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Neuroestimulação nos Transtornos Mentais e na Cognição

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DEDICATÓRIA

À minha família

Em especial aos meus pais, meu filho, meu marido e minha irmã

Aos meus amigos

Aos meus mestres

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RESUMO

CIRILLO, Patricia Carvalho. **Neuroestimulação nos Transtornos Mentais e na Cognição.** Rio de Janeiro, 2019. Tese (Doutorado em Psiquiatria) – Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2019.

As pesquisas com neuromodulação visam encontrar terapias alternativas para pacientes com transtornos psiquiátricos que não responderam aos tratamentos padrão. Dessa forma, os objetivos foram avaliar a eficácia da Estimulação Magnética Transcraniana repetitiva (EMTr) e da Estimulação Transcraniana por Corrente Contínua (ETCC) no tratamento de transtornos Psiquiátricos e na melhora cognitiva. Em um estudo randomizado, duplo-cego, placebo-controlado, sujeitos saudáveis foram submetidos a três sessões de ETCC, sendo duas de estimulação ativa, um para cada hemisfério cerebral, e uma sessão estimulação placebo. Adicionalmente, os voluntários realizaram uma tarefa cognitiva no computador antes e após cada estimulação para avaliar o controle inibitório com uma tarefa de sinal de parada. Concomitantemente, o eletroencefalograma (EEG) foi gravado para avaliar possíveis biomarcadores. Em um estudo aberto, pacientes idosos com Transtorno Depressivo Resistente (TDR) foram tratados com EMTr e avaliados antes e após o tratamento em relação à evolução clínica e cognitiva. Além disso, foram realizadas duas revisões sobre a eficácia da EMTr. Uma meta-análise analisou a eficácia desta técnica neuromodulatória nos transtornos ansiosos e no Transtorno do estresse pós-traumático (TEPT). E uma revisão qualitativa avaliou as evidências na literatura do emprego da EMTr nas diversas fases do Transtorno Bipolar (TB). A EMTr mostrou-se eficaz no tratamento do TRD e na melhora da velocidade de processamento de idosos com TDR. A modulação com ETCC em sujeitos saudáveis mostrou melhora de performance, aumentando a acurácia, após estimulação do cortex prefrontal dorsolateral (CPFDL) esquerdo e aumento do tempo de reação nas tentativas sem sinais de parada devido à modulação da atenção e controle inibitório proativo. A meta-análise mostrou tamanho de efeito moderado para o tratamento do TEPT com EMT e grande para o tratamento do Transtorno de Ansiedade Generalizada (TAG). Enquanto os estudos para aplicação da EMT no TB não apresentaram resultados consistentes. Não havendo, até o momento, indícios da eficácia da EMT em nenhuma fase do TB. Dessa forma, as evidências sobre o uso da EMT e da ETCC para melhora clínica ou cognitiva mostrou-se

promissora no TDR em idosos, GAD, TEPT e voluntários saudáveis. Enquanto ainda é incipiente para os demais transtornos. De qualquer maneira, mais estudos são necessários para verificar a eficácia destes métodos neuromodulatórios e para determinar os parâmetros ideais.

Palavras-chave: Estimulação Magnética Transcraniana; Estimulação Transcraniana por corrente contínua; Transtorno depressivo maior; Cognição; Envelhecimento.

ABSTRACT

CIRILLO, Patricia Carvalho. **Neuroestimulação nos Transtornos Mentais e na Cognição.** Rio de Janeiro, 2019. Tese (Doutorado em Psiquiatria) – Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2019.

The researches with neuromodulation aim to find alternative therapies for patients with psychiatric disorders that have not responded to standard treatments. Thus, the objectives were to evaluate the efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS) in the treatment of psychiatric disorders and for cognitive improvement. In a randomized, double-blind, placebo-controlled study, healthy subjects underwent three sessions of tDCS, two with active stimulation, over the right and left hemispheres, and one sham stimulation. In addition, volunteers performed a cognitive computer task before and after each stimulation to assess inhibitory control with the Stop signal task. Concomitantly, the electroencephalogram (EEG) was recorded to evaluate possible biomarkers. In an open-label study, elderly patients with Treatment-resistant depression (TRD) underwent rTMS. Clinical and cognitive outcomes were assessed at baseline and post-treatment. In addition, the author conducted two reviews to evaluate the efficacy of rTMS in psychiatric disorders. A meta-analysis examined the efficacy of this neuromodulatory technique in anxiety disorders and posttraumatic stress disorder (PTSD). And a qualitative review evaluated the literature evidence of TMS in all Bipolar Disorder (BD) phases. rTMS showed efficacy in the treatment of TRD and in enhancing processing speed of elderly patients. Modulation with tDCS in healthy subjects showed improvement in performance, increasing accuracy after stimulation of the left dorsolateral prefrontal cortex (DLPFC) and increased reaction time in the no-stop attempts due to attentional modulation and proactive inhibitory control. The meta-analysis showed moderate effect size for the treatment of PTSD with TMS and large for the treatment of Generalized Anxiety Disorder (GAD). Meanwhile, the studies that evaluated the application of TMS in BD did not present consistent results. There are no indications of TMS as an effective treatment to any stage of BD. Finally, the use of TMS and tDCS for clinical or cognitive improvement seems promising for TRD in the elderly, GAD, PTSD, and healthy volunteers. While it is still incipient for the other disorders. However, more studies are needed to verify the efficacy of these neuromodulatory methods and to determine optimal parameters.

Keywords: Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation; Major depressive disorder; Cognition; Aging.

