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TESE DE DOUTORADO

EFEITO ELETROFISIOLÓGICO E COGNITIVO DA ESTIMULAÇÃO TRANSCRANIANA POR CORRENTE CONTÍNUA (ETCC) COMBINADA AO TREINAMENTO DA MEMÓRIA DE TRABALHO NA FIBROMIALGIA: ENSAIO CLÍNICO RANDOMIZADO

Vinicius Souza dos Santos

Porto Alegre – 2017

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Vinicius Souza dos Santos

Orientador: Prof. Wolnei Caumo, M.D.,PhD**.** Tese apresentada como requisito parcial para obtenção do título de Doutor em Medicina: Ciências Médicas, pelo Programa de Pós-Graduação em Medicina: Ciências Médicas da Universidade Federal do Rio Grande do Sul.

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BANCA EXAMINADORA

Profa. Dra. Luciana Paula Cadore Stefani

(PPGCM-UFRGS)

Prof. Dra. Maria Helena Rigatto

(PPGCM-UFRGS)

Profa. Dra. Joice Segabinazi

(PUC-RS)

Prof. Dr. Rafael Vercelino

(FADERGS)

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RESUMO

Introdução: A fibromialgia é uma síndrome complexa que envolve componentes sensorial-discriminativo, afetivo-motivacional, cognitivo-avaliativo e social. O modelo fisiopatológico mais aceito atualmente engloba mecanismos centrais de modulação e amplificação da dor juntamente com a sensibilização periférica. Além da dor, déficits de memória e atenção são encontrados em cerca de 50-80% destes pacientes, os quais podem aumentar a vulnerabilidade a novos sintomas e prejudicar o enfrentamento da doença. Terapias atuais buscam contra- regular esse processo mal adaptativo, entretanto com relativo sucesso terapêutico. Diante disso, são necessárias novas possibilidades terapêuticas para tratar esses déficits cognitivos, bem como para um melhor entendimento da fisiopatologia. O desenvolvimento deste estudo originou dois artigos, os quais constituem esta tese.

Estudo I

Objetivos: Avaliar as mudanças neurofisiológicas intra e entre grupos induzidas pela estimulação transcraniana de corrente continua (ETCC) combinada a um treino da memória de trabalho nos sinais eletrofisiológicos das pacientes com fibromialgia.

Métodos: Foi realizado um estudo piloto com 14 pacientes com idade ente 18 e 65 anos com diagnóstico de FM de acordo com os critérios da colégio Americano de Reumatológia 2010, alocadas aleatoriamente em dois grupos de intervenção: ETCC-ativa combinada com treino de memória de trabalho (MT) (n=5;2 participantes excluídas por dados inconsistentes) e ETCC-*sham* combinada com treino de MT (n=7). A intervenção consistiu em oito sessões de ETCC-ativa aplicadas sobre o córtex pré-frontal dorsolateral esquerdo (CPFDLE), na intensidade de 2mA durante 20 min. Avaliou-se pré e pós-intervenção o sinal eletrofisiológico através do eletroencefalograma (EEG), percepção do nível da dor, pensamento catastrófico sobre a dor, sintomas de ansiedade e de depressão.

Resultados: Observou-se uma mudança estatisticamente significativa na área sob a curva (AUC) da amplitude da onda do P300, um componente de potencial relacionado a

evento (ERP), na condição ETCC-*sham* + treino de MT comparada à linha de base, no canal Pz (p=0.016). Esta diferença não foi observada para o grupo ETCC-ativa + treino de MT. No entanto, houve reduções significativas nos níveis de dor, ansiedade, depressão e catastrofismo após o tratamento com ETCC-ativa. Além disso, os níveis de dor após o tratamento correlacionaram-se inversamente com a AUC da onda do P300, independente do grupo de tratamento, o que indica que quanto maior este sinal eletrofisiológico menor o nível de dor.

Conclusões: Estes resultados indicam que o tratamento ativo pode contra-regular a hiperexcitabilidade das redes neurais envolvidas no processamento da dor em pacientes com FM e reduzir a dor e outros sintomas clínicos correlatos

Estudo II

Objetivos: Foi avaliado se a combinação da ETCC-ativa combinada a um treino de memória de trabalho poderiam produzir um efeito de maior magnitude comparada a ETCC-*sham* combinada a um treino de memória de trabalho no desempenho da memória episódica, de curto e longo prazo.

Métodos: Neste ensaio clínico randomizado participaram 40 pacientes com idade ente 18 e 65 anos com diagnóstico de FM de acordo com os critério do Colégio Americano de Reumatologia 2010, dividas randomicamente em dois grupos: ETCC-ativo combinada a um treino de memória (n=19;1participante foi excluída porque quebrou a perna) e ou ETCC-*sham* combinada a um treino de memória de trabalho (n=20). A ETCC consistiu em oito sessões de estimulação aplicadas sobre o córtex pré-frontal dorsolateral esquerdo (DLPFC), na intensidade de 2mA durante 20 min. Avaliou-se pré e pós o desempenho da memória episódica imediata e tardia, fluência verbal, memória de trabalho e o nível do fator neurotrófico derivado do cérebro (BDNF).

Resultados: Observou-se que a ETCC-ativa combinada a um treino de memória de trabalho melhorou de forma significativa (p=0,02) o desempenho da memória de curto prazo no teste de Rey A1-A5(desfecho primário), considerando a média (17,30) e desvio padrão (15,01) do delta (Δ), quando comparado ao grupo *sham* Assim como, melhorou

de forma significativa o desempenho no teste de fluência verbal ortográfica (p=0,02) e semântica (p=0,03), considerando as médias (23,46 e 14,08) e desvio dos Δ (27,94 e 23,78) respectivamente. Esses dados significativos foram encontrados quando controlado pelo índice ajustado do BDNF e anos de estudo. O efeito do tratamento ativo sobre a memória de curto prazo foi dependente dos níveis de fator neurotrófico do cérebro basal para o teste de Rey A1-A5, no entanto, os níveis séricos desta neurotrofina não se correlacionaram com o desempenho nos testes de fluência verbal.

Conclusões estudo: Este estudo mostrou que o efeito da ETCC-ativa combinada a um treino de memória de trabalho melhorou a função de redes envolvidas na memória de curto prazo e fluência verbal. Também sugerem que o efeito da ETCC-ativa combinada a um treino de memória de trabalho, nos testes de memória de curto prazo, são dependentes das condições de plasticidade do sistema na linha de base.

Palavras-chave: Fibromialgia, memória de trabalho, treinamento da memória de trabalho, Estimulação transcraniana por corrente contínua.

Registro do estudo: *clinical trials.gov* – NCT 02880917

ABSTRACT

Introduction: Fibromyalgia is a complex syndrome that involves sensory-discriminative, affective-motivational, cognitive-evaluative, and social components. The most accepted pathophysiological model currently focuses on central mechanisms of modulation and amplification of pain together with peripheral sensitization. In addition to pain, memory and attention deficits are found in about 50-80% of these patients, which can increase vulnerability and impair the search for resources to cope with the disease. The current therapies of fibromyalgia seek against regular this maladaptive process, however with relative therapeutic success. Due to this, new therapeutic possibilities are necessary to treat these cognitive deficits as well as the better understanding of the pathophysiology. The development of this study originated two articles which constitute this thesis.

Study I

Objectives: We evaluated intra and intergroup neurophysiological changes induced by transcranial direct-current stimulation (tDCS) combined with work memory training in the electrophysiological signs of patients with fibromyalgia.

Methods: A pilot study was conducted with 14 patients aged 18 and 65 years with FM diagnosis according to the criteria of the American College of Rheumatology 2010, divided randomly into two groups: tDCS-active combined with a work memory training(WM) (n = 5; 2 participants excluded for inconsistent data) and tDCS-sham combined with a WM training (n = 7). The tDCS consisted of eight stimulation sessions applied on the left dorsolateral prefrontal cortex (DLPFC), at 2mA intensity for 20 min. The electrophysiological signal through electroencephalogram (EEG), perception of pain level, catastrophic thinking about pain, anxiety and depression symptoms were evaluated before and after intervention.

Results: A statistically significant change was observed in the area under the curve (AUC) of the P300 wave amplitude as a measure of the event-related potential (ERP) in the sham -tDCS combined with a work-memory training compared to the baseline, in the Pz channel (p = 0.016), however, this difference in effect was not observed for active-

tDCS combined with work-memory training. However, there were significant reductions in levels of pain, anxiety, depression and catastrophism after treatment with active-tDCS. In addition, pain levels after treatment correlated inversely with P300 wave AUC, regardless of treatment group, indicating that the higher this electrophysiological signal the lower the level of pain.

Conclusions: These results indicate that active treatment may counter-regulate the hyperexcitability of neural networks involved in pain management in patients with FM and reduce pain and other related clinical symptoms.

Study II

Objectives: We assessed whether the combination of active -tDCS combined with a working memory training could produce a comparative magnitude greater effect sham-tDCS combined with a working memory training in the performance in episodic memory performance, short and long term.

Methods: In this randomized clinical trial, 40 patients aged 18 to 65 years with FM diagnosis according to the criteria of the American College of Rheumatology 2010 were randomly divided into two groups: Active-tDCS combined with a memory training (n = 19; 1 participant was excluded because broke their leg) and or sham-tDCS combined with a working memory training (n = 20). The tDCS consisted of eight stimulation sessions applied on the left dorsolateral prefrontal cortex (DLPFC), at 2 mA intensity for 20 min. Episodic memory performance, verbal fluency, working memory and the level of brain-derived neurotrophic factor (BDNF) were evaluated before and after treatment.

Results: It was observed that the Active-tDCS combined with a working memory training improved significantly ($p = 0.02$) the performance of the short term memory test in the delta (Δ) Rey A1-A5 (primary outcome), considering the mean (17.30) and standard deviation (15.01) compared to the sham group. As well as, it significantly improved performance in the Δ orthographic fluency test ($p = 0.02$) and semantics ($p = 0.03$), considering the means (23.46 and 14.08) and standard deviation (27. 94 and 23.78) respectively. These significant data were found when controlled by the adjusted

BDNF index and years of study. The effect of active treatment on short-term memory was dependent on basal levels BDNF for the Rey A1-A5 test, however, serum levels of this neurotrophin did not correlate with performance on verbal fluency tests.

Conclusions: This study showed that the effect of active- tDCS combined with a working memory training improved the function of networks involved in short-term memory and verbal fluency. They also suggest that the effect of active- tDCS combined with a working memory training in short-term memory tests are dependent on baseline system plasticity conditions.

Key words: Fibromyalgia, working memory, working memory training, Transcranial direct-current stimulation.

Register: clinical trials. gov– NCT 02880917

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LISTA DE ABREVIATURAS

ACR- *American College of Rheumatology* (Colégio Americano de Reumatologia)

ACC- *Anterior Cingulate Cortex* (Córtex cingulado anterior)

AMPA- Ácido α-amino-3-hidroxi-5-metil-4-isoxazol propiônico

AMPc- Monofosfato cíclico de adenosina

B-PCP: S *Brazilian Profile of Chronic Pain: Screen* (Escala do Perfil da Dor Crônica para o Português Brasileiro)

BP-PCS *Brazilian Portuguese Pain Catastrophizing Scale(Escala de Pensamento catastrófico sobre dor validado para o* Português Brasileiro)

BDNF- *Brain-derived neurotrophic factor* (fator neurotrófico derivado do cérebro)

CPFDL- Córtex pré-frontal dorsolateral

CPM- *Conditioned pain modulation* **(**modulação condicionada da dor)

Ca2+- Íons Cálcio

Cl^-- Íon cloreto

DNIC- *Diffuse Noxious Inhibitory Controls* (Controle inibitório nocivo difuso)

DLPFC- *Dorsolateral prefrontal córtex(*Córtex pré-frontal dorsolateral)

EEG- Eletroencefalograma

ERPs- *Event-related potentials* (Potenciais relacionados a eventos)

EAV- Escala análogo visual

EMT- Estimulação magnética transcraniana

ETCC- Estimulação Transcraniana por Corrente Contínua

FM- Fibromialgia

FMS- Fibromiálgicos

FNC- Fator neurotrófico de crescimento

FDA- *Food and Drug Administration*

HCPA- Hospital de Clínicas de Porto Alegre

IDCG- Índice de dor crônica generalizada

IDG- Índice de dor generalizada

IDATE- Inventário de Ansiedade Traço-Estado

LTP- Long Term Potentiation (Potencialização de longo prazo)

LCR- Líquido cefalorraquidiano

MINI- *Mini International Neuropsychiatric Interview* validado para o português

mA- Miliampere

M1- Córtex motor primário

MT- Memória de trabalho

Mg2+- Íons magnésio

Na+ - Íons Sódio

NK1- Receptor Neuroquinina 1

NGF- Nerve growth factor **(**Fator de Crescimento Nervoso)

NMDA- N-metil D-Aspartato

PAG- Periaqueductal Grey *Matter* (Substância cinzenta periaquedutal)

K- Potássio

QIF- Questionário de Impacto da Fibromialgia

QST- Quantitative sensory test (Teste sensorial quantitativo)

REDCap- *Research Electronic Data Capture*

RVM- Rostral ventromedial

S100β Proteína S100 Beta

SS- Severidade de sintomas

SNC Sistema Nervoso Central

SFC- Síndrome fadiga crônica

SP- Substância P

TNF- -α**-** *Tumor necrosis factor alfa* (Fator de necrose tumoral alfa)

TSQ- Teste Sensorial Quantitativo (*Quantitative sensory test)*

GTP **-** Trifosfato de guanosina

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APRESENTAÇÃO

Esta tese será estruturada em seis capítulos

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CAPÍTULO I – INTRODUÇÃO

A fibromialgia (FM) é caracterizada por dor musculoesquelética generalizada, difusa e crônica, com duração superior a três meses, tipicamente associada à fadiga, distúrbios do sono, alterações de humor, dificuldades de memorização, atenção entre outros sintomas cognitivos (Wolfe 2010). Deste modo, a FM é uma patologia complexa que envolve processos sensorial-discriminativo, afetivo-motivacional, cognitivo-avaliativo e sociais (Ferreira et al. 2002).

As abordagens terapêuticas atuais da fibromialgia buscam contra regular os processos de neuroplasticidade disfuncionais, através de técnicas multimodais que incluem combinação das modalidades farmacológicas, dentre as quais tem sido recomendada pela *Food and Drug Administration (FDA)* os antidepressivos duais (duloxetina e milnacipran), anticonvulsivantes (pregabalina e gabapentina) (Bellato et al. 2012) e dentre as técnicas não farmacológicas tem sido demonstrado algum nível de evidência para as terapias cognitivo-comportamentais, estimulação magnética transcraniana (EMT) e estimulação transcraniana de corrente contínua (ETCC) (Hassett and Gevirtz 2009). Até o presente momento os melhores resultados têm sido alcançados por meio da combinação de técnicas e as falhas têm sido atribuídas ao desconhecimento da fisiopatologia da doença ou ao uso de técnicas que não alcançam os potenciais mecanismos que sustentam as múltiplas facetas desta síndrome(Recla 2010 ;Häuser et al. 2009).

Embora a fisiopatologia da FM não esteja completamente elucidada, ocorre uma disfunção no processamento da sinalização nociceptiva, a qual é responsável pela manutenção do quadro álgico e pela resposta amplificada ao estímulo nociceptivo. Essa sensibilização envolve diversos mecanismos como o *wind up*, potenciação de longo prazo (LTP), facilitação de longo prazo, normalmente vinculados ao enfraquecimento do sistema modulatório descendente da dor. De acordo com evidências recentes, a partir de medidas psicofísicas e neurofisiológicas, estas sugerem que a mesma esteja relacionada à disfunção dos sistemas

modulatórios descendentes da dor (Caumo et al., 2016). Também, com a função prejudicada dos mecanismos de inibição em nível cortical, como demonstrado pela redução da inibição intracortical mensurada por meio da estimulação magnética transcraniana (EMT) (Caumo et al., 2017). Vale ressaltar que o nível de prejuízo da inibição parece ser mais acentuado na FM do que o observado em outras patologias como na osteoartrite, pois em ambas, a desinibição intracortical suplanta os níveis observados em sujeitos saudáveis (Caumo et al., 2016).

Além destas evidências, os pacientes com FM apresentam déficits cognitivos importantes e dentre eles o que chama a atenção é a memória, o qual pode aumentar a vulnerabilidade e prejudicar a busca de recursos de enfrentamento da doença e assim como do processamento de informações(Ji et al. 2003). Assim, para construir um racional abrangente e com plausibilidade biológica, o estudo da FM demanda uma integração de estratégias para captar os sintomas e sinais clínicos e de recursos tecnológicos com o objetivo de compreender os mecanismos fisiopatológicos de maneira mais completa, assim como na busca de estratégias terapêuticas mais eficazes. Dentre os recursos tecnológicos estão as medidas eletrofisiológicas, psicofísicas, dosagem de marcadores séricos de plasticidade como o Fator neurotrófico derivado do cérebro (BDNF), Proteína S100 (S100β), as quais parecem mensurar importantes facetas do processo fisiopatológico e do conjunto de sintomas da FM.

A partir deste racional escolhemos duas técnicas terapêuticas (a ETCC e o treinamento da memória de trabalho) que parecem ser uma alternativa viável para melhorar a memória e o processo disfuncional da FM. Esta escolha fundamenta-se na plausibilidade neurobiológica que a fisiopatologia da FM envolve vias de processamento disfuncionais que aumentam a susceptibilidade a respostas amplificadas à dor (Junior M.H, Goldenfum, and Siena 2012) com prejuízo da atenção e da memória.

Evidências recentes tem demostrado também efeitos aditivos com a combinação da ETCC como outros tipos de intervenções, sejam elas: cognitivas, atividade física e programa de reabilitação da dor (Riberto 2011;Luedtke et al.

2015;Mendonca et al. 2016). Nesta perspectiva, um estudo recente realizado pelo grupo de pesquisa Dor e Neuromodulação demostrou um efeito aditivo da ETCC ativa sobre o córtex pré-frontal dorsolateral (CPFDL) combinado com uma tarefa que induz a ativação de vias de controle inibitório (Silva et al. 2017a). Ainda que nosso estudo seja preliminar, demonstrou que a terapia combinada melhorou o desempenho das redes de atenção com consequente aumento no limiar de dor. Assim, a ETCC pode privilegiar e modular os circuitos pré-frontais com capacidade para melhorar a tolerância e minimizar o componente emocional da experiência dolorosa e espera-se que a combinação com o treinamento da memória possa levar a ganhos adicionais para os pacientes fibromiálgicos.

Considerando que se trata de tema relevante e que persistem lacunas do conhecimento, tanto na compreensão dos processos fisiopatologicos quanto terapêuticos esta tese teve dois objetivos principais, que originaram dois artigos que estão apresentados de acordo com as normas dos periódicos de submissão, cujos objetivos são: Avaliar se a combinação do treinamento de memória de trabalho com a ETCC ativo teria um efeito maior do que a ETCC *sham* no desempenho da memória episódica, curto e de longo prazo e avaliar as mudanças neurofisiológicas induzidas pelo ETCC combinado com treinamento da memória de trabalho nos sinais eletrofisiológicos dos pacientes com fibromialgia.

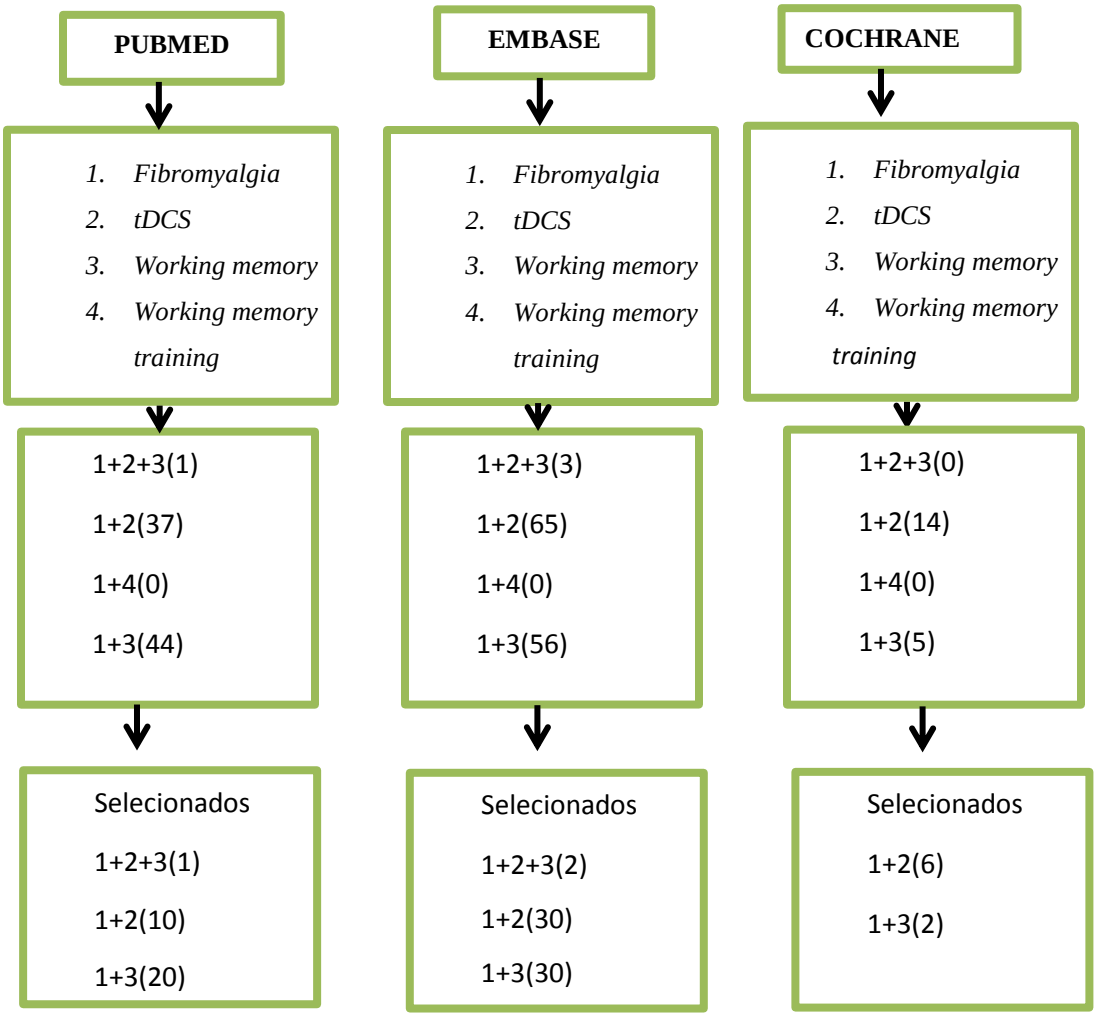
Esta tese está apresentada de acordo com o modelo preconizado pelo PPGCM da FAMED UFRGS.

