanto, não encontramos estudos que considerassem essa variante genética na resposta à ETCC até o momento. Mais estudos que avaliem como diferentes genótipos podem modular a resposta à ETCC são necessários para elucidar se eles têm um efeito essencial que ajudaria a definir protocolos individualizados e eficazes.

Considerando todo o exposto, a técnica de estimulação transcraniana de corrente contínua aplicada em diferentes sítios de estimulação, como DLPFC e M1, não apenas demonstrou eficácia na redução dos sintomas depressivos, mas também no controle dos sintomas da fibromialgia e na melhora de comportamentos alimentares disfuncionais, especialmente modulando aspectos relacionados ao *food craving*. Frente a isso, mais pesquisas que possibilitem o desenvolvimento de intervenções terapêuticas para promover o equilíbrio do sistema motivacional da dopamina e/ou a melhora da sintomatologia associada à FM, se fazem necessárias para possibilitar uma melhora global no comportamento alimentar desses pacientes, prevenindo ou tratando o ganho de peso e a obesidade.

2.5 Equipamento de ETCC para uso Domiciliar

Visando a operacionalização do uso prolongado em nível domiciliar, nosso laboratório em parceria com a Engenharia Biomédica do HCPA desenvolveu um aparelho com dois canais

independentes, portátil e alimentado por baterias recarregáveis, possibilitando aplicação em ambiente domiciliar. O dispositivo está registrado na Agência Nacional de Vigilância Sanitária (Anvisa) sob o número n.º80079190028. Este dispositivo foi desenvolvido e validado para uso doméstico, conforme demonstrado pela sua utilização anterior em diversos ensaios realizados pelo nosso grupo (BRIETZKE *et al.*, 2020; CARVALHO *et al.*, 2018; CAUMO *et al.*, 2022). O aparelho monitora a impedância de contato a uma taxa de amostragem de 1 mA e interrompe a sessão caso a impedância ultrapasse um valor pré-determinado de 1 mA por um intervalo de 5 segundos ou se a corrente elétrica sofrer alteração superior a 10%. O equipamento registra o tempo e a duração do uso, bem como o tempo da sessão, permitindo o monitoramento da adesão. Desde julho de 2020, quando esse protocolo estava em andamento, o aparelho está sendo comercializado após aprovação da ANVISA e concessão de direitos à empresa que o obteve a concessão.

3. JUSTIFICATIVA

Conforme descrito anteriormente, está estabelecido na literatura que a presença de excesso de peso/obesidade exerce um impacto negativo na progressão e no prognóstico de pacientes com FM, acarretando custos adicionais para o sistema de saúde e agravando a qualidade de vida. Evidências atuais demonstram possíveis vias fisiopatológicas compartilhadas por essas duas patologias, bem como uma sinalização dopaminérgica alterada.

O polimorfismo Taq1A no gene do DRD2 afeta a transmissão dopaminérgica, especialmente nas áreas pré-frontais e estriatais do cérebro, e também pode predispor a uma maior ingestão calórica, menor resistência a alimentos hiperpalatáveis, aumento da percepção e sensibilidade à dor, além de sintomas depressivos e ansiosos. Portanto, é importante rastrear a presença desse polimorfismo em indivíduos com FM, que apresentam um comportamento alimentar disfuncional e subsequente ganho de peso. Se confirmado, isso pode abrir caminho para a elaboração de novas estratégias de cuidado que envolvam técnicas modulatórias de mudança de comportamento. A utilização da ETCC para o tratamento da dor e a modulação do comportamento alimentar disfuncional já apresenta evidências na literatura.

A possibilidade de usar a ETCC domiciliar em pacientes com fibromialgia possui várias vantagens, pois além de ser não invasiva, é indolor, simples e de baixo custo. Além disso, considerando que esses pacientes geralmente têm dificuldade de locomoção, o uso desta técnica representa um grande diferencial na adesão ao tratamento.

4. MARCO CONCEITUAL

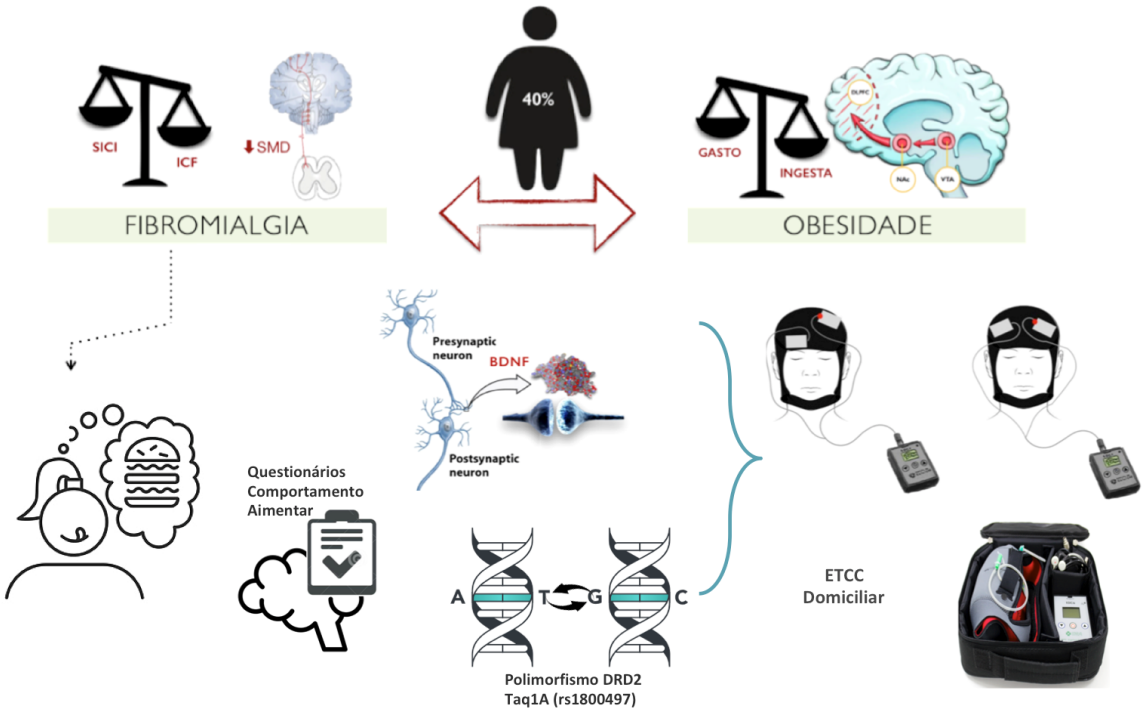

Figura 4. Marco Conceitual

5. OBJETIVOS

5.1 GERAL

Avaliar o efeito de 20 sessões de ETCC domiciliar aplicada sobre o córtex pré-frontal dorsolateral (DLPFC) esquerdo ou no córtex motor primário (M1) sobre a gravidade dos sintomas alimentares disfuncionais em mulheres com fibromialgia.

5.2 ESPECÍFICOS

1. Avaliar se o polimorfismo genético Taq1A alelo A1 (rs1800497) no gene do receptor D2 da dopamina atua como mediador na resposta à ETCC, aplicadas no DLPFC e no M1, no comportamento alimentar disfuncional na FM;
2. Investigar o papel das variações na neuroplasticidade entre os indivíduos, indexadas por alterações no fator neurotrófico derivado do cérebro (BDNF) ao longo do tratamento;
3. Analisar a relação entre o polimorfismo Taq1A (rs1800497) no gene do receptor D2 da dopamina e a resposta à ETCC no comportamento alimentar, considerando a gravidade dos sintomas da fibromialgia, incluindo incapacidade, sintomas depressivos, nível de sensibilização central e medidas de dor;
4. Investigar se a gravidade dos padrões disfuncionais do comportamento alimentar (*Three Factor Eating Questionnaire-21* e *Food Craving Questionnaire* – traço e estado) e o excesso de peso e circunferência abdominal estão correlacionados com o fator neurotrófico derivado do cérebro (BDNF) sérico e com o polimorfismo Taq1A (rs1800497) no gene do receptor D2 da dopamina.

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7. ARTIGOS

7.1 ARTIGO 1

A Framework for Exploring the Link Between Taq1A Polymorphism (rs1800497) and Eating Behavior in Women with Fibromyalgia

Submetido na *Nutritional Neuroscience*

A Framework for Exploring the Link Between Taq1A Polymorphism (rs1800497) and Eating Behavior in Women with Fibromyalgia

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Running title: Polymorphism Taq1A and eating behavior patterns in FM patients.

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ABSTRACT

Objective: To investigate if the severity of food cravings, disrupted eating patterns, and overweight status is correlated with serum brain-derived neurotrophic factor (BDNF), the severity of fibromyalgia (FM) symptoms, and the presence of the Taq1A genetic polymorphism.

Methods: This cross-sectional study included 106 women diagnosed with fibromyalgia (aged 30–65). Participants were divided into two groups based on the presence of the A1 allele on the Taq1A polymorphism (rs1800497): A1+ (n = 42) and A1- (n = 64). Instruments and assessments: the Food-Cravings Questionnaires (FCQ-state-S and FCQ-trait-T), the Three-Factor Eating Questionnaire-21 (TFEQ-R21), the Eating Disorder Examination Questionnaire (EDE-Q), the satiety perception (rated on a scale of 0–10) and anthropometric measures.

Results: A Generalized Linear Model (GLM), adjusting for mood, disability, and central sensitization, revealed a significant main effect of Taq1A genotype on food craving trait severity ($\chi 2 = 3.93$, $P < 0.04$). The A1+ genotype showed higher trait food cravings based on the adjusted marginal average and standard deviation [111.21 (38.03) on A+ compared to 91.21 (34.50) on A1-], respectively. Food craving severity correlated negatively with BDNF and positively with depressive symptoms, central sensitization, and pain-related disability. The A1 allele moderated satiety perception, central sensitization, restraint (EDE-Q), body mass index, and waist circumference.

Conclusion: A1+ carriers exhibited more intense food cravings associated with fibromyalgia symptoms, emphasizing the intricate connection between craving, disordered eating, and fibromyalgia severity. This study provides a framework integrating fibromyalgia symptoms, neuroplasticity, and dopaminergic signaling to explain the elevated prevalence of overweight status in individuals with fibromyalgia.

Key words: Fibromyalgia, food craving, disordered eating, polymorphism Taq1A.

1. INTRODUCTION

Fibromyalgia (FM) is characterized by widespread musculoskeletal pain, fatigue, cognitive impairment, and other symptoms associated with central sensitization (Yunus, 2008). Moreover, observational studies have found a strong link between fibromyalgia and obesity; up to 70% of FM patients are overweight or obese, which is higher than the rate of obesity and overweight in the general population (Narouze & Souzdalnitski, 2015). FM and obesity exhibit shared features, suggesting the presence of maladaptive processes. In this context, brain-derived neurotrophic factor (BDNF) emerges as a key player with relevance to both conditions (Elkfury et al., 2021). BDNF, integral to neuronal growth and maintenance, has been linked to disordered eating and is implicated in the neurobiological mechanisms underlying emotional aspects in FM and obesity. Simultaneously, genetic factors, specifically dopamine receptor genotypes, contribute to the intricate interplay between FM and obesity.

The mesocorticolimbic dopamine circuits that control motivation and cognitive processes have a large effect on how people eat and how much pain they feel (Volkow et al., 2008). Highly palatable foods, as well as pain and relief experiences, both have an impact on brain circuits that control motivation, salience, and decision-making (Leknes and Tracey, 2008). The Taq1A polymorphism (rs1800497) is a genetic variation found in the ANKK1 gene, close to the DRD2 gene, which codes for dopamine. This polymorphism has been extensively studied due to its association with differences in DRD2 density in the brain (Aliasghari et al., 2021). It is possible for people who have at least one A1 allele (A1+) to have 30% to 40% fewer DRD2 receptors in their striatum than people who do not have this allele (Jonsson et al. 1999), and this reduction in DRD2 density has been suggested as a potential risk factor for various addictive behaviors, including overeating (Noble et al. 1994). It is important to understand how the Taq1A polymorphism affects behaviors to fully understand how genetic, environmental, and

neurobiological factors interact to induce conditions like obesity and addiction. Notably, changes in dopamine signaling seem to play a part in FM, just as they do in obesity, eating disorders, food cravings, and addictive disorders (Volkow et al., 2017). Previous studies on people with fibromyalgia have found that DRD2 is more sensitive or present in denser concentrations and there is also a link between the number of dopamine D2/D3 receptors in women with fibromyalgia and their pain level as compared to healthy women (Ledermann et al., 2016). Since dopaminergic circuits are involved in the pathophysiology of both FM and obesity, more study is necessary to completely understand how food cravings and disordered eating can be influenced by neuroplasticity status, genetic variation, and FM symptoms (Ursini et al., 2011).

This study investigates the associations between the Taq1A (rs1800497) polymorphism, disordered eating, overweight, BDNF, and the severity of FM symptoms. We hypothesize that the severity of food cravings, disrupted eating patterns, and overweight status would be correlated with the serum BDNF, the severity of FM symptoms, and the Taq1A+ polymorphism.

2. METHODS

Study design

This cross-sectional study used the baseline data from one clinical trial registered under the ClinicalTrials.gov number NCT04192058. The protocol was approved by the Research Ethics Committee at the Hospital de Clinicas de Porto Alegre (HCPA), Porto Alegre, Brazil, with an Institutional Review Board registration number of 12625718.9.0000.5327 in the CAAE registry. Prior to participation, all subjects provided both verbal and written informed consent.

Setting, participants, and eligibility

Using the baseline data from the sample of one trial conducted in our institution between May 2019 and June 2022 via newspaper ads and the HCPA outpatient pain clinic in Porto Alegre, Brazil, subjects were diagnosed with fibromyalgia by a certified pain specialist using the American College of Rheumatology criteria (ACR-2016). Inclusion criteria were: women aged 30–65, right-handed, literate, and reporting pain scores ≥ 50 mm on a 0–100 mm visual analog pain scale (VAS 0–100 mm) on most days over the preceding three months. Exclusion criteria included: shift work, current or recent pharmacological treatment for obesity, history of bariatric surgery, pregnancy, present illicit substance/alcohol use, uncontrolled clinical/psychiatric diseases, rheumatoid arthritis, lupus, autoimmune/neurological/oncological conditions, and COVID-related symptoms.

Instruments and assessments

Eating behavior, anthropometric measures, psychological, and clinical assessments were performed by two trained research assistants blinded for the outcomes. All instruments used were validated to the Brazilian population.

Dependent and independent variables

The study's dependent variable was the food craving trait scores (primary outcome). Secondary outcomes included food craving state scores, and both measured by the Food-Cravings Questionnaires (FCQ), while eating behavior domains (cognitive restraint, uncontrolled eating, and emotional eating) were measured by the Three-Factor Eating Questionnaire-21 (TFEQ-R21). Additional measures included satiety, assessed by a numerical rating scale, and Body mass index (BMI). The study's primary factor of interest was the Taq1A (rs1800497) genetic variant, with other covariates consisting of pain catastrophizing, disability due to pain, impact of fibromyalgia symptoms on quality of life, depressive symptoms, sleep quality, symptoms of central sensitization, and BDNF.

Assessment of primary and secondary outcomes

a. The FCQ was implemented, consisting of two domains: the FCQ-trait-(T) assessment, with 39 questions across nine dimensions for assessing food-craving behavior patterns, and the FCQ-state-(S) assessment, with 15 questions in five dimensions for measuring current food cravings. Higher scores indicated stronger cravings.

b. The TFEQ-R21 assessment was used to assess three domains of eating behavior: uncontrolled eating (UE) (primary outcome), cognitive restraint (CR), and emotional eating (EE). Each domain was scored separately, with higher scores indicating a greater likelihood of disordered eating. Total scores for each domain could range from 0 to 100.

c. The EDE-Q test assessed eating psychopathology symptoms over the preceding 28 days. The instrument was comprised of four subscales: restraint, eating concern, shape concern, and weight concern. Scores were calculated by averaging responses within each subscale and across all subscales. Cutoff points provided thresholds for identifying elevated levels of eating psychopathology: the global scale (2.12), restraint subscale (1.49), eating concern (1.37), weight concern (2.63), and shape concern (2.12).

d. Volunteers responded to a single question regarding their satiety for non-specific, sweet, and savory foods using a 10-point Numerical Rating Scale (NRS), in which "0" indicated no desire or need to eat, and "10" denoted a very prominent desire or need to eat. Additionally, participants reported the times within a 24-hour period when these sensations were most and least prominent, following the protocol outlined by Jauch-Chara et al. (2014).

Anthropometric assessment

Height and weight assessment were performed by the same researcher using standardized techniques. BMI was also calculated based on these measurements. Additionally, waist

circumference (cm) was determined using an inelastic tape at the widest abdominal perimeter between the iliac crest and the last rib (Sanny, TR4013). The reported outcome was the average of three measurements.

Sociodemographic and medical comorbidities, psychological and sleep assessments, pain and central sensitization measurements, pain catastrophizing, and depressive symptoms

e. Participants in the study completed a standardized questionnaire providing information on medical comorbidities and sociodemographic data. Pain intensity was measured using a Numeric Pain Scale (NPS 0–10), in which a score of zero indicated no pain and a score of ten represented the highest level of pain experienced most of the time in the past week.
f. The Fibromyalgia Impact Questionnaire (FIQ) assessed the impact of fibromyalgia on quality of life.
g. The Profile of Chronic Pain: Screening (Br-PCP:S) was used to evaluate individuals' multidimensional pain experiences, including severity, disability, and emotional burden. The total score on this scale ranged from 0 to 93 points.
h. The Central Sensitization Inventory (BP-CSI) was employed to assess the symptoms of central sensitivity syndromes.
i. The Beck Depression Inventory-II (BDI–II) was employed to assess the severity of depressive symptoms.
j. Pain catastrophizing was evaluated using the Pain Catastrophizing Scale (B-PCS).
k. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality.

Determination of the Taq1A (rs1800497) genetic variant and serum BDNF

e. ***Taq1A Polymorphism (rs1800497):*** Blood samples were collected via venipuncture with EDTA-containing tubes and total DNA was extracted and purified using the PureLink® Genomic DNA Kit from Invitrogen, ThermoFisher Scientific. Then, the genotyping of the Taq1A (rs1800497) polymorphism was performed at the HCPA Experimental Research Center. A StepOnePlusTM Real-Time PCR System by Applied Biosystems Inc, Foster City, USA, along with a pre-designed TaqManTM SNP genotyping assay from Thermo Fisher Scientific (catalog 4351379, assay ID_C7486676), was used for genotyping. The AA and AG genotypes corresponded to A1+, while GG corresponded to A1-.

f. ***Serum BDNF concentration:*** Blood samples were collected using vacuum heparin gel tubes. After centrifugation for 15 minutes at 500 rpm, serum was obtained and immediately stored at -80 °C until the assay was performed. The serum concentration of BDNF was determined using the ELISA method, employing a human BDNF ELISA kit (CYT306, Chemicon/Millipore, Billerica, MA, USA). For the ELISA assay, optical density readings were obtained using either the GloMax®-Multi Microplate Reader from Promega or the Bio-Plex®-200 device from Bio-Rad. Total protein levels were measured using the Bradford method, with bovine serum albumin used as a standard following the manufacturer's instructions. The kit had a detection limit of 0.08 ng/mL for serum BDNF concentrations, with intra-assay and inter-assay coefficients of variation (CV) below 10% and 12%, respectively. Concentration values were expressed as pg/ml of protein.