LISTA DE ABREVIATURAS E SIGLAS

BAI	*Beck Anxiety Inventory*
BDI-II	*Beck Depression Inventory-II*
CPFDL	Cortex prefrontal dorsolateral
CPFDM	Cortex prefrontal dorsomedial
CT1	*Color trails test - subtest for sustained attention*
CT2	*Color trails test - subtest for divided attention*
CTT	*Color trails test*
DLPFC	*Dorsolateral prefrontal cortex*
DMPFC	*Dorsomedial prefrontal cortex*
EEG	*Electroencephalography ou* Eletroencefalograma
EEGLAB	Ferramenta para análise de ERPs do software MATLAB
EMTr	Estimulação Magnética Transcraniana repetitiva
ERN	*Error Related Negativity*
ERPs	*Event-related potentials* ou Potenciais relacionados a eventos
ETCC	Estimulação transcraniana por corrente contínua
GAD	*Generalized anxiety disorder*
HAMD-17	*Hamilton Depression Rating Scale*
ICA	*Independent Component Analysis*
IGT	*Iowa Gambling Task*
LMV	Limiar motor visual
LTD	*Long-term depression*
LTP	*Long-term potentiation*
MDD	*Major Depressive Disorder*
PSI	*Processing Speed Index*

PD	*Panic disorder*
Pe	*Error related positivity*
PTSD	*Post-traumatic stress disorder*
RMT	*Resting motor threshold*
SAD	*Social Anxiety Disorder*
SP	*Social phobia*
SST	*Stop Signal Task*
SSRT	*Stop Signal Reaction Time*
TB	Transtorno Bipolar
TBI	*Traumatic Brain Injury*
tDCS	*Transcranial direct current stimulation*
TDM	Transtorno Depressivo Maior
TEPT	Transtorno de estresse pós-traumático
TRD	*Treatment-resistant depression* ou Transtorno depressivo resistente
TMS	*Transcranial magnetic stimulation*
VMT	*Visual Motor Threshold*
WAISS-III	*Wechsler Adult Intelligence Scale - Third Edition*
WMI	*Working Memory Index*

SUMÁRIO

1. INTRODUÇÃO

ESTIMULAÇÃO MAGNÉTICA TRANSCRANIANA E ESTIMULAÇÃO TRANSCRANIANA POR CORRENTE CONTÍNUA

Os termos neuromodulação e neuroestimulação são utilizados para descrever procedimentos que utilizam estimulação magnética ou elétrica em regiões do cérebro o objetivo de tratar transtornos psiquiátricos ou neurológicos através da modulação da atividade cortical. Os métodos de neuroestimulação não-invasivos abordados nesta tese são a estimulação transcraniana por corrente contínua (ETCC) e a estimulação magnética transcraniana (EMT). Nenhum destes métodos necessita de anestesia. O paciente se senta em posição ereta e permanece consciente durante todo o procedimento.

Há evidências crescentes da eficácia dessas técnicas e seu potencial de neuroplasticidade(1). Pacientes com transtorno depressivo maior (TDM) que não responderam satisfatoriamente a tratamentos psicofarmacológicos apresentaram melhora clínica com a TMS(2).

A ETCC, utiliza corrente constante de baixa amplitude aplicadas em áreas corticais pré-definidas. Esse método consiste em uma bateria ligada a um eletrodo anódico que aumenta a excitabilidade cortical enquanto um eletrodo catódico diminui a excitabilidade(3). O ETCC ainda é um método experimental.

A estimulação magnética transcraniana (EMT) fornece pulsos magnéticos sobre as áreas corticais através de uma bobina posicionada no couro cabeludo. A EMT pode ser superficial ou profunda de acordo com a bobina utilizada. Ondas eletromagnéticas são transmitidas de uma bobina sobre o couro cabeludo(2). O Theta burst (TBS) é um tipo de TMS mais potente. Essa forma de TMS é tão eficaz quanto a rTMS com 10 Hz, mas a duração da sessão pode ser de 40 segundos a 6 minutos em comparação a 30 a 36 minutos com a rTMS(2). Tanto EMTr quanto o TBS podem ser inibitórios ou excitatórios. E podem ser tratamentos adjuntos ou monoterapia. Comumente, os medicamentos psicotrópicos são mantidos durante a realização do tratamento de neuroestimulação.

A intensidade da EMT é baseada em uma medida individual chamada limiar motor (LM). O limiar motor visual (LMV) é a intensidade mínima para visualizar a contração o polegar do paciente em 5 de 10 tentativas(2). A intensidade da EMT é calculada com um porcentual deste LMV, por exemplo 120%(4). O tratamento padrão da MDD com EMT consiste em 20-30 sessões diárias, ao longo de 4-6 semanas.

A EMTr é considerada um tratamento de primeira linha para pacientes com transtorno depressivo que não respondeu bem a pelo menos um antidepressivo(5). Já foi aprovada para o tratamento de MDD por diversas agências reguladoras como a FDA (EUA) e ANVISA (Brasil).

2 – Desenvolvimento

2.1 - Artigo 1

tDCS modulation of impulse control in healthy subjects and the role of the DLPFC: a randomized, double-blind, sham-controlled trial

Abstract

Background: The lack of impulse control is a key symptom in neuropsychiatric disorders. Neuroimage studies associated the dorsolateral prefrontal cortex (DLPFC) with response inhibition (impulse control). Also, Transcranial direct current stimulation (tDCS) is a promising method to improve cognitive functions.

Objective: We aimed to evaluate the effect of anodal tDCS over the DLPFC in the inhibitory response of healthy volunteers, comparing brain laterality and assessing Event-related potentials (ERPs) changes to identify biomarkers.