CAPÍTULO II- REVISÃO SISTEMATIZADA DA LITERATURA

1.ESTRATÉGIA PARA LOCALIZAR E SELECIONAR AS INFORMAÇÕES

Na revisão sistemática da literária, buscou-se ressaltar os principais aspectos relacionados com memória, estimulação transcraniana por corrente contínua (ETCC) fibromialgia e treinamento da memória. A seguinte pergunta foi abordada: Qual o efeito da combinação da estimulação transcraniana por corrente continua com treinamento cognitivo sobre a memória de trabalho em pacientes fibromiálgicos? Utilizou-se a estratégia PICOT ou PICO (EMBASE) descrevendo os seguintes termos: *Population: Fibromyalgia; Intervention: Transcranial direct current stimulation (tDCS) and Working memory training; Comparison: Sham; Outcome: Working memory*. Quando foram realizadas as buscas utilizandando: Paciente, Intervenção, Comparação e desfecho não foram encontrado publicações, então para não restringir a pesquisa foi realizada uma segunda busca incluindo população, intervenção e desfecho, uma terceira com população e desfecho e uma quarta com intervenção e população. A estratégia envolveu as seguintes bases de dados: MEDLINE (PubMed), EMBASE e COCHRANE, sem período delimitado. Foram realizadas buscas por meio dos descritores [MeSH (MEDLINE/PubMed) e EMTREE (EMBASE)]: *Fibromyalgia, Transcranial direct current stimulation (tDCS), Working memory, Working memory training.* Para apresentar o tema, usamos a revisão sistemática esquematizada na Figura 1.

Figura 1: Estratégia de busca de referências bibliográficas



2. EPIDEMIOLOGIA E ASPECTOS CONCEITUAIS DA FIBROMIALGIA

A FM é uma condição de dor crônica com prevalência mundial estimada de 2% a 8%, e dentre as doenças musculoesqueléticas é superada apenas pela osteoartrtite (Vicent et al. 2012;Cimmino, Ferrone, and Cutolo 2011). Apresenta uma relação homem/mulher de: 1:2-3 (Wolfe et al. 2013;Gupta et al. 2007). A faixa etária mais acometida é dos 30 aos 50 anos, aumentando progressivamente com a idade (Queiroz 2013). Baixa renda familiar e baixo nível de escolaridade(Mas et al. 2008;Neumann et al. 2008) também são fatores associados.

As síndromes dolorosas musculoesqueléticas generalizadas crônicas são objetos de estudo desde o início do século XX, quando a síndrome de dor lombar associada a pontos dolorosos a estímulos mecânicos foi denominada de fibrosite por Gowers (Chaitow 2002). Posteriormente, os pacientes acometidos por quadros semelhantes a esses receberam diagnósticos diversos. Em 1976, o termo fibromialgia foi sugerido para pacientes com dor crônica generalizada associados a pontos dolorosos. No entanto, somente na década subsequente, em 1990 o *American College of Rheumatology* (ACR) publicou os critérios para classificação da síndrome fibromiálgica (Wolfe , Smythe , Yunus , Bennett , Bombardier C 1990), sendo essencialmente clínico, considerando os seguintes critérios: presença de dor difusa há pelo menos três meses associada com dolorimento em 11 ou mais de 18 pontos sensíveis (*tender points*) em locais específicos e predeterminado (figura 2).

Figura 2. ***Tender Points na FM*.**

Adaptação do quadro "As Três Graças" Hans Von Aachen (1604). A figura aponta os *tender points* (demonstrados com pontos vermelhos) classificados pelos critérios do ACR(Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C 1990).

Em 2010, foram propostos novos critérios de classificação para FM, os quais foram aprovados pelo ACR como provisórios, estes diferiram dos critérios de 1990 nos seguintes itens: acréscimo de um índice de dor crônica generalizada (IDCG) o qual os escores variam de 0-19 para identificação dos pontos de dor, inclusão de uma avaliação da severidade de sintomas (SS) e exclusão dos *tender points* como critério diagnóstico (Wolfe 2010).

Na avaliação da SS incluiu-se fadiga, sono não reparador e sintomas cognitivos avaliados por meio de uma escala variando de 0 a 3 (0 = sem problemas; 1= problemas leves: geralmente leves ou intermitentes; 2= Moderados: problemas consideráveis, frequentemente presentes e / ou a um nível moderado; 3= graves: problemas persistentes, contínuos, que perturbam a vida). Além disso, também foram adicionados 41 sintomas somáticos gerais que são classificados em uma escala de zero a três (0= Sem sintomas; 1= Poucos sintomas; 2= Um número moderado de sintomas; 3= Um quantidade grande de sintomas). A pontuação da SS é a soma da gravidade dos três sintomas (fadiga, sono não reparador e sintomas cognitivos) mais a extensão (gravidade) dos sintomas somáticos em geral, com pontuação final entre 0 e 9(Wolfe 2010) (Tabela 1). Para os pacientes serem diagnosticados com FM segundo os critérios de 2010, eles devem apresentar os seguintes itens:

1. Níveis elevados de dor (IDCG≥7) mais níveis moderados de sintomas (SS≥5); ou níveis moderados de dor (IDCG entre 3-6) mais níveis elevados de sintomas (SS≥9);
2. Sintomas presentes em nível semelhante por pelo menos três meses;
3. O paciente não pode apresentar outra doença que explicaria a dor.

Tabela 1. Critérios de classificação para FM 2010 de acordo com *American College of Rheumatology*.

ÍNDICE DE DOR GENERALIZADA

Marque com X as áreas onde teve dor nos últimos 7 dias

ÁREA	SIM	NÃO	ÁREA	SIM	NÃO
MANDÍBULA E			MANDÍBULA D		
OMBRO E			OMBRO D		
BRAÇO E			BRAÇO D		
ANTEBRAÇO E			ANTEBRAÇO D		
QUADRIL E			QUADRIL D		
COXA E			COXA D		
PERNA E			PERNA D		
CERVICAL			DORSO		
TÓRAX			LOMBAR		
ABDOME					

Fonte: Adaptado de Heymann et al. 2010

Em 2011, foi proposta uma versão modificada dos critérios de 2010 para uso em estudos clínicos e epidemiológicos, fundamentada em uma avaliação de auto relato por meio do IDCG e dos sintomas através da SS, porém com uma versão simplificada de sintomas somáticos ocorridos nos últimos seis meses classificados como: 1=presença ou 0=ausência; com escore total variando de zero a três. Os sintomas somáticos mantidos foram cefaleia; dor ou cólicas no abdômen inferior e depressão. Os critérios de 2011 proporcionaram uma sensibilidade de 83%, uma especificidade de 67% e uma classificação correta de 74% (Wolfe et al. 2011).

Atualmente, os critérios propostos em 2011 foram revisados por Wolfe et al. 2016, deste modo três dessas condições devem estar presente para o diagnóstico da FM:

(1) Dor generalizada, em pelo menos quatro regiões;

(2) Os sintomas devem estar presentes em um nível similar por pelo menos 3 meses;

(3) Índice de dor generalizada (IDG) ≥ 7 e escore na escala de gravidade dos sintomas (SS) ≥ 5 ou IDG de 4-6 e escore SS ≥ 9 ;

(4) O diagnóstico de fibromialgia não exclui a presença de outras doenças clinicamente importantes.

Para determinar o índice de dor generalizada (IDG), o paciente é questionado em quantas áreas teve dor na última semana, a saber: cintura escapular direita e esquerda, braço direito e esquerdo, antebraço direito e esquerdo, quadril (glúteos, trocânter) direito e esquerdo, coxa direita e esquerda, perna direita e esquerda, mandíbula direita e esquerda, tórax, abdômen, regiões dorsal, lombar e cervical. Cada região equivale a um ponto no escore. A soma total dos escores varia de 0 a 19.

A escala de gravidade dos sintomas é determinada pela soma dos três sintomas: fadiga, sintomas cognitivos e cansaço ao despertar. O paciente deve responder sobre o grau destes sintomas na última semana: 0=sem problemas; 1= problemas leves; 2= problemas moderados, consideráveis; 3=problemas contínuos, generalizados (o escore varia de 0 a 9) mais a soma dos seguintes sintomas nos últimos 6 meses: depressão 0= não ;1=sim dor de cabeça 0= não ;1=sim dor ou cólicas na parte inferior do abdômen 0= não ;1=sim. O escore da gravidade dos sintomas final varia de 0 a 12(Wolfe et al. 2016).

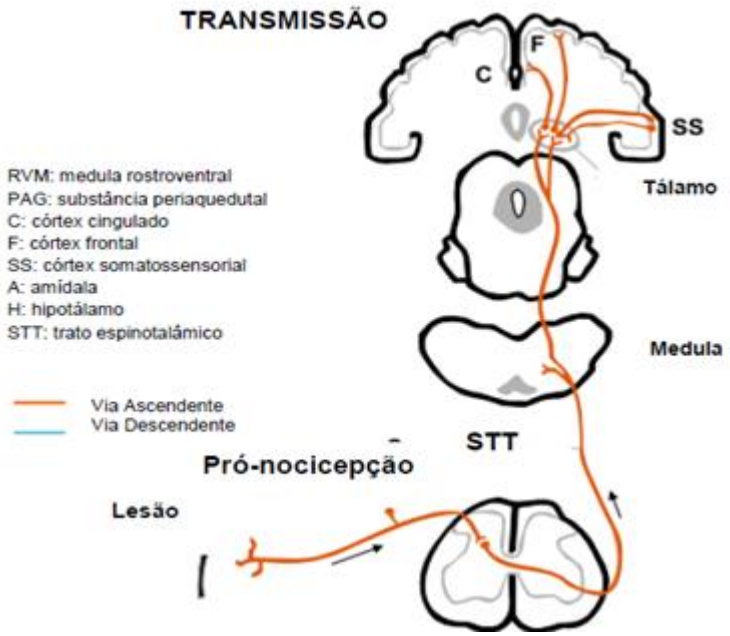
3. PROCESSAMENTO FISIOLÓGICO DA DOR: PRÓ-NOCICEPTIVO E ANTINOCICEPÇÃO.

3.1Pró-nocicepção

A propagação da dor é iniciada com a ativação de receptores fisiológicos, chamados nociceptores que estão localizados na pele, mucosas, órgãos, músculos entre outros. A decodificação dos estímulos térmicos, químicos e mecânicos detectados por terminações periféricas é o primeiro passo desse processo. Este mecanismo indutor facilitatório da dor também é chamado de pró-nocicepção (I. Jon Russell and Larson 2009). A transdução ascendente da dor gera um potencial de

ação de membrana conduzido desde os neurônios de primeira ordem que estão localizados no gânglio da raiz dorsal até os neurônios de segunda ordem localizados no corno dorsal da medula espinhal, posteriormente aos neurônios de terceira ordem localizados no tálamo e então aos de quarta ordem localizados no córtex(Merighi et al. 2008). (Figura 3).

Figura 3: Representação da pró-nocicepção



Fonte: Adaptado de Hoffman, Harrington, and Fields 2005

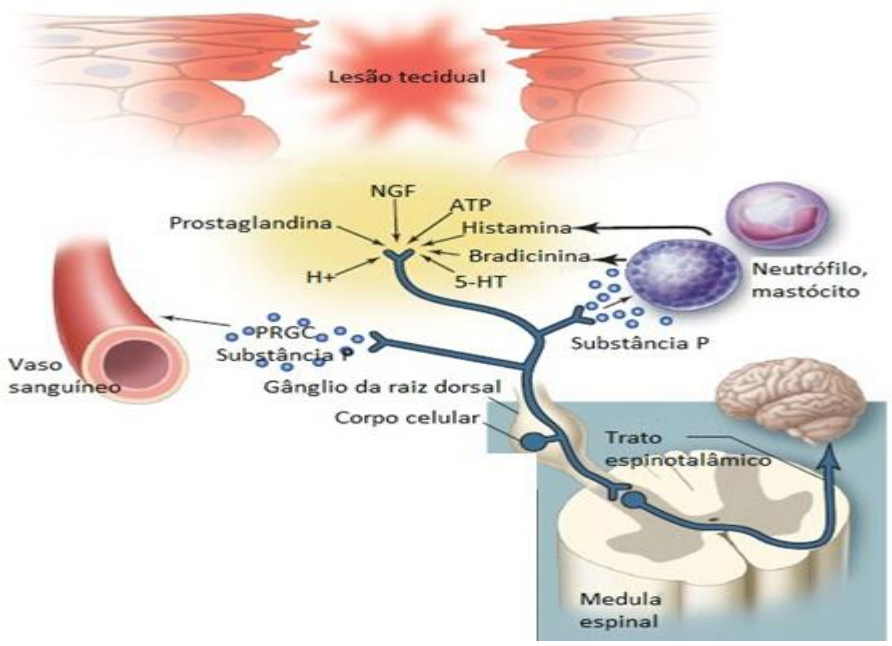
As fibras periféricas responsáveis por esse processo inicial são: mielinizadas de pequeno calibre (Aδ), amielizadas de pequeno calibre (C) e aferentes mielinizadas grossas (α e Aβ). A condução dos sinais nociceptivos é mediada através das duas primeiras. As fibras Aδ são nociceptores termomecânicos divididas em dois tipos: as fibras de limiar alto, respondendo apenas à estimulação mecânica intensa; e as fibras que respondem ao calor, tanto para as temperaturas nocivas, quanto para as temperaturas não nocivas, cujo potencial de ação é rapidamente conduzido (5-20 m / s) (Ploner et al. 2002). As fibras C conduzem estímulos captados por receptores polimodais (respondem aos estímulos nocivos mecânicos, térmicos, químicos e mecanorreceptores) e transmitem os sinais nociceptivos principalmente para neurônios nas lâminas II e III. (Julius 2001)(Figura 3).

Figura 4 : Axônios aferentes primários

Fonte: Adaptado de Julius 2001

Os nociceptores associados a fibras Aδ e C são ativados por estímulos potencialmente lesivos ou supralimiares havendo a liberação substâncias químicos, denominados algiogênicas, presentes no ambiente tissular, tais como: acetilcolina, bradicinina, histamina, serotonina, substância P, interleucinas, fator de necrose tumoral (TNFα), fator de crescimento nervoso (NGF) e monofosfato cíclico de adenosina (AMPc) (Serpell 2006 ;Clin 2015). Estes mediadores também promovem alterações na permeabilidade vascular, no fluxo sanguíneo e no recrutamento de células inflamatórias. Deste modo, há uma exacerbação da resposta ao estímulo doloroso por consequência da sensibilização periférica (Aida et al. 1999).

Figura 5.Ativação estímulos potencialmente lesivos ou supralimiares



Fonte: Adaptado de Bruce 1996. ATP = trifosfato de adenosina; NGF = fator de crescimento de nervo (nerve growth fator).

Uma vez no corno dorsal da medula espinhal, a sinapse nociceptiva nesta área tem basicamente dois diferentes caminhos de funcionamento. Quando uma descarga de curta duração e ou baixa frequência chega ao terminal pré sináptico, apenas o glutamato é liberado. Na ausência de Substância P (SP), o glutamato abre os canais para AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) e cainato, resultando em uma despolarização de curta duração da membrana do neurônio pós-sináptico, devido ao influxo de íons sódio (Na+) para o interior da célula. O neurônio volta a seu estado prévio de excitabilidade após a interrupção do estímulo. Nesse processo de ativação normal, canais NMDA (N-metil-D-aspartato) permanecem fechados, bloqueados por íons magnésio (Mg2+) (Banauskas and Nistri 1998). A maioria das sinapses AMPA com a superfície do neurônio central é inefetiva ou silente. Entretanto, em uma situação patológica pode tornar tais sinapses ativas, levando à formação de novas conexões do neurônio com a periferia, mecanismo que parece ser fundamental no processo de sensibilização central(Zhuo and Li 1998) e na formação da dor difusa.

Por outro lado, glutamato e SP são liberados concomitantemente quando um estímulo prolongado ou de alta frequência adentra a terminação pré-sináptica nociceptora. Ao ligar-se ao receptor metabotrópico proteína-G (trifosfato de guanosina – GTP) acoplado, neurocinina 1 (NK1), a SP ativa uma cascata intracelular, levando à formação de quinases e despolarização de longa duração dos neurônios do corno dorsal da medula espinhal. Simultaneamente, o acúmulo intracelular de Na+ despolariza a membrana e há um influxo de cálcio (Ca2+) para o interior da célula com deslocamento do Mg2+ e abertura do canal NMDA. Caso se prolongue, os eventos levam à sensibilização dos neurônios pós-sinápticos (Banauskas and Nistri 1998)

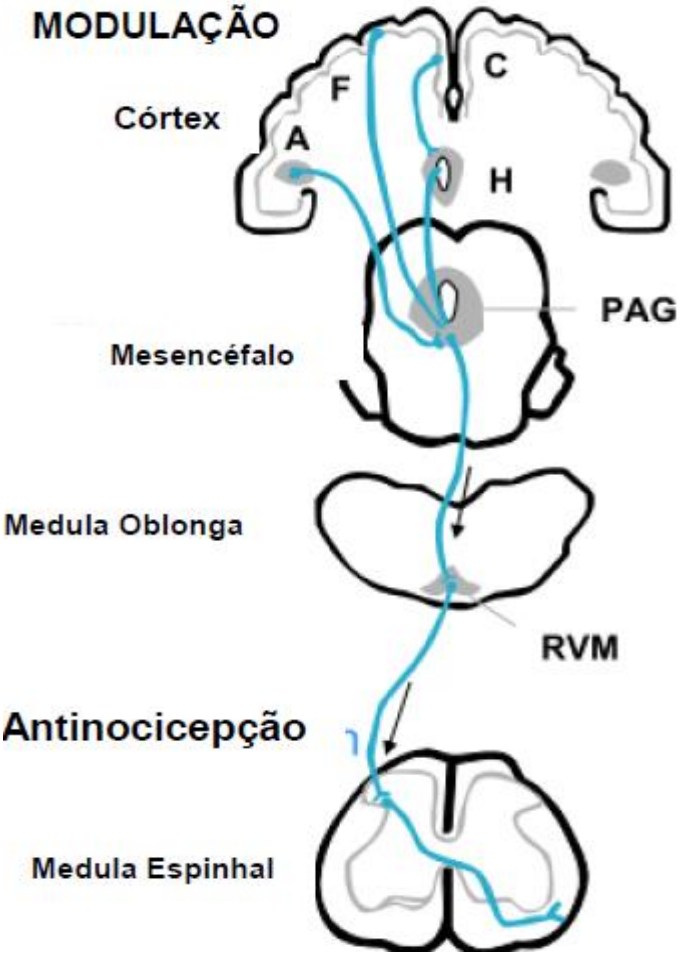
Ainda no corno dorsal da medula espinhal, as fibras nociceptivas ascendem pelos tratos espinotalâmicos, espinorreticular, espinomesencefálico, e sistema espinopontoamigdaliano e então para o córtex somatossensorial primário (SI), secundário (SII), ínsula e para o córtex cingulado anterior (ACC) (I. Jon Russell and Larson 2009). Dados anatômicos e eletrofisiológicos demostram que essas regiões corticais recebem *input* nociceptiva direto do tálamo. Deste modo, os neurônios talâmicos distribuem as informações nociceptivas em SI, SII, ínsula e ACC que estão envolvidos respectivamente nos aspectos sensoriais e discriminativos da dor, aprendizagem e memória do evento doloroso, reações autonômicas aos estímulos nocivos e nos aspectos afetivos relacionados a dor e a dimensão afetiva e seleção de resposta a dor (I. Jon Russell and Larson 2009).

3.2 Antinocicepção

Paralelamente ao processo de transmissão ascendente da dor, a modulação da via descendente pode manifestar-se através de ações sobre terminações nociceptivas (pré-sináptica), facilitando ou inibindo a liberações de neurotransmissores a partir do cérebro para a medula espinhal e periferia ou sobre neurônios espinhais, através de mecanismos pós sinápticos, sejam eles inter neurônios ou neurônios de projeção (Bee and Dickenson 2009).

As vias descendentes originam-se de diferentes áreas cerebrais, incluindo a substância cinzenta periaquedutal (PAG)(Fields 2004), núcleo magno da rafe, estruturas da medula rostral ventromedial (RVM) (Vanegas and Schaible 2004), hipotálamo e estruturas corticais. Estas estruturas exercem influências tanto excitatórias quanto inibitórias(Vanegas and Schaible 2004; Kobayashi 2012;Mobbs et al. 2009)

Figura 6.Modulação Descendente



Fonte: Adaptado de Hoffman, Harrington, and Fields 2005

Entre os mecanismos inibidores, um dos mais conhecidos é o controle inibitório de dor endógena, chamado de *Diffuse Noxious Inhibitory Controls*

(DNIC). Este é um fenômeno fisiológico que foi descrito em animais na década de 70, estabelece que estímulos dolorosos exerçam efeitos inibitórios sobre outros estímulos (Ombrellaro 1988). A *conditioned pain modulation* (CPM) aborda protocolos psicofísicos da dor em humanos, e expressa o fenômeno DNIC o qual é desencadeada quando um estímulo heterotópico condicionante é aplicado em áreas remotas do corpo, ativando fibras nociceptivas Aδ e/ou C(Ombrellaro 1988;Bouhassira 1992).

A CPM é observada quando há redução na intensidade da dor percebida no estímulo teste, quando na presença de um estímulo heterotópico (contralateral) doloroso condicionante. O fenômeno é mais eficiente quanto maior for a supressão da dor percebida no estímulo teste, frequente resumida em "dor inibe dor". A resposta da CPM em humanos é parcialmente mediada pelo sistema opióide descendente (Tambeli, Levine, and Gear 2009) e em parte, pelas vias serotoninérgicas e noradrenérgicas (Bouhassira 1992; Kuraishi et al. 1995). As disfunções das vias moduladoras descendentes da dor estão presentes em várias condições de dor crônicas, dentre ela encontra-se a FM. Vários estudos comparando a efetividade do CPM em pacientes com FM e com controles demonstraram que este sistema está prejudicado em fibromiálgicos (Chalaye et al. 2014; Potvin and Marchand 2016;Hilgenberg-Sydney, Kowacs, and Conti 2016;Normand et al. 2011) e é refletida pela reduzida da eficiência CPM.