Statistical analyses

Descriptive statistics were used to summarize socio-demographic characteristics, employing t-tests, Chi-squared tests, and Fisher's exact tests for comparisons between groups. The Shapiro-Wilk test assessed data normality, with most dependent variables not meeting criteria for

parametric analysis. Spearman correlation coefficients examined relationships between covariates (e.g., BDNF, sleep quality, pain catastrophizing, depressive symptoms, central sensitization scores) and dependent variables (e.g., FCQ state and trait, TFEQ-R21, and domains), satiety, and BMI.

Generalized linear models (GLMs) were used to assess Taq A1 polymorphisms (A+ and A-) in relation to eating behavior, considering the potential mediation of clinical symptoms (BDNF, central sensitization, pain catastrophizing, sleep quality, depressive symptoms). Covariates were selected based on statistical and biological plausibility criteria. Chi-square tests effect size was measured using Cramer's V. Moderation analysis explored how the A1 allele influenced the relationship between disordered eating behavior and previously linked factors. IBM SPSS Statistics 26 and SPSS Process Macro were used for analyses. Multiple comparisons were adjusted using the Bonferroni test. A Type I error rate of 5% was accepted.

A post-hoc power analysis was run because was a lack of previous studies on food craving patterns in relation to the Taq1A (rs1800497) genetic variants Taq A1 A+ and A- in FM cases. Thus, we analyzed the power of GLM analysis to verify if the genetic variant Taq A1 was linked to the severity of food craving patterns in FM. This power analysis revealed that, in a sample of 106 patients, based on the adjusted effect size of the GLM, which was equal to 0.4 ($\chi 2$ = 3.93, DF = 1, P < 0.04) for a type I error equal to 0.05, the power of the study was 98% (Xu et al., 2022).

3. RESULTS

3.1. Demographic, clinical, and psychiatric characteristics

We initially screened 250 patient candidates for our study; of these, 144 patients were excluded because 116 did not meet inclusion criteria and 28 had symptoms associated with SARS-CoV-2. Our final sample consisted of 106 females. Based on the Taq1A (rs1800497) genetic variant, 42

were found to have Taq A1 A+, and 64 were found to have A-. Table 1 summarizes the clinical features and demographics. As shown in Table 1, we noticed a trend imbalance in BDNF levels despite no differences between the groups.

_____insert table 1 here_____

3.2. Assessment of state and trait food cravings and eating behavior domains

Table 2 presents the univariate analysis of comparisons of groups according to Taq1A polymorphism (rs1800497) for A1+ and A1- variants. These outcome measurements consisted of state and trait food cravings and various eating behavior domains, including cognitive restraint, uncontrolled eating, and emotional eating. Additionally, it was compared to the perception of satiety. We did not find significant differences in these measures.

----------Insert table 2 ----------

3.3. Assessment of relationship between independent variables to identify potential confounders.

We used Spearman correlation analysis to identify covariates that could change the relationship between the outcomes (food cravings, eating behavior domains, and BMI) and the Taq1A polymorphism (rs1800497). The parameters included in the correlation analysis encompassed scores related to pain catastrophizing, disability due to pain, depressive symptoms,

sleep quality, heat pain tolerance, and BDNF. The results of this analysis are presented in Table 3.

----------Insert Table 3----------

3.4. Food craving patterns according to the Taq1A polymorphism (rs1800497) A1+ and A1- genotypes

3.4.1. Primary outcome

A GLM revealed a significant main effect of the Taq1A polymorphism (rs1800497) food craving patterns (FCQ-T scores) according to genotypes A1+ (n = 42) and A1- (n = 62) ($\chi 2$ = 3.93, DF = 1, P < 0.04). The adjusted marginal means of trait food cravings in the genotypes A+ were 111.21 (SD, 38.03) and 91.21 (34.50), respectively. The severity of the food craving score was negatively correlated with serum BDNF. In contrast, it exhibited positive correlations with depressive symptoms, central sensitization level, and the level of disability due to pain.

In the final GLM, only the covariates that had a significant relationship with the food craving score were retained. There was a large ES on food cravings for the A1+ compared to the A- genotypes ($\chi 2$ = 3.99; ES = 0.40). Similarly, a large ES was observed for clinical symptoms related to fibromyalgia on the food craving pattern (as shown in Table 4). In summary, disordered eating in fibromyalgia was positively correlated with the severity of symptoms related to mood, disability, and central sensitization.

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

3.4.2 Secondary Outcomes

The GLM analysis showed that the Taq1A polymorphism (rs1800497) was not linked to state of food cravings, uncontrolled eating, emotional eating, cognitive restraint, and BMI. The adjusted results from the general linear models (GLMs) are presented in Table 5.

These models retained variables associated with the respective outcomes: state of food cravings, uncontrolled eating, and emotional eating. No covariable was retained in the model with cognitive restraint as the outcome, so we did not present this outcome in the table. Both the state of food cravings and emotional eating exhibited an inverse correlation with BDNF. Additionally, the state of food cravings was associated with pain catastrophizing, depressive symptoms, and disability due to pain.

The interaction analysis of the Taq A1 polymorphism, as presented in Table 5, reveals a noteworthy influence of the Taq A1 A+ genotype on the correlation between BMI, BDNF, and the severity of disability due to pain. Specifically, when examining the correlation between serum BDNF and BMI in isolation, a positive relationship is observed. However, the introduction of the Taq A1 A+ genotype modifies this correlation, indicating an interactive effect between the Taq A+ polymorphism and BDNF.

Moreover, the level of disability due to pain is initially positively correlated with BDNF. However, the introduction of the Taq A+ polymorphism transforms this correlation into a negative association with BMI. This suggests moderator effect of this polymorphism with the neuroplasticity (as indicated by BDNF levels), and the impact of pain-related disability on BMI.

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

3.5. Secondary analysis: A1 Genotype's Moderating Influence on the Link Between Anthropometric Measures, Eating Behavior, and Central Sensitization Severity

We performed regression analyses to examine the impact of the A1 genotype on the association between eating behavior, anthropometric measures, and the severity of fibromyalgia symptoms. Table 6 displays the results, highlighting a moderating effect of the A1 genotype in these relationships. Figure 2 (A, B, C) visually demonstrates how the linear relationship shifts direction based on the presence of the A1 allele.

----------Table 6 ----------

----------Figure 2----------

4. DISCUSSION

These findings underscore the complex relationships among Taq1A polymorphism (rs1800497), clinical symptoms, neuroplasticity state, and eating behavior in the context of fibromyalgia. (i) It was found that people with the Taq1A polymorphism (rs1800497) A1+ genotype were more likely to have stronger food cravings. They add to the evidence that higher BMI, waist circumference measurements, food cravings, uncontrolled eating, and emotional eating are all linked to more severe depressive symptoms, pain exaggeration, central sensitization symptoms, and disability due to pain. (iii) They revealed the moderator effect of A1+ genotype in the relationship between eating behavior, anthropometric measures, disability due to pain and central sensitization symptoms. Besides, the considerable effect sizes (ES) observed in these measures emphasize a strong connection between clinical symptoms of fibromyalgia and disordered eating.

The novelty of this study is its construction of a framework integrating the severity of symptoms due to fibromyalgia with changes in the state of neuroplasticity and Taq1A polymorphism (rs1800497) to comprehend their relationships to food craving and disordered eating paradigms according to the Taq1A polymorphism (rs1800497) A+ and A-. More precisely, from a conceptual perspective, our findings could explain the pathophysiological processes underlying disrupted eating in fibromyalgia that are linked with the neuroplasticity state indexed by serum BDNF. These results show how the Taq1A polymorphism can affect eating behavior that leads to overeating and how these behaviors are linked to symptoms of fibromyalgia. In a broader sense, these findings contribute to a greater understanding of the pathophysiological processes that lead to disordered eating in people with fibromyalgia, which is in line with a heuristic biopsychosocial model. These findings are valuable for improving diagnosis and potentially accelerating the translation of results into clinical practice. The way this study was organized, as well as the complicated relationships between the variables, make it impossible to establish clear cause-and-effect links. However, the fact that these factors were associated with a higher BMI suggests such links are likely to exist. The severity of fibromyalgia's core symptoms, such as disability due to pain, depressive symptoms, central sensitization, and pain catastrophizing, can help doctors assess which patients are more likely to have greater problems related to eating behaviors. This information could thus be used as biofeedback to help such patients heal through therapy and rehabilitation. Likewise, these findings suggest that an increased prevalence of disordered eating, overweight, and obesity in fibromyalgia patients is linked to the Taq1A polymorphism, combined with the severity of cardinal symptoms of fibromyalgia.

These findings strongly link the Taq1A genotype (rs1800497) A+ allele to changes in eating behavior and food cravings. This is consistent with other research that has shown that brain dopamine plays a role in eating behaviors in both healthy (Volkow et al., 2003) and overweight

people (Marqués-Iturria et al. 2015). Additionally, previous research found that possessing fewer striatal D2 receptors was linked with food cravings (Yeh et al. 2016). Thus, overeating observed in fibromyalgia patients carrying Taq1A supports the idea that people carrying this polymorphism might have trouble controlling eating. Similarly, these results show that this association may be stronger for people who are constantly stressed, like those with fibromyalgia and pain (Groesz et al. 2012). Thus, this disrupted eating could be linked to disinhibition in brain circuits, including the cingulate gyrus (CG) and the dorsolateral prefrontal cortex (DLPFC). These brain regions are essential for controlling cravings and preventing oneself from doing something (Koob and Volkow 2016). Other studies have shown that the A1 allele of the Taq1A polymorphism reduces the number of D2 receptors, which makes subjects more likely to have problems with their eating and become addicted (Obregón et al., 2022; Montalban et al., 2023). This hypothesis is biologically plausible, as dopamine plays a crucial role in various brain functions, including motivation, reward, and pleasure. Thus, the link between the allele A+ Taq1A genotype and disordered eating patterns could be related to disruptions in the dopamine system (Lowe et al., 2013). Conversely, people lacking the A1 allele may experience fewer intense food cravings, potentially positively impacting weight control (Davis et al., 2007).

Our results demonstrate that the Taq1A polymorphism and disordered eating are positively correlated with score fibromyalgia symptom, such as pain catastrophizing, depressive symptoms, central sensitization, and pain-related disability. The symptoms in question have been previously associated with an imbalance in excitability and inhibition, as evidenced by neurophysiological measures, such as cortical excitability, efficiency of descending pain inhibitory systems, and serum BDNF levels (Zanette et al., 2014; Cardinal et al., 2019; Soldatelli et al., 2021). Accordingly, previous studies suggest that this imbalance is characterized by the strengthening of glutamatergic neuronal excitatory transmission and the weakening of the gamma-aminobutyric acid (GABAergic) system. This intricate process forms the foundation of the imbalance, emphasizing the interplay between the Taq1A polymorphism

and BDNF. Additionally, these findings highlight the crucial role of the interplay between Taq1A polymorphism and BDNF in mediating the relationship between the imbalance of excitability and inhibition and the severity of clinical symptoms associated with pain and disordered eating behaviors. Despite the complex relationship between neurobiological processes, such as neuroplasticity processes, genetic polymorphisms, and the positive correlation between the severity of fibromyalgia symptoms and disruptive eating behavior, according to previous studies, these factors form a cascade of events as part of the maladaptive coping strategy of compensatory eating behavior, which is connected to chronic stress (Amy and Kozak, 2012; O'Loughlin and Newton-John, 2019). Moreover, other factors may modulate these relationships, such as reduced physical activity or side effects of medications used to manage chronic pain, which increase appetite or weight gain (McLoughlin et al., 2011; Arnold et al., 2012).

In contrast, the present study found that relationship between serum BDNF and disordered eating appeared to follow an opposite trend. This finding aligns with recent meta-analyses indicating lower serum BDNF levels in subjects with eating disorders as compared to those without (Shobeiri et al., 2022). Such findings are consistent with the literature, highlighting BDNF as a crucial regulator of eating behavior (Saito et al., 2009; Monteleone and Maj, 2013). Previous animal studies further support this, demonstrating that BDNF knockouts induced hyperphagia and obesity, while BDNF administration decreased food intake and body weight (Nakagawa et al. 2000; Kernie 2000). A relevant finding of the present study is that the serum BDNF was conversely correlated with trait food craving and BMI. This is in line with the literature, which has shown that individuals with obesity tend to have lower levels of serum BDNF compared to those with a healthy weight (Golden et al., 2010; McAllan et al., 2018). This association has led to investigations into the potential impact of BDNF on bodyweight regulation and metabolism (Wang and Zhou, 2002). From the same perspective, it has been

demonstrated that BDNF is involved in the regulation of appetite and energy balance (Urabe et al., 2013).

When we looked at the interaction analysis, we saw that the Taq1A polymorphism changed the direction of the correlation between BMI and BDNF. Besides, a similar effect was found in the correlation between BMI and the severity of pain-related disabilities in Taq1A+ individuals. This moderator effect fits with what Wang et al. (2001) say about how genetic differences can affect neurobiological pathways and physiological responses. This is an interesting example of how genetic factors, mainly the Taq1A polymorphism, can change the links between neurological factors like BDNF, obesity symptoms, and disabilities caused by pain. This fits the idea that genetic differences can be essential moderators, changing the complex relationship between BMI and health outcomes, as Johnson et al. (2011) have shown. These moderator effects are crucial for determining the complicated links between genetics, obesity, and health problems. This fits with the bigger picture of how genes and the environment interact, highlighting the importance of looking at the effects of genetic differences on health outcomes from a broad perspective.

It is important to acknowledge the limitations of this study regarding its design and the interpretation of these results. First, despite the initial hypothesis, which postulated that we would find differences in eating behavior domains between groups with and without the Taq1A polymorphism, the study did not find such distinctions. This lack of difference may be attributed to a type II error due to insufficient power for some secondary outcomes. Second, it is possible that, despite control efforts, the effect of confounding factors (i.e., psychiatric comorbidities, psychotropic medications, and psychiatric symptoms) that could influence the relationship of Taq1A genetic variant on eating behaviors persisted, a residual confounding effect of these factors. Third, we included only women; although such homogeneous sampling reduces the potential for confounding bias, it also limits the external validity. Even though it is limited, they can be extrapolated for most fibromyalgia, which is still prevalent at higher rates in women than

in men (Ruschak et al., 2023). Also, the absence of a follow-up period limited our ability to gain a better understanding of the impact of the relationship between the Taq1A polymorphism and the dysfunctional neuroplasticity as factors affecting disordered eating and overweight in the long-term.

In conclusion, A1+ carriers exhibited more intense food cravings associated with fibromyalgia symptoms, emphasizing the intricate connection between craving, disordered eating, and fibromyalgia severity. This study provides a framework integrating fibromyalgia symptoms, neuroplasticity, and dopaminergic signaling to explain the elevated prevalence of overweight status in individuals with fibromyalgia.

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Table 1. Sample characteristics according to the presence or absence of Taq A1 polymorphism (n=106).

	A1+ group (n=42)	**A1- group** (n=64)	***p-value***
Frequency (%)	39.60	60.40	
Demographic and anthropometric data			
Age (years)[¥]	48.5 (43.75-56.00)	51.5 (39.25-57.75)	0.97
Body Weight[¥]	75.32 (68.60-81.58)	73.75 (64.22-85.75)	0.95
Height (m)[*]	1.58 (0.60)	1.61 (0.60)	0.10
BMI (Kg/m^2)[¢ *]	29.60 (3.92)	29.63 (5.45)	0.97
Waist circumference (cm)[*]	96.23 (9.10)	97.79 (12.97)	0.51
Formal education (years)[*]	12.57 (4.00)	11.92 (4.90)	0.48
Clinical, psychiatric, and psychological data			
Psychiatric disorder	32/42	51/64	0.67
Anxiety	20/42	29/64	0.77
Depression	26/42	21/64	0.82
Bipolar mood disorder	1/42	0/64	0.19
Panic disorder	7/42	9/64	0.44
Tobacco	11/42	10/64	0.20
Alcohol	19/42	20/64	0.26
Substances	7/42	6/64	0.21
Hypertension	9/42	15/64	0.70
Diabetes Mellitus	2/42	5/64	0.27
Fibromyalgia Impact Questionnaire – FIQ[¥]	17.00 (13.00-20.50)	16.00 (12.25-19.75)	0.48
Pain Catastrophizing Scale Total Score– PCS[¥]	37.00 (31.00-42.00)	37.00 (28.25-43.00)	0.96
Rumination - PCS [¥]	12.50 (10.00-14.00)	12.00 (9.25-14.00)	0.75
Magnification- PCS[¥]	9.00 (6.00-10.00)	9.00 (6.00-10.00)	0.92
Helplessness- PCS[¥]	16.00 (13.00-19.00)	17.50 (12.00-20.00)	0.99

Pittsburgh Sleep Quality Index -PSQI*	13.51 (3.75)	12.83 (3.43)	0.35
Brazilian Portuguese Central Sensitization Inventory – BP-CSI¥	65.00 (57.00-73.00)	69.5 (52.5-77.00)	0.43
Beck Depression Inventory – BDI II *	26.01 (11.23)	25.96 (10.64)	0.95
Psychotropic medication			
Antidepressants	25/42	42/64	0.91
Tricyclic antidepressants	6/42	12/64	0.10
Dual Action Antidepressants	17/42	18/64	0.15
Selective serotonin reuptake inhibitors	8/42	20/64	0.18
Benzodiazepines	6/42	11/64	0.71
Anticonvulsants	12/42	21/64	0.30
Opioids	12/42	15/64	0.43
Laboratorial			
Serum brain-derived neurotrophic facto ¥	31.48 (23.86-58.99)	44.77 (25.80-75.34)	0.22

* Parametric data were assessed by Student's T test for independent samples; values represented as mean standard (± standard deviation (SD)).
¥ The Mann-Whitney U test was performed in non-parametric data; values represented as median (IQR 25-75). "A1+ group" = genotypes with the presence of A1 allele in the DRD2 polymorphism (A1/A1 and A1/A2) and "A1-group" = genotypes with absence of Taq A1 polymorphism (A2/A2).

Table 2. Measurements of state and trait food cravings, eating behavior domains and satiety perception according to the Taq1A polymorphism (rs1800497), A1+ and A1-. (n=106).

Dependent variables	**A1+ group** (n=42)		**A1- group** (n=64)		***P-value***
	Mean (SD)	**Median** $_{(IQ15-75)}$	**Mean (SD)**	**Median** $_{(IQ15-75)}$	
Food Craving Questionnaires - FCQ					
Food Craving State - FCQ	37.38 (10.29)	37.50 (15; 36)	37.53 (12.10)	36 (18 ; 60)	0.82
Food Craving Trait - FCQ	92.16 (30.87)	87 (35.48 ; 175)	100.76 (37.97)	88.5 (18 ; 60)	0.41
Three Factor Eating Questionnaire - TFEQ-R21					
Cognitive Restraint - TFEQ-R21	41.01 (25.69)	39 (-9.39 ; 94)	43.55 (22.09)	44 (-6 ; 94)	0.61
Uncontrolled Eating - TFEQ-R21	36.80 (20.09)	37 (4 ; 89)	36.28 (20.56)	33 (0 ; 100)	0.82
Emotional Eating - TFEQ-R21	40.29 (30.31)	30.50 (-10.60 ;100)	42.77 (31.67)	39 (0 ; 100)	0.76
Satiety on Numerical Scale (0-10)	6.68 (2.19)	7 (0.5 ; 10)	6.70 (2.33)	7 (2 ; 10)	0.86

The Mann-Whitney U test was use to compare "A1+" = genotypes with the presence of A1 allele (A1/A1 and A1/A2) and "A1"= genotypes with absence of Taq A1 polymorphism (A2/A2).