Methods: Twenty-one healthy volunteers were evaluated at the Massachusetts General Hospital in this randomized, double-blind, sham-controlled crossover trial. Subjects attended to three visits in which they performed the Stop Signal Task (SST) before and after anodal tDCS modulation over the right or left DLPFC or sham. The sequence of stimulation was randomized, and we recorded electroencephalography (EEG) concurrently with the task. The primary outcome was the stop signal reaction time (SSRT). Other outcomes of interest were accuracy in Go and No-Go trails and Go reaction time (RT) and changes in ERPs amplitudes.

Results: Twenty subjects completed the study. In Go trails, accuracy significantly increased after left anodal tDCS modulation and remained the same after right when compared to sham. The RT for correct Go trials significantly increased for both left and right tDCS modulation compared to sham, with a greater level of statistical significance on the right. P200 amplitude corresponding to the average waveforms of F3, Fz, and F4 positions showed a significant increase when comparing right-tDCS to sham. In No-go trials, there were no behavioral changes, including SSRT, and there was a significant increase of P300 amplitude of the average waveforms of the prefrontal positions only for left stimulation. The adverse events were mild to moderate.

Conclusions: This study shows that a single session of anodal tDCS over the left DLPFC modulated accuracy more effectively than over the right in healthy subjects. Also, selective

attention and proactive inhibition increased significantly over the right DLPFC whereas no significant changes in motor response inhibition were observed with tDCS modulation over right or left DLPFC. The ERPs provide neurophysiological support for these findings. Therefore, tDCS significantly enhanced the capabilities of the stimulated brain area according to the respective dominant cerebral hemisphere as well as the cognitive functions required by the task.

Keywords: Transcranial direct current stimulation, Stop signal task, Response inhibition, Proactive Inhibition, Event-related potential

Introduction

Despite the evolution of treatments for neuropsychiatric disorders, there is still a lack of therapeutic options for cognitive dysfunction. In the past decade, multiple neuroimage studies have identified anatomical and functional areas uniquely related to cognitive networks(1, 2). Thanks to these neuroimage advances, brain modulation techniques have considerably evolved and are promising methods to treat cognitive impairments. A differential of neuromodulation methods is the capacity to direct the stimulus to neural targets selected according to the desired outcome(3). In addition to the absence of adverse events like weight gain and loss of libido, the leading causes of poor adherence to psychopharmacological treatments(4, 5). Transcranial direct current stimulation (tDCS) is an emerging brain modulation technique for the treatment of cognitive dysfunction as well as for the improvement of cognitive performance in healthy subjects(6). Compared to other brain stimulation methods, tDCS has advantages for having more straightforward handling, lower cost, being portable and safer(7).

tDCS is a non-invasive technique to modulate brain activity and connectivity and promote synaptic plasticity(8). This neuromodulation technique delivers weak, non-convulsive, constant electrical currents through electrodes placed on the scalp. The standard tDCS montage consists of two electrodes, one anode, and one cathode, positioned over pre-defined targets. The anodal tDCS elicits neuronal depolarization, increasing cortical excitability while the cathodal tDCS does the opposite(8). Usually, tDCS is applied for 10 to 30 minutes, at a current intensity from 1-2 mA, with saline-soaked sponges measuring up to 35 cm^2(8). tDCS mechanisms of action are partially understood, and it is known to produce an electric field that does not induce neuronal action potentials(9).

The electric field spreads on the scalp, skull, cerebrospinal fluid and around 45% of the delivered current crosses into the cortex (8, 10). One hypothesis for the mechanism of action is that tDCS has a diffuse action and changes the functional connectivity of the brain areas through which the current passes and of remote non-stimulated regions (8, 11, 12). Therefore, the effect of tDCS should be interpreted by the dynamics of neural networks and the integration between them rather than effects on specific brain foci(12). Of note, several elements can influence the electric field, like the size of the sponge, position, and size of the electrodes, the duration, intensity, and polarity of stimulation(12). As a practical example, larger sponges produce less focal stimuli and can simultaneously modulate nearby areas with diverse functions(13). Therefore, it is important to define these elements and optimize the electric field to achieve the desired behavioral or clinical outcome.

The lack of impulse control (response inhibition) is a key characteristic of several neuropsychiatric disorders like Attention Deficit *Hyperactivity* Disorder (*ADHD*), substance-use disorders, Borderline Personality disorder and Bipolar disorder(14). Impulsivity may lead to risk or inappropriate behavior and social maladjustment. The Stop signal task (SST) measures response inhibition through a mathematical model based on the motor reactions latency of the subject to the stimuli(15).

On computerized SST, participants are required to respond as fast as possible to a visual stimulus on the screen, pressing a mouse button (Go trial). Occasionally, a *stop signal* appears, and the participant should withhold their response (No-go trial). In Go trials, volunteers delay the motor response as a strategy to wait for the appearance of the stop signal, resulting in a non-statistically significant increase in reaction time (RT)(8, 16). Additionally, in No-go trials, the improvement in response inhibition performance is demonstrated by shortening stop signal reaction time (SSRT), since the participant must be quick to cancel the ongoing response when the stop signal appears. Studies have examined the modulatory effect of tDCS in motor inhibitory control using SST. The only consistent result is the decrease of SSRT after anodal tDCS over the right inferior frontal gyrus (rIFG) in healthy subjects, showed by six trials(17-22).