4. FISIOPATOLOGIA DA FIBROMIALGIA

Embora a FM seja uma patologia com grande impacto na vida dos pacientes sua fisiopatologia não está totalmente elucidada. O modelo fisiopatológico mais aceito atualmente enfoca em mecanismos centrais de modulação e amplificação da dor juntamente com a sensibilização periférica (M. H. Junior, Goldenfum, and Siena 2012). Ao nível de fibras periféricas, tem sido observado que pacientes fibromiálgicos quando comparado com controle, apresentam maior limiar de detecção ao frio, calor e menor limiar de dor à pressão, que caracteriza lesão do nervo periférico. Esses achados foram confirmados com biópsia de pele que evidenciaram menor número de fibras nervosas não mielizadas (Eyler et al. 2013).

Além das alterações periféricas, existe um processo de sensibilização central como mecanismo associado as queixas de dor em pacientes fibromiálgicos (J. Ablin, Neumann, and Buskila 2008). A sensibilização central é uma resposta exacerbada do sistema nervoso central a uma variedade de estímulos tais como: pressão, temperatura e luz (Staud and Smitherman 2002;Nijs, Van Houdenhove, and Oostendorp 2010). O mecanismo de sensibilização central é clinica e fisiologicamente caracterizado por alodínia, hiperalgesia, somação temporal e dor referida em diversos segmentos do corpo, levando a dor generalizada (Meeus and Nijs 2007). Logo, fatores centrais também podem resultar em fadiga, distúrbios do sono e do humor, dificuldade de concentração e memória, provavelmente porque os mesmos neurotransmissores que controlam a dor e a sensibilidade sensorial também controlam essas variáveis (Yunus 2007;Yunus 2008).

Alterações em vias descendente da dor também estão envolvidas no processo de sensibilização central, onde o mau funcionamento das vias neuronais descendentes pode levar uma maior facilitação e menor inibição dos sinais nociceptivos transmitido para o cérebro (Zusman 2002). O paradigma *Conditioned pain modulation* (CPM) é frequentemente utilizado para avaliar a eficácia do sistema inibitório descendente da dor e baseia-se no mecanismo que "dor-inibe-

dor"(Schweinhardt 2011). Estudos em pacientes com fibromialgia demostram uma ativação ineficaz do sistema modulatório descendente dos pacientes fibromiálgicos quando comparados com controle (Chalaye et al. 2014);(Potvin and Marchand 2016)(Hilgenberg-Sydney, Kowacs, and Conti 2016)(Normand et al. 2011).

Estudos demonstram evidências para a excitação aumentada no SNC de pacientes com FM. Esses pacientes têm concentrações aproximadamente três vezes maiores de SP no líquido cefalorraquidiano (LCR) em comparação com controles saudáveis(Vaerøy et al. 1988)(I J Russell et al. 1994)Mountz et al. 1995). Níveis elevados de glutamato e glutamina também foram demonstrados no cingulado posterior, na insula posterior e na amígdala em pacientes com FM, avaliados por meio de espectroscopia de ressonância magnética de prótons (Fayed et al. 2010; Harris et al. 2009;Valdés et al. 2010). Os níveis de metabólitos de neurotransmissores que tipicamente inibem a transmissão da dor, como a norepinefrina e a dopamina, estão significativamente reduzidos no LCR de pacientes com FM quando comparado com controles sem FM (I J Russell et al. 1992).

O sistema inibitório do SNC nestes pacientes também está alterado, indivíduos com FM apresentam níveis mais elevados de encefalinas no LCR quando comparados com controles (Baraniuk et al. 2004), o que sugere um excesso de opióides endógenos na FM. Harris et al, 2007 avaliou a disponibilidade do receptor opióide em pacientes com FM por tomografia por emissão de pósitrons , e observou que os FM apresentaram níveis reduzidos do receptor opióide na amígdala, no cingulado e no núcleo acumbens, estes receptores podem estar altamente ocupados por opióides endógenos numa tentativa de reduzir a dor ou ainda com sua expressão diminuída após estimulação prolongada(R. E. Harris et al. 2007).

O GABA é o maior neurotransmissor inibitório, e seu papel no processamento da dor têm sido reconhecido há algum tempo (Goudet et al. 2009), em pacientes fibromiálgicas seus níveis estão diminuídos na ínsula anterior direita (231), área cerebral importante no processamento da dor (Richard E. Harris et al.

2009;Valdés et al. 2010). Outros mecanismos fisiopatológicos descritos na literatura também podem contribuir para a fisiopatologia da fibromialgia, como fatores psicológicos e genéticos.

Sabe-se que os aspectos cognitivos têm grande relevância no processamento e na modulação da dor. Além da dor persistente, os fibromiálgicos frequentemente sofrem déficits cognitivos, incluindo dificuldades de concentração, atenção e memória, que parece estar relacionado com a gravidade da dor (Clauw 2014). Assim, a hipótese é que mau funcionamento do sistema de inibição endógeno da dor e a dor crônica impedem o desempenho cognitivo ótimo, sendo corroborada pelas mudanças funcionais (T. Schmidt-Wilcke et al. 2007;Luerding et al. 2008)e morfológicas encontradas em pacientes fibromiálgicos (Linnman et al. 2009),(Cifre et al. 2012). Sabe-se também que os aspectos cognitivos como catastrofismo e o medo são fatores que pioram o prognóstico destes pacientes (Clauw 2014).

Estudos epidemiológicos e genéticos tem demostrado uma correlação forte entre a predisposição familiar e a fibromialgia (J. N. Ablin, Cohen, and Buskila 2006). Parente de primeiro grau de pacientes com fibromialgia apresentam um risco oito vezes maior de desenvolvê-la, (Arnold et al. 2004). Entretanto, a associação entre o polimorfismo genético e o aumento do risco de desenvolver fibromialgia ainda não está bem estabelecida.

Em suma, embora existam mecanismos fisiopatogênicos plausíveis que expliquem o desencadeamento e sustentação dos processos neurobiológicos disfuncionais, ainda não existe um consenso pleno sobre os mecanismos fisiopatogênicos da FM, nem sobre estratégias terapêuticas que permitam reverter ou conter os processos mal adaptativa e de neuroplasticidade já instauradas. Embora seja uma síndrome que envolve mutliplos sistemas neurobiológicos e que cursa com dor difusa, fadiga, catastrofismo e alterações de sono, o objeto de interesse desta tese e a cognição.

5. MEMÓRIA DE TRABALHO EM FIBROMIALGIA

A memória de trabalho (MT) ou também chamada de memória de curto prazo é definida com um sistema que permite a manipulação temporária de informações visuais, verbais e armazenamento as quais são necessárias para realização de tarefas complexas como aprendizado, raciocínio e planejamento(Swanson 1999;Zayed et al. 2013;Wang and Gathercole 2013).

Para avaliação da memória de trabalho optamos pelo modelo multicomponente de memória de trabalho desenvolvido por Baddeley, (2011) que é composto por 4 componentes: executivo central, a alça fonológica, o esboço visuoespacial e o buffer episódico.O executivo central desempenha funções como flexibilidade e atenção seletiva, capacidade de evocar informações guardadas na memória de longo prazo e controlar a alça fonológica e esboço visuoespacial. A alça fonológica armazena determinada quantidade de sons por um período de tempo e processa as informações que podem ser apresentadas visualmente ou auditiva. O esboço visuoespacial armazena informações visuais, espaciais e provavelmente relacionadas a percepção dos movimentos chamada de cinestesia. O buffer episódico realiza a integração e armazenamento de informações verbais e visuoespacial provenientes dos subsistemas de memória de longo prazo ou do meio externo. O buffer episódico é o único que permite o armazenando geral, ou seja, de várias fontes em um único episódio dos subsistemas alça fonológica e esboço visuoespacial(C. A. M. Junior and Melo 2011).

São vários os testes que avaliam a MT segundo Abreu e Matos (2010). O mais comum é o Span de Dígitos das baterias Wechsler. Outro teste utilizado é *n-back* é um meio de investigação que possui componentes visuais e auditivos, verbais e não verbais sendo uma importante ferramenta para avaliar processos mais complexos de memória de trabalho principalmente exigem do executivo central o monitoramento dos itens que ficam para trás e que necessitam ser apertados por um botão sempre que ocorre uma repetição. Quanto maior o número de itens maior a carga do executivo central e maior a ativação frontal.

Com o intuito de investigar a relação do córtex pré-frontal, mais especificamente o córtex pré-frontal dorso lateral, com a MT, Campanhã et al. (2012) relatam estudo no qual foi investigado se uma lesão virtual do CPFDL poderia prejudicar o desempenho de pessoas saudáveis em uma tarefa de MT. Como resultado, houve um aumento do número de erros ao realizar a tarefa *n-back* sob estimulação magnética transcraniana do CPFDL esquerdo, o que indica que esta área é fundamental em pelo menos um aspecto da MT.

Estudos com testes neuropsicológicos como medidas de avaliação das funções executivas, verificaram comprometimento significativo memória, memória de trabalho e planejamento em adultos em diferentes patologias e dentre elas a fibromialgia. (Gallagher e Blader, 2001; Hervey et al, 2004; Seidman et al., 2004; Adler, 2010; Silva et al., 2012).

Bertolucci e de Oliveira relataram que 50-80% dos pacientes com FM apresentam um declínio memória de trabalho e atenção (Bertolucci and Oliveira 2013). O lobo pré-frontal é responsável pela ação reguladora do comportamento, o controle das funções executivas, planejamento de ações futuras, regulador da atenção e memória entre outras funções básicas instintivas (Fuster 2008).

Estudo de Seo et al.,2012, desenvolvida com paciente com fibromialgia investigou as diferenças nos correlatos neurais da memória de trabalho entre pacientes com FM e indivíduos saudáveis, usando ressonância magnética funcional. Os resultados deste estudo sugerem que o déficit de memória de trabalho encontrado em pacientes com FM pode ser atribuída a diferenças na ativação neural em redes de memória na região frontal e pode resultar em alteração da percepção da dor nestes pacientes, quando associados a depressão e ansiedade(Seo et al. 2012).

Corroborando com tais achados, as deficiências cognitivas também são conhecidas por estarem associadas à gravidade da dor, na população com dor crônica. Entretanto a associação entre o desempenho cognitivo e medidas experimentais de dor são pouco investigadas. Um estudo recente de Ickmans et al. 2015 com pacientes com Síndrome de Fadiga Crônica (SFC) com e sem

Fibromialgia, e saudáveis avaliou a associação entre o desempenho cognitivo baseado na atenção seletiva e sustentada, inibição cognitiva e na capacidade de memória de trabalho com as medidas experimentais de dor como: limiares de dor a pressão e *conditioned pain modulation* (CPM). No grupo com SFC+FM a capacidade de inibição da dor endógena foi significativamente associada com inibição cognitiva. Os autores relatam que a inibição da dor pode ser um preditor significativo do mau funcionamento cognitivo. As hipóteses deste estudo são que o mau funcionamento da via descentes inibitória da dor impossibilita um bom funcionamento cognitivo e a que sobreposição de regiões cerebrais para o processamento da dor e cognição pode explicar uma piora na inibição em presença de dor crônica (Ickmans et al. 2015).

Nesse sentido, pacientes com FM, conforme Seo et al. (2012), apresentaram um desempenho diminuído em uma variedade de testes de MT em relação ao grupo controle, demonstrando que a MT pode estar prejudicada em pacientes com FM. A reabilitação por meio do treino cognitivo poderia melhorar esta habilidade. Contudo, há várias questões no que se refere à eficácia deste treino nesta população, bem como quais processos ou sistemas apresentariam uma melhora(Seo et al. 2012).A modalidade do estímulo é relevante, neste sentido, uma vez que a alça fonológica e o esboço visuoespacial são componentes relativamente independentes (Baddeley, 2011).

6. AVALIAÇÃO DA MEMÓRIA DE RECONHECIMENTO, LONGO PRAZO E FLUÊNCIA VERBAL EM PACIENTES FIBROMIÁLGICOS

Existem alguns modelos descritos na literatura para avaliar as demais funções cognitivas, mas nesse projeto optamos pelo modelo Miyake(Miyake et al. 2000), posteriormente modificado Fisk e Sharp (Fisk and Sharp 2004), e com referência ao artigo de Aboulafia-Brakha e colaboradores(Aboulafia-Brakha et al. 2011) para avaliar as funções executivas a qual englobam 4 fatores interdependentes: Deslocamento, inibição, atualização e acesso. O deslocamento envolve a capacidade de engajar e desengajar de diferentes tarefas, sendo necessárias para isto algumas habilidade cognitivas tais como: atenção, flexibilidade mental, rapidez de processamento.A inibição refere-se a habilidade de inibir respostas automáticas ou destratoras que possam interromper o curso eficaz de uma ação. A atualização trata-se da habilidade para monitorar e codificar informações, e substituir informação antigas não relevantes por novas que sejam importantes. O acesso trata das representações de memória de longo prazo e está envolvida em tarefas de fluência verbal (Tesio et al. 2015).

Tesio et al.,2015 avaliou o desempenho neuropsicológico em pacientes com fibromialgia nos seguintes domínios: Memória de longo prazo, memória de trabalho, atenção e função executiva em relação ao controle. Os resultados deste estudo confirmam a presença de comprometimento na atenção, memória de trabalho e de algumas domínios da função executivas tais como: deslocamento e atualização em pacientes fibromiálgicos em comparação aos saudáveis(Tesio et al. 2015).

Ademais, um recente artigo de revisão da literatura avaliou as disfunções cognitivas em fibromialgia e dentre esses tópicos avaliaram a memória episódica, a qual é capacidade de lembrar de eventos ou episódios específicos. Em geral, os achados sobre a memória episódica sugerem um pequeno déficit em pacientes com FM, contudo não parecem ser tão robustos quanto os achados com memória de trabalho(Glass 2009b).

Além disso, esses déficits cognitivo, principalmente de memória e atenção, têm sido associados a outros sintomas clínicos tais como qualidade do sono, níveis de ansiedade, depressão e catastrofismo a dor (Glass 2009b). Grace e colegas relataram que ansiedade foi correlacionada com medidas de memória e concentração em pacientes fibromiálgicos(Grace et al. 1999). Suhr e colaboradores também relataram que sintomas depressivos estão relacionados à memória na FM (Suhr 2003). Do mesmo modo, Dick e colaboradores encontraram uma relação entre depressão, ansiedade e função cognitiva (Dick et al. 2008). Por outro lado, Park e colegas avaliaram o desempenho cognitivo e sua relação com sintomas depressivos e de ansiedade, não foi observado correlação com o desempenho em qualquer das medidas cognitivas em paciente com fibromialgia(Park et al. 2001). Em suma, parece que as variáveis psicológicas, como a depressão e ansiedade podem contribuir para a disfunção cognitiva na FM, mas atualmente isso ainda não está totalmente elucidado. Diante disso, desenvolvemos um protocolo de pesquisa com um conjunto de testes neuropsicológicos controlando para os principais fatores confundidores descritos na literatura.

7. AVALIACAO DO PROCESSAMENTO COGNITIVO POR MEIO DE POTENCIAIS RELACIONADOS A EVENTOS

Estudos com marcadores eletrofisiológicos e de neuroimagem tem sido utilizados para avaliar as funções cognitivas em pacientes com síndrome de dor crônica. Os potenciais relacionados a eventos (ERPs) vem sendo um dos meios mais objetivos de avaliar as funções cognitivas e mediar a atividade eletrofisiológica do sistema nervoso central, através do eletroencefalograma (EEG) (Seo et al. 2012;Pinheiro et al. 2016).

Os potenciais relacionados a eventos (*event-related potentials* ou ERPs) são deflexões de onda do Eletroencefalograma (EEG) de pequena voltagem geradas em resposta a estímulos específicos e associadas ao tempo após ocorrência de determinado evento seja ele motor, sensitivo ou cognitivo. Acredita-se que ERPs

são as reproduções da soma de potenciais pós-sinápticos produzidos por um grande número de neurônios piramidais em sincronia (Peterson et al., 1995). ERPs podem ser divididos em duas categorias: as ondas rápidas que ocorrem em até 100ms após o estímulo e estão associadas ao processo sensitivo, e as ondas lentas que refletem o processamento das informações cognitivas, como o P300 (Sur and Sinha 2009).

As técnicas dos ERPs são muito úteis para estudar as bases fisiológicas dos processos cognitivos, uma vez que esses potenciais são um indicador das mudanças da atividade elétrica cerebral associadas, com relação temporal específica, com estímulos físicos ou processos cognitivos, em outras palavras, permite a avaliação da relação entre a atividade cerebral e o processo psicológico em tempo real(Rodríguez et al., 2006). Para fins deste trabalho, a onda utilizada será a P300 ou P3, que se apresenta como uma onda positiva, sua amplitude varia entre 5 e 20uv, sua latência varia entre 300 ms e 900 ms (Luck, 2005). Mudanças na latência e amplitude desse componente têm sido associadas com variáveis cognitivas como memória, tomada de decisão e atenção(Jaeger and Parente 2010). A deflexão positiva P300 tem sido associada com processamento atencional e de memória (Polich 2007) para estímulos incomuns, importantes ou de seleção de informação(Berti, 2016), sendo a tarefa *oddball* auditiva uma das mais utilizadas para avaliar esse processo. A tarefa consiste na apresentação de uma série de estímulos auditivos de dois tipos - frequentes e infrequentes. Os frequentes ou padrão é apresentado com um tom de 1000 hertz e ocorrem em cerca de 80% do casos, enquanto o infrequente ou raro em 20%.

Nessa tarefa pode ser solicitado ao individuo que pressione um botão especifico (processo ativo) ou apenas contar o número de estímulos infrequentes (passivo). No modo passivo, espera-se que os estímulos raros captem a atenção automaticamente, permitindo estudar como o estímulo influencia na atenção envolvendo um processo *bottom-up* e na modalidade ativa do paradigma, espera-se estudar os processos controlados do tipo *top-down* (Carretié, 2011).

Dois estudos (Alanoğlu et al. 2005;Yoldas et al. 2003) onde foi analisado P300 em uma tarefa de *oddball* auditiva em pacientes com fibromialgia, demostrou diminuição de amplitudes e latências mais longas em P300 em fibromiálgicos quando comparados a indivíduos saudáveis, demostrando que FMS apresentam déficits de processamento atencional. Apesar das descobertas mencionadas acima, as pesquisas realizadas seguindo o paradigma de *Oddball* auditivo em pacientes com fibromialgia ainda são escassos, tornando difícil uma característica comum que permita agrupá-los para compará-los e tirar conclusões robustas.

8. MARCADOR BIOLÓGICO DE PLASTICIDADE ASSOCIADO À DOR

Diversas moléculas têm sido relacionados ao processamento da dor, entre elas o Fator Neurotrófico derivado do Cérebro (BDNF), considerado potencial marcado de neuroplasticidade (Merighi et al. 2008). O BDNF é uma neutrofina que está amplamente distribuído no sistema nervoso central e está sendo reconhecida com importante marcador de plasticidade neuronal relacionada a receptores NMDA em vias nociceptivas ascendente e descendentes (Brietzke et al. 2016). Seu efeito neuroplástico está associado ao equilíbrio nas sinapses excitatórias (glutamatérgico) e inibitórias (gabaérgica)(Binder and Scharfman 2004). No contexto da sensibilização central, como é o caso dos FMS, as células da micróglia são ativadas por astrócitos que também podem liberar BDNF, o que reduz a expressão de cotransportadores como íon cloreto(Cl-) e exportadores potássio (K+) e cloreto(Cl-) (KCC2) na região do corno dorsal da medula. Isto resulta em um acúmulo intracelular de Cl- que limita os efeitos inibitórios gabaérgicos nesses nociceptores promovendo a desinibição (Latremoliere and Woolf 2009).

Estudo recente do nosso grupo(Caumo et al. 2016a), avaliou a excitabilidade do córtex motor e os níveis de BDNF em dor crônica musculoesquelética de acordo com a patologia estrutural e nesse contexto encontra-se a FM. Os resultados foram: BDNF inversamente correlacionado com a inibição intracortical e com mudanças na escala numérica de dor durante no CPM-teste, sugerindo uma maior desinibição no córtex motor e no sistema inibitório

descendente da dor em FM e síndrome de dor miofascial do que em paciente com osteoartrite e saudáveis. Além disso, em pacientes com FM os níveis séricos de BDNF estão aumentados (Haas et al. 2010),(Laske et al. 2007) e inversamente correlacionados com os limiares de dor a pressão(Zanette et al. 2014).

9. A ESTIMULAÇÃO TRANSCRANIANA COM CORRENTE CONTÍNUA E A COMBINAÇÃO COM O TREINAMENTO DA MEMÓRIA DE TRABALHO COMO RECURSO TERAPÊUTICO

Os pacientes FMS apresentam déficits em tarefas que requerem memória de trabalho e atenção (Glass 2009a). Uma das regiões envolvidas com o processamento dessas atividades é o córtex pré-frontal. Diante disso, a estimulação transcraniana por corrente contínua (ETCC) em CDLPF é uma das várias técnicas de estimulação cerebral não invasiva desenvolvida nos últimos anos, que permite a modulação da atividade e excitabilidade cortical dessa área, resultando em alterações de funções psicológicas e processos comportamentais (Shin, Foerster, and Nitsche 2015). O uso desta técnica na prática clínica apresenta vantagens, pois além de ter sido comprovada sua função modulatória, possui um baixo custo, poucos efeitos colaterais, e potenciais de eficácia em diversas especialidades médicas (Brunoni et al. 2012).

O aparelho do ETCC possui dois eletrodos que devem ser posicionados sobre o escalpo do paciente. Esses eletrodos são imersos em uma esponja de 5-35 cm2 umedecidos em água ou em solução de cloreto de sódio para conduzir corrente de aproximadamente 9 volts. A densidade da corrente varia de 1-2 mA e os eletrodos são mantidos presos no escalpo por uma banda elástica (F Fregni et al. 2006). Um eletrodo é o ânodo (eletrodo positivo) e o outro é o cátodo (eletrodo negativo). O fluxo de corrente move-se do ânodo para o cátodo passando pelo escalpo, provocando aumento da excitabilidade cortical com a estimulação anódica e o efeito oposto com a catódica (Nitsche et al. 2008). Ou seja, a estimulação catódica diminui o potencial de repouso da membrana e os neurônios são

hiperpolarizados, já o estímulo anódica causa despolarização pelo aumento do potencial de membrana. Geralmente o ânodo fica localizado sobre a área alvo do córtex motor primário (M1) e/ou (CPFDL) quando se objetiva melhorar os sintomas álgicos e cognitivos respectivamente (Poreisz et al. 2007).