Table 3: Spearman correlation analysis of outcome measures (food craving, eating behavior domains and BMI) with potential confounding factors (n=106).

		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(12)	(13)
1	Food Craving State	1											
2	Food Craving Trait	.68**	1										
3	Cognitive Restraint	-.05	.07	1									
4	Uncontrolled Eating	.57**	.63**	-.03	1								
5	Emotional Eating	.47**	.66**	.06	.60**	1							
6	Body Mass Index (IBM)	.10	.18	.08	-.02	.27**	1						
7	Brazilian Pain Catastrophizing Scale - BP-PCS	.32**	.17	-.08	.28*	.07	-.02	1					
8	Pittsburgh Sleep Quality Index (PSQI)	-.05	-.08	.05	-.09	.02	.07	-.14	1				
9	Central Sensitization Inventory (CSI)	.28**	.33**	-.12	.11	.20*	.08	.52**	-.08	1			
10	Brazilian Portuguese version of the Profile of Chronic Pain: Screen B-PCP:S -Br	.20*	.22*	.03	.02	.05	.15	.11	.30**	.08	1		
11	Beck Depression Inventory-II (BDI–II)	.29**	.32**	-.19*	.26**	.20*	-.08	.52**	-.15	.58**	-.08	1	
12	Brain-derivate-neurotrophic-factor (BDNF)	-.11	-.19*	-.04	-.09	-.19*	-.02	.07	.06	.04	.09	-.02	1
13	Heat pain tolerance (°C)	.12	.06	-.06	.04	.07	.06	.13	-.22*	.06	-.08	.08	-.03

Table 4. Generalized linear model analysis to assess the relationship of scores in the Food Craving Questionnaire - Trait (FCQ-T) according to the Taq1A polymorphism (rs1800497) A1+ (n=62) and A1- (n=64) and severity of symptoms related to mood, disability, and central sensitization (n = 106).

Primary outcome							
Food Craving Questionnaire - Trait (FCQ-T)							
	Beta	**SEM**	**CI 95%**	**Wald χ2**	**df**	**P**	**ES**
A1+ group (n=42)	-20.056	10.157	(-39.96 to -0.14)	3.99	1	.048	0.4
A1 – group (n=62)	0[reference]						
Brain-derivate-neurotrophic-factor (BDNF)	-.296	.121	(-.53 to -0.06)	5.93	1	.015	0.49
Brazilian Portuguese version of the Profile of Chronic Pain: Screen B-PCP:S -Br.	.483	.213	(.07 to 0.90)	5.13	1	.023	0.45
Central Sensitization Inventory (CSI)	.458	.235	(.03 to 0.92)	3.80	1	.048	0.39
Beck Depression Inventory-II (BDI–II):	1.094	.382	(.34 to 1.85)	8.17	1	.004	0.58
Interaction analysis							
A1+ group vs. Brain-derivate-neurotrophic-factor (BDNF)	.258	.174	(-.08 to 0.60)	2.19	1	.138	-----
A1- group vs. Brain-derivate-neurotrophic-factor (BDNF)	0[reference]						

Primary outcome – generalized linear model analysis to compare responders and non-responders. The Cramer's V was used as a measure of effect size for chi-square tests. The size effect was interpreted as follows: Standards for interpreting Cramer's V proposed by Cohen (1988) are the following. DF (degrees of freedom) = 1 (0.10 = small effect) (0.30 = medium effect) (0.50 = large effect). https:// www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-R5.php. P < 0.05 indicates significant differences between treatments in the estimated marginal means adjusted for multiple comparisons by the Bonferroni test.B: regression coefficient, SE: standard error, CI: confidence interval, χ 2 : Wald chi-square, df: degrees of freedom.

Table 5. Secondary Outcomes: Food craving state, uncontrolled eating, emotional eating, satiety, and BMI according to the Taq1A polymorphism (rs1800497) A1+ (n=62) and A1- (n=64) (n = 102).

Secondary outcome							
Food Craving Questionnaire - State (FCQ-S)							
	Beta	**SEM**	**CI 95%**	**Wald χ^2**	**df**	**P**	**ES**
A1+ group (n=42)	-2.98	3.263	(-9.38 to 3.41)	.837	1	.36	---
A1 – group (n=62)	$0^{reference}$						
Brain-derivate-neurotrophic-factor (BDNF)	-.078	.0415	(-.15 to -0.002)	3.53	1	.04	.37
Profile of Chronic Pain: Screen PCP:S	.171	.0822	(.01 to 0.33)	4.327	1	.03	.42
Beck Depression Inventory-II (BDI–II)	.245	.1317	(-.2 to -0.03)	3.66	1	.04	.38
Pain catastrophizing Scale – PCS	.179	.0994	(-.16 to -0.04)	3.47	1	.02	.37
Interaction analysis							
A1+ group vs. Brain-derivate-neurotrophic-factor (BDNF)	.060	.0577	(-.05 to 0.17)	1.064	1	.30	---
A1- group vs. Brain-derivate-neurotrophic-factor (BDNF)	$0^{reference}$						
Three Factor Eating Questionnaire (TFEQ) uncontrolled eating (UE)							
	Beta	**SEM**	**CI 95%**	**Wald χ^2**	**df**	**P**	**ES**
A1+ group (n=42)	-4.430	6.302	(-16.78 to 7.92)	.494	1	.482	---
A1 – group (n=62)	$0^{reference}$						
Profile of Chronic Pain: Screen B-PCP:S -Br	.093	.0390	(.02 to 0.17)	5.722	1	.017	.45
Three Factor Eating Questionnaire (TFEQ)- emotional eating (EE)							
	Beta	**SEM**	**CI 95%**	**Wald χ^2**	**df**	**P**	**ES**

A1+ group (n=42)	.116	6.419	(-12.46 to 12.69)	.000	1	.986	----
A1 – group (n=62)	0[reference]						
Brain-derivate-neurotrophic-factor (BDNF)	-.214	.0924	(-.39 to -0.03)	5.366	1	.021	.46
Central Sensitization Inventory (CSI)	.514	.1971	(.13 to 0.90)	6.803	1	.009	.52
Satiety on Numerical Scale (0 to 10)							
	Beta	**SEM**	**CI 95%**	**Wald χ^2**	**df**	**P**	**ES**
A1+ group (n=42)	.098	.4234	(-.73 to 0.93)	.054	1	.816	
A1 – group (n=62)	0[reference]						
Beck Depression Inventory-II (BDI–II):	-.076	.0251	(-.13 to -0.03)	9.082	1	.003	.61
Central Sensitization Inventory (CSI)	.043	.0175	(.09 to 0.18)	5.998	1	.014	.49
Body Mass Index (BMI)							
	Beta	**SEM**	**CI 95%**	**Wald χ^2**	**df**	**P**	**ES**
A1+ group (n=42)	7.474	4.880	(-2.09 to 17.04)	2.345	1	.126	----
A1 – group (n=62)	0[reference]						
Brain-derivate-neurotrophic-factor (BDNF)	-.027	.0207	(-.07 to -0.02)	3.664	1	0.03	.38
Profile of Chronic Pain: Screen PCP:S	.103	.0509	(.03 to 0.20)	4.074	1	.044	.40
Interaction analysis							
A1+ group vs. Brain-derivate-neurotrophic-factor (BDNF)	.057	.0239	(.01 to 0.14)	5.748	1	.017	.48
A1- group vs. Brain-derivate-neurotrophic-factor (BDNF)	0[reference]						
A1+ group vs. Profile of Chronic Pain: Screen PCP:S	-.139	.0660	(-.27 to -0.03)	4.460	1	.035	.42
A1- group vs. Profile of Chronic Pain: Screen PCP:S	0[reference]						

Degrees of freedom (Df), Beta coefficient (B), The standard error of the mean (SEM); Effect size (ES) according to guidelines (Cohen) equivalent phi value .1 represents a small effect, = .3 represents a medium effect and = .5 represents a large effect. Effect Size Calculator (campbellcollaboration.org). It indicates that the ES was not calculated by not detect difference between treatment

Table 6. Moderation model effects in A1+ group on anthropometric measures (n=42).

Conditional effects (W)	**Coefficient B**	**SE**	**t**	**P**
Satiety*BPCSI	0.05	0.02	2.22	0.03
Restraint (EDE)*BMI	0.15	0.05	2.71	0.008
Restraint (EDE)*Waist Circumference	0.05	0.03	2.21	0.013

"A1+ group" = genotypes with the presence of A1 allele in the DRD2 polymorphism (A1/A1 and A1/A2). BPCSI= Brazilian Portuguese Central Sensitization Inventory. EDE= Eating Disorder Questionnaire.

Figure 1.

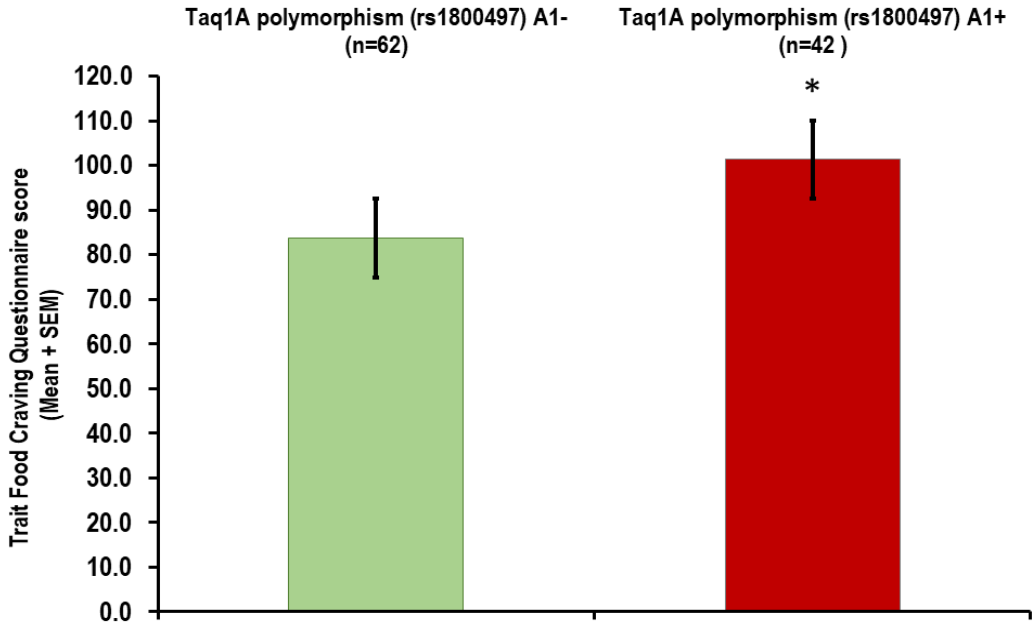

Figure 1. Food craving patterns (FCQ-T scores) according to genotypes A1+ (n = 42) and A1- (n = 62). Error bars represent the standard error of the mean. An asterisk denotes significant differences in all interventions ($P < 0.05$). A generalized linear model (GLM) was used for the analyses, and the Bonferroni test was used for post-hoc multiple comparisons.

Figure 2.

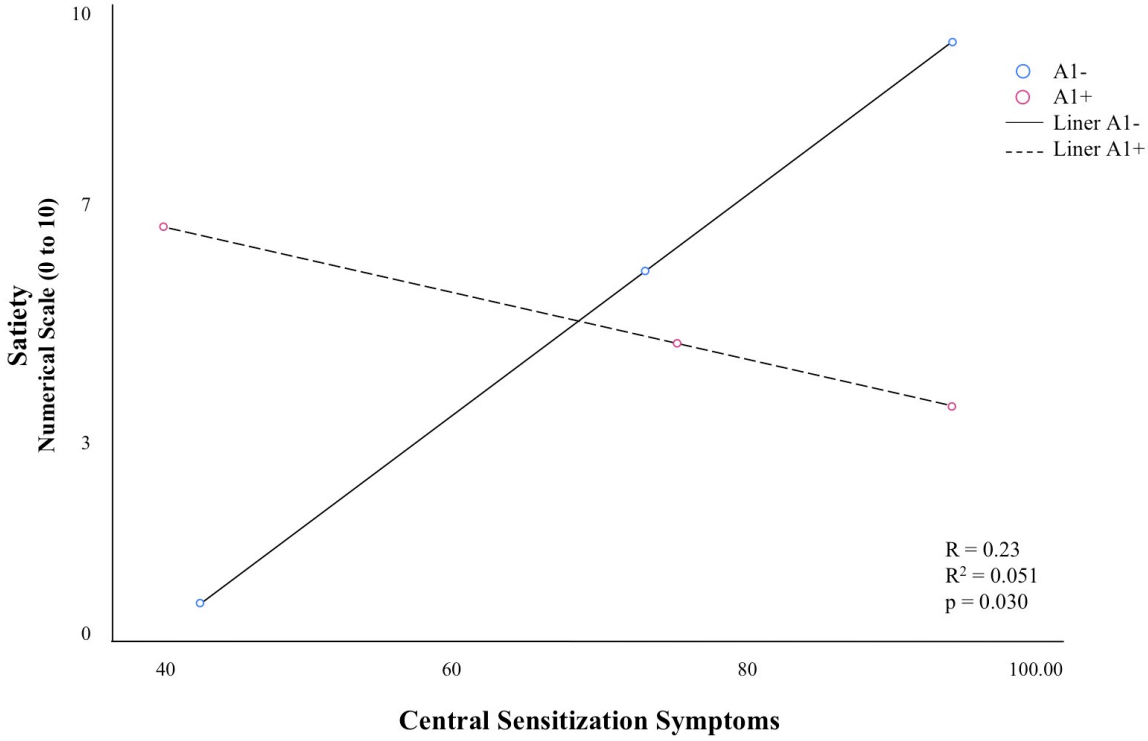

Figure 2. (A)

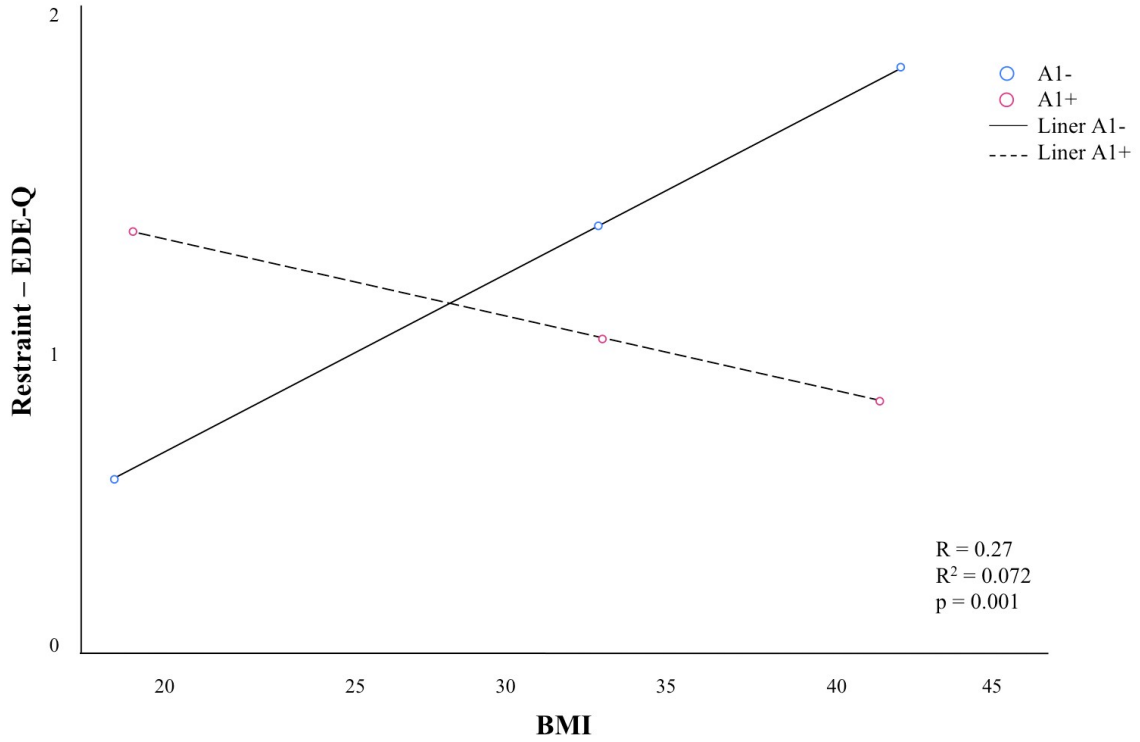

Figure 2. (B)

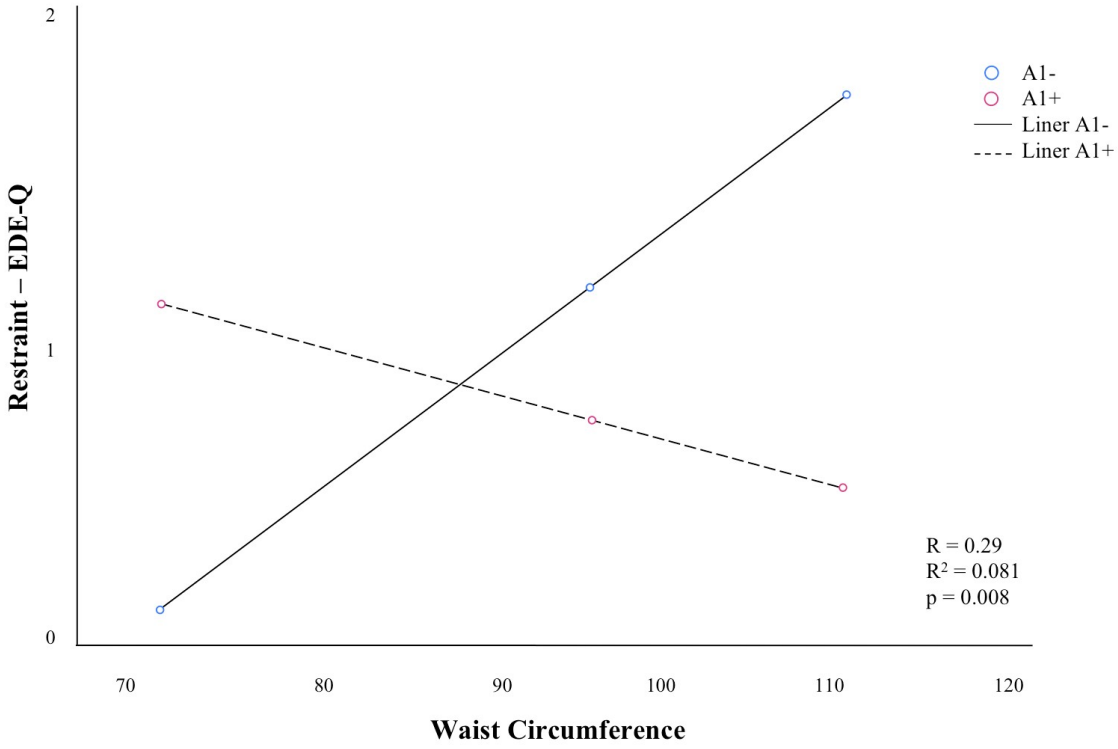

Figure 2. (C)

Legend Figure 2. The analysis of the moderator effect of genotype A1 in a sample of 106 subjects classified according to genotypes A+ (n=42) and A1- (n=64). This effect was analyzed concerning eating behavior, anthropometric measures, and the severity of central sensitization symptoms. They revealed that the relationship between these measures' changes direction according to the A1 allele. Specifically, when individuals have the A1+ genotype, the correlation between these variables is negative. Conversely, the correlation is positive for those with the A1 genotype.