The dorsolateral prefrontal cortex (DLPFC) has been associated with response inhibition due to the activation of this cortical area during SST in several studies of functional brain imaging(23). This prefrontal hub is a “top-down” control area that integrates internal and external information(1). In SST, this cortex area processes a visual stimulus into a motor control action. Until now, two studies assessed the effect of tDCS anodal and cathodal stimulation on SST in healthy subjects. One single-blind, sham-controlled study compared anodal and cathodal tDCS over the left DLPFC with 1mA, for 10 minutes(24). Only anodal tDCS increased Go RT. Another single-blind sham-controlled study compared anodal and cathodal tDCS over the right DLPFC and the rIFG with 1.5 mA, for 20 minutes(22). They found shorter SSRT after anodal tDCS over rIFG and no significant changes in Go or NoGo trials after anodal or cathodal tDCS over right DLPFC. The parameters applied in both studies may have been underdosed(22, 24, 25). Therefore it is possible that greater intensity and duration improve outcomes. Based on these results, it is necessary to evaluate whether the increase in Go RT only after anodal tDCS over the left DLPFC is due to the laterality of stimulation.

Accordingly, our study was designed to evaluate the effect of tDCS modulation over the DLPFC on the cognitive control of healthy volunteers. For an in-depth understanding, we

compared the laterality of stimulation (left versus right DLPFC) and concurrently recorded electroencephalography (EEG) to assess the relation of behavioral effects to the stage of perception in the time course processing. Hence, the first aim of this study was to compare the inhibitory control effects of anodal tDCS to the right or left DLPFC and sham in healthy volunteers. Secondly, to relate the changes in Event-related potentials (ERPs) to the behavioral ones to identify possible biomarkers.

METHODS

Participants

We evaluated 21 healthy volunteers (nine females, aged 19-71 years), at the Massachusetts General Hospital (MGH), from July to October 2017. To enroll in the study, healthy volunteers should have 18 to 75 years of age. The exclusion criteria were 1) contraindications for tDCS (history or epilepsy, metallic implants in the head and neck, brain stimulators, vagus nerve stimulators, ventriculoperitoneal shunt, pacemakers, pregnant or breastfeeding), 2) diagnosis of psychiatric or neurological disorder, 3) ongoing treatment with any psychotropic medications; 4) active substance dependence (except for tobacco); 5) inability to participate in testing procedures. All patients signed informed consent, and the ethics committee of MGH approved the study. The initial evaluation included the following questionnaires to ensure that the volunteers were healthy: (1) 86-item Behavior Rating Inventory of Executive Function Adult Form (BRIEF-A) to assess executive function; (2) Barrat Impulsiveness Scale, version 11 (BIS-11) to evaluate cognitive and motor impulsivity; (3) Quick Inventory of Depressive Symptoms -Self-Rated (QIDS-SR) and (4) Patient Health Questionnaire (PHQ9) to assess mood; (5) questions 12 through 14 of the Concise Health Risk Tracking (CHRT) for suicidality, (6) a question about irritable or elated mood to screen for mania and (7) MINI International Neuropsychiatric Interview to screen neuropsychiatric disorders.

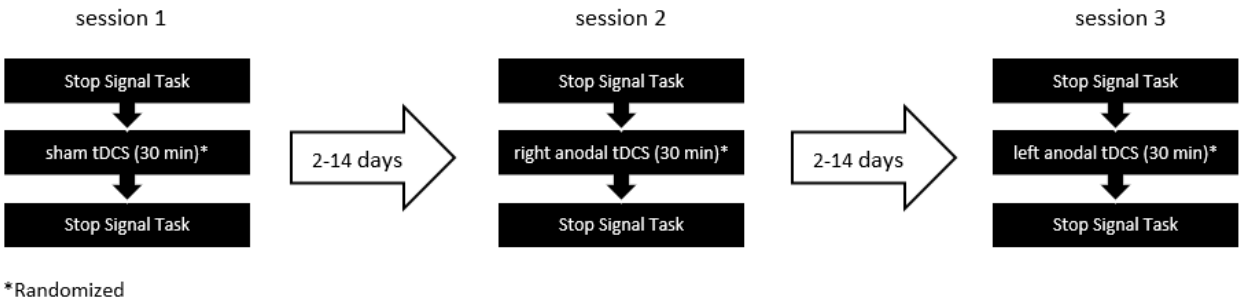
Sample size and power calculation

The analysis is based on our preliminary data on reaction time, accuracy and ERPs amplitudes for 20 subjects comparing post versus pre-active or sham tDCS(26). Assuming a sample standard deviation of 5, with 20 subjects we will have 80% power to detect an absolute size of 2 or greater and 90% power to detect an effect size of 3.3 or greater, based on a paired t-test at the 0.05 two-tailed significance level. Given that in our preliminary data the most

prominent effect sizes observed were differences in reaction time of 8 ms, differences in accuracy of 5 points, and differences in ERP amplitudes of 9uV, we evaluated that 20 subjects would be enough to detect the expected differences post to pre-DCS and comparing active versus sham tDCS.

Experimental Design

In this randomized, double-blind, sham-controlled, crossover trial, subjects attended to three visits with an interval between two visits of 60 hours to 2 weeks. In every visit, they performed the same cognitive task before and after tDCS. All subjects received three tDCS stimulations (two active over the right or left DLPFC and one sham). The order of stimulation was randomized with computer software.