Fregni et al. 2006 avaliaram a ETCC no tratamento da dor decorrente de traumatismo raquimedular utilizado estimulação anódica sobre o M1 e catódica sobre a região supraorbital contralateral a 2mA por 20 minutos, durante cinco dias consecutivos. Os autores verificaram melhora significativa dos níveis de dor após estimulação ativa, mas não após estimulação placebo. Houve também efeito analgésico cumulativo durante a estimulação que permaneceu por até duas semanas após término do tratamento. Esse mesmo protocolo foi adotado em um estudo com pacientes fibromiálgicas divididas em três grupos: estimulação anódica em M1, estimulação no CPFDL (posicionando o eletrodo catódico na região supraorbital) e estimulação *sham*. Os autores observaram melhora do nível de dor até três semanas após o término do tratamento no grupo ativo em M1(F Fregni et al. 2006).Valle et al., 2009 realizaram um estudo com ETCC a 2mA, por 20 minutos, durante 10 dias, em mulheres com fibromialgia, onde foi observado um importante efeito analgésico e melhora da qualidade de vida no grupo ativo em relação ao *sham* (Valle et al. 2009).

Além dos benefícios na diminuição nos níveis de dor, a ETCC é uma técnica de neuromodulação com resultados promissores para aprimorar o desempenho atencional e de memória de trabalho. Considerando o papel da região pré-frontal na memória de trabalho, Fregni e colaboradores investigaram o efeito da ETCC anódica sobre região do CPFDL em voluntários saudáveis e o desempenho na memória de trabalho através do tarefa n-back. Os resultados foram que a estimulação sobre o CPFDL esquerdo aumenta a precisão na tarefa em relação ao grupo *sham*(Felipe Fregni et al. 2005). A estimulação combinada ao treino cognitivo em saudáveis, foi relatado por Campanhã et al. (2012) em um estudo que investigou o benefício da ETCC associada a uma tarefa de MT chamada *n-back*. Como

resultado do estudo obteve-se evidências de que quando a ETCC é administrada durante o desempenho de uma tarefa de MT o seu efeito pode resultar em um melhor desempenho em outra tarefa equivalente aplicada em um momento posterior.

Evidências recentes tem demostrado também efeitos aditivos da combinação da ETCC com outros tipos de intervenção, sejam elas cognitivas, atividade física e programa de reabilitação da dor (Riberto 2011;Luedtke et al. 2015;Mendonca et al. 2016). Nesta perspectiva, um estudo recente realizado pelo nosso grupo encontrou um efeito aditivo da ETCC ativa sobre o CPFDL combinado com uma tarefa que induz a ativação de vias de controle inibitório (Silva et al. 2017a). Ainda que nosso estudo seja preliminar, demonstrou que a terapia combinada melhorou a performance das redes de atenção e aumentou o limiar de dor. Assim, a ETCC pode privilegiar e modular os circuitos pré-frontais com capacidade para melhorar a tolerância e minimizar o componente emocional da experiência dolorosa. Espera-se que a combinação com o treinamento memória possa levar a ganhos adicionais para os pacientes fibromiálgicos.

Entretanto, até o presente momento existe uma lacuna no conhecimento quanto ao uso do efeito combinado da ETCC associado ao treinamento memória de trabalho em paciente com fibromialgia. Sabe-se que isoladamente ambas as intervenções (ETCC e treinamento da memória de trabalho) tem demostrados resultados promissores na melhora do desempenho cognitivo em especial na memória e atenção. Diante disse, são necessários novos protocolos que utilizem o treinamento da memória de trabalho concomitante ao ETCC em CPFDL para avaliar se a combinações de técnicas podem levar efeitos aditivos, e assim diminuição nos déficits cognitivos em FMS, visto que este fator está sendo descrito na literatura como um dos mantenedores do quadro álgico destes pacientes.

CAPÍTULO III

1. JUSTIFICATIVA

A fibromialgia é uma síndrome complexa que envolve componentes afetivos, sensoriais, sociais e cognitivos. Caracteriza-se por dor crônica generalizada associada a sintomas com fadiga, alterações do humor, alterações de sono, ruptura do ritmo circadiano e baixo desempenho cognitivo. Um dos sintomas que chama a atenção nesses pacientes além da dor são os problemas de memória e atenção, pois estão presente em cerca de 50 -80%. Esse fator pode aumentar a vulnerabilidade e prejudicar a busca de recursos de enfrentamento da doença e assim como do processamento de informações.

Os déficits de memória e atenção também estão associados a pobre qualidade do sono e dor sendo que essa queixas trazem grande repercussões para as atividades diárias desse pacientes, pois prejudica o seu rendimento no trabalho, relações interpessoais e sua qualidade de vida. Deste modo, o tratamento atual da fibromialgia visa reduzir os sintomas de dor e as complicações associada dessa síndrome. A utilização dos antidepressivos dual e as anticonvulsivantes associadas a medidas não farmacológicas visam diminuir a problemas relacionados às múltiplas facetas que envolvem essa síndrome. Até o presente momento os melhores resultados têm sido alcançados por meio da combinação de técnicas e as falhas têm sido atribuídas ao desconhecimento da fisiopatologia da doença ou ao uso de técnicas que não alcançam os potenciais mecanismos que sustentam as múltiplas facetas desta síndrome.

Nesta perspectiva, um estudo recente realizado pelo nosso grupo encontrou um efeito aditivo da ETCC ativa sobre o córtex pré-frontal dorsolateral (CPFDL) combinado com uma tarefa que induz a ativação de vias de controle inibitório (Silva et al. 2017a). Ainda que o estudo seja preliminar, demonstrou que a terapia combinada melhorou o desempenho de redes de atenção com consequente aumento no limiar de dor. Assim, a ETCC pode privilegiar e modular os circuitos pré-frontais

com capacidade para melhorar a tolerância e minimizar o componente emocional da experiência dolorosa.

Deste modo, esperamos que o a ETCC combinada com o treinamento da memória também possa levar ganhos adicionais para pacientes fibromiálgicos e assim trazer uma nova possibilidade terapêutica para minimizar os efeitos dos déficits de memória assim como melhor a sintomatologia encontrado nesses pacientes.

Além disso, para construir um racional abrangente e com plausibilidade biológica, o estudo da FM demanda uma integração de estratégias para captar os sintomas e sinais clínicos e de recursos tecnológicos com o objetivo de compreender os mecanismos fisiopatológicos de maneira mais completa, assim como na busca de estratégias terapêuticas mais eficazes. Dentre os recursos tecnológicos estão as medidas neurofisiológicas, por meio da Eletroencefalografia (EEG), a dosagem de marcadores séricos de plasticidade BDNF, as quais parecem mensurar importantes facetas do processo fisiopatológico e do conjunto de sintomas da FM.

Sendo assim, o presente estudo avaliou se a combinação do Treinamento de memória de trabalho combinado com o ETCC teria um efeito maior do que a ETCC- *sham* no desempenho da memória episódica, curto e de longo prazo. Também avaliamos as mudanças neurofisiológicas induzidas pelo ETCC combinado com treinamento da memória de trabalho nos sinais eletrofisiológicos dos pacientes com fibromialgia e o desempenho da memória episódica curto e de longo prazo pode estar relacionado ao BDNF sérico no linha de base. O mapa conceitual construído a partir da base teórica que sustenta este estudo encontra-se na figura 7.

2. MAPA CONCEITUAL

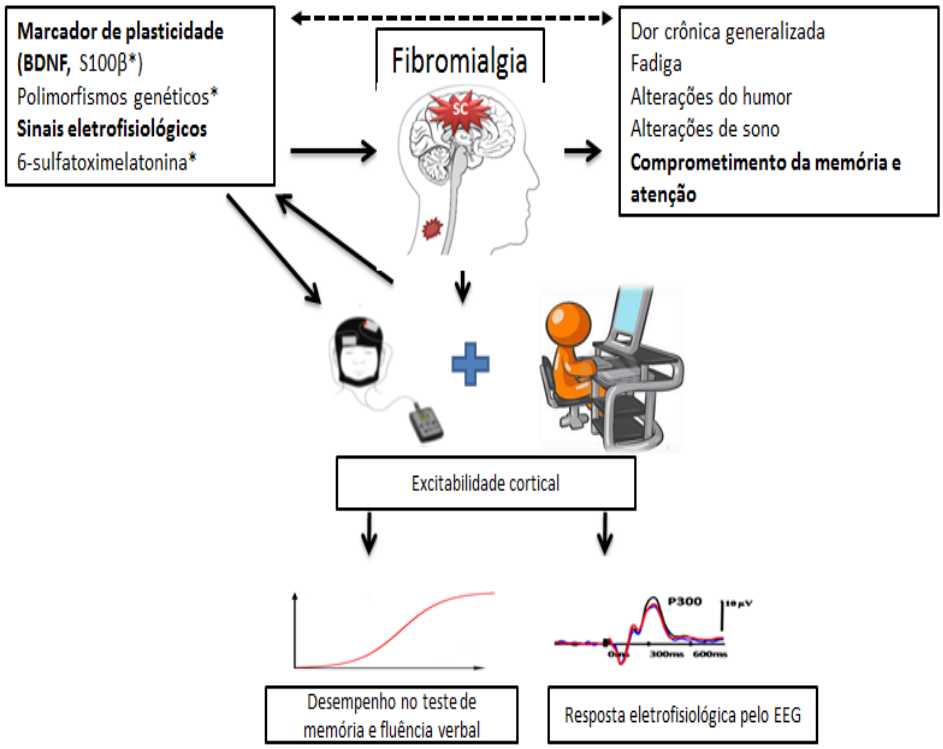


Figura 7. Mapa conceitual. * Marcadores de plasticidade que não foram utilizados neste projeto. Palavras em negrito foram o foco deste projeto.

3. OBJETIVOS

3.1 Objetivo Primário:

Avaliar se a combinação do treinamento de memória de trabalho com a ETCC ativo teria um efeito superior a ETCC *sham* no desempenho da memória episódica, de curto e longo prazo.

3.2 Objetivos secundários:

Comparar os efeitos do tratamento ETCC ativo e *sham* e treinamento memória de trabalho; e verificar os efeitos nos seguintes desfechos:

Cognitivos:

- Avaliar o desempenho na memória de trabalho,atenção sustentada e divida e fluência verbal;
- Avaliar o desempenho da memória episódica curto e de longo prazo pode estar relacionado com o BDNF sérico no linha de base.

Eletrofisiológicos:

- Avaliar as mudanças neurofisiológicas induzidas pelo ETCC combinado com treinamento da memória de trabalho nos sinais eletrofisiológicos dos pacientes com fibromialgia;
- Avaliar a associação entre a amplitude do P300 e a percepção do nível da dor, pensamento catastrófico sobre a dor, sintomas ansiosos e depressivos.

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CAPÍTULO IV

ARTIGO 1 ORIGINAL EM INGLÊS

Combined treatment with transcranial direct current stimulation and cognitive training in fibromyalgia patients: electrophysiological and cognitive-affective changes

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Authors

Vinicius Souza dos Santos[1,2],Maxciel Zortea[1,2], Felipe Vasconcelos Torres[1,2], Amanda Lino de Oliveira[2,3], Guilherme Lannig[4], Sandra Carvalho[5] , Jorge Leite[5] , Iraci Lucena da Silva Torres[1,6], Felipe Fregni[7], Gustavo Gauer[8], Prisla Ücker Calvetti[2,] , Wolnei Caumo[1,2,9,10 *]

Affiliations

1 Post-graduation Program in Medicine: Medical Sciences, Federal University of Rio Grande do Sul (UFRGS)

2 Laboratory of Pain & Neuromodulation, Clinical Hospital of Porto Alegre (HCPA)

3 Graduation Program in Physiotherapy, UFRGS

4 Graduation Program in Psychology, UFRGS

5 Neuropsychophysiology Laboratory, CIPsi, School of Psychology (EPsi), University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal 7 Pharmacology of Pain and Neuromodulation: Pre-clinical Investigations, UFRGS

6 Associate Professor, Pharmacology Department, Instituto de Ciências Básicas da Saúde, UFRGS, Porto Alegre, Brazil.

7 Associate Professor of Physical Medicine & Rehabilitation, Associate Professor of Neurology Harvard Medical School. Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA.

8 Post-Graduation Program in Psychology, UFRGS

9 Anesthesiologist, Pain and Palliative Care Service at Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil.

10 Associate Professor of Pain and Anesthesia in Surgery Department, School of Medicine, UFRGS, Porto Alegre, Brazil

*Correspondence: Wolnei Caumo MD, Ph.D., Laboratory of Pain & Neuromodulation, School of Medicine at UFRGS, Professor of Pain and Anesthesia in Surgery Department, Hospital de Clínicas de Porto Alegre, Street Ramiro Barcelos, Porto Alegre, RS, 90035-003, Brazil. wcaumo@hcpa.edu.br

Abstract

Fibromyalgia (FM) is a chronic pain condition with a complex disorder involving sensory-discriminatory, motivational-affective, cognitive-evaluative and social dimensions. Objective: This pilot study investigated the central electrophysiological signal changes induced by transcranial direct current stimulation (tDCS) combined with a working memory (WM) training in patients with Fibromyalgia and the association between electrophysiological signal and pain level, pain catastrophizing, anxiety and depression. Methods: In a randomized sham-controlled double-blinded clinical trial, 12 FM patients received 8 sessions of anodal tDCS over the dorsolateral pre-frontal cortex (DLPF) with an online application of the Dual N-Back task. We applied an auditory oddball task to evaluate the P300 event-related potential (ERP). Electrophysiological signal, pain perception, catastrophizing, anxiety and depression were measured before and after treatment. Results: The area under the curve (AUC) of the ERP was higher after sham-tDCS applied concurrently the Dual N-Back task as compared to the baseline, whereas no significant difference was observed for the active-tDCS stimulation. Very similar curves for the 400-600ms post-deviant stimulus interval were observed for both groups in all derivations, except for the Pz-derivation. Also, significant reductions in pain report, pain catastrophizing and anxiety scores were found only after the active treatment. Pain levels after treatment correlated inversely with the magnitude

of the electrophysiological signal, indicating increased P300 AUC is associated with higher pain reported. Conclusion: The applications of anodal tDCS over the DLPFC combined with cognitive training may counter-regulates the hyperexcitability of central nervous system networks in FM patients, and possibly reduce pain and other clinical symptoms.

Registration in Clinical trials.gov: NCT 02880917

INTRODUCTION

Fibromyalgia (FM) is a chronic pain condition with worldwide prevalence between 2% to 5%, more prevalent in women (Neumann and Buskila 2003), and characterized by generalized chronic pain, fatigue, depression and other cognitive symptoms (Häuser, Thieme, and Turk 2010). Thereby, it is a complex disorder involving sensory-discriminatory, motivational-affective, cognitive-evaluative and social dimensions. Although its pathophysiology and etiology is not well understood, the current hypotheses state that abnormal mechanisms involved in central pain processing in FM result in amplified pain sensitivity(Meeus and Nijs 2007; Henry, Chiodo, and Yang 2011). The dorsolateral prefrontal cortex (DLPFC) is a brain area that affects overall pain perception and the pain experience (Boggio, Zaghi, and Fregni 2009; Borckardt et al. 2011). It has been found that increased activity of the DLPFC after behavioral therapy for pain increased the cortical control over pain experience (Seminowicz et al. 2013). Although the efficacy of tDCS for treating pain symptoms has been demonstrated in several chronic conditions, including FM (Lefaucheur et al. 2017), there is growing evidence showing that its analgesic effects might promote an additive effect combined with if other types of intervention (cognitive intervention, physical activity, pain rehabilitation program) (Riberto 2011; Luedtke et al. 2015; Mendonca et al. 2016). An additive of effect of active tDCS over the DLPFC combined with a task focusing on inhibitory processes already has been reported from previous work from our group, demonstrating that the combined intervention improved the orienting and executive attentional networks, while it enhanced the control of pain perception (Silva et al. 2017b). Some studies also indicate tDCS effects are state dependent (Shahbabaie et al. 2014; Learmonth et al. 2015). Thus, the tDCS might prime and modulate prefrontal circuitry, enhancing the capacity to tolerate and downregulate the emotional component of the pain experience.

Nevertheless, studies are needed to understand the relationship between these non-invasive therapeutic approaches and the electrophysiological markers for

chronic pain syndromes (for a systematic review, see 15). In this sense, these biomarkers can help to comprehend the relationship between the dysfunctional intracortical mechanisms involving GABAergic and glutamatergic pathways that have been associated with FM (Mhalla et al. 2010). Two previous studies (Alanoğlu et al. 2005; Yoldas et al. 2003) analyzed event-related potentials (ERPs) in an auditory oddball task. This paradigm usually produces a positive deflection 300ms after the deviant stimulus (P300), which indicates attentional and memory processing (Polich 2007). These studies reported diminished amplitudes and longer latencies for P300 when compared to healthy subjects. Nevertheless, the study of P300 component as a neurophysiological marker to a maladaptive brain implicated in chronic pain has never been proposed (Costigan, Scholz, and Woolf 2009). The EEG data may be used not only to identify some aspects of maladaptive plasticity, but it may also be a feasible, low cost alternative in the follow–up of patients with chronic pain (Lelic 2014).

Thus, the main goal of this pilot study was to investigate the neurophysiological changes induced by tDCS combined with a cognitive training on central electrophysiological signals in patients with FM. We assume an increased amplitude and shorter latencies in P300 ERP component will be found after active-tDCS application, as well as an association between the amplitude of the P300 component and pain level perception, pain catastrophizing, anxiety and depression.

METHOD

Study design

This pilot study consisted of a randomized sham-controlled double blinded clinical trial (ClinicalTrials.gov registration NCT 02880917), which was approved by the hospital Research Ethical Committee (no. 14-0369). Figure 1 shows the flowchart.

---- Insert Figure 1 ----

Study sample

FM subjects were recruited by directly contacting them from the institutional chronic pain clinic, by referrals from other clinic units, and through media advertising. FM diagnosis adhered to 2010 American College of Rheumatology criteria (Wolfe et al. 2010). All subjects were screened for eligibility by phone. Other inclusion criteria were: females that reported pain score on the Numerical Pain Scale (NPS 0-10) greeter than 5 on most days during the last month, and aged between 18 and 70 years-old. Exclusion criteria were: severe behavioral disturbs, neurological commitment (traumatic brain injury, epilepsy or convulsive crises, stroke and degenerative syndromes), chronic inflammatory disease (lupus, rheumatoid arthritis), previous adverse reactions due to tDCS application, usage of brain metallic implant or pacemaker, and use of medication for attentional deficit/hyperactivity disorder. Patients who revealed more than 25% of poor quality of the EEG signal due to artifacts or noise (criteria is presented below) were excluded.

Treatment

For each of the 8 treatment sessions, a tDCS (TCT Research Limited©, Hong Kong) combined with a cognitive training task intervention was applied. tDCS was delivered using the anode electrode positioned over the left DLPFC (F3 according to the 10–20 system for EEG) and the cathode electrode at right supraorbital region (Fp2). The electrodes were placed into–35 cm^2 sponges soaked in saline solution for better current conductivity. Rubber bandages were used to hold the electrodes in place for the duration of stimulation. For the active-tDCS condition, a constant current of 2mA was applied for 20 min. For sham stimulation the electrodes were placed in the same position, but the stimulator was turned off after a ramp-up of 30s of stimulation (Gandiga, Hummel, and Cohen 2006).

The cognitive training consisted of an online application of a Dual N-Back task (Susanne M. Jaeggi et al. 2007), which started 3 minutes after the beginning of the tDCS application (instructions were presented before the beginning of the application). A laptop (15 inches screen, distance of ~60cm ahead) with software E-Prime 2.0 Standard presented two types of stimuli, simultaneously. Visual stimuli were blue squares presented in eight different positions, and auditory stimuli consisted of the letters D, P, Q, G, V, C, T and K presented binaurally via headphones. Patients had to decide for each trial if the stimuli were the same as n-trials before (memory workload), by pressing the keyboard "A" button for visual and "L" for auditory (and do not press any button when none of the alternatives apply). The task had 20 blocks with 20 trials each, of which 10 were "no target", 4 were "visual target only", 4 "auditory target only" and 2 "dual target", and had a duration of about 25 minutes. The memory workload information was presented in the beginning of each block, and a feedback (percentage of correct responses) was presented in the end of each block. Because of the adaptive nature of the cognitive training, workload level increased when the previous block had 90% correct responses or higher and decreased when less than 70% was achieved. Training started with 1-back in the first 3 blocks, and 2-back after block 4. Practice trials were not used, due to the inherent learning process of the cognitive training.

Primary and secondary outcomes

The primary outcome consisted of the area-under-the-curve (AUC) of the P300 ERP component for central electrophysiological signal. Secondary outcomes were the VAS for pain level perception and the scores for pain catastrophizing thoughts and symptoms of anxiety and depression. All this outcomes were measured before and after treatment.

Outcomes assessment

Central electrophysiological signal (primary outcome)

Signal was acquired from Fz, Cz, Pz and Oz derivations (channels Fp1 and Fp2 were also monitored for eye blinks artifacts) through Ag/AgCl electrodes embedded in gel and attached to the scalp using a neoprene headcap. Minimum hair removal was done as needed. Electrodes were connected to a digital data-acquisition system, ENOBIO 20 (Neuroelectrics®, Barcelona), which sent the signal via Bluetooth interface to a laptop equipped with the NIC 2.0 software (Neuroelectrics®, Barcelona). The EEG recordings were digitally stored at 0.5 kHz sampling resolution in a computer hard drive for off-line analysis.