(A) The linear relationship between self-perceived satiety on a numerical scale (0 to 10) and central sensitization symptoms according to the A1 allele (+ or -).
(B) The linear relationship between the domain Restraint evaluated by EDE-Q and BMI according to the A1 allele (+ or -).
(C) The linear relationship between the domain Restraint evaluated by EDE-Q dominion and waist circumference according to the A1 allele (+ or -).

7.2 ARTIGO 2

Impact of Multiple-Session Home-Based Transcranial Direct Current Stimulation (M-HB-tDCS) on Eating Behavior in Fibromyalgia: A Factorial Randomized Clinical Trial

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Impact of multiple-session home-based transcranial direct current stimulation (M-HB-tDCS) on eating behavior in fibromyalgia: A factorial randomized clinical trial

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ABSTRACT

Background: Multiple-session home-based self-applied transcranial direct current stimulation (M-HB-self-applied-tDCS) has previously been found to effectively reduce chronic pain and enhance cognitive function. However, the effectiveness of this method for disordered eating behavior still needs to be studied.
Objective: This study aimed to assess whether 20 sessions of M-HB-self-applied-tDCS, administered over four weeks to either the left dorsolateral prefrontal cortex (L-DLPFC) or primary motor cortex (M1), could improve various aspects of eating behavior, anthropometric measures, and adherence.
Methods: We randomly assigned 102 fibromyalgia patients between the ages of 30 and 65 to one of four tDCS groups: L-DLPFC (anodal-(a)-tDCS, n = 34; sham-(s)-tDCS, n = 17) or M1 (a-tDCS, n = 34; s-tDCS, n = 17). Patients self-administered 20-min tDCS sessions daily with 2 mA under remote supervision following in-person training.
Results: Generalized linear models revealed significant effects of M-HB-self-applied-tDCS compared to s-tDCS on uncontrolled eating (UE) (Wald $\chi 2 = 5.62$; df = 1; P = 0.018; effect size, ES = 0.55), and food craving (Wald $\chi 2 = 5.62$; df = 1; P = 0.018; ES = 0.57). Regarding fibromyalgia symptoms, we found a differentiated impact of a-tDCS on M1 compared to DLPFC in reducing food cravings. Additionally, M-HB-a-tDCS significantly reduced emotional eating and waist size. In contrast, M1 stimulation was more effective in improving fibromyalgia symptoms. The global adherence rate was high, at 88.94%.
Conclusion: These findings demonstrate that M-HB-self-applied-tDCS is a suitable approach for reducing uncontrolled and emotional eating, with greater efficacy in L-DLPFC. Furthermore, these results revealed the influence of fibromyalgia symptoms on M-HB-self-applied-tDCS's, with M1 being particularly effective in mitigating food cravings and reducing fibromyalgia symptoms.

1. Introduction

Fibromyalgia (FM) occurs concurrently with widespread chronic pain, psychological distress, cognitive impairment, sleep disturbances, fatigue, and depressive symptoms [1–3]. Up to 70% of FM patients are overweight, and 40% are obese [4–7]. Additionally, patients often

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1. Introduction

Fibromyalgia (FM) occurs concurrently with widespread chronic pain, psychological distress, cognitive impairment, sleep disturbances, fatigue, and depressive symptoms [1–3]. Up to 70% of FM patients are overweight, and 40% are obese [4–7]. Additionally, patients often experience disrupted eating behavior [8]. This coexistence of disordered eating reflects a complex interplay between various neural structures and mechanisms, including the prefrontal cortex (PFC) and anterior cingulate cortex (ACC).

Chronic pain can increase emotional eating due to an excessively active ACC, as individuals try to alleviate pain-related distress [9–11]. Dysregulation in the ACC and related structures, crucial for emotion and impulse control, may contribute to overconsumption of palatable foods, resembling a tolerance response [9,10,12]. These cortical areas are central to reward, emotion, motivation, cognitive functions [13] and pain processing [14]. The transcranial direct current stimulation (tDCS) has shown specific effects depending on the targeted brain regions. Left dorsolateral prefrontal cortex (L-DLPFC) tDCS enhances cognition and reduces depressive symptoms [15–17]. In a meta-analysis, active stimulation, either rTMS or tDCS, on both hemispheres outperformed sham across diverse populations (alcohol, nicotine, illicit drugs, eating addictions) [18]. Despite the biological plausibility of PFC-targeted neuromodulation for disordered eating [19–21], the ongoing debate centers on lateralization to a specific hemisphere (left vs. right).

A-tDCS on primary motor cortex (M1) has been found to effectively reduce pain in fibromyalgia [13,15]. Besides, it has been found to improve the connection between M1 and the thalamus [16], change how subjects feel heat and pressure [17], and provide long-term relief from chronic pain [18]. According to electric field modeling studies using PET, it might also impact important brain regions like the ACC, thalamus, insula, and DLPFC [22,23]. These cortical areas are central to reward, emotion, motivation, and cognitive function [13]. Thus, modulation of M1 holds promise and is an intuitive way to improve pain symptoms and mitigate eating dysfunction in FM. Alternatively, stimulation of the DLPFC improves mood, thinking, and decision-making [18,22]. According to a previous study, single-session anodal-(a-)-tDCS over the right DLPFC reduces food cravings, which may help recipients consume fewer calories [17,24]. To make tDCS easier for more patients, a tested, home-based (HB)-tDCS device allows doctors to change settings, make the device safer, and monitor how patients follow instructions [13,25,26]. In addition, a recent study found that M1 is more effective than L-DLPFC in alleviating chronic pain among fibromyalgia patients [27]. L-DLPFC stimulation enhances cognitive performance [26,28] and reduces pain catastrophizing and pain-related disability [29,30]. The rationale behind choosing M1 and L-DLPFC for stimulation in our protocol was based on the above and in the absence of available data on the effects of multiple-session home-based self-applied (M-HB-self-applied-tDCS) targeting M1 and PFC on their dysfunctional eating behavior.

Thus, this study aimed to compare the efficacy of M-HB-self-applied-tDCS (twenty sessions) over the L-DLPFC or M1 compared to sham-(s)-tDCS in improving uncontrolled eating and food cravings in fibromyalgia patients. Additionally, this study assessed the impact of M-HB-self-applied-tDCS on cognitive restraint, emotional eating, food craving states, body mass index (BMI), and waist circumference. We also explored the potential correlation between the improvement of fibromyalgia symptoms and the influence of tDCS on eating behavior. This study monitored adherence using session recording software throughout each treatment session.

2. Materials and methods

2.1. Study design

The protocol of this randomized, double-blind, parallel-group, sham-controlled clinical trial (RCT) was approved by the Research Ethics Committee at the Hospital de Clinicas de Porto Alegre (HCPA), Porto Alegre, Brazil. The Institutional Review Board and Research Ethics Committee registration was: 12625718.9.0000.5327 CAAE registry. All subjects provided verbal and written informed consent prior to their participation.

2.2. Setting, participants, and eligibility

This study included 102 adult females between the ages of 18 and 65 who were right-handed and possessed reading and writing abilities. Recruitment took place through two primary channels: the outpatient pain clinic at HCPA, Porto Alegre, Brazil, and newspaper advertisements. As inclusion criteria, participants were required to meet the diagnostic criteria for fibromyalgia defined by the 2016 American College of Rheumatology (ACR-2016). Furthermore, inclusion necessitated a minimum score of 50 mm on a 0–100 mm visual analog pain scale (VAS 0–100 mm) during most days in the three months preceding enrollment. Additionally, participants had to commit to not altering their doses of antidepressant and anticonvulsant medications for the duration of the study.

Exclusion criteria barred individuals with contraindications for non-invasive brain stimulation, as per established guidelines [31]. Participants were ineligible if they had uncontrolled clinical or psychiatric diseases, suicidal ideation with plans, present illicit substance use, shift work, a medical history of rheumatoid arthritis, lupus, autoimmune diseases, neurological or oncological conditions, or prior bariatric surgery. Patients were also ineligible if they met the diagnostic criteria for eating disorders (DMD) outlined in the Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR (2022) [32].

2.3. Sample size justification

The sample size was estimated for two primary outcomes based on prior studies [28,33] for a two-tailed hypothesis test (alpha = 5%, beta = 20%). For uncontrolled eating in the TFEQ - R21 domain and for an effect size (ES) of 0.6 and a standard deviation of SD = 20, the required sample size was estimated to be 92 patients. For an ES = 0.63 in the Food-Cravings Questionnaire (FCQ-T) score (SD = 35.7), the estimated required sample size was 90 patients. To account for multiple outcomes, potential dropouts, and non-normal distribution, we increased the sample by 10%, resulting in a final sample size of 102 (34 in the a-tDCS groups and 17 in the s-tDCS groups).

2.3.1. Randomization

Randomization was accomplished using an online tool (www.sealedenvelope.com), creating a 2:1:2:1 allocation ratio to randomize participants into four groups: (1) active DLPFC, (2) sham DLPFC, (3) active M1, and (4) sham M1. An external, professionally conducted randomization and randomized number codes were sealed in envelopes with the patient's entry sequence number.

2.3.2. Blinding

Researchers received pre-programmed equipment from an assistant, ensuring they remained unaware of whether they were administering active or s-tDCS. Participants and researchers were thus blinded to the type of stimulation. Participants were asked to guess whether they received a-tDCS or s-tDCS at the treatment end and rated their confidence level on a Likert scale from 1 (“not sure at all”) to 5 (“completely sure”).

2.4. Electrode positions and HB-tDCS stimulation protocol

The HB-tDCS device used in this study was developed by the Biomedical Engineering department at the HCPA, Porto Alegre, Brazil and is registered with the Brazilian National Health Surveillance Agency (ANVISA, N°80079190028). This device has been successfully employed in previous RCT conducted by the research groups [13,23,25,26]. Electrode placements followed the 10–20 EEG system, with the anode at F3 and the cathode at F4, or the anode at C3 and the cathode at Fp2. Electrodes delivered 2 mA of current in 20 min. Both active and sham tDCS conditions were employed, with the same electrode montage used for both. During s-tDCS, the device provided 30 s of stimulation at specific intervals. Electrodes, sized at 35 cm^2, were coated with a saline-soaked sponge and affixed to a neoprene elastic cap. Electrode placement on the cap was marked with red for the anode and black for the cathode. Participants were encouraged to contact the research team as needed and keep records of any adverse effects. Detailed instructions for self-administration at home were provided, along with a video guide (https://youtu.be/3Wtji4esOGE). Additional details on the device and the protocol can be found in the supplementary material (Annex I). The timeline of the protocol is presented in Fig. 1.

2.5. Instruments and assessments

Two trained researchers blinded to the experimental groups conducted eating behavior, anthropometric measures, psychological, and clinical assessments. All assessment instruments used were validated for the Brazilian population.

2.6. Outcomes

Primary outcomes included uncontrolled eating and food craving patterns, while secondary outcomes included cognitive restraint and emotional eating, as assessed by the TFEQ-21 domains. Other secondary outcomes involved food craving states, body mass index (BMI), and waist circumference.

2.7. Primary and secondary outcomes

a. The TFEQ-R21 was used to assess three domains of eating behavior: uncontrolled eating (UE) (primary outcome), cognitive restraint (CR), and emotional eating (EE). Each domain was scored separately, with higher scores indicating a greater likelihood of disordered eating. Total scores for each domain could range from 0 to 100 [34,35].
b. The Food-Cravings Questionnaires (FCQ) was also implemented, consisting of two domains: FCQ-trait-(T), with 39 questions across nine dimensions for assessment of food-craving behavior patterns, and the FCQ-state-(S), with 15 questions in five dimensions for measuring current food cravings. Higher scores indicated stronger cravings [36].

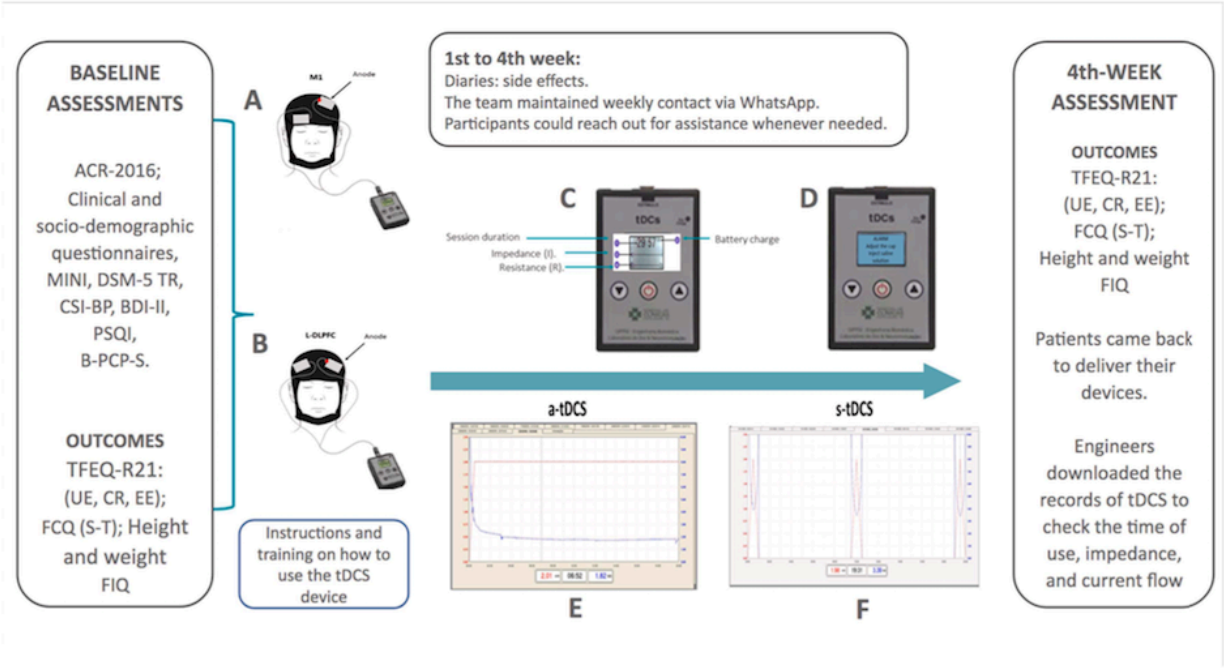

Fig. 1. Timeline the study. **Sites of stimulation: (1A)** Anodal transcranial Direct Current Stimulation (a-tDCS) with the anode placed over M1 (C3) and cathode over fP2. **(1B)** Anodal tDCS with anode over left DLPFC (F3) and cathode over right DLPFC (F3). **Device Features: (1C)** High resistance. **(1D)** Alarm warning: adjust the cap and inject extra saline. **(1E)** Typical curves of current intensity versus contact impedance during a-tDCS. **(1F)** Typical curves observed in s-tDCS at baseline, 10 min post-stimulation, and at the end of the treatment. The time points of assessments. Baseline: questionnaire to assessed clinical and socio-demographic characteristics, analgesic use, eating disorders according to Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR (2022) - anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), avoidant restrictive food intake disorder (ARFID), and other specified feeding and eating disorders (OSFED), were outlined in the DSM-5 TR (American Psychiatric Association, 2022), heat pain threshold (HPT) by Quantitative Sensory Testing [(QST). Instruments: Fibromyalgia Impact Questionnaire (FIQ); Central Sensitization Inventory (CSI), for Brazilian population (CSI-BP); Beck Depression Inventory- (BDI-II), Brazilian Pain catastrophizing Scale – BP-PCS; Pittsburgh Sleep Quality Index (PSQI). State and Trait Food-Cravings Questionnaires (FCQ-S and FCQ-T); Three Factor Eating Questionnaire (TFEQ - R21): Assesses three domains of eating behavior: cognitive restraint (CR), uncontrolled eating (UE) and emotional eating (EE).

c. The Fibromyalgia Impact Questionnaire (FIQ) comprises diverse questions addressing various dimensions of fibromyalgia symptoms, such as pain severity, fatigue, morning tiredness, stiffness, sleep disturbances, mood, etc. The maximum score on the FIQ was 100 [37].

2.8. Anthropometric assessments

Height and weight assessments were performed by the same researchers using standardized techniques. Body Mass Index (BMI) was calculated based on these measurements, while waist circumference (cm) was additionally determined using an inelastic tape at the widest abdominal perimeter between the iliac crest and the last rib. The reported outcome was the average of three measurements.

2.9. Clinical and sociodemographic data, pain assessments, central sensitization, sleep quality, psychological symptoms, eating disorder diagnoses, and psychiatric diagnoses

A standardized questionnaire was used to collect sociodemographic and medical data, and a Numerical Pain Scale (NPS 0–10), with 0 indicating no pain and 10 the worst pain, was used to evaluate pain severity. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality [38]. The Brazilian Portuguese-Central Sensitization Inventory (BP-CSI) was used to evaluate central sensitization symptoms [39], the Beck Depression Inventory-II (BDI–II) was used to evaluate depressive symptoms [40], and the Pain Catastrophizing Scale (B-PCS) was used to measure pain-related catastrophizing [41]. Psychiatric diagnoses were established using the Mini-International [42], and eating disorders were assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) criteria (2022) [32].

2.10. Statistical analyses

Normality was assessed with the Shapiro-Wilk test, and continuous variables were compared using ANOVA or non-parametric tests. Categorical variables were analyzed with the chi-square or Fisher's exact tests. A factorial generalized linear model (GLM) was used to investigate the impact of treatment (i.e., of a-tDCS and s-tDCS) according to stimulation area (i.e., DLPFC and M1), as well as their interaction. The delta value (end average minus beginning average) was used as a measure of outcomes. The modified intention-to-treat analysis (m-ITT) included subjects completing ≥50% of sessions, with missing data imputation using regression model coefficients (**details in Annex II**). All analyses were Bonferroni-adjusted for multiple testing (5% significance threshold). Data analysis was conducted using SPSS version 22.0.

3. Results

3.1. Demographic and clinical characteristics of the subjects

Out of the 250 participants screened, 148 were excluded, with 110 failing to meet inclusion criteria; these included 101 patients with uncompensated chronic diseases and lacking fibromyalgia diagnostic criteria, and nine with eating disorders diagnosed per the DSM-5-TR criteria. Among the remaining 102, five dropped out before completing the 20-session tDCS protocol. The progression of participants throughout various stages of the research is presented in Fig. 2.

The analysis, which compares treatment groups with baseline data (i.e., demographic, clinical characteristics, psychological state, sleep quality, pain scores) did not show significant differences among the groups. Data are present in Table 1. The impact of M-HB-self-applied-tDCS on outcomes within groups is detailed in the supplementary material (Annex II).