Behavioral Paradigm

The Stop Signal Task measures the ability to inhibit an ongoing response. Participants must press the right or left laptop mouse button as quickly as possible when letters "Z" or "A" appears respectively (Go trial). However, whenever "A" or "Z" is followed by "X," which is the stop signal, participants must withhold their response (No-go trial). The stop signal delay (SSD) starts at 400 ms and varies according to the subject's performance, increasing or decreasing by 50 ms respectively after a successful or unsuccessful answer, within a range of 50 to 500 ms. This adjustment occurs to enable them to successfully inhibit the response in approximately 50 % of the No-go trials. The Stop-Signal task consisted of 160 Go trials (80%) and 40 No-go trials (20%) performed in Presentation software (Neurobehavioral Systems, San Francisco, CA). The primary outcome measure is the SSRT and other outcomes of interest are accuracy of Go and No-Go trials and reaction time on Go-trials.

Before the beginning of the study, a researcher not involved in collecting data set the tDCS protocols in the software, with the names A, B, and C and created a spreadsheet with the randomization these names. The electrodes montage was always the same, and the clinician responsible for the stimulation followed the randomization of protocols A, B and C. The opening of the blind code of the study was carried out after data collection completion. The experiment was performed in a silent room

with two paired laptops, one to perform the task and another with the tDCS software with the double-blind modality and EEG monitoring. Subjects sat with a distance of 75 cm from the screen with the task and could not see the other laptop, positioned behind them. Trained clinicians set up the room, applied tDCS and monitored tolerance to stimulation and quality of the acquired data during the sessions. At the end of each session, subjects completed the tDCS Adverse Events Questionnaire(27).

tDCS protocol and EEG

We used a hybrid 8-channel tDCS-EEG Starstim® system (Neuroelectrics, USA) with Ag/AgCl electrodes (contact area 3.14 cm^2) for the tDCS stimulation and EEG recording. Smaller sized electrodes allow for an increased focality of the stimulation compared to standard bigger sponges commonly used in tDCS studies (12). We used the tDCS bipolar montage targeting the left or right DLPFC with the anode placed on the scalp at the F3 or F4 position and the cathode on the contralateral supraorbital area at FP2 or FP1, according to the international 10-20 EEG coordinate system. Figure 1 shows the electric field underlying corticomotor excitability changes for tDCS stimulation targeting the left and right DLPFC. The active bipolar tDCS delivered an electric current of 2mA and was applied for 30min. For the sham condition, the current was applied only for a 15 second fade in and fade out at the beginning and end of the 30 minutes, to simulate the possible experience of local tingling sensation that real stimulation produces but without sustained effect on cortical activity. To accomplish double-blinding, an independent investigator previously configured the tDCS protocols and named them with letters (A, B and C) in the software. Once the templates have been defined, the operator selected the one specified in the randomization. EEG was recorded before and after tDCS modulation simultaneously to the Stop-Signal task execution with eight electrodes located at Fp1, Fp2, F3, F4, Fz, P3, P4, and Oz, with a right mastoid reference and at a sampling frequency of 500 samples/second.

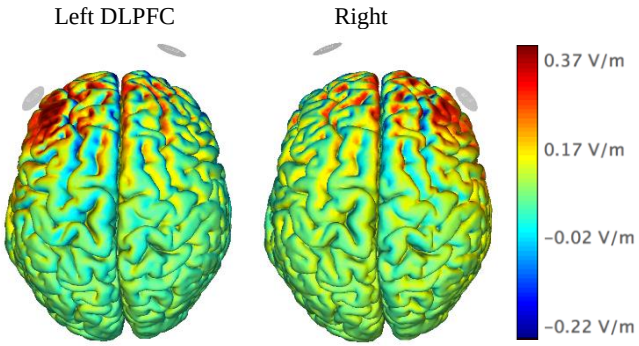


Figure 1 Electrical field model. Modeling of the normal component of the electrical field (V/m) created by the montage targeting the left DLPFC (Anodal F3, Cathodal Fp2) and right DLPFC (Anodal F4, Cathodal Fp1).

Statistical analyses

Behavioral analysis

Data were analyzed using R software. We modeled the reaction time (RT) in Go trials with a Generalized Linear Model with Mixed Effects (GLMM) with a Gamma distribution, with Subjects as a random factor and the interaction between Time Point (PRE/POST stimulation) and Stimulation Type (Left/Right/Sham) as a fixed factor. We have previously shown that the gamma distribution is particularly well-suited to modeling reaction times during conflict tasks (28-30). Accuracy (percentage of correct responses) was also modeled using a generalized logistic regression with mixed effects and a binomial distribution, with Subjects as a random factor and the interaction between Time Point (PRE/POST stimulation) and Stimulation Type (left/right/sham) as a fixed factor.

The Akaike Information Criterion (AIC) was used to assess the complexity added by each factor to the GLMM models (31, 32). By convention, a factor was included in the model if it did not increase the model's AIC by more than 5 points and it had a significant effect (33). If an interaction factor met the criterion for inclusion in the model, its individual main categorical effects were also included for parametrization purposes. If an interaction was significant, multiple pairwise post-hoc tests were conducted, with correction for multiple comparisons using the 'mvt' method from the *lsmeans* package in R (34). Coefficients were considered significant when $p<0.05$ (confidence interval of 95%).

As there is no record to represent the inhibition of the response of No-go trials, the SSRT is indirectly estimated by the race model in which average SSD is subtracted from median reaction time of Go-trials(35). Hereafter, SSRT was statistically analyzed using a two-way analysis of variance (ANOVA) with the stimulation condition (left/right/sham) and time point (PRE/POST stimulation) as factors.