Oddball task, data acquisition and ERPs analysis: An Acer® laptop (14 inches screen, distant 60 cm ahead of the patient) was connected to the register laptop via TPC port to register the event. An auditory oddball task was presented using E-Prime 2.0 (Psychology Software Tools Inc., Sharpsburg, PA). Stimuli were 320 1000hz (standard) and 80 2000hz (deviant) sinusoidal "beeps" presented for 500 ms through earphones in a jittered inter-stimulus-interval (ISI; 2000 to 3000 ms) and randomly, divided in four blocks of 100 stimuli each (keeping the 4:1 proportion). Patients were instructed to pay attention and count how many deviant stimuli appeared in each block. A preview of the sounds was used to confirm the participant understood which was the target stimulus. All analyses were done using built in and custom written routines in MATLAB (Mathworks, Inc) after initial signal processing using EEGLAB and ERPLAB plugins. EEG recordings were notch-filtered at 60 Hz offline. Signals that were too noisy or that contained too much movement artifact were excluded from the analysis. These were inferred by visual inspection of the traces along with the presence of abnormally high power in lower frequencies (0–3 Hz), or by amplitudes greater than 50 uV.

Pain level, pain catastrophizing, anxiety and depression (secondary outcomes)

Pain level was assessed with a visual-analogue scale (VAS) in a line 10cm long. Patients marked with a pen how much pain they felt at the moment, ranging from "no pain/comfortable" to "a lot of pain/extremely uncomfortable". The Brazilian Portuguese Pain Catastrophizing Scale (BP-PCS) (25) was administered to

assess pain catastrophizing. The scale consists of 13 items in 4-points Likert scale of thoughts and feelings presented when patients feel pain. It provides a total score ranging from 0 to 52, as well as scores for the Rumination, Magnification and Helplessness subscales. Anxiety was measured with a short version of the State-Trait Anxiety Inventory (STAI) (Kaipper et al. 2010). Patients had to report using a 4 or 3-points Likert scale how they feel "right now" (State scale, 13 items, ranging from 13 to 49) and how they usually feel (Trait scale, 12 items, ranging from 12 to 36). Rasch analysis was implemented to reduce the number of items, maintaining the psychometric quality (Kaipper et al. 2010). Finally, depressive symptoms were measured with the Beck Depression Inventory II (BDI-II; (Gorenstein et al. 2011) Gorenstein, Pang, Argimon, & Werlang, 2011). The scale contains 21 items in a 4-point Likert scale (total score ranging from 0 to 63) to which patients reported how they feel during the last two weeks.

Other clinical and psychological assessments at baseline

We evaluated baseline characteristics, such as age, years of education and number of medication using a standard sociodemographic questionnaire and comorbidities using the M.I.N.I International Neuropsychiatric Interview (Amorim 2000b). Other baseline instruments were the Fibromyalgia Impact Questionnaire (Marques et al. 2006) for the functional impact of fibromyalgia, and the Brazilian Profile of Chronic Pain: Screen (B-PCP:S; (Caumo et al. 2013a) to characterize functional limitations related to severity of pain, emotional stress and pain interference in life.

Randomization and blinding

Before the recruitment phase, the randomization was generated using a computer system by researchers who did not administer the intervention. They put the sequence in separately opaque sealed envelopes. The simple randomization method was applied, with patients assigned to the one of the two groups with a rate of 1:1. For blinding purposes, the envelopes containing the patients' protocol numbers were opened by an auxiliary researcher, who also programmed the tDCS

device for active or sham stimulation. The researcher who applied the treatment and the researcher who conceived the pre and post evaluations were unaware of this information. Blinding of patients was done using the sham stimulation described in the Treatment session.

Data treatment and statistical analyses

Exploratory descriptive analyses were implemented in order to describe the variables and test for normality parameters. Shapiro-Wilk statistics, frequency histograms and box-plot graphs were used. Inferential tests included factorial within (2 levels: pre and post-treatment) and between (2 levels: active and sham-tDCS) analyses of variance (ANOVAs) for the primary (EEG parameters) and secondary outcomes (pain perception, catastrophizing, anxiety and depression). Lastly, Spearman correlations (considering the small sample size) between the primary and the secondary outcomes were applied. Significance level was considered $P < 0.05$, bi-caudal, and effect sizes using squared-Eta (η^2) were described.

RESULTS

Two (assigned to the active-tDCS group) out of the 14 patients were excluded due to too much noise in the EEG acquisition. Table 1 presents descriptive data of the baseline measures and inferential statistics comparing these measures between groups. No significant differences were found, indicating groups were equivalent at baseline.

---- Insert Table 1 ----

Primary outcome: Effects of the combined treatment on central electrophysiological signal

After analysis of artifact, we excluded 6.16% of trials. To determine if tDCS had any effect on P300 wave, we analyzed the averages for each Group (Sham, N=7; tDCS, N=5) and Type of stimulus (standard or deviant), and calculated the

Area Under the Curve (AUC) for the 400-600 ms post-stimulus interval. Our results showed very similar curves for both sham and active-tDCS groups in all derivations for the same kind of stimuli, except in the Pz-derivation for the deviant stimulus after the treatment (p=0.016, Paired-Samples T Test). Our findings pointed to an increased P300 wave for the sham group in the parietal area when re-exposed to the oddball task, a finding that did not occur in the active-tDCS group **(Figure 1).**

---- Insert Figure 2 ----

Secondary outcomes: Effects of the combined treatment on pain perception, catastrophizing, anxiety and depression

We compared the scores on the VAS (pain), BP-PCS, STAI and BDI-II to assess, respectively, pain perception, pain catastrophizing thoughts and symptoms of anxiety and depression, with ANOVAs 2 (Group: a-tDCS and s-tDCS) x 2 (Time: pre and post-treatment). Table 2 presents the statistical information of these comparisons. As follows, for VAS (pain), in an independent manner, patients had lower pain scores after treatment and after tDCS intervention compared to sham condition. The interaction term showed to be marginally significant $F(1, 10)=4.56$; $p=0.058$; $\eta^2=0.31$. Pairwise comparisons, using Bonferroni correction, revealed that a-tDCS had reduced the level of pain after treatment ($p=0.003$) and that after treatment this score was lower when compared to the s-tDCS group ($p=0.013$).

The BP-PCS: total score showed significant main effect for Time and a significant interaction term, $F(1, 10)=10.92$; $p<0.008$; $\eta^2=0.52$. Further comparisons revealed that only in the a-tDCS group, there was a significant ($p<0.001$) decrease in catastrophizing scores from pre to post-treatment. The intervention affected differently the dimensions of pain catastrophizing.In summary, all patients diminished Magnification thoughts from pre to post-treatment (main effect: $F[1, 10]=16.473$; $p=0.002$; $\eta^2=0.62$), but only a-tDCS group reduced Rumination ($p=0.001$) and Helplessness ($p<0.001$) thoughts after treatment (interaction for Rumination: $F[1, 10]= 6.36$; $p=0.030$; $\eta^2=0.39$, and for Helplessness F[1,

10]=15.17; p=0.003; η^2=0.60). In addition, Helplessness scores after treatment were significantly lower than s-tDCS group (p=0.049).

Trait and state anxiety scores were analyzed separately. For the former, there was a main effect for Time, and an interaction between Time and Group, F(1, 10)=5.03; p=0.049; η^2=0.33, with no main effect of Group (as showed in Table 2). Pairwise analysis revealed only a-tDCS group had a reduction in the trait anxiety scores from pre to post-treatment (p=0.007). In relation to state anxiety, independently of the group, patients had reduced state anxiety after the treatment. The interaction term was marginally significant, F(1, 10)=5.03; p=0.066; η^2=0.30, and pairwise comparisons indicated the sham group had lower scores at the post-test when compared to pre-test (p=0.002). Finally, in relation to BDI-II scores, patients with FM had lower depression scores after the treatment, independent of the group. A marginally significant interaction was observed, F(1, 10)=4.44; p=0.061; η^2=0.31, but the pairwise comparisons only reinforced the changes from pre to post-test in the a-tDCS (p<0.001) and s-tDCS (p=0.016).

---- Insert Table 2 ----

Correlations between P300 area-under-the-curve (AUC) and pain perception, catastrophizing, anxiety and depression

To investigate if the P300 component was related to the other dependent variables in the post-intervention evaluation of the study, which could have a mediating role between the intervention and the electrophysiological data, Spearman correlations were calculated, considering the small sample size. Table 3 presents these correlation indices. As can be seen, the higher the pain scores in the VAS (pain) post-intervention, the higher the AUC in channels Cz, Pz and Oz pos-intervention. Figure 3 plots this relation. None of the other measures were associated with this EEG parameter.

---- Insert Table 3 ----

---- Insert Figure 3 ----

DISCUSSION

This study found that the P300 ERP amplitude, indexed by the AUC, was higher after sham-tDCS applied concurrently with a working memory training task as compared to the baseline, whereas similar effect was not observed in the active-tDCS stimulation. Although the physiological analysis in this study was exploratory and preliminary, these results suggest that tDCS produce a cumulative modulation effect state-dependent (Shahbabaie et al. 2014; Learmonth et al. 2015). Although these results were contrary to our previous hypothesis, they constitute a tool for exploring the physiological and therapeutic effect of the state-dependent stimulation. Also, they open a way to explore properties observed when one uses combined intervention, such as their entrainment, accumulation, and interaction with stimulus intensity. Regardless of the null effect of active tDCS combined with the cognitive training in the primary outcome, these interventions changed clinical indicators, as observed by significant reductions in the level pain scores, trait anxiety scores and improvement in rumination and helplessness dimensions of pain catastrophizing. One possible explanation for this result is that the effect of cognitive task induced maximum homeostatic stimuli via neurobiological systems, which are common targets for both interventions, and it induced a ceiling effect (Meiron and Lavidor 2013a). Also, the tDCS might prime the modulation of prefrontal circuitry, resulting in an enhanced capacity to tolerate and downregulate the emotional component of the pain experience (Shahbabaie et al. 2014). There is a possibility that active tDCS applied over the DLPFC modulates prefrontal circuitry and downregulates the emotional component of pain experience, at the same time that it alleviates pain via activation of the descending pain suppression system (Hadjipavlou et al. 2006)**.**

There are few studies focusing on chronic pain and P300 component. Some researchers have shown that attentional deficits in patients with chronic pain may explain the increase of P300 amplitude, considering that the deviant stimuli imposes

greater distraction (Veldhuijzen et al. 2006). Crombez, Van Damme, & Eccleston (2005) raised a hypothesis of *hypervigilance* that could account for some of the cognitive impairments of chronic pain patients. These authors argue that because hypervigilance is unintentional, pain processing can interfere with task stimuli processing, which may leave the patient more vulnerable to distractions, especially to new and rare stimuli. Although we did not have a healthy control group, our findings are in line with this view, in terms of the observed increase in P300 amplitude from pre to post-intervention for the sham-tDCS group. This conclusion is more likely to be the case if we consider another hypothesis, which assumes an imbalance of GABAergic and glutamatergic brain systems in FM leads to an over-functioning of the excitatory system (Mhalla et al. 2010). Therefore, for the sham group, having received only the cognitive training produced an increase in the electrophysiological response, as they already have a magnified excitatory response.

For the active-tDCS group, there was no difference from pre to post stimulation in the P300 amplitude. One possible explanation is that tDCS produced a "blocking effect", which prevented the neuronal networks associated with the P300 to discharge overly. It should be kept in mind that our findings suggest a higher P300 amplitude is associated with worse self-reported pain. Therefore, decreasing its amplitude (or not allowing it to increase) would be beneficial. In opposition to our findings, the study of Chan et al. (2012) reported an inverse correlation, although they measured the electrophysiological potentials following nociceptive stimuli to the foot, with no obvious relation to attentional or memory processes. In our auditory oddball paradigm, high order cognitive processes, such as attentional and mnemonic, are hypothesized to be associated with P300 characteristics, recruiting particular neuronal networks partially independent of the perceptual or motor systems (Verleger, Jaśkowski, and Wascher 2005). The present study is part of a larger research, focusing on pain and cognitive changes, thus we used the Dual n-back as a cognitive training known to increase fluid intelligence and working memory capacity (S. M. Jaeggi et al. 2008). Its impact on the frontal cortico-subcortical circuits should not be ignored. Thereby, an alternative

explanation would be an overload of these circuits after active-tDCS combined with a very difficult task. However, the combined treatment induced significant changes in pain and other clinical aspects, which is theoretically more plausible in the presence of top-down regulatory mechanisms, indicating higher or preserved attention.

Our results demonstrated a significant reduction in pain reports after eight days of treatment with anodal tDCS over the DLPFC compared to sham, similar to the findings of Valle et al., (2009). It could be the case that stimulation in DLPFC modulates affective-emotional aspects of pain, regulating, for example, the unpleasantness associated with pain (Lima and Fregni 2008). This conclusion is reinforced by the improvement of functional aspects related to the chronic feeling of pain in our study, such as catastrophizing thoughts and anxiety. Closely related to that is the role of the DLPFC as an inhibitory circuit able to intrinsically reduce pain sensation. A recent study by Martins et al. (2013) used an intervention with Transcranial Magnetic Stimulation (TMS) over the DLPFC and found a decrease of pain perception after one session of active TMS in healthy participants compared to sham. They argue that this area is associated with cortico-limbic inhibitory circuits and has a top-down mechanism that can actively reduce pain perception. Usually, the primary motor cortex (M1) area is the focus of most of the anodal stimulations for pain reduction purposes (Caumo et al. 2016b). Nevertheless, the DLPFC has also been a target for pain relief, as recent reviews inform (Seminowicz and Moayedi 2017). In the present study, we step further by showing the association with electrophysiological signals, which has implications for the understanding of mechanisms, as well as diagnosis and treatment of FM.

The DLPFC has an important role in cognitive and affective modulation of pain aspects. Our results are in line with this assumption, as we found reductions in catastrophizing thoughts and anxiety symptoms after active tDCS. Patients reduced pain catastrophizing scores by 74.21% and trait anxiety by 12.5% after active-tDCS. This effect has clinic and functional implications for the management of pain in FM

patients. Catastrophizing and anxiety have a close relation, conceptually (catastrophic thoughts were initially identified in patients with depression and anxiety) (Michael JL Sullivan 2009), as well as empirically via questionnaire assessments (Drahovzal, Stewart, and Sullivan 2006). So, it is expected an associated effect of active tDCS. Interestingly, only trait anxiety was reduced after active treatment. By definition, state anxiety is a transient emotion (Endler and Kocovski 2001), which could be modulated by many factors at the time of the assessment, differently from trait anxiety, which is related to a predisposition to respond to the environment (Endler and Kocovski 2001). Considering pain catastrophizing and trait anxiety are general behavioral tendencies, it could be suggested that our combined treatment had an effect on pain and threat-related personality characteristics. Nevertheless, it remains unclear if the reductions in pain catastrophizing thought and anxiety symptoms are consequences of the pain perception reduction itself.

We need to take into account the small sample size we obtained. Two participants had to be excluded due to poor signal quality at the signal acquisition phase, preventing from including their data into any analysis. Therefore, lack of power may have been a limitation here, especially when one considers the P300 amplitude. Also considering it is a pilot study, future investigations need to confirm this exploratory findings and clarify the role of P300 as an electrophysiological marker for therapeutic changes after transcranial electric stimulations. Other methodological limitations may be related to the lack of a FM control group, which prevents from generalizing the results and claiming findings are specific of this syndrome. Also, we need to consider that our study has also an exploratory nature and thus it is possible that it has increased type I error.

Final considerations

Chronic musculoskeletal pain is one of the main complaints of patients with FM. However, other symptoms are also associated with these complaints, including fatigue, sleep disorders, cognitive dysfunction, anxiety and depressive episodes (M.

H. Junior, Goldenfum, and Siena 2012; Tobias Schmidt-Wilcke and Clauw 2011). Applications and treatments with anodal tDCS over the DLPFC have been showed promising results in reducing levels of anxiety, depression, and catastrophism in other syndromes, such as major depression and bipolar disorder (D'Urso et al. 2013; Magdalena S. Volz, Farmer, and Siegmund 2016). Our study corroborates with those findings. Considering the innovation of the study, we conclude the use of EEG is a possible marker of pain perception and clinical improvement and can be considered of great interest for clinicians and researchers of the field.

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Declaration of interests

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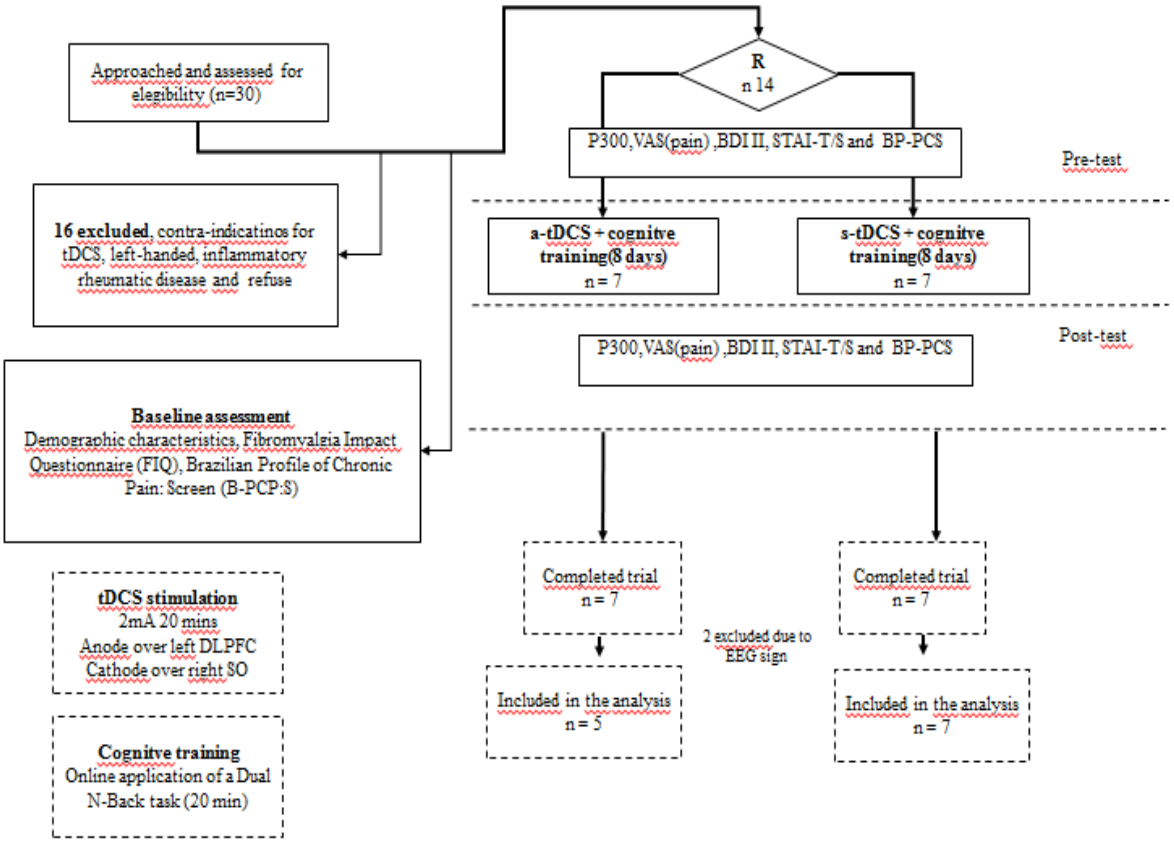

Figure 1. Flowchart of the study design.

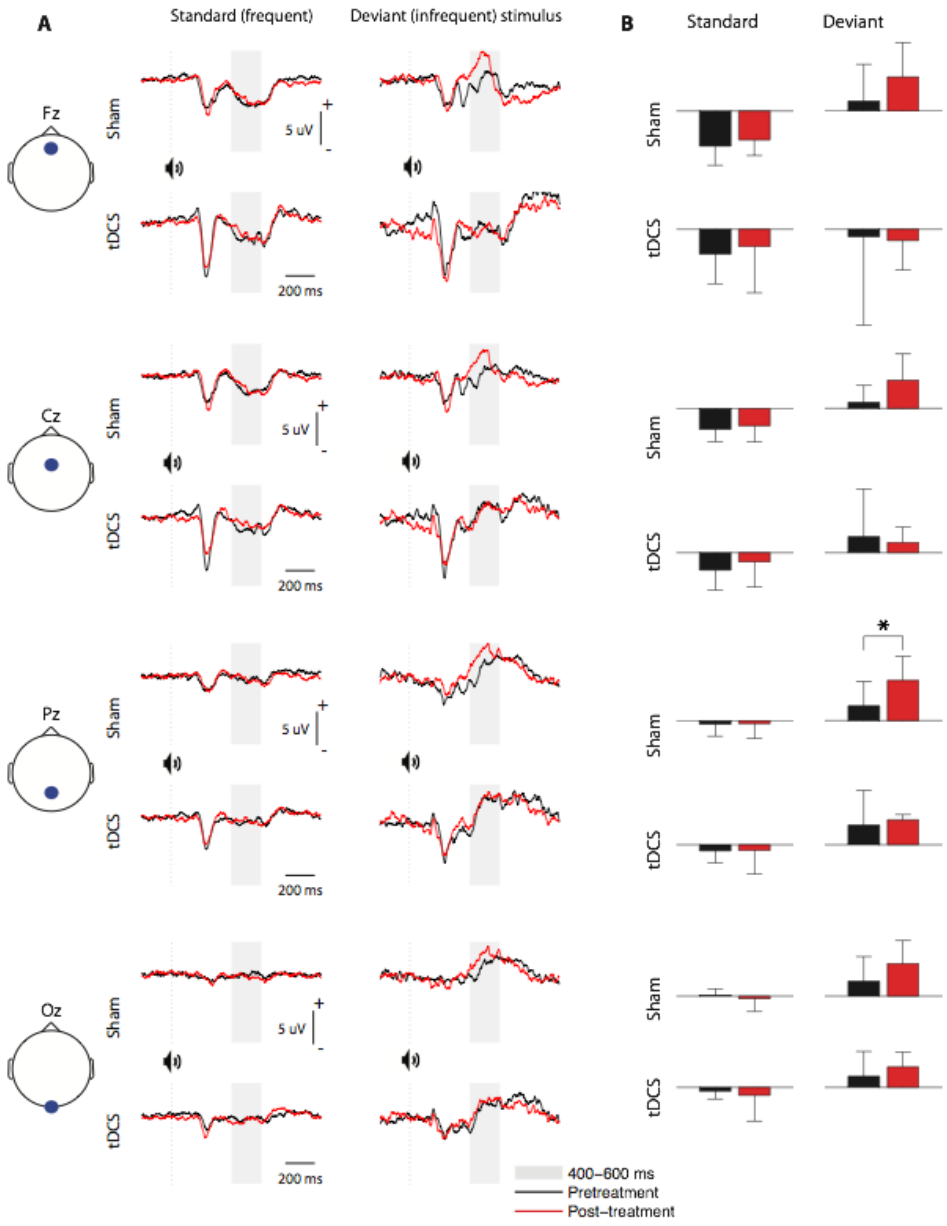

Figure 2. Grand averages comparing pre and post-treatment (line plots) for Fz-, Cz-, Pz- and Oz-derivations, as indicated by schematic representation figures to the left. P300 interval (400-600 ms) is highlighted by a gray background (A). Area Under Cuve (AUC) for the P300 interval (400-600 ms). AUC differs between pre and post-treatment for the Sham group and deviant stimulus (infrequent) in the Pz-

derivation (B). Each inset compares pre (black) and post- (red) treatment of the same group and derivation. Bar plots represent Mean ± Standard Deviation. (*) $p < 0.05$ (Paired Samples T test).