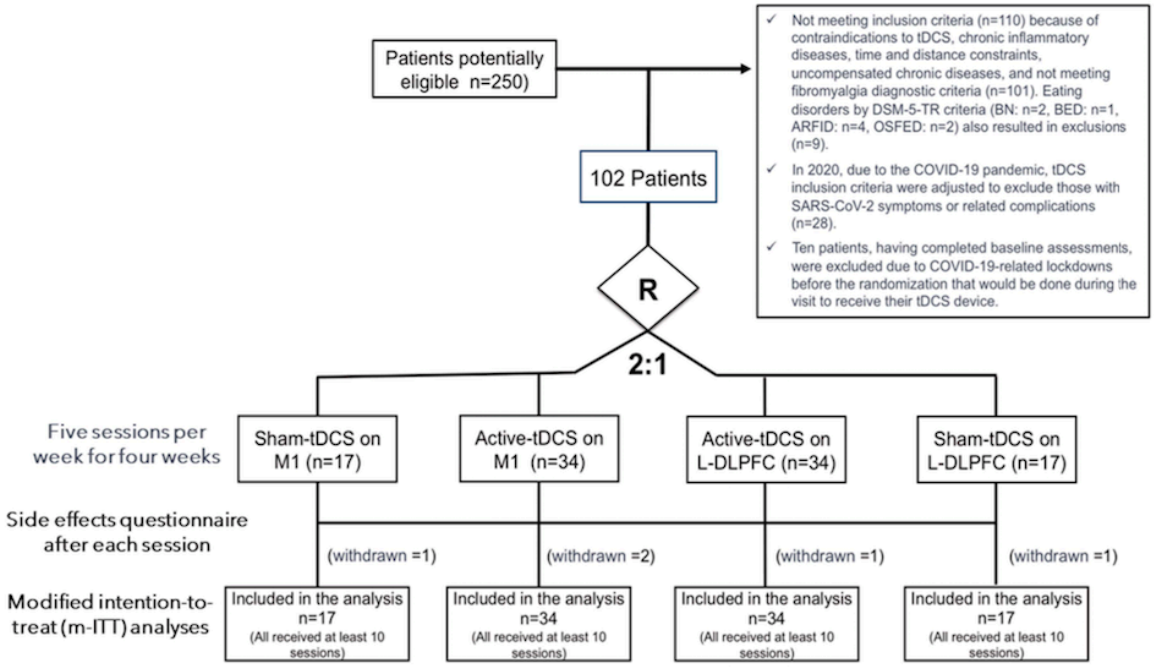

Fig. 2. Flowchart of study. Randomization (R) and Intention-to-Treat (ITT) analyses. Despite their withdrawal, they fulfilled the inclusion criteria for the intention-to-treat analysis by completing at least 50% of the sessions (10 sessions) and met the criteria for modified (m-ITT), as pre-defined. Before the COVID-19 restrictions, twenty patients had completed the protocol.

Table 1
Baseline epidemiological and clinical characteristics, psychological state, sleep quality, pain scores, according to area of stimulation (M1 or DLPFC) and the treatment group (a-tDCS and s-tDCS). Data are presented as the mean (SD) or frequency (n = 102).

Characteristics	Primary motor cortex (M1)		Prefrontal dorsolateral cortex (DLPFC)	
	a-tDCS (n = 34)	sham-tDCS (n = 17)	a-tDCS (n = 34)	sham-tDCS (n = 17)
Age (years)	48.98 (10.08)	49.70 (8.97)	48.56 (8.93)	40.61 (9.70)
Body mass index (Kg/m2)	29.39 (4.90)	31.17 (5.05)	29.68 (4.51)	28.34 (4.54)
Waist Circumference (cm)	97.41 (12.08)	95.41 (12.87)	97.03 (11.38)	98.00 (9.91)
Formal education (years)	12.06 (4.92)	13.25 (4.17)	12.18 (4.68)	13.11 (4.57)
Working condition				
Working	15 (44.1)	6 (35.3)	15 (44.1)	11 (64.7)
Unemployed	7 (20.6)	2 (11.8)	9 (26.5)	1 (5.9)
Health license	9 (26.5)	6 (35.3)	8 (23.5)	2 (11.8)
Retired	3 (8.8)	3 (17.6)	2 (5.9)	3 (17.6)
Smoking (yes/no)	9 (26.5)/25 (73.5)	4 (23.5)/13 (76.5)	7 (20.6)/27 (79.4)	3 (17.6)/ 14 (82.4)
Alcohol use (yes/no)	4 (23.5)/13 (76.5)	4(23.5)/13 (76.5)	13 (38.2)/ 21 (61.8)	7 (41.2)/ 10(58.8)
Diagnosis of psychiatric disorder according to MINI (yes/no) ®	26 (76.47)/ 8 (23.52)	12 (70.6)/5 (29.4)	28 (82.4)/6 (17.6)	13 (76.5)/ 4 (23.5)
Panic Disorder (yes/no)	4 (11.76)/ 30 (88.23)	3 (17.6)/14 (82.4)	3 (8.82)/31 (91.18)	2 (11.75)/ 15(88.25)
Major Depression Disorder (yes/no)	24 (72.7)/9 (27.3)	10 (58.8)/7 (41.2)	22 (64.7)/ 12(73.54)	11(64.7)/6 (35.3)
Anxiety Disorder (yes/no)	13 (38.2)/ 21(61.8)	8 (47.1)/9 (52.9)	17 (50)/17 (50)	8 (47.1)/9 (52.9)
Analgesic medication use				
Opioid analgesic (yes/no)	7(20.52)/ 27 (79.48)	3 (17.6)/14 (82.4)	11 (32.4)/ 23(67.6)	5 (29.4)/ 12(70.6)
Analgesic non-opioid (yes/no)	30 (88.23)/ 4(11.76)	15 (88.2)/2 (11.8)	31 (91.2)/3 (8.82)	16 (94.11)/1 (5.88)
Use drug active on the nervous system (yes/no)**				
Selective Serotonin Reuptake Inhibitor (yes/no)	7 (20)/28 (80)	4 (23.5)/13 (76.5)	11 (32.4)/ 23(67.6)	4 (23.5)/ 13 (76.5)
Tricyclic or dual antidepressants (yes/no)	16 (47.06)/ 18 (52.94)	9 (52.94)/8 (47.06)	12 (35.29)/ 22 (64.70)	6 (35.29)/ 11(64.70)
Benzodiazepine (yes/no)	4 (11.4)/30 (88.6)	2 (11.8)/15 (88.2)	7 (20)/27 (79.4)	4 (23.53)/ 13 (76.47)
Antipsychotic (yes/no)	1 (2.94)/33 (97.06)	0 (0)/17 (100)	3 (8.8)/31 (91.2)	1 (5.9)/34 (97.1)
Zolpidem (yes/no)	1 (2.94)/33 (97.06)	4 (23.5)/13 (76.5)	2 (5.9)/32 (94.1)	2 (11.8)/ 15 (88.2)
Pregabaline (yes/no)	8 (23.52)/ 26(76.47)	6 (35.3)/11 (64.7)	10 (29.4)/ 24(70.6)	8 (47.1)/9 (52.9)
History of chronic disease (yes/no)	27 (67.5)/ 13(32.5)	11 (55)/9 (45)	23 (67.6)/ 11 (32.4)	10 (55.6)/ 8(44.4)
Hypertension (yes/no)	10 (25)/30 (75)	5(25)/15 (75)	11 (32.4)/ 23 (67.6)	3(16.7)/15 (83.3)
Diabetes Mellitus (yes/no)	2 (5.7)/32 (94.12)	2(5.7)./32 (94.12)	2(11.1)/16 (88.9)	3(8.8)31 (91.2)
Tireoide disease (yes/no)	2 (11.75)/ 15 (88.25)	3(8.82)/31 (91.17)	4 (11.8)/30 (88.2)	2 (11.75)/ 15 (88.25)
Asthma (yes/no)	4 (11.76)/ 30 (88.23)	3 (17.6)/14 (82.4)	3 (8.82)/31 (91.18)	2 (11.75)/ 15 (88.25)
ACR	23.33 (2.95)	23.70 (3.67)	22.41 (3.96)	22.50 (4.24)
Widespread Pain Index	13.45(3.08)	13.88 (2.69)	13.21(3.11)	14.12 (3.03)
Severity Symptoms Scale	10.03 (1.57)	9.47 (1.94)	9.62 (1.49)	9.53 (1.87)
Psychological measures, central sensitization, pain scores, and sleep quality and number of valid sessions of a-tDCS				

Table 1 (*continued*)

Characteristics	Primary motor cortex (M1)		Prefrontal dorsolateral cortex (DLPFC)	
	a-tDCS (n = 34)	sham-tDCS (n = 17)	a-tDCS (n = 34)	sham-tDCS (n = 17)
Central Sensitization inventory (CSI-BP) score	64.37 (11.15)	64.77 (16.40)	61.28 (12.29)	68.03 (15.15)
Beck Depression Inventory-II	25.97 (10.78)	25.16 (11.56)	28.76 (11.36)	24.67 (8.76)
Pittsburgh Sleep Quality Index – PSQI	10.93 (4.48)	11.29 (4.37)	10.74 (4.36)	10.13 (4.14)
Pain Catastrophizing Scale – PCS	38.23 (8.64)	33.21 (10.80)	34.78 (12.62)	34.89 (10.45)
Pain on visual analogue scale (VAS))	8.52 (1.28)	8.45 (1.44)	8.54 (1.23)	8.41 (1.23)
Number of valid sessions of a-tDCS¥	17.17 (3.58)	16.79 (4.72)	17.93 (2.92)	17.06 (2.83)

Mini-International Neuropsychiatric Interview (MINI).
® Patients could have none, one or multiple psychiatric diagnoses.
**Some patients were using more than one type of drug.
¥ For a valid 20-min a-tDCS session, impedance levels should remain between 3 and 2 kΩ for at least seventy percent of the total stimulation duration.

Table 2 displays the averages of primary and secondary outcomes, encompassing assessments of eating behavior, the impact of fibromyalgia symptoms on daily life and disability, and anthropometric measures.

3.1.1. Primary outcomes: assessment of M-HB-self-applied-tDCS impact on TFEQ-21-UE and FCQ-T scores

A GLM analysis revealed the impact of M-HB-self-applied-a-tDCS on both primary outcomes, UE, and trait-food craving (Table 3), with large effect sizes of 0.55 and 0.57, respectively.

Interaction analysis between stimulation area and intervention groups revealed that M-HB-self-applied-a-tDCS was more effective in reducing UE when applied over L-DLPFC than M1, with a moderate effect size (ES = 0.35).

3.1.2. Primary outcomes: evaluating the influence of fibromyalgia symptom severity on the effect of tDCS on TFEQ-21-UE and FCQ-T scores

The data in Table 4 indicate a positive link between the impact of fibromyalgia symptoms on UE. The interaction analysis on the impact of fibromyalgia symptoms according to stimulation area showed a significant effect for food craving, with a differentiated impact on the M-HB-self-applied-a-tDCS in M1 compared to DLPFC. This interaction analysis indicated a moderate ES (0.35) in favor of M-HB-self-applied-a-tDCS on M1 compared to L-DLPFC.

3.1.3. Secondary outcomes: impact of M-HB-self-applied-tDCS on the CR, EE, changes in state food craving, waist circumference, and BMI

Table 5 displays the treatment effects on secondary outcomes. M-HB-self-applied-a-tDCS effectively reduced EE scores with a large effect size (0.40), but this effect was not observed in CR or state craving. A significant, moderate ES were found on CR with L-DLPFC stimulation compared to M1 (ES = 0.35), and this effect persisted even in the interaction analysis between the group and stimulation area (ES = 0.32).

The M-HB-self-applied-a-tDCS was significantly more effective than M-HB-self-applied-s-tDCS in improving symptoms related to fibromyalgia. However, interaction analysis indicated that a-tDCS over M1 was more effective at enhancing fibromyalgia symptoms than over L-DLPFC.

Furthermore, a-tDCS demonstrated greater effectiveness than s-tDCS in reducing waist size regardless of the stimulation area, with a moderate effect size of 0.35.

Table 2
Three Factor Eating Questionnaire (TFEQ-21) - Uncontrolled Eating (UE), Cognitive restraints (CR), emotional eating (EE); Food Craving State-Trait Scale, impact of fibromyalgia symptoms on quality live and disability, waist circumference and BMI. Data are presented as mean (SD) [before (B) and after (A)-intervention]. Delta (Δ)-mean values represent scores A minus B (n = 102).

Primary outcome			
Delta (Δ) value of three Factor Eating Questionnaire (TFEQ-21) - Uncontrolled eating (UE)			
Stimulation area	Mean (SD) before (B) treatment	Mean (SD) after (A) treatment	Δ-value (A-B)
(1) a-tDCS-L-DLPFC (n = 34)	29.30 (23.05)	63.74 (14.91)	−34.44 (30.88)
(2) s-tDCS- L-DLPFC (n = 17)	28.83 (23.06)	58.39 (15.30)	−29.55 (36.14)
(3) a- tDCS-M1 (n = 34)	25.46 (22.24)	60.98 (17.13)	−35.52 (26.80)
(4) s-tDCS-M1) n = 17)	43.35 (23.08)	56.43 (16.69)	−13.07 (37.99)
Delta (Δ) value of Food Craving Questionnaire - Trait (FCQ-T)			
(1) a-tDCS-L-DLPFC (n = 34)	99.57 (38.15)	86.95 (34.78)	−12.61 (17.42)
(2) s-tDCS- L-DLPFC (n = 17)	94.52 (32.96)	93.47 (40.32)	−1.05 (26.15)
(3) a- tDCS-M1 (n = 34)	95.50 (34.90)	78.05 (47.28)	−17.44 (38.84)
(4) s-tDCS-M1) n = 17)	102.58(34.34)	103.88 (41.44)	1.29 (16.84)
Secondary outcomes			
Three Factor Eating Questionnaire (TFEQ-21) -Cognitive restraints (CR)			
(1) a-tDCS-L-DLPFC (n = 34)	39.67(18.82)	60.71 (11.24)	−23.37 (3.99)
(2) s-tDCS- L-DLPFC (n = 17)	33.27(23.89)	61.76 (13.87)	−25.25 (6.55)
(3) a- tDCS-M1 (n = 34)	36.47(17.89)	59.64 (12.63)	−23.16 (3.76)
(4) s-tDCS-M1) n = 17)	48.04(17.99)	60.78 (9.51)	−12.74 (4.66)
Three Factor Eating Questionnaire (TFEQ-21) - Emotional Eating (EE)			
(1) a-tDCS-L-DLPFC (n = 34)	29.28 (29.06)	67.80 (28.53)	−40.92 (49.71)
(2) s-tDCS- L-DLPFC (n = 17)	33.97 (29.57)	56.86 (34.48)	−22.89 (63.04)
(3) a- tDCS-M1 (n = 34)	35.60 (28.69)	52.61 (29.27)	−17.52 (48.88)
(4) s-tDCS-M1) n = 17)	45.75 (27.18)	49.02 (31.98)	−3.47 (58.36)
Food Craving Questionnaire – State (FCQ-S)			
(1) a-tDCS-L-DLPFC (n = 34)	36.47 (11.76)	32.66 (11.76)	−3.80 (8.87)
(2) s-tDCS- L-DLPFC (n = 17)	39.35 (9.54)	35.92 (12.53)	−3.42 (9.43)
(3) a- tDCS-M1 (n = 34)	37.17 (11.88)	31.81 (15.87)	−5.35 (15.80)
(4) s-tDCS-M1) n = 17)	39.11 (12.70)	34.00 (11.34)	−5.11 (10.24)
Fibromyalgia Impact Questionnaire (FIQ) – on quality of life and disability			
(1) a-tDCS-L-DLPFC (n = 34)	73.22 (11.91)	63.70 (13.70)	−9.52 (13.12)
(2) s-tDCS- L-DLPFC (n = 17)	73.59 (10.20)	69.24 (11.76)	−4.35 (10.80)
(3) a- tDCS-M1 (n = 34)	77.70 (7.15)	61.09 (13.15)	−16.60 (12.31)
(4) s-tDCS-M1) n = 17)	76.24 (7; 96)	69.23 (7.94)	−7.01 (4.60)
Waist Circumference			
(1) a-tDCS-L-DLPFC (n = 34)	97.40 (12.08)	97.28 (11.05)	−0.38 (5.18)
(2) s-tDCS- L-DLPFC (n = 17)	95.41 (12.87)	95.79 (14.25)	−1.40 (5.14)
(3) a- tDCS-M1 (n = 34)	97.03 (11.38)	94.48 (12.73)	−2.34 (5.79)

Table 2 (*continued*)

Primary outcome			
Delta (Δ) value of three Factor Eating Questionnaire (TFEQ-21) - Uncontrolled eating (UE)			
Stimulation area	Mean (SD) before (B) treatment	Mean (SD) after (A) treatment	Δ-value (A-B)
(4) s-tDCS-M1) n = 17)	98.0 (9.91)	96.50 (10.13)	0.39 (3.31)
Body Mass Index (BMI)			
(1) a-tDCS-L-DLPFC (n = 34)	29.68 (4.58)	29.76 (4.86)	−.04 (.47)
(2) s-tDCS- L-DLPFC (n = 17)	28.52 (5.14)	29.73 (5.07)	−.07(.59)
(3) a- tDCS-M1 (n = 34)	29.19 (4.79)	29.79 (4.86)	−.16 (1.4)
(4) s-tDCS-M1) n = 17)	43.35 (23.08)	30.67 (4.98)	.16 (.40)

Primary motor cortex (M1); Left dorsolateral prefrontal cortex (L-DLPFC).

Table 3
Factorial Generalized linear model: Treatment Effects (M-HB-a-tDCS or s-tDCS) by Stimulation Area (M1 or DLPFC) on Three-Factor Eating Questionnaire (TFEQ-21) Uncontrolled Eating and Food Craving Trait Scale (n = 102).

Primary outcomes								
Delta (Δ) value of three Factor Eating Questionnaire (TFEQ-21) - Uncontrolled eating (UE)								
	EMM	*Beta*	*SEM*	*CI 95%*	*Wald χ2*	*df*	*P*	*ES*
Intervention groups: a-tDCS/s-tDCS	−37.21 (3.69)/-20.43 (5.22)	−29.69	9.048	(-47.43 to −11.96)	10.773	1	.001	0.55
Area of stimulation: L-DLPFC/ M1	−31.49 (4.52)/ −26.15 (4.52)	−18.24	10.448	(-38.72 to 0.08)	3.050	1	.081	–
Interaction analysis between stimulation area and intervention groups		25.82	12.79	(0.74 TO 50.90)	4.07	1	0.04	0.35
Delta (Δ) value of Food Craving Questionnaire - Trait (FCQ-T)								
Intervention groups: a-tDCS/s-tDCS	−18.79 (3.15)/0.11 (4.42)	−25.68	7.697	(-40.76 to −10.59)	11.132	1	.001	0.57
Area of stimulation: L-DLPFC/ M1	−7.13 (3.82)/ −11 (3.84)	−2.35	8.843	(-19.68 tp 14.98)	.071	1	.790	–
Interaction analysis between stimulation area and intervention groups		13.53	10.858	(-7.74 to 34.81)	1.553	1	.213	–

Primary motor cortex (M1); Left dorsolateral prefrontal cortex (L-DLPFC).
Estimated marginal means (EMM).
Degrees of freedom (Df); Standard error for mean (SEM); confidence interval (95% CI).
Effect size (ES) according to guidelines (Cohen) equivalent phi value .1 represents a small effect = 0.3 represents a medium effect and = 0.5 represents a large effect.
-- It indicates that the ES was not calculated by not detecting a significant difference.

3.2. Assessment of adverse events and safety

We observed a significant difference in the burning sensation between the M-HB-self-applied-a-tDCS on M1 group and those undergoing a-tDCS on L-DLPFC or receiving sham treatments on either L-DLPFC or M1 (refer to Table 6). However, the occurrence of most symptoms showed similarity between a-tDCS and M-HB-self-applied-s-tDCS, with the majority classified as mild or moderate, even in patients discontinuing treatment due to a burning sensation.

Table 4
Factorial Generalized linear model: Treatment Effects (M-HB-a-tDCS or s-tDCS) by Stimulation Area (M1 or DLPFC) on Three-Factor Eating Questionnaire (TFEQ-21) UE and trait-food craving according to the severity of fibromyalgia symptoms (n = 102). (n = 102).