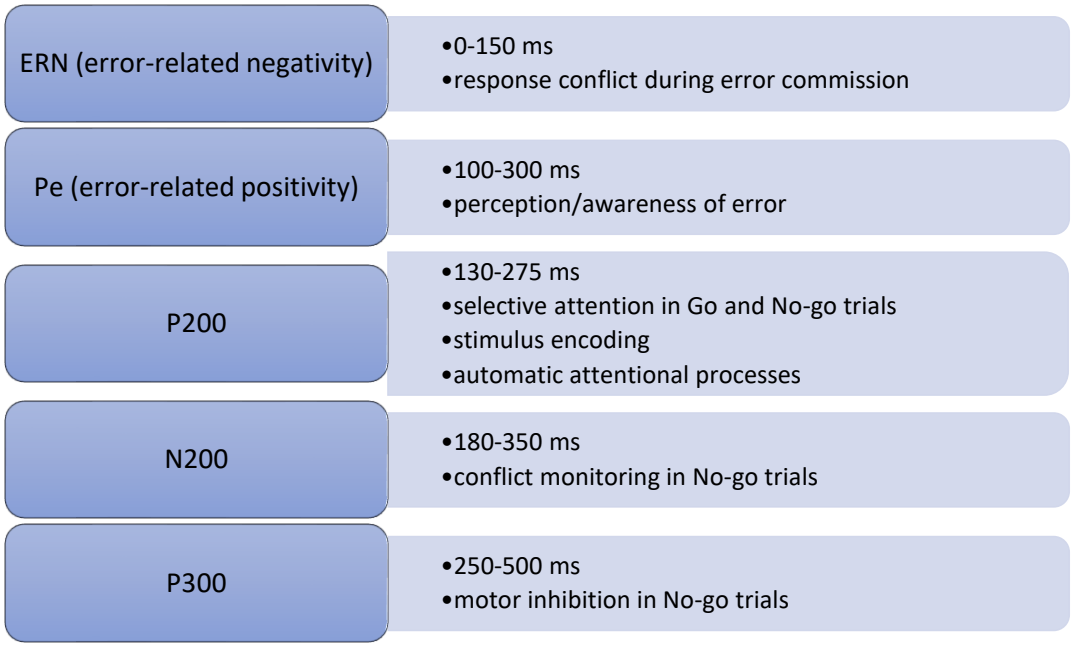
Event-related potentials analysis

EEG was processed offline with EEGLAB and MATLAB (The Mathworks, Inc.). In preprocessing, we applied Independent Component Analysis (ICA) to remove artifacts with a 1-20 Hz filter and extracted epochs from -200 ms to 800 ms. Epochs were detrended and normalized by dividing them by the standard deviation of each epoch. The mean of a 200 ms baseline was removed from each epoch, and epochs exceeding +/- 150 μV were discarded.

The mean amplitude of ERPs of EEG was estimated with a linear mixed model and a normal distribution. Given that the highest amplitude changes were observed in the frontal positions, the ERP analysis was focused on the average of F3, Fz and F4 positions. Only trials with incorrect responses were included in the Error-Related Negativity (ERN), and error related positivity (Pe) analysis. The waveforms components were measured separately for each tDCS condition and time point (PRE/POST stimulation).

We analyzed P200, N200, P300, ERN, and Pe, which characterize the inhibitory and attentional functions in conflict tasks according to prior literature (36). P200 is a positive-going electrical potential that peaks at about 130-275 ms after the onset of the stimulus in Go and No-go trials, indexing mechanisms for early allocation of attention and consciousness of stimulus as well as selective attention: the higher its amplitude, the more efficient is the visual search (37). N200 is a negative-going ERP deflection peaking 180–350ms post-stimulus that most predominantly appears in No-go trials, indexing the monitoring of conflict between activation of ongoing response and the need to inhibit that response (38). P300 appears 250 ms to 500 ms after the stimulus most predominantly in No-go trials. There is no consensus about the meaning of P300, although this is known to be related to the stopping process (39). The ERN is a negative deflection in the ERP that occurs following error commission, time-locked to an individual's response. It typically peaks between 0-150 ms after the erroneous response begins and it is thought to be a marker of response conflict that occurs during error commission (40). The ERN is often followed by a positive peak, known as the error-related positivity or Pe, a positive deflection that can peak 100-300 ms after making the incorrect response. The Pe amplitude is thought to reflect the perception or recognition of the error(41). Figure 2 summarizes the ERPs components and their respective functional significance according to literature, as well as the time window used for their analysis.

Figure 2: ERP functional significance and time window



Demographic characteristics

The comparison of the age and the distribution of the total scales scores were performed with the Mann-Whitney test. The level of significance for all tests was less than 5%, which allows a confidence interval (CI) of 95%.

RESULTS

We analyzed the effect of tDCS on the performance of the Stop Signal task of the 20 healthy subjects that completed the study.

Demographic analysis

The sample consisted mainly of singles (60%), currently working (65%), not Hispanic (85%) and the most frequently reported races were Caucasian (45%) or Asian (35%). There was no significant difference in the demographic characteristics between male and females.

Table 1 – Demographic characteristics of the study population

Characteristics (n=21)	Study population n (%)
Age	
Mean age + SD (years)	33.4 ± 14.9
Range	19-71
Gender	
Male	12 (57.1 %)
Female	9 (42.9 %)
Hispanic/Latino	
Yes	4 (19.0 %)
No	17 (81.0 %)
Race	
White/Caucasian	9 (42.9%)
Black/African American	2 (9.5%)
Asian/Native Hawaiian/other Pacific Islander	7 (33.3%)
More than one Race	3 (14.3%)
Currently working	
Yes	14 (66.7 %)
No	7 (33.3 %)
Marital status	
Never married	13 (61.9 %)
Married once	5 (23.8 %)
Divorced/separated	2 (9.5 %)
Live-in relationship	1 (4.8 %)

Go trials

Accuracy of Go trials

Figure 3 represents the comparison of the accuracy post- to pre-stimulation on Go trials according to tDCS conditions. Left anodal modulation led to a significant increase in accuracy compared to sham (p=0.0001) which increased from 92% to 96%. This improvement is notable since it has a high value in the baseline. Also, sham stimulation led to a significant decrease in post-stimulation accuracy (p=0.0022), probably due to fatigue. Interestingly, although the anodal stimulation of the right DLPFC did not significantly improve post-stimulation accuracy, there is a significant difference when compared to sham (p=0.0069), suggesting that tDCS stimulation targeting the right DLPFC may have contributed to the maintenance of performance. The effect of left stimulation is also significantly different compared to right stimulation (p=0.0001).