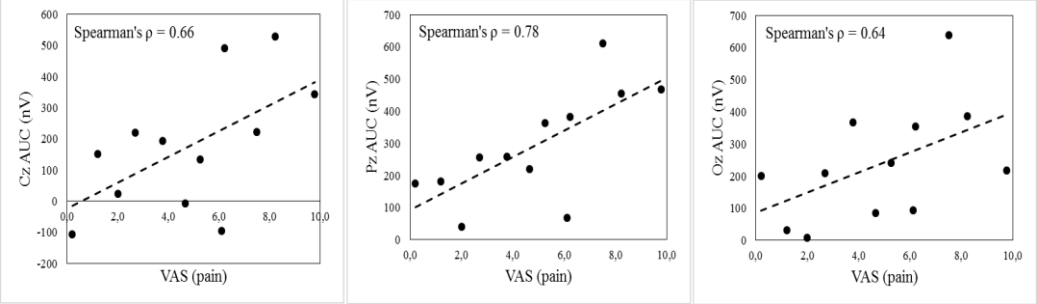

Figure 3. Correlations between electrophysiological measures for P300 component and pain perception. Dashed line is the best-fit linear approximation for the data. VAS (pain): pain visual-analogue scale; AUC: area-under-the-curve.

Table 1 Sociodemographic and health characteristics of the sample at baseline (n = 12)

	Active-tDCS (n=5) M (SD)	Sham-tDCS (n=7) M (SD)	*T*	*p*
Age	46.40 (12.4)	42.29 (9.1)	0.67	0.520
Years of education	10.20 (5.7)	11.43 (2.6)	-0.49	0.672
FIQ	67.79(15.2)	69.15(14.3)	-0.16	0.877
B-PCP:S	66.84 (12.3)	74.89 (19.1)	-0.79	0.446
BP-PCS	31.80 (10.6)	28.29 (19.3)	0.48	0.645
STAI-T	25.60 (5.8)	24.29 (7.6)	0.32	0.753
STAI-S	35.00 (4.7)	38.71 (8.6)	-0.87	0.405
BDI-II	26.40 (9.6)	29.86 (17.6)	-0.32	0.753
VAS (pain)	7.16 (0.9)	7.74 (1.9)	-0.61	0.554
Medication for pain n (%)*				
Anti-inflammatory	4 (80%)	3 (42.85%)		
Antidepressant	4 (80%)	7 (100%)		
Anticonvulsant	1 (20%)	2 (28.57%)		
Opioid	1 (20%)	2 (28.57%)		
Psychiatric comorbidities n (%)				
Major depressive episode	3 (60%)	5 (71.42%)		
Major depressive episode with Dysthymia	1 (20%)	1 (14.28%)		
Maniac-depressive disorder	1 (20%)	1 (14.28%)		
Panic Disorder without agoraphobia	-	1 (14.28%)		
Panic Disorder witht agoraphobia	1 (20%)	1 (14.28%)		
Social phobia	-	2 (28.57%)		
Obsessive compulsive disorder	-	1 (14.28%)		
Post-traumatic stress disorder	1 (20%)	2 (28.57%)		
Mood disorder	1 (20%)	1 (14.28%)		
Generalized anxiety disorder	1 (20%)	1 (14.25%)		

Note: FIQ = Fibromyalgia Impact Questionnaire; B-PCP:S = Brazilian Profile of Chronic Pain: Screen; BP-PCS = Brazilian Portuguese Pain Catastrophizing Scale; STAI-T/S = State-Trait Anxiety Inventory: Trace/State; BDI-II = Beck Depression Inventory; VAS (pain) = pain visual-analogue scale; Anti-inflammatory drugs include dipyrone, paracetamol and aceclofenac; Antidepressants include fluoxetine and nortriptyline; Anticonvulsants include gabapentin, pregabalin and duloxetine; Opioid include codeine and Tylex®; Psychiatric comorbidities = frequency of comorbidities assessed through the M.I.N.I. International Neuropsychiatric Interview. * Some patients were using more than one type of drug.

Table 2.Effects of treatment on pain perception, catastrophizing, anxiety and depression(sham-tDCS n = 7; active-tDCS n = 5)

		Pre-treatment	Post-treatment	MD from Pre to post	Main effect for Time		Main effect for Group	
		M (SE)	M (SE)	%	p	η^2	P	η^2
Pain Visual-Analogue Scale – VAS (pain)	Sham	7.74 (0.6)	6.44 (0.8)	16.78	0.004	0.59	0.021	0.43
	Active	7.16 (0.7)	2.51 (1.0)	65.03				
Pain Catastrophizing Scale – BP-PCS (total)	Sham	27.71 (6.1)	21.71 (4.8)	21.65	0.001	0.75	0.571	-
	Active	31.8 (7.2)	8.2 (5.6)	74.21				
State-Trait Anxiety Inventory – STAI (State)	Sham	38.71 (2.7)	30.14 (2.9)	22.14	0.006	0.55	0.900	-
	Active	35.00 (3.3)	32.80 (3.4)	6.29				
State-Trait Anxiety Inventory – STAI (Trait)	Sham	24.29 (2.6)	23.86 (2.5)	0.02	0.015	0.46	0.986	-
	Active	25.60 (3.1)	22.40 (3.0)	12.5				
Beck Depression Inventory – BDI-II	Sham	29.86 (5.7)	21.29 (4.0)	28.70	0.001	0.77	0.278	-
	Active	26.40 (6.7)	8.20 (4.7)	68.94				

Notes: MD (%) = percentage of mean difference between pre and post-intervention. p-value based on ANOVAs 2 x 2.

Table 3 .Correlations between P300 area-under-the-curve (AUC) measures for the deviant stimulus and pain perception, catastrophizing, anxiety and depression scores. All measures are post-intervention (n=12)

	Cz	Pz	Oz	Fz
Pain Visual-Analogue Scale -VAS (pain)	0.66*	0.78*	0.64*	0.49
Pain Catastrophizing Scale – BP-PCS	-0.17	0.11	0.26	0.05
State-Trait Anxiety Inventory – STAI (State)	-0.20	0.09	0.17	-0.38
State-Trait Anxiety Inventory – STAI (Trait)	0.14	0.32	0.25	0.01
Beck Depression Inventory – BDI-II	-0.07	0.27	0.22	0.12

Notes: 95% confidence intervals for the three significant correlations were: Cz x VAS (pain) = [0.14 - 0.89]; Pz x VAS (pain) = [0.38 - 0.93]; Oz x VAS (pain) = [0.11 - 0.89].

* $p < 0.05$, based on Spearman correlations.

ARTIGO 2 ORIGINAL EM INGLÊS

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Transcranial direct current stimulation effect combined with memory training on the cognitive in performance is neuroplasticity dependent in fibromyalgia: a randomized clinical trial

Authors

Vinicius Santos[1,2], Maxciel Zortea[1,2], Rael Lopes[2,3], Cátia Cilene dos Santos Naziazeno[2], Julia Saldanha[1,2], Sandra Carvalho[4,5], Jorge Leite[4,5], Iraci Lucena da Silva Torres[6,7], Andressa Souza [2,8], Prisla Ücker Calvetti[2], Felipe Fregni[5], Wolnei Caumo[1,2,9]*

Affiliations

1 Post-graduation Program in Medicine: Medical Sciences, Federal University of Rio Grande do Sul (UFRGS)

2 Laboratory of Pain & Neuromodulation, Clinical Hospital of Porto Alegre (HCPA)

3 Graduation Program in Psychology, UFRGS

4 Laboratory of Neurophysiology, University of Minho

5 Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School

6 Post-Graduation Program in Biological Sciences: Physiology, UFRGS

7 Pharmacology of Pain and Neuromodulation: Pre-clinical Investigations, UFRGS

8 Post-Graduation Program in Health and Human Development, La Salle University

9 Pain and Palliative Care Service at Hospital de Clínicas de Porto Alegre (HCPA),

*Correspondence: Wolnei Caumo MD, Ph.D., Laboratory of Pain & Neuromodulation, School of Medicine at UFRGS, Professor of Pain and Anesthesia in Surgery Department, Hospital de Clínicas de Porto Alegre, Street Ramiro Barcelos, Porto Alegre, RS, 90035-003, Brazil. wcaumo@hcpa.edu.br

Abstract

Cognitive dysfunction in fibromyalgia has been reported, especially memory. Anodal transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) has been effective in enhancing this function. We tested the effects of eight sessions of tDCS and cognitive training on immediate and delayed memory, verbal fluency and working memory and its association with brain-derived neurotrophic factor (BDNF) levels. Forty females with fibromyalgia were randomized to receive eight sessions of active or sham tDCS. Anodal stimulation (2mA, 20mins) was applied over the DLPFC and online combined with a working memory training (WMT). Pre and post-treatment neurocognitive tests were administered. Data analysis on deltas considering years of study and BDNF as covariates, indicated active-tDCS + WMT significantly increased immediate memory indexed by Rey Auditory Verbal Learning Test score when compared to sham. This effect was dependent on the basal BDNF levels. In addition, the model showed active stimulation increased orthographic and semantic verbal fluency scores (with Controlled Word Association Test) and short-term memory (with Forward Digit Span). The combination of both techniques seemed to produce effects on specific cognitive functions related to short-term and long-term episodic memory and executive functions, which has clinical relevance for top-down treatment approaches in FM.

Introduction

Fibromyalgia (FM) is a chronic pain condition with 2 to 5% prevalence in general population, being more frequent in women [1,2]. It comprises widespread chronic pain, fatigue, depression, anxiety, impaired cognition, disrupted sleep and other somatic complaints[3]. In general, the most frequent complains related to cognitive aspects include a poorer recall, forgetfulness and difficulty with concentration and the ability to stay attentive. Despite the pathophysiology of FM is not completely understood, an imbalance in the excitatory/inhibitory central nervous system (CNS) has being considered[4].This imbalance comprises a phenomenon of central sensitization syndrome (CCS). The CSS is an amplification of neural signaling within the central nervous system associated with hypersensitivity to pain [5]. In fact, the CCS includes psychological distress, sleep disturbance, fatigue, allodynia and hyperalgesia [6]. Its severity has been positively correlated with selective and sustained attention and less bottom-up sensitization. The impaired sustained attention was associated positively with deep-tissue hyperalgesia and deficient conditioned pain modulation [7]. Furthermore, a higher score in the Central Sensitization Inventory (CSI) in chronic pain was positively correlated with level of dysfunction in the descending pain modulatory system, as well with higher levels of serum brain-derived neurotrophic factor (BDNF)[8].

Although multiple mechanisms of synaptic plasticity are involved in the CCS, the BDNF has a central role in strengthening glutamatergic synapses, while it weakens GABAergic synapses. The increase of this neurotrophic factor inverts the polarity of GABA currents in dorsal horn neurons[9]. Also, convergent pieces of evidence suggest that BDNF and its neurotrophic receptor tyrosine kinase (TrkB) are essential to maintain the network activity in the prefrontal cortex (PFC) [10]. Also, PFC neurons have intrinsic properties that allow them to initiate, maintain and terminate sustained nonadapting firing. At the same time, it has inhibitory synaptic network control wielded by GABAergic interneurons to regulate “reverberant” neuronal firing. The PFC is provided of extensive dopaminergic projections and other inputs for tuning the state of a network sensible to detect triggers and to initiating activity. Due to the fact this region is responsible for many functions, it has been extensively used as a target for

cognitive enhancement approaches via transcranial direct current stimulation (tDCS) [11,12,13,14]

Accordingly, the tDCS applied on DLPFC improved the working memory (WM) learning curves in healthy adults, who trained on a spatial or verbal adaptive n-Back Task [15]. Similarly, two studies with healthy subjects showed that the anodal stimulation on the left dorsolateral prefrontal cortex (DLPFC) improved the WM performance [16] and the number of correct responses during a 3-Back Task while cathodal stimulation over the same brain area did not produce any change [12]. More robust effects have been reported with the combination of stimulation and a cognitive task [11].One of the most used tests for working memory training is the n-Back Task. found that the tDCS associated with a WM task produced a better performance in another equivalent task applied at a later time. Additionally, recently our research group showed an additive effect of tDCS on DLPFC combined with a task that induces the activation of inhibitory control pathways in FM[13] The study also shows that the combination of interventions improved performance of attention networks associated with an increase in pain threshold. We hypothesize tDCS may modulate prefrontal circuits, enhancing tolerance and minimizing the emotional component of pain experience. However, there is a gap in terms of exploring baseline neuroplasticity characteristics that could be related to tDCS's effect on the DLPFC combined with a WM training. Moreover, multiples sessions of this combined treatment may have advantages over a singular session.

In this explanatory trial, we aimed to test if a treatment with active-tDCS combined with a working memory training (WMT) would increase immediate and delayed memory scores, as well as working memory, verbal fluency and divided attention capacity, when compared to sham-tDCS + WMT. We also aimed to test if the treatment effect is dependent on the serum BDNF levels. We hypothesize that neuroplasticity state measured by BDNF have a modulatory role for the effect of tDCS in cognitive performance. In other words, the higher the BDNF serum levels, the larger the anodic tDCS effects on memory and the other cognitive functions.

Results

Demographic and clinical characteristics

Thirty-nine patients completed the study (one patient had dropout from the a-tDCS group due to a leg injury). Clinical and demographic characteristics of the sample according to the intervention group were compared and are shown in Table 1. Data indicates baseline features were equivalent between groups.

---- Insert Table 1 ----

Effect of treatment on immediate and delayed memory (primary outcomes), verbal fluency and working memory (secondary outcomes) measures

Immediate and delayed recall of episodic memory assessed with the Rey Auditory-Verbal Learning Test (RAVLT), orthographic and semantic category verbal fluency assessed with the Controlled Oral Word Association Test (COWAT), WM via the Paced Auditory Serial Addiction Test (PASAT) and short-term and WM assessed with the Forward (FDS) and Backward Digit Span (BDS) were compared between treatment groups. To avoid baseline differences, we used deltas (Δ) based on the mean differences calculation [(post-test – pre-test)/pre-test]. Independent samples *t*-tests were applied and P values are presented in Table 2. No significant differences were detected for any of these cognitive scores.

---- Insert Table 2 ----

Effect of treatment on immediate and delayed memory (primary outcomes) and verbal fluency, WM and short-term memory (secondary outcomes) measures considering BDNF levels and years of study

Firstly, due to many factors may influence serum BDNF level, we have adjusted its value in a linear regression model with stepwise method, which included age, number of medications and frequency of medication use, presence of psychiatric diagnosis and baseline depressive symptoms (using the BDI-II) and functional incapacity (using the B-PCP:S). The final model showed presence of psychiatric diagnosis ($B=-3.64$; $P<0.007$) and number of medications ($B=9.30$; $P<0.019$) significantly explained BDNF levels ($R^2=0.22$). Thus, the adjusted values of BDNF were used for the following analyses. We also included years of study as a covariate because raw scores were used (instead of standardized scores), which may be affected by educational level.

In order to test the influence of BDNF levels as a modulator for the treatment's

effect, we used a multivariate analysis of covariance (MANCOVA) for the cognitive scores as dependent variables. We tested main effects for treatment (active-tDCS + WM training and sham-tDCS + WM training) and years of study, and the interaction between treatment and BDNF adjusted index. The MANCOVA revealed that treatment had a significant influence in the model [Wilk's Lambda=0.488; F(9,24)=2.80; P =0.021; η^2=0.512], as well as the interaction term treatment*BDNF adjusted index [Wilk's Lambda=0.264; F(9, 24)=2.52; P=0.005; η^2=0.486]. Years of study was non-significant (P=0.069). The influence of the factor treatment and covariates (years of study and BDNF adjusted index) together for each cognitive score is presented in Table 3. Accordingly, the model was significant for verbal fluency measures (COWAT orthographic and semantic), immediate recall (RAVLT A1_A5) and short-term memory (with the FDS score), considering Δs.

---- Insert Table 3 ----

In Table 4, we investigated in depth how group factor and covariates are associated with the cognitive scores, using univariate linear regression analyses as parameters estimates. As can be seen, belonging to the a-tDCS + WM training group was associated with an increased change in orthographic verbal fluency and immediate recall, independently of the educational and the BDNF level. Year of study was negatively associated with changes in orthographic verbal fluency score. Moreover, BDNF adjusted index correlated negatively with changes in immediate memory recall for the active tDCS and positively with the sham-tDCS group, while it correlated negatively with changes in FDS for the sham tDCS group only.

---- Insert Table 4 ----

Associations between BDNF adjusted index and episodic memory scores

For exploratory purposes, Pearson correlations between BDNF adjusted index level and immediate memory recall scores were applied for each treatment group. Figure 1 depicts this interaction, where the correlation was only significant for the active tDCS group.

---- Insert Figure 1--------

Discussion

The present study aimed to test if a treatment tDCS coupled with a WM cognitive task would have additive effects that benefit memory, attention and executive functions for patients with FM when compared to cognitive training alone. In fact, data suggests this was the case regarding the higher increase in immediate memory capacity and verbal fluency after active treatment compared to sham. Interestingly, the effects over short-term memory was partially dependent on baseline levels of serum BDNF, considering that this neurotrophic factor was associated with changes in RAVLT A1_A5 score only for the active tDCS and with changes in short-term digit span memory just for the placebo group. BDNF was not correlated with verbal fluency. Also, years of study did not influence significantly the effect of interventions in the multivariate model.

Our findings are congruent with other studies that found a better effect of tDCS combined with a cognitive training on WM and other cognitive performances[17,18,19]. Recent studies have showed that tDCS combined with a cognitive training task is more efficient to improve the pain threshold in FM compared to sham stimulation[20,21] . Particularly, in Silva et al. (2017)'s [20] study, anodal tDCS applied on the DLPFC coupled with a training task for inhibitory control (a Go No-Go) improved the executive and orienting attentional networks performance after a single session. In addition, previous researchers have found that for healthy volunteers the DLPFC anodal stimulation combined with an adapted verbal n-Back Task for training improved recall performance of word pairs [22,23,24].In healthy individuals, anodal tDCS over Broca's region (left hemisphere) improved the phonemic and semantic fluency, however, when they stimulated the right homologue hemisphere they have not found a similar effect [25]. It is possible that the impact of treatment observed in our study may also be associated with the lateralization of verbal material processing. This hypothesis is plausible since our sample comprises right-hand subjects only, which have mostly formal aspects of language being processed by the left-hemisphere [24]. Considering this rationale, the stimulus modality (verbal and visual) of the WM training task may interacts in a particular way with the site of the stimulation (left or right DLPFC). For example, the tDCS task-congruent intervention had a

stronger and long-lasting enhancement of cognitive outcomes[24]. However, the effect reported by Meiron and Lavidor[24] was observed in healthy subjects. Our study comprised only verbal tasks for cognitive assessment. So, further studies would be necessary to test the hemisphere lateralization hypothesis for memory and executive functions in FM using similar tasks with visual stimuli.

Despite the positive findings regarding cognitive processes, some have found null results. Using a similar methodology of the present study, Elmasry, Loo, and Martin (2015) [26]concluded that ten sessions of online tDCS combined with a cognitive training (Dual n-Back Task) were not able to change neither WM nor executive function measures significantly. However, active tDCS improved the Dual n-Back discrimination ability (d') [26] (26). This finding is quite similar to our univariate data, where no significant difference was found for the differences from pre to post-treatment assessments between groups. So, it is possible to argue that baseline factors associated with the central neurophysiological state are likely to influence this sort of treatment. This argument is supported by a growing body of evidence suggesting that tDCS produces a state-dependent impact when considering cognitive outcomes [27]. Based on this assumption, in our analysis, we found that a factor closely related to neuroplasticity state (BDNF) have influenced the effectiveness of treatment.

Baseline BDNF had a relevant effect on short-term memory indices. The RAVLT A1_A5, which assess the cumulative short storage capacity after a word list is presented five times to the patient, is a renowned instrument for episodic memory assessment [28]. Our data suggests tDCS induced a higher increase in this function from pre to post-intervention compared to sham. However, this effect was only significant when the interaction term, considering BDNF levels, is included. When we observe Table 2 *t*-tests, changes due to active or sham treatment have roughly the same magnitude. But when the interaction between Treatment and BDNF is considered (Table 4), it becomes clearer this neurotrophine had an opposite effect over these changes for each group. Figure 3 illustrates that higher levels of BDNF at baseline assessment were associated with smaller changes from pre to post-intervention, while for sham-tDCS changes the effect was inverse.