Primary outcomes

Delta (Δ) value of three Factor Eating Questionnaire (TFEQ-21) - Uncontrolled eating (UE)

	Beta	SEM	CI 95%	Wald $\chi 2$	df	P	ES
Intercepted model	−46.090	11.4442	−23.660	16.220	1	.000	–
Intervention groups: a-tDCS/s-tDCS [reference]	−13.133	6.4549	−.482	4.139	1	.042	0.34
Area of stimulation: L-DLPFC/M1 [reference]	19.898	14.3037	47.933	1.935	1	.164	–
Impact of fibromyalgia symptoms on quality of life and disability by FIQ	2.011	.7312	3.444	7.565	1	.006	0.47
Interaction analysis: impact of fibromyalgia symptoms on quality of life and disability and treatment effect							
M1/L-DLPFC [reference]	−1.763	.9794	.157	3.239	1	.072	–
Delta (Δ) value of Food Craving Questionnaire - Trait (FCQ-T)							
Intercepted model	−27.817	9.8798	(-47.18 to −8.45)	7.927	1	.005	0.48
Intervention groups: a-tDCS/s-tDCS [reference]	−14.006	5.5232	(-24.83 to −3.81)	6.430	1	.011	0.43
Area of stimulation: L-DLPFC/M1 [reference]	26.215	12.1918	(2.32–50.11)	4.623	1	.032	0.37
Impact of fibromyalgia symptoms on quality of life and disability by FIQ	1.842	.6399	(.59–3.09)	8.287	1	.004	0.49
Interaction analysis: impact of fibromyalgia symptoms on quality of life and disability and treatment effect							
M1/L-DLPFC [reference]	−1.723	.8447	(-3.38 to −0.07)	4.162	1	.041	0.35

Fibromyalgia Impact Questionnaire (FIQ).
Primary motor cortex (M1); Left dorsolateral prefrontal cortex (L-DLPFC).
Estimated marginal means (EMM).
Degrees of freedom (Df); Standard error for mean (SEM); confidence interval (95% CI).
Effect size (ES) according to guidelines (Cohen) equivalent phi value .1 represents a small effect, = 0.3 represents a medium effect and = 0.5 represents a large effect.
-- It indicates that the ES was not calculated by not detecting a significant difference.

3.3. Assessment of adherence

Analysis did not indicate any significant difference between the groups regarding the number of sessions, as shown in Table 1. Three patients (two in the M-HB-self-applied-a-tDCS group and one in the M-HB-self-applied-s-tDCS group) received fewer than five sessions. In the group that received a-tDCS over the DLPFC and M1, the total number of sessions was 1300, of which we recorded 1174 valid sessions (90.30%). In the group that received M-HB-self-applied-s-tDCS on the DLPFC and M1, there were 587 valid sessions, whereas the total number of sessions was 680 (86.32%). The total number of scheduled sessions for all samples, considering a-tDCS and M-HB-self-applied-s-tDCS, was 1980, with 1761 valid sessions recorded in total. Thus, total adherence for all subjects was 88.94%.

3.4. Assessment of the qualitative description of blinding integrity

Patients who received M-HB-self-applied-a-tDCS on M1 and left DLPFC could guess correctly 96% of the time and 94.1% of the time. In contrast, M-HB-self-applied-s-tDCS on M1 and left DLPFC groups

Table 5
Factorial Generalized linear model: Treatment Effects (M-HB-a-tDCS or s-tDCS) by Stimulation Area (M1 or DLPFC) on the cognitive restraints (CR), emotional eating (EE), food craving state, the impact of fibromyalgia symptoms on quality of life and disability, waist circumference, and BMI (n = 102).

Secondary outcomes

Three Factor Eating Questionnaire (TFEQ-21) -Cognitive restraints (CR)

	EMM	Beta	SEM	CI 95%	Wald $\chi 2$	df	P	ES
Intervention groups: a-tDCS/s-tDCS	−22.10 (2.72)/-20.61 (3.85)	−10.42	6.6807	(-23.51 to 2.67	2.43	1	0.19	–
Area of stimulation: L-DLPFC/M1	−24.76 (3.34)/ −17.96 (3.34)	−15.74	7.7142	(-30.86 to −0.62)	4.16	1	0.03	0.35
Interaction analysis between stimulation area and intervention groups		17.88	9.4480	(-.64 to −36.39)	3.58	1	0.04	0.32
Three Factor Eating Questionnaire (TFEQ-21) - Emotional Eating (EE)								
Intervention groups: a-tDCS/s-tDCS	−34.36 (3.75)/ −17.76 (5.30)	−21.42	9.1888	(-39.43 to −3.41)	5.434	1	.020	0.40
Area of stimulation: L-DLPFC/M1	−32.46 (4.59)/ −19.66 (5.59)	−17.62	10.610	(-38.41 to 3.17)	2.758	1	.097	–
Interaction analysis between stimulation area and intervention groups		9.64	12.9949	(-15.82 to 35.11)	.551	1	.458	–
Food Craving Questionnaire – State (FCQ-S)								
Intervention groups: a-tDCS/s-tDCS	−6.43 (1.39)/ −4.27 (1.97)	−3.946	3.4260	(-10.66 to 2.76)	1.327	1	.249	–
Area of stimulation: L-DLPFC/M1	−3.61 (1.71)/-7.09 (1.71)	1.692	3.9561	(-6.06 to 9.44)	.183	1	.669	–
Interaction analysis between stimulation area and intervention groups		3.562	4.8452	(-5.93 to 13.05)	.540	1	.462	–
Fibromyalgia Impact Questionnaire (FIQ) – on quality of life and disability								
Intervention groups: a-tDCS/s-tDCS	12.73 (0.72)/ 15.17 (1.0)	−4.912	1.7377	(-8.31 to −1.50)	7.989	1	.005	0.48
Area of stimulation: L-DLPFC/M1	15.24 (.87)/ 12.66 (0.86)	.118	2.0066	(-3.81 to 4.05)	.003	1	.953	–
Interaction analysis between stimulation area and intervention groups		4.926	2.4703	(.08–9.76)	4.077	1	.042	0.34
Waist Circumference								
Intervention groups: a-tDCS/s-tDCS	−1.56 (0.56)/-0.42 (0.78)	−2.769	1.3561	(-5.42 to −0.11)	4.170	1	.041	0.35
Area of stimulation: L-DLPFC/M1	−.98 (0.68)/ −0.99 (0.68)	−1.619	1.5580	)-4.67 to 1.43)	1.080	1	.299	–
Interaction analysis between stimulation area and intervention groups		3.280	1.9130	(-.46 to 7.03)	2.940	1	.086	–
Body Mass Index (BMI)								

(*continued on next page*)

Table 5 (*continued*)

Secondary outcomes								
Three Factor Eating Questionnaire (TFEQ-21) -Cognitive restraints (CR)								
	EMM	*Beta*	*SEM*	*CI 95%*	*Wald χ2*	*df*	*P*	*ES*
Intervention groups: a-tDCS/s-tDCS	0.04 (.11)/ 0.43 (0.19)	−.113	.2774	(-.65 to 0.43)	.167	1	.683	–
Area of stimulation: L-DLPFC/ M1	−0.0 = 16 (.13)/0.33 (0.13)	−.242	.3182	(-.86 to 0.38)	.576	1	.448	–
Interaction analysis between stimulation area and intervention groups		.147	.3887	(-.61 to 0.90)	.144	1	.705	–

Primary motor cortex (M1); Left dorsolateral prefrontal cortex (L-DLPFC).
Degrees of freedom (Df); Standard error for mean (SEM); confidence interval (95% CI).
Effect size (ES) according to guidelines (Cohen) equivalent phi value .1 represents a small effect, = 0.3 represents a medium effect and = 0.5 represents a large effect.
-- It indicates that the ES was not calculated by not detecting a significant difference.

Table 6
Side effects presented as percentage (%), and the incidence or severity of side effects classified as mild, moderate, and severe (n = 102).

Symptoms	Group	Mild	Moderate	Severe	P-value¥
Headache					
	(1) a-tDCS-L-DLPFC (n = 34)	47.1%	47.1%	5.9%	0.07
	(2) s-tDCS- L-DLPFC (n = 17)	50.0%	33.3%	16.7%	
	(3) a- tDCS-M1 (n = 34)	35.0%	37.5%	27.5%	
	(4) s-tDCS-M1) n = 17)	40.0%	35.0%	25.0%	
Tingling					
	(1) a-tDCS-L-DLPFC (n = 34)	5.9%	64.7%	29.4%	0.09
	(2) s-tDCS- L-DLPFC (n = 17)	16.7%	38.9%	44.4%	
	(3) a- tDCS-M1 (n = 34)	27.5%	40.0%	32.5%	
	(4) s-tDCS-M1) n = 17)	25.0%	55.0%	20.0%	
Itching					
	(1) a-tDCS-L-DLPFC (n = 34)	5.9%	58.8%	35.3%	0.09
	(2) s-tDCS- L-DLPFC (n = 17)	16.7%	55.6%	27.8%	
	(3) a- tDCS-M1 (n = 34)	27.5%	40.0%	32.5%	
	(4) s-tDCS-M1) n = 17)	25.0%	50.0%	25.0%	
Burning	(1) a-tDCS-L-DLPFC (n = 34)				
	(1) a-tDCS-L-DLPFC (n = 34)	5.9%	82.4%	11.8%	0.03*
	(2) s-tDCS- L-DLPFC (n = 17)	16.7%	77.8%	5.6%	
	(3) a- tDCS-M1 (n = 34)	27.5%	57.5%	15.0%	
	(4) s-tDCS-M1) n = 17)	25.0%	75.0%	0.0%	
Redness					
	(1) a-tDCS-L-DLPFC (n = 34)	5.9%	58.8%	35.3%	0.08
	(2) s-tDCS- L-DLPFC (n = 17)	16.7%	55.6%	27.8%	
	(3) a- tDCS-M1 (n = 34)	27.5%	40.0%	32.5%	
	(4) s-tDCS-M1) n = 17)	25.0%	50.0%	25.0%	

¥ The P-values show the difference in the comparisons between groups using χ2.
Numbers identify the groups: (1) a-tDCS on L-DLPFC, (2) s-tDCS on L-DLPFC, (3) a-tDCS on M1, and (4) s-tDCS on M1. The asterisk* indicates a significant difference for s-tDCS on M1 compared to groups 1, 2, and 4.

showed a high rate of incorrect guesses (87.5% and 93.3%, respectively).

Participants, regardless of the stimulation site, reported a confidence level of 92.6% for a-tDCS and 88.5% for s-tDCS.

4. Discussion

In this study, self-applied M-HB-self-applied-a-tDCS on the L-DLPFC effectively reduced UE and EE in patients with fibromyalgia. These findings make a significant contribution by showing that M-HB-self-applied-a-tDCS has different effects on trait food cravings depending on the severity of fibromyalgia symptoms, with a higher impact on food cravings in the M1 group. They underscore the importance of tailoring stimulation areas for precise intervention in specific disordered eating behaviors and highlight the feasibility of M-HB-self-applied-a-tDCS.

4.1. tDCS impact on disordered eating behavior in fibromyalgia

The effect of M-HB-self-applied-a-tDCS on UE and EE, especially when applied to the L-DLPFC, gives us useful information for creating targeted interventions for people struggling with disordered eating behaviors. This shows the importance of looking at specific brain regions that control UE [20,43]. These results align with prior randomized clinical trials and meta-analyses conducted by health professionals in medical centers [44,45]. Additionally, they find support on the ground of neurobiological processes that take place in the prefrontal cortex (PFC), which has been the focus of tDCS treatment for eating disorders [46,47]. From a functional perspective, the potential therapeutic benefit of stimulating the PFC is that it is a key brain region associated with impulsive decision-making and self-control processes [48]. Moreover, the PFC is believed to play a substantial role in delayed reward discounting (DRD) rates with tDCS use [49,50]. It is not clear what the best area is to apply tDCS for disordered eating behaviors, with results showing mixed trends. Previous studies have shown that either inhibiting the L-DLPFC or stimulating the right-(r)-DLPFC can mitigate disordered eating symptoms related to DRD. Thus, this is an interesting research focus for determining if stimulating the right or left PFC could produce better results for specific symptoms of determined eating disorders. Another positive aspect of our study is that it offers M-HB-self-applied-a-tDCS, a therapeutic approach of low cost with great potential for feasible long-term use. This is in line with earlier research that found a dose-response effect in overweight people, showing that, after one week of daily a-tDCS in the r-DLPFC, participants consumed fewer calories and said they were less hungry [51]. This approach is also supported by the concept that the number of consecutive tDCS sessions seems to be linked to consistent results with longer effects [15]. Although the present study lacks a follow-up, previous studies have shown that tDCS effects may persist for up to 30 days after stimulation [52].

We noted that M-HB-self-applied-a-tDCS did not have a significant effect on cognitive restraints. However, a significant reduction with a moderate ES (0.35) was observed in the stimulation of L-DLPFC, regardless of whether participants received active a-tDCS or a s-tDCS. The interaction analysis between stimulation area and type of stimulation sustained a moderate SE, which likely supports a significant placebo effect in the outcome. According to previous literature, the placebo effect observed in randomized controlled trials may reflect the influence of individuals believing they are receiving an active treatment [53]. Thus, positive expectations and beliefs can lead to neurotransmitter release, which is involved in neural activity and cognitive processing, contributing to perceived cognitive improvement, which was indexed in the CR domain. Other effects that can also influence the treatment effect and magnify the placebo effect are disease progression, symptom fluctuations, regression to the mean, and response bias in self-reported symptoms [53]. Even though the placebo effect has been discussed frequently, its real impact remains in debate. Thus, this is a phenomenon that needs to be better understood. Notably, literature on the placebo effect is contentious in several aspects. A previous meta-analysis suggested that the placebo effect is usually small and connected to subjective outcomes [54], while studies with depressed patients who were not responding to treatment showed a placebo effect with a large ES, and was consistent across various treatment modalities, including tDCS [55]. The placebo effect is real, and it may differ depending on the treatment type used (e.g., pills or devices). Our results suggest that

more research is needed to understand how the different factors that cause the placebo effect work together and what it means for creating effective treatment plans in clinical settings.

4.2. Varied effects of M-HB-a-tDCS on eating behavior in relation to fibromyalgia symptom severity

The results highlight that fibromyalgia symptoms can influence the efficacy of M-HB-self-applied-a-tDCS in mitigating food cravings. This aligns with previous research indicating a more favorable impact of M-HB-self-applied-a-tDCS on M1 compared to L-DLPFC for improving fibromyalgia symptoms [27–29]. Although the exact mechanism is not fully understood, it is plausible that pain diminishes the pleasure derived from food sensory experiences, possibly reducing feelings of satiety [56]. The hypothesis that alleviating fibromyalgia symptoms may decrease cravings for hyperpalatable foods finds support in data from the U.S. National Health and Nutrition Examination Survey, suggesting a nuanced relationship between elevated ultra-processed food intake and mild depression, heightened mental health challenges, and anxiety [57]. Effective pain management, therefore, may positively influence eating behaviors. This interplay of functions provides a potential explanation for the observed association between M1 stimulation and reduced food craving. So, these findings contribute to the research field by demonstrating how a-tDCS applied in one brain area can impact signals in other brain regions. This offers a novel perspective on how electrical stimulation could potentially remodel dysfunctional neural networks across different brain areas.

Furthermore, as demonstrated by a previous electric field modeling study using PET, M1 stimulation might impact other brain regions like the ACC, thalamus, insula, and DLPFC [22,23]. It is therefore plausible that M1 stimulation may induce neuroplastic changes that reorganize the somatosensory cortex and at the same time modulate neural circuits associated with reward and craving, including the nucleus accumbens and prefrontal cortex [19]. These results are clinically relevant to individualized planning of the best stimulation area in a clinical setting. As these results help understand how a-tDCS can be applied in a brain area, they may have ripple effects, impacting the functional dynamics of interconnected brain regions. In our study, these treatment effects could be linked to electrode size, which is crucial for stimulation focus and cortical excitability [58]. The cumulative therapeutic impact of M-HB-self-applied tDCS may have amplified these effects [58].When interpreting findings, consider these methodological aspects, acknowledging their potential applicability to fibromyalgia populations, although they offer insights into a-tDCS benefits for disordered eating in diverse health contexts.

4.3. M-HB-self-applied-a-tDCS is a feasible and safe approach

This study demonstrated robust data with high adherence rates exceeding 86.32% in both a-tDCS and s-tDCS treatment groups, showcasing the efficacy and viability of M-HB-self-applied-a-tDCS [59]. The results support the benefits of M-HB-self-applied-a-tDCS, highlighting increased accessibility, scalability, long-term use, reduced travel costs, application flexibility, and significantly enhanced treatment adherence. M-HB-self-applied-a-tDCS side effects were generally mild to moderate, consistent with rates observed in studies supervised by medical professionals [58]. Additionally, these findings align with previous studies utilizing M-HB-self-applied-a-tDCS [27,29,30,33].

It's important to note that the study employed a pre-planned modified intent-to-treat (m-ITT) analysis with an adjusted protocol, encompassing all patients who completed at least ten sessions. The choice of ten sessions for ITT was guided by most of the literature supporting clinical symptom improvement in chronic pain [60,61]. This method is not as strict as classical ITT, but it suggests that M-HB-self-applied-a-tDCS could be useful in clinical settings with at least a minimum number of sessions.

4.4. Limitations

In interpreting our findings, several methodological considerations and limitations must be acknowledged that may have impacted the study's outcomes. *First,* we intentionally employed an unbalanced randomization approach, favoring M-HB-self-applied-a-tDCS over M-HB-self-applied-s-tDCS for feasibility. This decision was aimed at enhancing protocol adherence by maximizing the number of participants receiving potentially beneficial treatment. The 2:1 allocation ratio was chosen based on the rationale that fibromyalgia entails significant suffering, thereby ensuring a larger active group to better identify and assess potential side effects. *Second,* despite providing comprehensive training on tDCS device use, we lacked remote monitoring of sessions, and therefore caution against direct comparisons with supervised studies. *Third,* the exclusive enrollment of female participants sought to mitigate sex-related biases, considering known differences in a-tDCS effects on the DLPFC in women. *Fourth,* imbalances in psychiatric medication use were addressed through randomization and delta value analysis, minimizing potential impact on conclusions. *Fifth,* the high rates of incorrect guessing indicate effective blinding. While the high confidence rates in both groups may influence outcomes by potentially inflating the placebo effect, it's noteworthy that these rates were similar between the a-tDCS and s-tDCS groups. This similarity implies an equalizing effect, making it improbable that their confidence could alter our conclusions significantly. Finally, The COVID-19 pandemic's mobility limitations prevented a follow-up period, restricting insights into the long-term impact of the intervention on outcomes. These methodological considerations highlight the need for cautious interpretation and support future studies with extended follow-ups, particularly in specific disordered eating behaviors.

4.5. Conclusion

These findings demonstrate that M-HB-self-applied-a-tDCS is a suitable approach for reducing uncontrolled and emotional eating, with greater efficacy than L-DLPFC. Furthermore, they revealed the influence of fibromyalgia symptoms on M-HB-self-applied-a-tDCS's, with M1 being particularly effective in mitigating food cravings and reducing fibromyalgia symptoms.