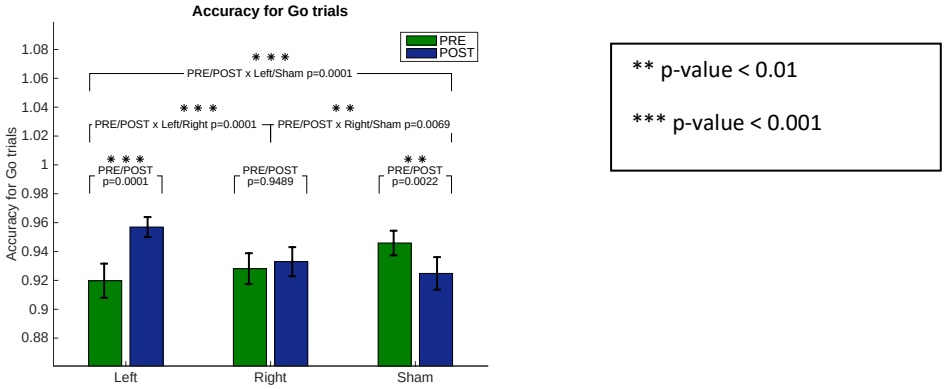


Figure 3: Accuracy of Go trials according to tDCS conditions

Reaction time of Go trials

In figure 4, we can see that the reaction time for correct Go trials significantly increased for both left (p=0.0301) and right tDCS modulation (p=0.0015) compared to sham.

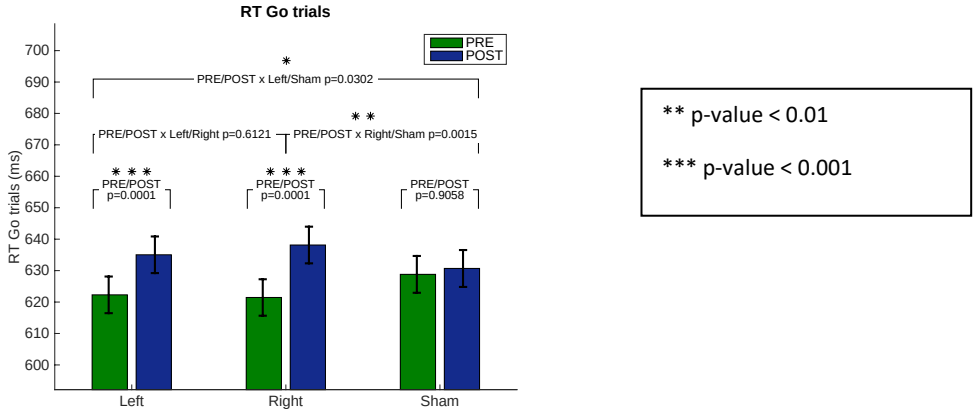


Figure 4: Reaction time for Go trials according to tDCS conditions

Frontal ERPs of Go trials

Figure 5a shows increased amplitude of P200 post- to pre-tDCS at F3 for left stimulation and F4 for right stimulation and a decreased amplitude for sham in both channels. The increase was greater for the right. Although, no amplitude changes were statistically significant (p-values - F3: sham=0.2649, left=0.6371, right=0.1090; F4: sham=0.1431, left=0.6358, right=0.1217). The analysis of P200 amplitude corresponding to the average waveforms of F3, Fz, and F4 positions also showed an increase at F3 and F4 following the laterality of stimulation and decrease after sham condition, with significant change only when comparing right-tDCS

to sham (p=0.0155)(Figure 5b). This modulation of P200 amplitude only after right may be related to the greater increase of Go trials RT post-right-stimulation.

The increase of P200 amplitude comparing post- to pre-stimulation is shown in Figure S1 at Supplemental materials. Despite the mirrored electrode montage of both hemispheres, the increase in the amplitude of P200 after left-tDCS is localized in the left frontal, and parietal lobes and more lateral while after right-tDCS is spread, reaching the occipital lobe and crossing the midline.