We expected that higher BDNF serum level would be related with better performance on memory tests, and this apparent discrepancy from the literature may be related to the clinical population of FM. There is some literature indicating a positive relation between BDNF level with verbal memory and learning capacity in healthy subjects[29,30]. Moreover, there has evidence that the volume of the left hippocampus mediates the association between BDNF and spatial memory [31]. However, all these previous findings were revealed in healthy individuals. It should be considered FM is known as a syndrome that comprises a central sensitization process associated with higher levels of BDNF compared to controls [8]. Simultaneously, higher levels of BDNF have been related to either higher pain scores and disability in FM [32]. Therefore, especially for this population, and perhaps other similar pain syndromes, higher levels of this neurotrophin may impact negatively on the tDCS effect, leading to smaller changes in cognitive outcomes. Although BDNF is said to be responsible for synaptic plasticity, neuronal connectivity, and dendritic arborization, it may also produce high excitability state (hyperexcitability), which in turn induces vulnerability to stressful events and excitotoxicity to the system. This effect occurs in the hippocampus region, which is central to memory processes, such as consolidation [33]. BDNF is also widespread in central and peripheral nervous system, and present in many neural systems [34] and its concentration may affect each neural network differently. Considering that, it seems plausible to conclude that in patients with FM, high levels of BDNF are not only associated with pain increase and maintenance but may also be associated with an adverse neurophysiological environment for therapeutic approaches. Another measure of immediate recall evaluated here is the FDS. The BDNF was inversely correlated with the change in this test only for the sham group. Considering that no simple effect for treatment was found, we deductively concluded that a higher BDNF level at baseline could reduce the changes from pre to post-intervention. However, it remains unclear yet why this relationship was observed only for the sham group. First point to be raised concerns the differences between tasks. Despite evaluating similar recall abilities in both cases, RAVLT involves meaningful stimuli (words), learning curves (by repeating the stimuli), a free-order recall method and complex associative strategies, whereas FDS is a auditory test that classically measures phonological components of short-term

memory[35] This idea may help to understand the different role of BDNF for the RAVLT A1_A5 score for the sham group, which had a positive relation. When we consider the associations between BDNF and cognitive measures for the sham group, another explanation could be related to the fact that these patients did received an intervention, that is the cognitive training. Besides, it should be considered that serum BDNF accounts only partially for the central nervous system concentration of the neurotrophin [36,37] .

We have also found effects of our treatment in other cognitive systems, and that was independent of BDNF levels. The COWAT is a measure of verbal fluency and covers a wide range of cognitive functions, including verbal ability and executive control [38]. Some authors reviewed cognitive processes evaluated with verbal fluency tasks. They suggest category fluency tasks, such as the semantic COWAT we used, reflect better the verbal ability, while letter fluency, on which our orthographic test is based, reveals more executive aspects [39]. They discuss the semantic verbal fluency is associated with more anterior-ventrally localized networks of the frontal cortex, while letter fluency is located more posterior-dorsally. Thus, it is plausible to consider that a DLPC anodal stimulation combined with a WM task that equally recruits the DLPFC area (apart from other regions, see Constantinidis and Klingberg 2016),[40] would have a more salient impact over executive functions, than language-related functions. Patients with FM are known to have executive attention and WM difficulties[41] what may explain why we have only found effects of our treatment for orthographic verbal fluency. On the other hand, the diffuse effect of tDCS should not be neglected, which means DLPFC stimulations may increase excitability in various regions of the frontal lobe. Because fluency tasks have time restrictions, higher general processing speed associated with increased excitability would benefit the active group.

In overall, the effect of tDCS observed in the current study may suggest that the active-tDCS combined with a WMT induced a greater inhibitory control over the neural networks involved in the cognitive processing. This hypothesis might be plausibility if we considered that the FM is the prototypical syndrome of CSS [42], which encompasses an impaired function of neurons and circuits in

nociceptive pathways, with an increase in either membrane excitability and synaptic efficacy, and reduced inhibition [43]. In fact, the neurobiological mechanism of FM [29] involves an imbalance between excitatory and inhibitory systems, by a dysfunction in the GABAergic and glutamatergic pathways [44]. In this sense, therapeutic use of active-tDCS may induce long-lasting after-effects. It was found long-term potentiation and depression and involvement of NMDA-receptor channels related to the tDCS effects, as well as domaminergic and cholinergic systems [45]. The stimulation is able to change the neuronal calcium influx, protein synthesis, blood flow, the level of brain oxygenation. The results can, however, differ between healthy and individuals with some central nervous system dysfunction , such as FM patients [46].

Also, the present study represents progress to the question of non-invasive treatment in FM patients about transfer effects. As we found performance enhancements in functions other than WM tasks, transfer effects to other cognitive processes are plausible to be considered. RAVLT, COWAT, and FDS measure functions other than WM. However, this idea should be regarded cautiously, because we have not found effects for PASAT or backward digit span scores, which measure different aspects of WM [47,41]. Another limitation of our study was that the Dual n-Back Task used for training purposes is a highly demanding task, especially for older patients not familiarized with the computer. Even considering the adaptive version, starting at 1-back and increasing according to accuracy performance, none of the patients was able to achieve more than 2-back WM load. This task may have exhausted the limits of WM and cognitive processing, not allowing performance gains. These inferences are also limited due to the lack of a healthy control group (it is not possible to know if treatment effects are exclusive for FM patients) and a sham cognitive training (other types of cognitive intervention focusing on different functions could have similar results). Also, we had a sample of women, which limits our conclusions to this gender, although it should be highlighted that FM has a higher prevalence in females [1].

Conclusion

Overall, our results highlight two important conclusions. First, eight session of

anodal tDCS over the left DLPFC combined with WM training has a modulatory effect on short-term memory capacity and verbal fluency after active treatment compared to sham stimulation. The secondary effect BDNF had a relevant effect in our model when we consider short-term memory indices. Also, these findings suggest that the effects of tDCS combined with a WM training relation to transfer effects to other cognitive processes are plausible to be considered.

Methods

Design, overview, setting and participants

The methods and results sections are reported according to the CONSORT guidelines. All subjects provided written informed consent before participating in this randomized, double blind, sham-controlled, two arm parallel design with allocation ratio of 1:1. The study was approved by the Research Ethics Committee at Hospital de Clínicas de Porto Alegre (HCPA) (Institutional Review Board IRB 140369). The current controlled trial is registered at Clinical Trial (No. NCT02880917).

We recruited 40 adultsaged between 18 and 65 years-old outpatients of the HCPA were invited via advertisement to participate. Sample size was calculated based on previous with 0.25 effect size compare the effect of active tDCS and sham with alpha level of 0.05 and 80% power. FM was diagnosed according to American College of Rheumatology criteria [48]. Subjects were required to have a score at least 50mm on the 0-100mm visual analogue scale for pain (VAS, which 0 means “no pain” and 100 means “worst possible pain”) during most of the days over the last three months [49]. Subjects were allowed to remain on analgesic medications, including drugs for which they were refractory, and these medications could not be adjusted during the study. Major depressive disorders were accepted as secondary to FM. Subjects with history of substance abuse or evidence of other pain-related disorder were excluded. Females pregnant, in breast-feeding or with a history of neurologic or oncologic disease, ischemic heart disease, kidney or hepatic insufficient were also excluded.

Intervention: tDCS stimulation and cognitive training Dual N-back task.

For each of the 8 treatment sessions, a tDCS (TCT, Hong Kong, China) combined with a cognitive training task intervention was applied. tDCS was delivered using the anode electrode positioned over the left DLPFC (F3 according to the 10–20 system for EEG) and the cathode electrode at right supraorbital region (Fp2). The electrodes were placed into–35 cm2 sponges soaked in saline solution for better current conductivity. Rubber bandages were used to hold the electrodes in place for the duration of stimulation. the active-tDCS condition, a constant current of 2mA was applied for 20 min. For sham stimulation the electrodes were placed in the same position, but the stimulator was turned off after a ramp-up of 30s of stimulation [50]. To evaluate the safety of tDCS, we used the Systematic Assessment for Treatment with tDCS questionnaire based on previously reported adverse events.

The cognitive training consisted of an online application of a Dual N-Back task [51] ,). A laptop (15 inches screen, distance of ~60cm ahead) with software E-Prime 2.0 Standard presented two types of stimuli, simultaneously. Visual stimuli were green squares presented in eight different positions, and auditory stimuli consisted of the letters D, P, Q, G, V, C, T and K presented binaurally via headphones. Patients had to decide for each trial if the stimuli were the same as n-trials before (memory workload), by pressing the keyboard "A" button for visual and "L" for auditory (and do not press any button when none of the alternatives apply). The task had 20 blocks with 20 trials each, of which 10 were "no target", 4 were "visual target only", 4 "auditory target only" and 2 "dual target", and had duration of about 25 minutes. The memory workload information was presented in the beginning of each block, and a feedback (percentage of correct responses) was presented in the end of each block. Because of the adaptive nature of the cognitive training, workload level increased when the previous block had 90% correct responses or higher and decreased when less than 70% was achieved. (Figure 2).

---- Insert Figure 2--------

Randomization.

Before the recruitment phase, the randomization was generated using a computer system by researchers who did not administer the intervention. They put the

sequence in separately opaque sealed envelopes. The simple randomization method was applied, with patients assigned to the one of the two groups with a rate of 1:1.

Blinding. Envelopes containing the patients' protocol numbers were opened by an auxiliary researcher, who also programmed the tDCS device for active or sham stimulation .Allocation concealment was assured by intervention being assigned only after enrollment..Furthermore, to assess whether blinding was effective, at the end of the experiment subjects were asked to guess whether they had received a-tDCS or sham and to rate their confidence level using a 5-point Likert scale (from no confidence at all to completely confident).

Baseline instruments and assessments (**clinical)** All tests used have been validated for the Brazilian population. At the baseline, the instruments used were: Pittsburgh Sleep Quality Index[52] to assess the sleep quality; Beck Depression Inventory-II (BDI-II)[53], for the assessment of depressive symptoms; The Brazilian validated version of the Fibromyalgia Impact Questionnaire (FIQ)[54], to assess quality of life of FM patients; the Brazilian Portuguese version of the Pain Catastrophizing Scale (BP-PCS)[55], for the catastrophic thinking, State-Trait Anxiety Inventory (STAI) for the assessment of Anxiety [56]; Brazilian Profile of Chronic Pain: Screen (B-PCP:S)[57] to characterize functional limitations related to severity of pain, emotional stress and pain interference in life; Pain level was assessed with a visual-analogue scale (VAS); Mini-International Neuropsychiatric Interview (M.I.N.I.) to detect psychiatric disorders60; Medical comorbidities and demographic data were assessed using a standardized questionnaire. Heat pain threshold; Heat pain tolerance ;BDNF marker of plasticity

Outcomes: The primary outcome was the effects of the intervention (a-tDCS + WM training vs. s-tDCS + WM training) on the performance of the Rey Auditory-Verbal Learning Test (RAVLT). **The second outcome** was performance of the Paced Auditory Serial Addiction Test (PASAT)[58] , Controlled Oral Word Association Test (COWAT), Forward Digit Span (FDS), Backward Digit Span(BDS) and serum level of BDNF.

The Rey Auditory-Verbal Learning Test(primary outcome): RAVLT is a test for the evaluation of episodic memory, with components related to short- and long-term memory and recognition. The 15 words of the test were read slowly, and patients were asked to repeat them after reading, regardless of the order (A1). The same procedure was repeated in the following steps A2, A3, A4 and A5. A second list of words (B1), distracting, was then applied, in which the patient was asked to evoke only the words from this list. After we asked the patients to speak the words of the first list, but now without presenting them (A6). About 20 to 30 minutes after such a step, patients again had to recall the words from the first list (A7). Finally, a list of 50 words was presented then the patient should judge whether the word belonged or not to the first list [28].,

Controlled Oral Word Association Test (COWAT)(second outcomes): Involves word fluency in two categories: orthographic and semantic. In the orthographic category, patients were instructed to speak as many words as possible for 1 minute, starting with the letters F, A and S. In the semantic category, subjects were instructed to speak the highest number of words for the class of animals for 1 minute. This test is specifically used to assess verbal fluency [59].

Forward and backward digit span(second outcomes): The FDS consists of eight series for direct order and seven for reverse order, with a gradual increase of number of digits in each series. The FDS is applied first, followed by the BDS, which was administered independently if the examinee fails completed in the Forward order [47]. The maximum score in the subtest is 30 points, and the maximum gross result in the direct order is 16 points in reverse order is 14 points.

Paced Auditory Serial Addiction Test (PASAT) (second outcomes): This test is specifically used to evaluate sustained and divided attention, working memory and processing speed.In this test, the stimuli are numbers from one to nine, presented in random and predetermined sequence. The task was to perform the sum of the numbers presented, two by two, disregarding the result of the calculation. The test was started by displaying the numerical sequence every 3 seconds. It displays the version A and B. Specifically this project we use the

version in the first consultation and B in the second to prevent habituation. The score will be determined by the number of correct answers, with the maximum score in each part being 60 points**.**

Serum levels of brain-derived neurotrophic factor(BDNF) (second outcomes): Blood samples were collected at baseline and by the end of treatment. Serum BDNF was determined by the Enzyme-Linked Immunoabsorbent Assay (ELISA) using a ChemiKine BDNF Sandwich ELISA Kit, CYT306 (Chemicon/Millipore, Billerica,MA, USA). The lower detection limit of the kit is 7.8 pg/mL for BDNF.

General Procedure. Participants initially volunteered by signing the consent form. Following this, they responded to the baseline assessments and were checked for necessary exclusion criteria. Then, they were randomly allocated to one of the experimental groups, either receiving sham s or active stimulation .Measures of working memory through the Dual N-back were obtained during the tDCS. Blinding was also incorporated and side effects following tDCS were recorded.. Figure 3 presents the flowchart of the study.

---- Insert Figure 3--------

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Author Contributions

V.S.S., M.Z. and W.C. conceived and designed the study, participated in the sequence alignment, performed the statistical analysis, and coordinated and

drafted the manuscript; R.L. and C.C.S.N. collected and registered the data; J.S. helped in the data analysis; S.C. and J.L helped conceive and design the study and drafted the manuscript; I.L.S.T., P.U.C., F.F. conceived the study, participated in its design and coordinated and reviewed the manuscript; A.S. helped with the blood laboratorial analyses and reviewed the manuscript.

Declaration of interests

We affirm that we did not have support from any other organization for the submitted work.

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Figure 1. Scatter plots indicating the Pearson (r) correlations between changes in episodic memory immediate recall assess with the Rey Auditory Verbal Learning Test (RALVT) and changes in BDNF adjusted index.

Figure 2. The Dual n-Back Task scheme.

Figure 3. Flowchart showing recruitment and progress through the study. Controlled Word Association Test (Cowat) ; Rey Auditory Verbal Learning Test (RAVLT); Paced Auditory Serial Addiction Test (PASAT); Brain-derived neurotrophic factor(BDNF); Heat pain threshold (HPTh) and tolerance (HPTo).

Table 1. Demographic and Clinical characteristics (n=40).

	Active-tDCS (n=20)	**Sham-tDCS (n=20)**	***p***
Demographic			
Age (years)	49.15 (8.43)	50.05 (11.19)	0.77
Body weight (Kg)	28.47 (4.18)	27.73(5.20)	0.62
Years of study	10.60(4.36)	10.75(2.86)	0.89
Clinical			
Clinical comorbidity (yes /%)	11(55)	15 (75)	0.18
Hypertension (n/%)	6 (30)	7(35)	
Hypothyroidism (n/%)	1 (5)	3(15)	
Asthma (n/%)	1 (5)	2(10)	
Gastritis (n/%)	2 (10)	0(0)	
Diabetes(n/%)	1 (5)	0(0)	
Other (n/%)	0(0)	3(15)	
Beck Depression Inventory – BDI – II	24(9.84)	28(12.96)	0.22
Brazilian Portuguese version of the Pain Catastrophizing Scale (BP-PCS)	30.65(11.89)	31.30(14.91)	0.88
Fibromyalgia Impact questionnaire(FIQ)	63.43(18.29)	66.16(15.31)	0.61
State-Trait Anxiety Inventory – STAI			
STAI – State	33.45(6.31)	34.30(7.61)	0.70
STAI – Trait	25.25(4.64)	26.85(6.17)	0.36
Brazilian Profile of Chronic Pain: Screening (B-PCP:S**)**	69.01(14.15)	70.57(16.10)	0.76
Pittsburgh Sleep Quality Index – PSQI	12.05(4.34)	11.60(4.07)	0.73
Alcohol Consumption (yes/%)	8(40)	6(30)	0.50
Smoking (yes/%)	6(30)	6(30)	1
Biochemical			
Serum BDNF	28.70(12.43)	30.41(12.48)	0.67
Measures of pain			
Pain score on VAS (0 to100 cm)	7.30(1.66)	7.21(1.66)	0.86
QST: Heat Pain threshold	33.13(1.13)	33.19(1.05)	0.85
QST: Pain tolerance	44.29(3.19)	44(3.0)	0.76
Psychiatric disorder according to the MINI *			
Major depressive episode	11(55%)	16(80%)	0.91

Major depressive episode with dysthymia	7(35%)	6(30%)	0.73
Maniac-depressive disorder	3(15%)	3(15%)	1
Post-traumatic stress disorder	3(15%)	3(15%)	1
Generalized anxiety disorder	6(30%)	9(45%)	0.32
Medication			
Analgesic use (yes/%)	12(60)	10(50)	0.52
> 4 times a week in the last 3 months t (n/%)	5(25)	7(35)	0.24
< 4 times a week (n/%)	7(35)	3(15)	0.36
Aminophen/Dipirone(n/%)	3 (15)	5 (25)	
Non-steroidal anti-inflammatory drugs(n/%)	9 (45)	5 (25)	
Central nervous system active medication(yes/%)	16(80)	16(80)	
Antidepressant (n/%)	9(45)	10(50)	
Anticonvulsant (n/%)	5 (25)	4(20)	
Benzodiazepine (n/%)	2 (10)	2(10)	

Notes. QST = Quantitative Sensory Testing; VAS: visual analog scale; BDNF = Brain-derived neurotrophic factors. Values are given as mean (standard deviation) or frequency (%).. Independent samples t-Tests for mean values and Chi-Squared or Fisher's tests for frequency values. * Most frequent Psychiatric disorder according to the Minnesota International Neuropsychiatric Invetory (MINI – DSM-IV).

Table 2. Independent *t*-Tests Between Active and Sham-tDCS + WMT Groups for the Differences (Deltas) of Cognitive Scores from Pre to Post-Treatment (n =39). Data presented as mean (M) and standard deviation (SD).

	Active-tDCS + WMT (n=19) M(SD)			Sham-tDCS + WMT (n=20) M(SD)			
Cognitive Measures	**Pre-treatment**	**Pos-treatment**	**Delta (Δ)**	**Pre-treatment**	**Pos-treatment**	**Delta (Δ)**	**Between-groups P values for ΔsΔ P**
Δ COWAT Orthographic	28.80(11.24)	34.05(9.65)	23.46(27.94)	31.30(10.88)	34.31(11.88)	10.74(19.70)	0.11
Δ COWAT Semantic	16.80(6.07)	18.90(5.85)	14.08(23.78)	17.55(5.66)	17.26(5.15)	0.95(16.32)	0.52
Δ RAVLT A1	6.50(1.67)	9.20(2.56)	45.55(40.60)	6.80(2.09)	8.26(1.96)	25.52(35.96)	0.11
Δ RAVLT A1_A5	50.10(10.29)	58.40(8.74)	17.30(15.01)	45.70(10.15)	53.26(9.21)	18.03(15.33)	0.88
Δ RAVLT A7	9.65(2.88)	12.20(2.30)	28.37(23.67)	8.70(2.57)	10.94(2.73)	25.23(24.13)	0.68
Δ RAVLT Recognition	13.30(1.78)	14.10(1.20)	6.17(13.21)	13.50(1.27)	13.89(1.41)	2.72(10.75)	0.37
Δ PASAT	28.73(13.04)	33.50(12.61)	18.42(26.93)	28.15(11.30)	32.72(12.10)	18.21	0.98
Δ FDS	6.90(1.74)	6.45(1.50)	-4.39(18.29)	6.90(2.29)	6.00(1.69)	-9.62	0.45
Δ BDS	4.60(1.35)	5.05(1.82)	15.66(49.17)	4.30(1.62)	4.73(2.02)	12.36(39.61)	0.81

Notes. Δ = deltas; COWAT = Controlled Word Association Test; PASAT = Paced Auditory Serial Addiction Test; RAVLT = Rey Auditory Verbal Learning Test; FDS = Forward Digit Span; BDS = Backward Digit Span.Δ P- value* is the comparison of the deltas

Table 3. Analysis of Covariance (ANCOVA) Models for the Association of Treatment, Years of Study and BDNF adjusted index on Deltas of Cognitive Scores (n = 39)

Cognitive Measures	**Type III Sum of Squares**	***df***	**Mean Square**	**F**	***P***	$\eta^2_{partial}$
Δ COWAT Orthographic	6257.07	4	1564.27	3.26	0.024	0.29
Δ COWAT Semantic	4241.91	4	1060.48	3.05	0.031	0.28
Δ RAVLT A1	8996.26	4	2249.07	1.47	0.233	0.16
Δ RAVLT A1_A5	2534.90	4	633.72	3.42	0.020	0.30
Δ RAVLT A7	6695.88	4	1673.97	1.80	0.152	0.18
Δ RAVLT Recognition	151.84	4	37.96	0.23	0.921	0.03
Δ PASAT	3699.63	4	924.91	1.50	0.225	0.16
Δ FDS	5716.00	4	1429.00	4.01	**0.010**	0.33
Δ BDS	12014.31	4	3003.58	1.54	0.213	0.16

Notes: df = degrees of freedom; Δ = deltas; COWAT = Controlled Word Association Test; PASAT = Paced Auditory Serial Addiction Test; RAVLT = Rey Auditory Verbal Learning Test; FDS = Forward Digit Span; BDS = Backward Digit Span. Statistics refer to the Corrected Model, with Treatment (active and sham-TDCS + WMT) and Treatment*BDNF adjusted index as factors and Years of Study as covariate.

Table 4. Univariate Linear Regression Models for the Effects of Treatment Groups (Active and Sham-tDCS + WMT), Years of Study (as a Covariate) and the Interaction Treatment*BDNF on Deltas of Cognitive Measures (n= 39)

Dependent Variable	B	SEM	F	P
Δ COWAT Orthographic				
Intercept	1.12	28.32	0.04	0.969
Active tDCS	75.36	35.77	2.10	0.043
Sham tDCS[a]	.	.	.	.
Education (years)	- 2.43	1.01	- 2.39	0.022
Active tDCS * index BDNF	- 0.91	0.77	- 1.18	0.244
Sham tDCS * index BDNF	1.54	0.90	1.27	0.211
Δ COWAT Semantic				
Intercept	-17.56	24.14	-0.72	0.472
Active tDCS	45.25	30.49	1.49	0.145
Sham tDCS[a]	.	.	.	.
Education (years)	1.45	0.86	1.68	0.103
Active tDCS * index BDNF	-0.93	0.65	-1.42	0.164
Sham tDCS * index BDNF	- 0.01	0.77	- 0.01	0.999
Δ RAVLT A1_A5				
Intercept	-6.37	17.62	-0.31	0.720
Active tDCS	74.29	22.26	3.33	0.002
Sham tDCS[a]	.	.	.	.
Education (years)	-0.80	0.63	-1.28	0.210
Active tDCS * index BDNF	-1.39	0.47	-2.90	0.007
Sham tDCS * index BDNF	1.15	0.53	2.04	0.049
Δ FDS				
Intercept	78.12	24,430	3,198	0.003
Active tDCS	- 46.00	30.85	-1.49	0.146
Sham tDCS[a]	.	.	.	.
Education (years)	-1.49	0.87	-1.31	0.199
Active tDCS * index BDNF	-0.77	0.66	-1.16	0.251
Sham tDCS * index BDNF	-2.61	0.78	-3.35	0.002

Notes: df = degrees of freedom; SEM = standard error of the mean; COWAT = Controlled Word Association Test; RAVLT = Rey Auditory Verbal Learning Test; FDS = Forward Digit Span.
[a] Comparative group, to which values are referenced to.