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CRediT authorship contribution statement

Manoela N.da Jornada: Conceptualization, Data curation, Investigation, Writing – original draft. **Luciana C. Antunes:** Conceptualization, Supervision, Writing – original draft. **Camila Alves:**

Conceptualization. **Iraci L.S. Torres:** Writing – review & editing. **Felipe Fregni:** Conceptualization, Writing – review & editing. **Paulo R. S Sanches:** Conceptualization, Methodology. **Danton P Silva:** Funding acquisition. **Wolnei Caumo:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors involved in this study disclose the following potential conflicts of interest: Dr. Caumo, affiliated with the National Council for Scientific and Technological Development (CNPq), Brazil, and Dr. Silva Torres reported receiving grants from the National Council for Scientific and Technological Development, as well as from the Foundation de Amparo à Pesquisa do Estado do Rio Grande do Sul. Dr. Sanches also received grants from the National Council for Scientific and Technological Development during the conduct of the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.02.001.

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7.3 ARTIGO 3

Procedure and protocol to use the Home-Based-tDCS

Submetido na MethodsX

Procedure and protocol to use the Home-Based-tDCS

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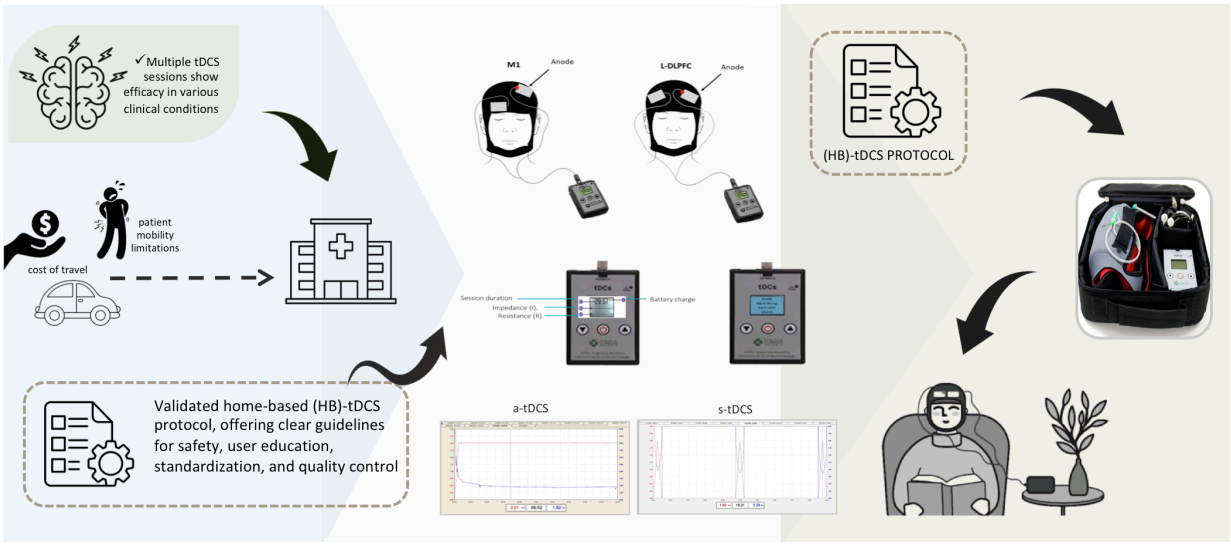
Abstract

The benefits of delivering transcranial direct current stimulation (tDCS) treatment at home are highlighted:

- Emphasizing reduced burdens
- Improved compliance
- Enhanced access for diverse populations

We presented a validated home-based (HB)-tDCS protocol, offering clear guidelines for safety, user education, standardization, and quality control. The protocol includes details on the home-based tDCS device characteristics, electrode positions, stimulation protocols, and user training. Notably, it emphasizes user selection considerations, the importance of well-defined protocols permitting patient-scheduled sessions, and adherence monitoring. The document also outlines a structured study protocol, incorporating baseline assessments, training sessions, and approaches to monitoring protocol compliance. In conclusion, the perspectives on tDCS with a structured protocol at home might contribute significantly to advancing neuromodulation practices.



Specifications table

Subject area	*Neuroscience*
More specific subject area	*Neuromodulation*
Name of your protocol	*Procedure and protocol to use the Home-Based-tDCS*
Reagents/tools	*The device for Home-Based-tDCS is registered with the Brazilian National Health Surveillance Agency (Anvisa) under number N°80079190028.*
Experimental design	*We presented a validated home-based (HB)-tDCS protocol, offering clear guidelines for safety, user education, standardization, and quality control.*
Trial registration	-
Ethics	*The relevant informed consent was obtained from the subjects.*
Value of the Protocol	• *Reduced burdens* • *Improved compliance* • *Enhanced access for diverse populations*

1. Background

Several studies have explored transcranial direct current stimulation (tDCS) in various clinical settings. They have demonstrated effectiveness (Level A) in treating depression. They are likely effective (Level B) for conditions such as neuropathic pain, fibromyalgia, migraines, Parkinson's disease (both motor and cognitive symptoms), stroke (motor), epilepsy, schizophrenia, alcohol and drug addiction, and obesity [1–5]. However, the widespread adoption of tDCS faces challenges due to the necessity of multiple sessions and the cost of travel to medical centers for patients and the healthcare system.

To overcome this barrier, home-based tDCS (HB-tDCS) devices have been developed to provide greater convenience for patients and reduce the need for frequent travel to medical centers [6]. Despite this advancement, clear guidance for practical therapeutic applications of HB-tDCS remains challenging [7]. Establishing a standardized protocol for HB-tDCS is crucial to enhance treatment compliance and improve accessibility, especially for individuals in remote areas or those facing physical, cognitive, or chronic health challenges requiring long-term tDCS use [8].

While many home-based tDCS (HB-tDCS) approaches involve interactions between supervisors and users, the devices must be programmable in a personalized way. They should incorporate safety features to prevent protocol changes without supervision. Meanwhile, patients need channels to seek support if necessary. Our experience in randomized controlled trials supports the positive outcomes of home-based tDCS [9–12].

Success in HB-tDCS hinges on carefully selecting the user, considering their physical and cognitive capacities to operate the device safely. A comprehensive protocol for home-based tDCS is essential, covering safety, education, standardization, ethics, quality control, community engagement, accessibility, and regulatory compliance.

1. Safety: The protocol offers clear guidelines for the safe and correct utilization of tDCS equipment, mitigating potential risks and adverse effects of improper application.

2. User Education: Publicizing the protocol allows users to access detailed information on proper tDCS use, fostering user education. This ensures individuals understand the procedure, set appropriate parameters, and adhere to best practices.

3. Standardization: A standardized protocol maintains consistency in tDCS application, which is critical for research studies, clinical trials, and therapeutic interventions. This consistency ensures reliable and comparable results across different settings.

4. Ethical Considerations: Transparently sharing the protocol enhances ethical considerations surrounding the use of tDCS. It ensures users are well-informed about the procedure, potential benefits, and possible risks, enabling them to make informed decisions.

5. Quality Control: A published protocol acts as a reference for quality control, allowing researchers, clinicians, and users to adhere to established guidelines and ensure correct and consistent device utilization.

6. Community Engagement: Publicizing the protocol encourages engagement with the broader scientific and user communities. It promotes collaboration, feedback, and protocol improvement based on collective knowledge and experiences.

7. Accessibility: Publicizing the protocol ensures that information is accessible to a wider audience, including researchers, healthcare professionals, and individuals interested in using tDCS for various purposes. This facilitates democratized access to knowledge and promotes inclusivity.

8. Regulatory Compliance: Regulatory standards often require detailed protocols for the use of medical devices. Publicizing the protocol helps meet these standards, ensuring regulatory compliance.

The protocol presented was developed and validated by the team of Pain and Neuromodulation Lab at Hospital de Clinicas de Porto Alegre (HCPA) in partnership with the Biomedical Engineering department of the HCPA, Brazil, for the use of tDCS.

2. Home-Based tDCS Device

The device for Home-Based-tDCS is registered with the Brazilian National Health Surveillance Agency (Anvisa) under number Nº80079190028. This device was developed and validated for use at home, as demonstrated by its previous use in different trials conducted by our group [9,11,13]. The device monitors contact impedance at a sampling rate of 1 mA and interrupts the session if the impedance exceeds a predetermined value of 1 mA for an interval of 5 seconds or if the electric current undergoes an alteration greater than 10%. The equipment records the time and duration of use, as well as the session time, which allows for adherence monitoring. Since July 2020, when this protocol was in progress, it has been commercialized by Mendes and Barbosa Produtos Médicos Ltda Quark Medical (Brazil). The tDCS equipment for home use is presented in Figure panel (**1, 2, 3, 4, 5 and 6**).

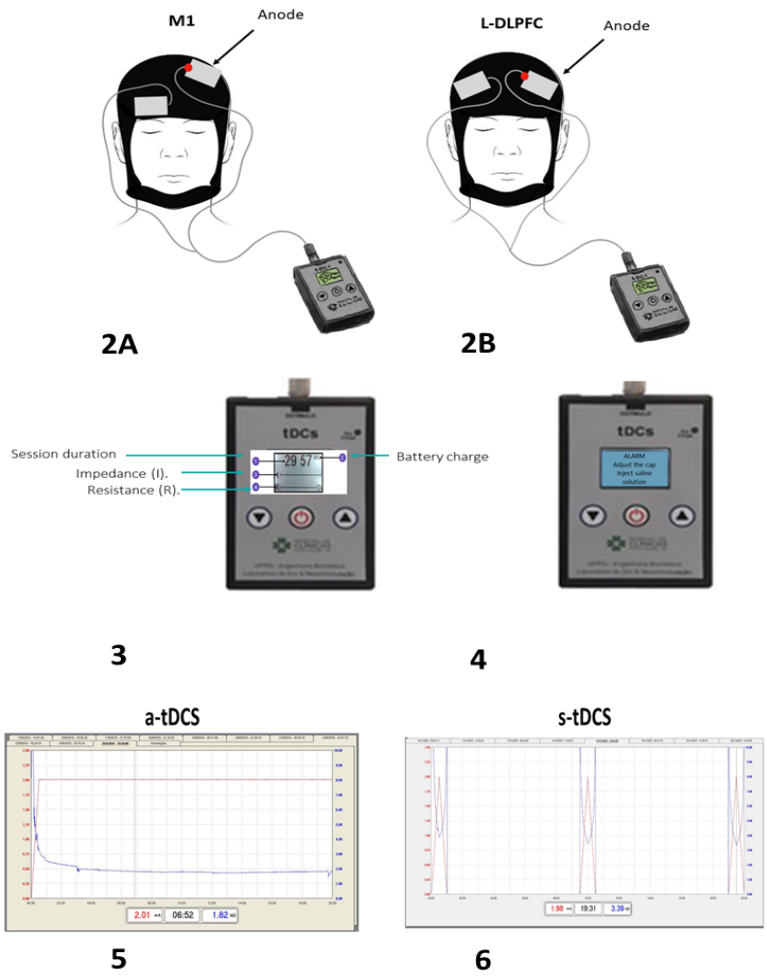


Figure panel (**1, 2, 3, 4, 5 and 6**).

(1) Schematic drawing of the electrode**.** Flexible Vinyl material, conductive rubber, and vegetal sponge.

(2) Cap Neoprene of 4 mm thickness manufactured by Biomedical Engineering Department of Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, with sites of stimulation: **(2A)** Anodal transcranial Direct Current Stimulation (a-tDCS) with the anode placed over M1 (C3) and cathode over fP2. **(2B)** Anodal tDCS with anode over left DLPFC (F3) and cathode over right DLPFC (F3). **Device Features: (3)** High resistance. **(4)** Alarm warning: adjust the cap and inject extra saline. **(5)** Typical curves of current intensity versus contact impedance during a tDCS. **(6)** Typical curves of current intensity versus contact impedance during 30 seconds in s-tDCS.

3. Electrodes position and HB-tDCS stimulation protocol

This study protocol used scalp electrodes positioned according to the 10-20 system for EEG, with the anode at F3 and the cathode at F4, or with the anode positioned on the left primary motor cortex (C3) and cathode over the right supra-orbital region (Fp2), and the current applied for 20 minutes at 2 mA (see Figure 1A, 1B). The study included both active tDCS and sham conditions, with the device programmed to offer 30 seconds of stimulation at the beginning, after 10 minutes, and after 20 minutes during the sham conditions. To ensure a sham condition, the same montage was used for both active tDCS and sham tDCS. Both active and sham tDCS had a ramp-up time of 20 seconds for the current to reach 2 mA, followed by a ramp-down time of 20 seconds. This protocol was designed to mimic active tDCS but without delivering sustained stimulation. The electrodes are 35cm2 and coated with a vegetable sponge moistened with saline solution administered by two silicone cannulas coupled to the electrode. The positioning of the electrodes in the stimulation sites was facilitated using a neoprene elastic cap available in varied sizes for proper adjustment to the patients' heads. To ensure the blinding of participants regarding the intervention they received the device was programmed to automatically turn on and off at each of the specified time points for both active and sham tDCS conditions. A biomedical engineer programed the device to provide a predetermined number of stimulation sessions, with a minimum interval of 16 hours between each consecutive session. This protocol was designed to ensure that participants did not receive tDCS sessions extra than the programmed in the protocol, which could potentially lead to adverse effects or interfere with the outcomes of the study. This approach was adopted to ensure that participants were unaware of whether they were receiving active or sham stimulation at any given time during the study.

The study's protocol included visits to the center for baseline assessment, training on how to use the device, and assessment at treatment end. The participants receive instructions on how to self-apply the tDCS, choose a quiet time in their daily schedule to apply the treatment session, and record adverse effects. The treatment protocol for tDCS at home involved several steps to ensure proper use and adherence to the protocol.

4. Structure of study protocol

The study's protocol consisted of a structured sequence:

Baseline Assessment: This began at the center, where participants were initially assessed.

Training Session (Visit 1): Volunteers received comprehensive training on using the tDCS device correctly. They were provided with instructions for self-administration at home. The cap size and electrode positions were determined, and participants were given a link to a video guide for self-administration *(https://youtu.be/3Wtji4esOGE).* They were also encouraged to contact the research team if needed.

Visit 2: Occurred four weeks after starting the tDCS protocol. Participants returned to the center for a treatment-end assessment and returned the device. Throughout the protocol, participants were required to use the device appropriately and keep records of any adverse effects experienced.

Cap Size and Electrode Positioning

The process of determining cap size and electrode positions involved several steps:

(i) Measuring the participant's head circumference to select the appropriate cap size (small, medium, or large).

(ii) Participants wore the cap while the researcher identified electrode positions following the 10-20 EEG system.

(iii) Electrode positioning on the cap was based on randomization, with scenarios such as anode at F3 and cathode at F4 or anode at C3 and cathode at Fp2 (see Figure 1A, 1B).

(iv) Electrodes were inserted into vegetable sponges and secured in the cap following the 10-20 EEG system.

(v) To avoid electrode placement errors, the anode was marked red, and the cathode was marked black.

(vi) Detailed instructions for self-administration of the tDCS device at home can be found here: https://www.jove.com/video/57614/home-based-transcranial-direct-current-stimulation-device-development.

Training and Self-Application of tDCS at Home

The training and instructions for participants to self-administer tDCS at home included the following steps:

(i) Participants received initial training on equipment usage and skin irritation identification.

(ii) The first treatment session was supervised with detailed instructions provided through a step-by-step video guide.

(iii) Participants were instructed to prepare the stimulation area by exposing it in front of a mirror.

(iv) The skin under the electrodes was cleaned with alcohol to remove creams, dirt, or grease.

(v) Participants were guided to wear the cap, positioning the seam between their eyebrows.

(vi) Approximately 6 ml of saline was added to the syringes connected to the sponges.

HB-tDCS Sessions and Compliance Monitoring

To ensure compliance with protocol during HB-tDCS sessions, we implemented several procedures:

(i) Participants were advised to choose a quiet and suitable time in their daily schedule for their treatment session.

(ii) The initial home-based session was conducted under remote supervision, allowing participants to seek assistance from the research team if needed.

(iii) A weekly contact through WhatsApp to track participants' progress and ensure they adhered to the treatment protocol.

(iv) Participants were encouraged to contact the research team for assistance.

(v) Participants were instructed to promptly document any adverse effects in a diary following each tDCS home session.

(vi) To verify the adherence to the following protocol, a biomedical engineer reviewed the records to confirm the session time, duration, current intensity, and contact impedance. The average impedance was employed to assess the quality of the delivered current. The impedance should range between 8 and 4 kΩ at the beginning of stimulation, with the target during treatment between 3 and 2 kΩ. For a valid 20-minute a-DCS session, impedance levels should be between 3 and 2 kΩ for at least half the time in the case of a duration of 10 min. The literature supports the choice of a 10-minute duration by demonstrating its effectiveness in

promoting neuroplasticity, with studies by Nitsche (2000) and Bikson (2016) adding to this understanding [2,14].

5. Perspectives

The Pain and Neuromodulation Lab at HCPA, Porto Alegre, Brazil, in collaboration with the HCPA's Biomedical Engineering department at HCPA, Porto Alegre, Brazil, developed and validated this structured protocol for tDCS at home that addresses important issues. Safety is prioritized through clear guidelines, mitigating the potential risks of improper tDCS application. Simultaneously, publicizing the protocol enhances user education, fostering understanding and adherence to best practices. Standardization is achieved, ensuring consistent tDCS application across diverse settings. The protocol transparently outlines ethical considerations, empowering users to make informed decisions. It serves as a reference for quality control and facilitates collaboration, feedback, and continual improvement in the scientific and user communities. It permits democratizing knowledge; the protocol enhances accessibility and ensures regulatory compliance with detailed requirements for medical device use. These perspectives on tDCS at home with a structured protocol contribute to advancing neuromodulation practices, ethical engagement, and accessibility.

Data availability: Any data related to the intervention and primary outcomes will be available upon request from Caumo (wcaumo@hcpa.edu.br) without any time restrictions.

CRediT Author Statement

The authors, Drs. Caumo, Manoela N. da Jornada, and Luciana C. Antunes, played integral roles in the study, with full access to all data and assuming responsibility for data integrity and accuracy.

The conceptualization and design of the study involved contributions from Caumo, Fregni, Torres, Sanches, Manoela N. da Jornada, and Luciana C. Antunes.

Acquisition, analysis, and interpretation of data were conducted by Caumo, Fregni, Torres, Manoela N. da Jornada, and Luciana C. Antunes.

For critical manuscript revisions, the intellectual input came from Caumo, Manoela N. da Jornada, Luciana C. Antunes, Silva Torres, and Fregni.

Statistical analysis was performed by Caumo and Fregni.

Caumo obtained the funding.

Conflict of Interest:

 The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
Caumo, Sila Torres, Dr Sanches had a patent for BR 20 2015 016450 0 licensed to Quark Medical. The tDCS device used in this study was developed and patented by Dr Sanches, MSc Pereira, Dr Silva Torres, and Dr Caumo, and these authors received royalties from Quark Medical (patent for BR 20 2015 016450 0 licensed to Quark Medical). MSc Pereira reported grants from Financiadora de Estudos e Projetos during the conduct of the study. No other disclosures were reported.

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8. CONSIDERAÇÕES FINAIS

Conforme abordado na presente tese, evidências tanto em indivíduos com FM quanto com obesidade, apontam para um desequilíbrio no sistema motivacional da dopamina, afetando circuitos cerebrais pré-frontais e límbicos, que regem os aspectos relacionados à cognição e à recompensa do comportamento alimentar.