Figure 1. Scatter plots indicating the Pearson (r) correlations between changes in episodic memory immediate recall assess with the Rey Auditory Verbal Learning Test (RALVT) and changes in BDNF adjusted index.

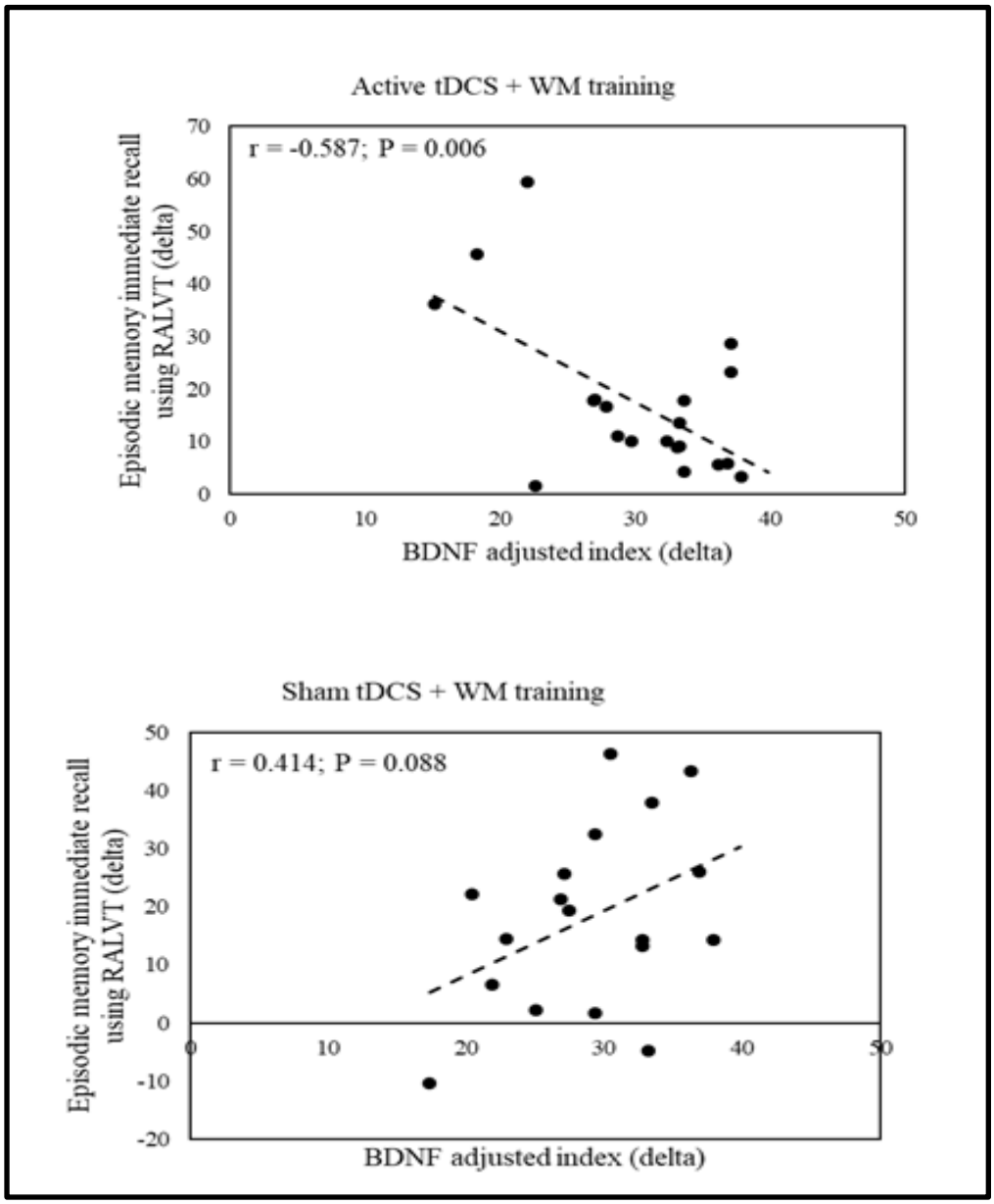
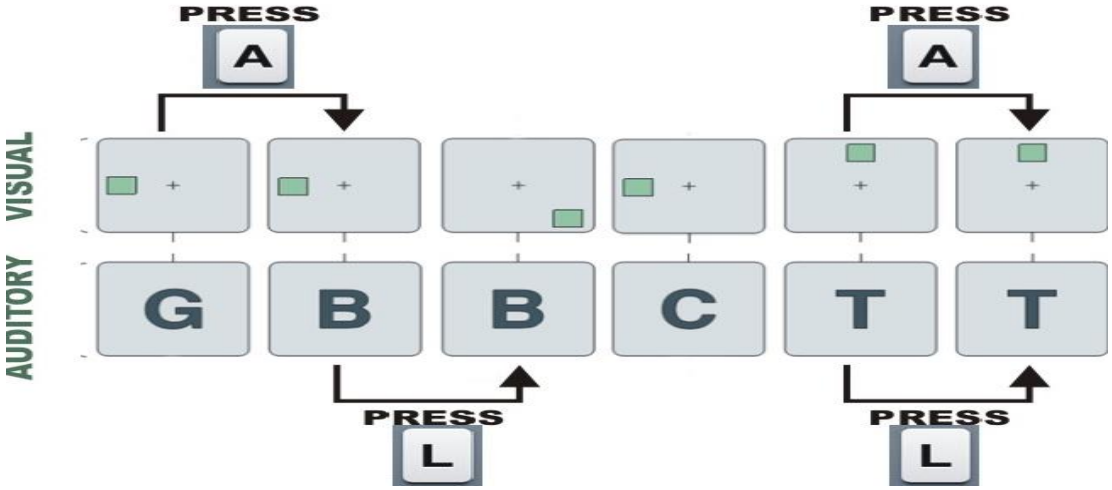


Figure 2 N-back task



Note:Presented two types of stimuli, simultaneously. Visual stimuli were green squares presented in eight different positions, and auditory stimuli consisted of the letters D, P, Q, G, V, C, T and K presented binaurally via headphones. Patients had to decide for each trial if the stimuli were the same as n-trials before (memory workload), by pressing the keyboard "A" button for visual and "L" for auditory (and do not press any button when none of the alternatives apply).

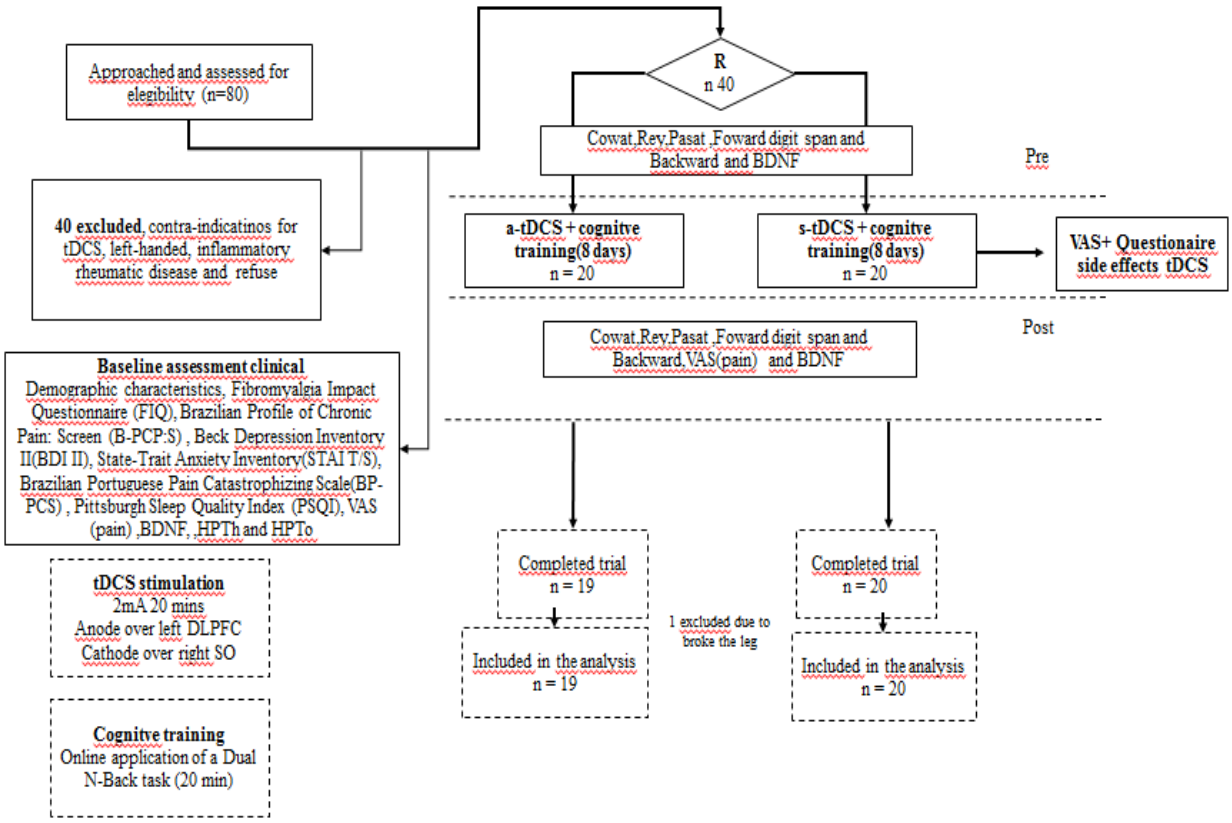


Figure 3. Flowchart showing recruitment and progress through the study. Controlled Word Association Test (Cowat) ; Rey Auditory Verbal Learning Test (RAVLT); Paced Auditory Serial

CAPÍTULO V

1. CONSIDERAÇÕES FINAIS

Os resultados obtidos com esta tese de doutorado permitem as seguintes conclusões:

O sinal eletrofisiológico como possível marcador de percepção da dor e melhora clínica em pacientes fibromialgicos;

Redução dos escores dos níveis dor, ansiedade, catastrofismo e depressão no grupo ativo (ETCC ativo + treinamento da memória de trabalho) em comparação ao *sham* (ETCC sham + treinamento de memória de trabalho*)* após 8 sessões de tratamento;

Maior amplitude no canal Pz no grupo *sham (*ETCC *sham* + treinamento de memória de trabalho) após o tratamento quando comparado com a linha de base efeito esse que não foi encontrado no grupo ativo. Esses dados sugerem que o ETCC produziu um efeito modulatório cumulativo que era estado dependente.

O grupo que recebeu o tratamento ativo(ETCC ativo + treinamento da memória de trabalho) aumentou o desempenho na capacidade de memória de curto prazo e de fluência verbal quando comparado ao grupo *sham (*ETCC *sham* + treinamento de memória de trabalho) após 8 sessões de tratamento.

O efeito do tratamento ativo (ETCC ativo + treinamento da memória de trabalho) sobre a memória de curto prazo foi estado dependente dos níveis séricos basais do BDNF para o RAVLT A1 ao A5 e para o grupo sham (ETCC *sham* + treinamento de memória de trabalho) para o intervalo de dígitos direto. Deste modo, o BDNF é um marcadores de plasticidade que influência parcialmente na resposta ao tratamento pois não influenciou a reposta sobre a fluência verbal.

2. PERSPECTIVAS FUTURAS

Esta tese de doutorado corrobora para o fortalecimento e solidificação de uma linha de pesquisa que estuda os mecanismos de neuroplasticidade mal-adaptativos e processos de neuromodulação em paciente com fibromialgia, também para o estudo da integração dos diversos mecanismos neurobiológicos, diagnósticos e terapêuticos usando técnicas de neuromodulação e que visam gerar conhecimento para alicerçar novas políticas de assistência e treinamento no manejo das dores crônicas.

Como perspectiva futura, esperamos fazer diferentes montagem de estimulação transcraniana por corrente continua como por exemplo em córtex motor primário, cortéx dorsolateral pré -frontal esquerdo e direito (bilateral) e a aplicação do treinamento memória de trabalho antes ou após a estimulação transcraniana para avaliar a resposta sobre as variáveis de memória e atenção. Também pretendemos avaliar a resposta de outros marcadores de plasticidade como estimulação magnética transcraniana, S100, 6 sulfatoximelatonina e polimorfismos genéticos.

Além disso, iremos aumentar o número de pacientes com fibromialgia para realização do teste com eletroencefalografia em busca de um melhor entendimento sobre a neuroassinatura do processomento do sinal eletrofisiológico de paciente com fibromialgia.

CAPÍTULO VI

ANEXOS

ANEXO I - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO:

NOME DO ESTUDO: **EFEITO DA ESTIMULAÇÃO TRANSCRANIANA COM CORRENTE CONTÍNUA (ETCC) ASSOCIADO AO TREINO COGNITIVO NO PROCESSAMENTO DA MEMÓRIA DE TRABALHO EM PACIENTES FIBROMIÁLGIAS**

Número do protocolo:_____

Instituição: Hospital de Clinicas de Porto Alegre- HCPA

Você está sendo convidada a participar de um estudo que avalia o efeito do tratamento da dor por meio de estímulos de baixa intensidade aplicados na cabeça em combinação com testes de computador.

1. OBJETIVOS DO ESTUDO

O objetivo deste estudo é analisar o possível efeito de 10 sessões de corrente contínua de baixa intensidade sobre a cabeça (ETCC) associada ao treinamento da atenção em pacientes com fibromialgia, conforme a figura 1que representa a ETCC. O efeito das sessões de ETCC e do treinamento de atenção serão avaliadas por questionários sobre qualidade do sono, sintomas de depressão, catastrofização, testes de atenção e de memória. Haverá perguntas sobre os seus sentimentos, nível de dor e os pensamentos que lhe surgem à cabeça sobre a dor que vem sentindo.

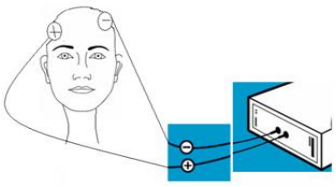


Figura 1.

2. EXPLICAÇÃO DOS PROCEDIMENTOS

Para participar da pesquisa, será necessário que você responda perguntas antes, durante e após o tratamento. Você virá ao Ambulatório dez vezes, cinco nesta semana, e outras cinco na próxima semana. Será necessário coletar duas amostras de sangue para avaliar a produção de sustâncias de defesa do organismo contra a dor. O volume de sangue será de 10 ml a cada coleta, o equivalente a duas colheres de sopa., que serão coletadas antes e após o tratamento com corrente contínua de baixa intensidade sobre a cabeça(ETCC) e do treinamento da atenção. Após coleta de sangue você responderá alguns questionários de ansiedade, e de atenção e fará um teste de atenção. Nos dias subsequente você realizará o tratamento com ETCC e o treinamento da atenção. No décimo dia a senhora fará a avaliação final com os mesmos

questionários e testes do primeiro dia que também serão explicados pelo pesquisador que estará atendendo você.

3. TRATAMENTO

Neste estudo você poderá ser sorteada para receber os 2 tratamentos ativo, conforme segue. A sessão de tratamento corrente contínua de baixa intensidade sobre a cabeça (ETCC) será realizada conforme o protocolo deste estudo, em dez sessões seguidas (exceto finais de semana), com o uso de eletrodos de borracha que ficam dentro de esponjas que são umedecidas com soro fisiológico, estes serão colocados na sua cabeça, através dos quais passará uma corrente elétrica fraca que pode no máximo causar uma leve coceira. Neste procedimento você não sofrerá choques, cortes ou cirurgias. O procedimento terá duração de 20 minutos. O tipo de estimulação transcraniana será de baixa corrente, de 1mA (miliAmper). Para você entender melhor, miliAmperes é uma medida de corrente elétrica. E a medida de 1mA equivalem a corrente gerada por uma bateria comum pequena. A mesma bateria usada em rádios, brinquedos eletrônicos, lanternas. Não será necessário ter maiores cuidados com o cabelo para a realização da intervenção, somente não usar gel ou cremes para cabelos naquele dia.

Na outra intervenção, que se chama de treinamento da atenção você ficará sentada em uma cadeira confortável na frente de uma tela de computador e terá que apertar a seta do teclado (para cima ou para baixo) quando desaparecer a figura do monitor. Você será previamente instruída para realizar essa intervenção. Você poderá também receber tratamento ativo ou o placebo. Dependendo do grupo de tratamento para qual a senhora for sorteada poderá receber os dois tratamentos placebos, este grupo receberá um tratamento em que o equipamento não emitirá estímulo e o teste de atenção será desenvolvido com outras imagens fora do contexto da pesquisa. Nem você nem o avaliador que lhe aplicará os questionários saberão qual intervenção a senhora recebeu.

Cada sessão de tratamento durará 1 hora, exceto a avaliação inicial e final que terá duração de 2 horas. Caso comprove o benefício das duas intervenções (ETCC e treinamento da atenção), esta será disponibilizada para os pacientes que receberam o tratamento placebo.

Recomendação:. A senhora deverá continuar todos os tratamentos para dor que você já utiliza(medicamentos, fisioterapia). O estudo propõe um tratamento adicional sem interromper o tratamento que você está recebendo pelo médico.

4. POSSÍVEIS RISCOS E DESCONFORTOS

O tratamento pode produzir algum desconforto durante a aplicação. Poderá ocorrer vermelhidão, sensações de coceira, leve formigamento no local onde serão colocados os eletrodos. Você também poderá sentir sonolência, porém, não necessita de acompanhantes.

5. POSSÍVEIS BENEFÍCIOS DESTES ESTUDOS

A intervenção visa analisar a possível alteração da atenção. Com os resultados deste estudo poderemos obter informações importantes sobre o quanto este procedimento poderá beneficiar pacientes com quadros de dor semelhantes ao seu.

6. EXCLUSÃO DO ESTUDO

O investigador responsável poderá excluí-la do estudo, sem o seu consentimento, quando julgar necessário, para o melhor encaminhamento do seu caso ou se a senhora não cumprir o programa estabelecido.

7. DIREITO DE DESISTÊNCIA

A senhora pode desistir de participar a qualquer momento da pesquisa. Sua decisão de não participar ou de deixar a pesquisa depois de iniciada não prejudicará o seu tratamento.

8. PRIVACIDADE

Todas as informações obtidas deste estudo poderão ser publicas com finalidades científicas, preservando os dados de identificação.

9. CONTATO DOS PESQUISADORES

Caso você tenha alguma dúvida poderá entrar em contato com os pesquisadores através dos telefone: **Profº Dr. Wolnei Caumo** 3359-8083 (2º andar do HCPA Laboratório de Dor & Neuromodulacao - sala 2201E) .Ou, ainda com o Comitê de Ética e Pesquisa do Hospital de Clínicas (de segunda à sexta-feira, das 8 às 17 horas).. Este é um órgão composto por profissionais de diferentes áreas de conhecimento e por representantes da comunidade, são responsáveis pela avaliação ética e metodológica dos projetos de pesquisa que envolva seres humanos - telefone 3359-8304.

10. RESSARCIMENTO DE DESPESAS

Você não terá despesas com a sua participação na pesquisa.

11. CONSENTIMENTO

Este termo de Consentimento Livre e Esclarecido será fornecido uma via para a Sra e uma via será arquivada pelo pesquisador, sendo as duas vias assinadas e rubricadas todas as páginas por ambos. Declaro ter lido – ou me foi lido – as informações acima antes de assinar este formulário. Foi-me dada ampla oportunidade de fazer perguntas, esclarecendo plenamente minhas duvidas. Por este instrumento, torno-me parte, voluntariamente, do presente estudo.

_____

Nome do paciente

_____

Assinatura do paciente

_____

Nome do pesquisador

_____

Assinatura do pesquisador

Porto Alegre, _____de _____de 20____.

ANEXO 2 -CONSORT

CONSORT 2017**checklist of information to include when reporting a randomised trial**

Section/Topic Item	Checklist item no.	CONSORT item	Reported on page No	
Title and abstract			**Artigo 1**	**Artigo 2**
	1a	Identification as a randomized trial in the title	66	97
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	67	98
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	70	99
	2b	Specific objectives or hypotheses	70	100
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	70	110
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-	-
Participants	4a	Eligibility criteria for participants	70-71	109
	4b	Settings and locations where the data were collected	79	109

Section/Topic Item	Checklist item no.	CONSORT item	Reported on page No	
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	71	109-110
Outcomes	5a 6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	72-3	111
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-	-
Sample size	7a	How sample size was determined	71	109
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-	-
Randomization:				
- Sequence generation	8a	Method used to generate the random allocation sequence	74	108-109
	8b	Type of randomization; details of any restriction (such as blocking and block size)	74	109
- 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	74	109

Section/Topic Item	Checklist item no.	CONSORT item	Reported on page No	
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	74	109
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	74	110-111
	11b	If relevant, description of the similarity of interventions	----	---
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	74	101-102
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-	101-102
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 analyzed for the primary outcome	75	101
	13b	For each group, losses and exclusions after randomization, together with reasons	75	101
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-	101

Section/Topic Item	Checklist item no.	CONSORT item	Reported on page No	
	14b	Why the trial ended or was stopped	-	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	75	101
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	70	102
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)	75-77	101-103
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	75-77	101-102
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	71	-
Discussion				

Section/Topic Item	Checklist item no.	CONSORT item	Reported on page No	
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	80-81	108
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	80-81	108
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	77-80	103-107
Other information				
Registration	23	Registration number and name of trial registry	72	105
Protocol	24	Where the full trial protocol can be accessed, if available	72	105

Section/Topic Item	Checklist item no.	CONSORT item	Reported on page No	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	80	113