O *estudo 1* (exploratório) fornece uma estrutura que integra os sintomas cardinais da fibromialgia, a neuroplasticidade e sinalização dopaminérgica, para avançar na compreensão da elevada prevalência de excesso de peso em indivíduos com fibromialgia. Observamos que os indivíduos com a presença do alelo A1 (A1+) no polimorfismo Taq1A (rs1800497) foram mais propensos a ter desejos alimentares (*food craving*) mais fortes. Medidas de IMC e circunferência abdominal mais elevadas, *food craving*, descontrole alimentar e alimentação emocional associaram-se a sintomas depressivos e dolorosos mais graves, sintomas de sensibilização central e incapacidade relacionada à dor. Ainda, o genótipo A1+ exerceu um efeito moderador na relação entre comportamento alimentar, medidas antropométricas, incapacidade relacionada à dor e sintomas de sensibilização central. A partir de uma perspectiva conceitual, nossos achados poderiam explicar os processos fisiopatológicos subjacentes à alimentação disfuncional na fibromialgia, que estão ligados ao status de neuroplasticidade indexado pelo BDNF sérico. Estes resultados mostram como o polimorfismo Taq1A pode afetar o comportamento alimentar, levando à alimentação excessiva e como esses comportamentos estão associados aos sintomas da fibromialgia.

No *estudo 2* (ensaio clínico) comprovamos a eficácia da ETCC domiciliar autoaplicada sobre M1 ou DLPFC esquerdo na melhoria de vários domínios do comportamento alimentar, incluindo restrição cognitiva, descontrole alimentar e alimentação emocional. Considerando a

influência dos sintomas da FM, apenas o grupo que recebeu estimulação em M1 apresentou melhora nos padrões de *Food Craving*. Hipotetizamos que tais efeitos no grupo que recebeu ETCC ativa sobre o M1 possam ser efeitos secundários da melhora relacionada à dor e, embora não tenhamos dados sobre medidas de nível de estresse, também é plausível que essa melhora tenha reduzido o estresse, que, assim como a dor, leva a comportamentos alimentares disfuncionais, maior consumo energético e consequente adiposidade. Embora o maior contingente de evidências utilizando ETCC para modulação do comportamento alimentar disfuncional tenha como alvo o DLPFC, ao se tratar de uma patologia complexa e com sintomas multifacetados como a fibromialgia, a estimulação no M1 mostra-se um sítio promissor.

Essas novas descobertas fornecem evidências sobre os benefícios e o impacto da ETCC domiciliar autoaplicada em comparação com os resultados de ensaios clínicos randomizados anteriores e meta-análises onde a estimulação foi aplicada por profissionais de saúde em centros médicos e sublinham a relevância clínica e a praticidade desta técnica.

No *estudo 3*, padronizamos o protocolo para o uso do equipamento de ETCC domiciliar, oferecendo diretrizes claras para segurança, educação do usuário, padronização e controle de qualidade. O protocolo inclui detalhes sobre as características do dispositivo ETCC domiciliar, posições dos eletrodos, protocolos de estimulação e treinamento do usuário; enfatiza considerações sobre a seleção do usuário, a importância de protocolos bem definidos que permitam sessões agendadas pelo paciente e o monitoramento da adesão. O documento também descreve um protocolo de estudo estruturado, incorporando avaliações iniciais, sessões de treinamento e abordagens para monitorar o cumprimento do protocolo. Acreditamos que um protocolo estruturado de ETCC domiciliar pode contribuir significativamente para o avanço das práticas de neuromodulação.

No entanto, os estudos possuem limitações. O *estudo 1* apresenta limitações quanto ao seu desenho, impossibilitando estabelecer relações de causa e efeito. Apesar da hipótese inicial, que postulava que encontraríamos diferenças nos domínios do comportamento alimentar entre grupos com e sem o polimorfismo Taq1A, o estudo não encontrou tais distinções. Esta falta de diferença pode ser atribuída a um erro tipo II devido ao poder insuficiente para alguns resultados secundários. Em segundo lugar, é possível que, apesar dos esforços de controle, persista o efeito de fatores de confusão que poderiam influenciar a relação da variante genética Taq1A nos comportamentos alimentares, um efeito de confusão residual desses fatores. Terceiro, incluímos apenas mulheres; embora essa amostragem homogênea reduza o potencial de viés de confusão, ela também limita a validade externa. Além disso, a ausência de um período de acompanhamento limitou a nossa capacidade de compreender melhor o impacto da relação entre o polimorfismo Taq1A e a neuroplasticidade mal-adaptativa como fatores que afetam o comportamento alimentar e o excesso de peso a longo prazo. No *estudo 2*, destacamos as seguintes limitações: primeiro, optamos intencionalmente por uma abordagem de randomização desequilibrada (2:1) para priorizar a viabilidade do estudo, dados os benefícios potenciais da ETCC. Além disso, o tamanho maior da amostra no grupo ativo melhorou nossa capacidade de identificar e avaliar possíveis efeitos colaterais. Em segundo lugar, embora tenhamos fornecido treinamento abrangente aos pacientes sobre como usar o dispositivo ETCC, não implementamos o monitoramento remoto das sessões durante todo o estudo. Terceiro, incluímos exclusivamente participantes do sexo feminino para mitigar potenciais vieses relacionados ao sexo. Finalmente, a ausência de um período de acompanhamento limitou a nossa capacidade de obter uma melhor compreensão do impacto a longo prazo da intervenção nos resultados.

Considerando o impacto negativo da dor, dos aspectos emocionais e do excesso de peso na FM, cuja relevância ao indivíduo e sociedade é inquestionável, é preciso avançar na

compreensão de seus mecanismos fisiopatológicos com vistas ao avanço terapêutico. O desenvolvimento de intervenções destinadas a reequilibrar o sistema motivacional da dopamina e/ou a melhora da sintomatologia associada à FM, como técnicas de indução de neuroplasticidade bem-adaptativa, podem representar um potencial terapêutico no tratamento do comportamento alimentar desses pacientes, prevenindo ou tratando o ganho de peso e a obesidade comórbida. Os achados dos dois estudos que fazem parte da presente tese abrem caminho para ensaios clínicos maiores que explorem os efeitos da ETCC domiciliar em diferentes sítios de estimulação e/ou em combinação com outras abordagens terapêuticas, incluindo terapia de aconselhamento nutricional, terapia cognitivo-comportamental, programas de exercícios físicos e tratamentos farmacológicos no futuro.

9. PERSPECTIVAS FUTURAS

A presente tese de doutorado forneceu os seguintes *insights* importantes: (i) a ETCC domiciliar reduziu efetivamente o *food craving* e melhorou o comportamento alimentar disfuncional em pacientes com fibromialgia. (ii) a ETCC domiciliar é uma abordagem viável para melhorar o comportamento alimentar. (iii) a ETCC domiciliar em M1 melhorou o impacto da fibromialgia na qualidade de vida e na circunferência da cintura. (iv) O efeito da ETCC anódica no comportamento alimentar disfuncional e no *food craving* pode estar associada ao polimorfismo Taq1A e à redução do BDNF.

Mais estudos clínicos nessa área se fazem necessários para servir de base para futuras estratégias efetivas de tratamento que incluam neuromodulação e técnicas de intervenção nutricional efetivas para essa população.

10. ANEXOS

10.1 ANEXO 1 — STROBE (Estudo 1)

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	85
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	86
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	87-88
Objectives	3	State specific objectives, including any prespecified hypotheses	88
Methods			
Study design	4	Present key elements of study design early in the paper	88
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	88
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	88
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	88-89
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	90-91
Bias	9	Describe any efforts to address potential sources of bias	88
Study size	10	Explain how the study size was arrived at	88
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	88-91

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	91
		(*b*) Describe any methods used to examine subgroups and interactions	91
		(*c*) Explain how missing data were addressed	91
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	91
		(*e*) Describe any sensitivity analyses	91
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	91-92
		(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	91-94
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	91-94
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	90-94
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*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	94-97
Discussion			

Key results	18	Summarise key results with reference to study objectives	97
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	101
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	97-102
Generalisability	21	Discuss the generalisability (external validity) of the study results	97-102
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	85

*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. ANEXO 2: CONSORT (Estudo 2)

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

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	119
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	119
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	120
	2b	Specific objectives or hypotheses	120
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	120
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	120
	4b	Settings and locations where the data were collected	120
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	120-122
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	121
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	120

	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	120
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	120
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	120
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	120
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	120
	11b	If relevant, description of the similarity of interventions	120
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	125-126
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	125-126
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	122
	13b	For each group, losses and exclusions after randomisation, together with reasons	122
Recruitment	14a	Dates defining the periods of recruitment and follow-up	2019-2022
	14b	Why the trial ended or was stopped	November 2022
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	122
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	122-126

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)	122-126
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	122
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	127
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	126
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	126-127
Other information			
Registration	23	Registration number and name of trial registry	NCT03843203
Protocol	24	Where the full trial protocol can be accessed, if available	With corresponding author
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	128

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*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. ANEXO 3: TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nº do CAAE: 12625718.9.0000.5327

Título do Projeto: IMPACTO DA ESTIMULAÇÃO TRANSCRANIANA DE CORRENTE CONTÍNUA DOMICILIAR NO COMPORTAMENTO ALIMENTAR DE MULHERES COM FIBROMIALGIA: UM ENSAIO CLÍNICO RANDOMIZADO FATORIAL

Você está sendo convidada a participar de uma pesquisa cujo objetivo é avaliar o impacto da estimulação transcraniana de corrente contínua (ETCC) aplicada sobre o DLPFC esquerdo ou M1 no comportamento alimentar disfuncional em mulheres com fibromialgia, considerando a eficácia e a segurança do uso deste tipo de intervenção. Ou seja, neste projeto, pretendemos avaliar o efeito da ETCC no comportamento alimentar, pois sabe-se que pacientes com fibromialgia possuem uma alta prevalência de excesso de peso/obesidade, o que pode interferir no curso e no prognóstico da doença.

Este projeto é realizado pelo Laboratório e Dor & Neuromodulação do Hospital de Clínicas de Porto Alegre (HCPA). Estamos realizando esse convite, pois a senhora já aceitou participar da pesquisa "Estudo de eficácia e efetividade da estimulação transcraniana de corrente contínua (ETCC) de longo prazo em nível domiciliar na fibromialgia: um ensaio clínico randomizado, explanatório" do mesmo grupo de pesquisa.

Se a senhora aceitar participar da pesquisa, os procedimentos envolvidos em sua participação são os seguintes:

Você preencherá 4 questionários sobre seus hábitos alimentares. Estes questionários possuem questões de marcar a resposta e podem ser respondidos em aproximadamente 1 hora. Será realizada uma coleta de sangue (15 mL, equivalente a 3 colheres de chá). O material biológico coletado será utilizado exclusivamente para essa pesquisa. Após as análises previstas, o material restante será descartado. Também serão medidos a sua circunferência abdominal bem como o peso e a altura. Esses procedimentos serão realizados no mesmo dia de uma das visitas do projeto que você já participa.

Adicionalmente, pedimos a sua autorização para acessar informações já coletadas no estudo anterior, tais como informações sociodemográficas e resultados de avaliações.

Depois de três meses, a senhora deverá realizar novamente o preenchimentos dos questionários e as medidas de circunferência abdominal e de peso.

Um possível desconforto poderá ser sentido na coleta de sangue, devido à introdução da agulha, com o possível surgimento de um hematoma (mancha roxa na pele) ou outro desconforto no local da coleta. Um outro desconforto associado à pesquisa é o tempo que deverá ser disponibilizado para a realização dos procedimentos propostos.

A participação na pesquisa não trará benefícios diretos às participantes, porém, contribuirá para o aumento do conhecimento sobre o assunto estudado, e, poderá beneficiar futuras pacientes.

Sua participação na pesquisa é totalmente voluntária, ou seja, não é obrigatória. Caso você decida não participar, ou ainda, desistir de participar e retirar seu consentimento, não haverá nenhum prejuízo ao atendimento que você recebe ou possa receber na instituição.

Não está previsto nenhum tipo de pagamento pela sua participação na pesquisa e você não terá nenhum custo com respeito aos procedimentos envolvidos.

Caso ocorra alguma intercorrência ou dano, resultante de sua participação na pesquisa, você receberá todo o atendimento necessário, sem nenhum custo pessoal.

Os dados coletados durante a pesquisa serão sempre tratados confidencialmente. Os resultados serão apresentados conjuntamente, sem a identificação dos participantes, ou seja, o seu nome não aparecerá na publicação dos resultados.

Caso você tenha dúvidas, poderá entrar em contato com o pesquisador responsável, Profº Dr. Wolnei Caumo ou com a pesquisadora Manoela Jornada, pelo telefone (51) 3359-6377, ou com o Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre (HCPA), pelo telefone (51) 33597640, ou no 2º andar do HCPA, sala 2229, de segunda a sexta, das 8h às 17h.

Esse Termo é assinado em duas vias, sendo uma para o participante e outra para os pesquisadores.

_____

Nome do participante da pesquisa

_____

Assinatura

_____

Nome do pesquisador que aplicou o Termo

_____

Assinatura

Local e Data: _____

_____

Assinatura

Local e Data: _____

10.4. ANEXO 4 - PRODUÇÃO DURANTE O PERÍODO DO DOUTORADO

39ª Semana Científica do HCPA

Gestão da pesquisa aplicada à saúde

De 30 de setembro a 4 de outubro de 2019

Certificamos que o trabalho **RELAÇÃO ENTRE SINTOMAS DEPRESSIVOS, ANSIOSOS E DE DOR COM ALIMENTAÇÃO EMOCIONAL E FOOD-CRAVING EM MULHERES COM FIBROMIALGIA: UM ESTUDO EXPLORATÓRIO** de autoria de **SAMARA MACHADO BRUCK; MANOELA NEVES DA JORNADA; BETINA FRANCESCHINI TOCCHETTO; LUCIANA DA CONCEIÇÃO ANTUNES; LETÍCIA RAMALHO; JÉSSICA LORENZI ELKFURY; WOLNEI CAUMO**, foi apresentado na modalidade E-POSTER na **39ª Semana Científica do HCPA**, realizada no Hospital de Clínicas de Porto Alegre, no período de 30 de setembro a 4 de outubro de 2019.

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

Profª. Patrícia Ashton-Prolla
Coordenadora do GPPG

a autenticidade deste documento pode ser verificada através da URL:
https://sgee.hcpa.edu.br/sgee/validar/BC3D7BDF

Promoção

Universidade: presente!

XXXI SIC
SALÃO DE INICIAÇÃO CIENTÍFICA

Salão UFRGS 2019 – Conhecimento Formação Inovação

CERTIFICADO

Certificamos que

SAMARA MACHADO BRUCK

apresentou o trabalho

RELAÇÃO ENTRE SINTOMAS DEPRESSIVOS, ANSIOSOS E DE DOR COM ALIMENTAÇÃO EMOCIONAL E FOOD-CRAVING EM MULHERES COM FIBROMIALGIA: UM ESTUDO EXPLORATÓRIO

orientado por

WOLNEI CAUMO

na modalidade "Apresentação oral e poster", com carga horária de 5 horas, no Salão UFRGS 2019: XXXI SALÃO DE INICIAÇÃO CIENTÍFICA DA UFRGS, realizado no período de 21/10/2019 a 25/10/2019.

Documento gerado sob autenticação KAA.980.283.693

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21 a 25 de outubro de 2019
Campus do Vale . UFRGS

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FACULDADE DE MEDICINA
DEPARTAMENTO DE NUTRIÇÃO

DECLARAÇÃO

DEPARTAMENTO DE NUTRIÇÃO

Declaro, para os devidos fins, que a **NUTRICIONISTA MANOELA NEVES DA JORNADA** colaborou como ministrante na disciplina de **Nutrição Clínica III,** do Curso de Nutrição desta Faculdade de Medicina, tendo abordado o tema *Terapia Nutricional nos Transtornos Alimentares*, por um período de 03 horas na data de 08 de maio de 2019.

Atenciosamente,

Profª. Drª Thais Steemburgo
Nutricionista CRN 433
UFRGS -

Profª Drª Thais Steemburgo

Professora da disciplina de Nutrição Clinica III

Ramiro Barcelos, 2400 - 4° andar - CEP 90035-003 - Porto Alegre - RS
tel. e fax: (51)3308-5122 e-mail: nutricao@famed.ufrgs.br

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Atenciosamente,

Profª. Drª. Thais Steemburgo
Nutricionista - CRN 4333
UFRGS

Profª Drª Thais Steemburgo

Professora da disciplina de Nutrição Clinica III

Ramiro Barcelos, 2400 - 4° andar - CEP 90035-003 - Porto Alegre - RS
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DEPARTAMENTO DE NUTRIÇÃO

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Atenciosamente,

Profª. Drª. Thais Steemburgo
Nutricionista CRN 4333
UFRGS

Profª Drª Thais Steemburgo

Regente e professora da disciplina de Nutrição Clínica III

Universidade Federal do Rio Grande do Sul

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Atenciosamente,

Thais Steemburgo

Profª Drª Thais Steemburgo

Regente e professora da disciplina de Nutrição Clínica III

Universidade Federal do Rio Grande do Sul

Ramiro Barcelos, 2400 - 4° andar - CEP 90035-003 - Porto Alegre - RS
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Atenciosamente,

Thais Steemburgo

Profª Drª Thais Steemburgo

Professora da disciplina de Nutrição Clínica III

Universidade Federal do Rio Grande do Sul

Ramiro Barcelos, 2400 - 4° andar - CEP 90035-003 - Porto Alegre - RS
tel. e fax: (51)3308-5122 e-mail: nutricao@famed.ufrgs.br

CERTIFICATE OF ORAL PRESENTATION

This is to certify that

Samara Bruck

presented the following abstract:

Efficiency of Home-Based Transcranial Direct Current Stimulation (TDCS) on Dysfunctional Eating Behavior in Women with Fibromyalgia

Co- authors: Calmila Fernanda Alves, Wolnei Caumo, Manoela da Jornafa, Rodrigo de Almeida, Leticia Ramalho

as an oral presentation at

15TH WORLD CONGRESS OF THE INTERNATIONAL NEUROMODULATION SOCIETY (INS)
21-26 MAY 2022, BARCELONA SPAIN

Carlos Tornero, MD, PhD
INS Congress Chair

David Abejón, MD, PhD
INS Congress Co-Chair

ins INS 15TH WORLD CONGRESS
21 – 26 MAY 2022, BARCELONA, SPAIN

BARCELONA

REPÚBLICA FEDERATIVA DO BRASIL
MINISTÉRIO DA EDUCAÇÃO

ATESTADO

Atestamos que

Manoela Neves da Jornada

Participou da **"Mostra de TCC do Curso de Nutrição"**, promovida pela Universidade Federal de Ciências da Saúde de Porto Alegre e organizada pelo Curso de Graduação em Nutrição, no período de 28 a 30 de setembro de 2022, na cidade de Porto Alegre-RS, na qualidade de **MEMBRO DA BANCA AVALIADORA**, do Trabalho "Impacto do comportamento alimentar e alterações de sono no desenvolvimento de obesidade em mulheres com fibromialgia", sob autoria de "Amanda Maule" e orientação de "Fernanda Michielin Busnello" e "Letícia Ramalho".

Porto Alegre, 28 de setembro de 2022.

UFCSPA

Profª Drª Fabiana Viegas Raimundo
Coordenadora do Curso de Nutrição

Profª Drª Fernanda Michielin Busnello
Coordenadora da Comissão de TCC

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DEPARTAMENTO DE NUTRIÇÃO

DECLARAÇÃO

DEPARTAMENTO DE NUTRIÇÃO

Declaro, para os devidos fins, que a **NUTRICIONISTA MANOELA NEVES DA JORNADA** colaborou como ministrante, de forma presencial, na disciplina de **Nutrição Clínica III,** do Curso de Nutrição desta Faculdade de Medicina, tendo abordado o tema *Terapia Nutricional nos Transtornos Alimentares*, um período de 03 horas na data de 26 de outubro de 2023.

Atenciosamente,

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