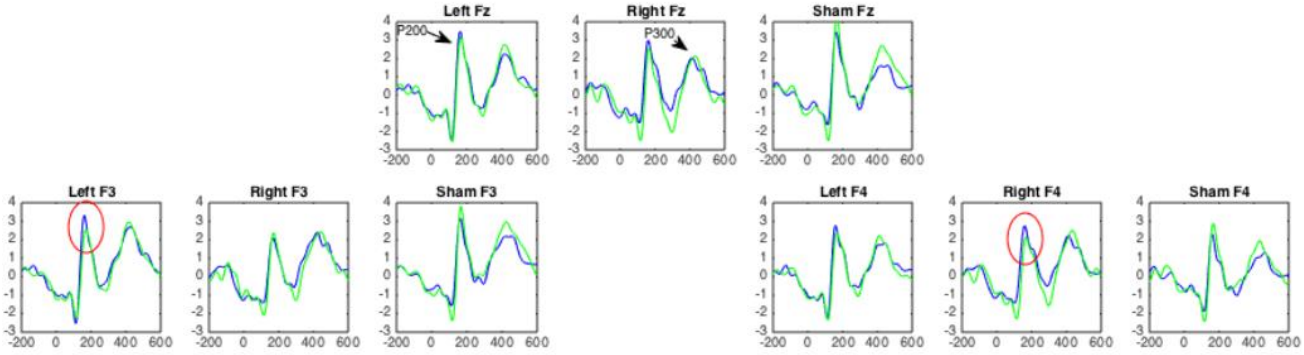


Figure 5a: Event-related potentials of Go trials time-locked to stimuli showing increased amplitude of P200 for left and right stimulation compared to sham, statistically significant only for left. Grand average waveforms correspond to F3, Fz and F4 positions alone.

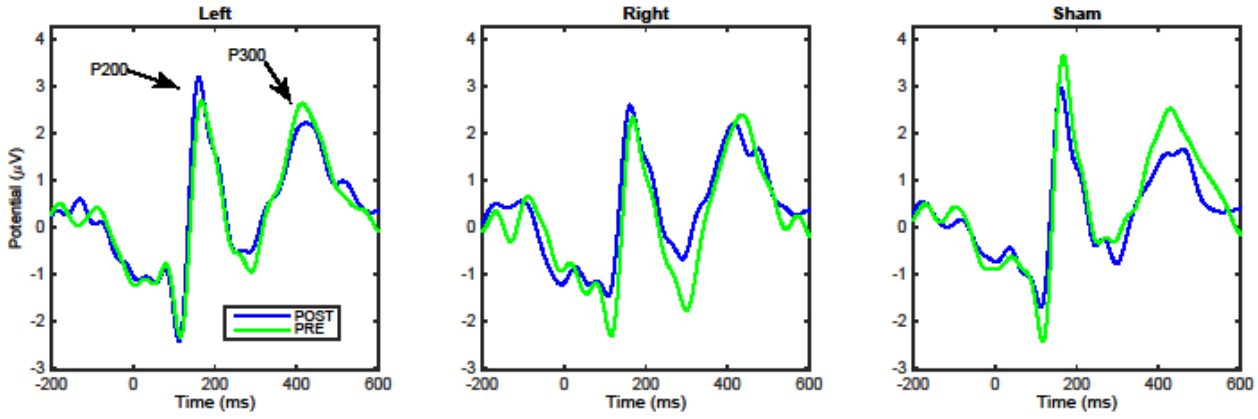


Figure 5b: Event-related potentials of Go trials time-locked to stimuli showing increased amplitude of P200 for left stimulation compared to sham. Grand average waveforms correspond to the average of F3, Fz and F4 positions.

No-go trials

Accuracy and stop-signal reaction time (SSRT) of No-go trials

In this study, there were no significant behavioral changes in No-go trials with any of the tDCS conditions. Figure 6 represents the comparison of the accuracy post to pre-stimulation

on No-go trials. Similarly, as shown in figure 7, there was no improvement in SSRT for any of the stimulation conditions.

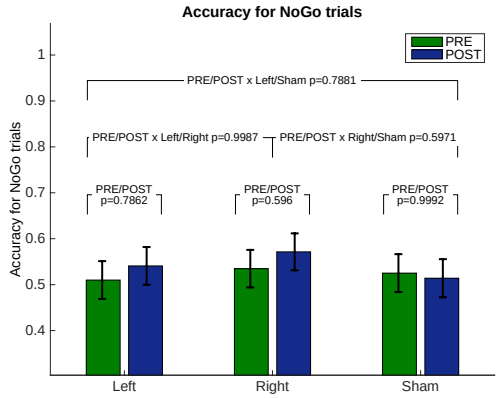


Figure 6: Accuracy of No-go trials according to tDCS conditions

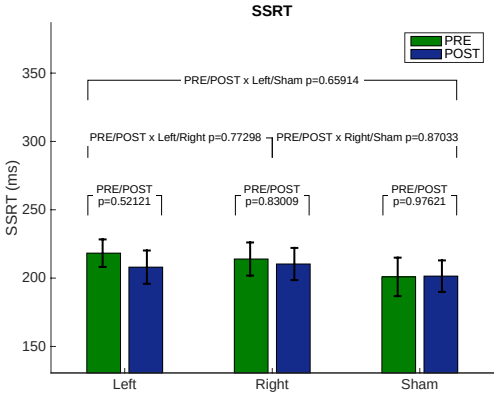


Figure 7: SSRT of no-Go trials according to tDCS conditions

Frontal ERPs of No-go trials

Figure 8 shows a significant increase of P300 amplitude for left stimulation (β=2.08uV, CI=[0.09, 4.06], p=0.0398) compared to sham. We can also observe an increase in P300 amplitude for right stimulation, but it is not statistically significant compared to sham (β=1.17uV, CI=[-0.82, 3.18], p=0.2500). In this case, there are no significant changes in P200 amplitude for left stimulation (β=1.28uV, CI=[-0.65, 3.22], p=0.1932) or right stimulation (β=1.56uV, CI=[-0.39, 3.52], p=0.1171) compared to sham. We can also observe that there are no significant changes in N200 amplitude for left (β=-0.08uV, CI= [-2.13, 1.96], p=0.936) or right stimulation (β=-0.15uV, CI=[-2.23, 1.92], p=0.882) compared to sham. The increase in P300 amplitude after active tDCS on No-go trials comparing post- to pre-stimulation is shown in Figure S2 at Supplemental materials.

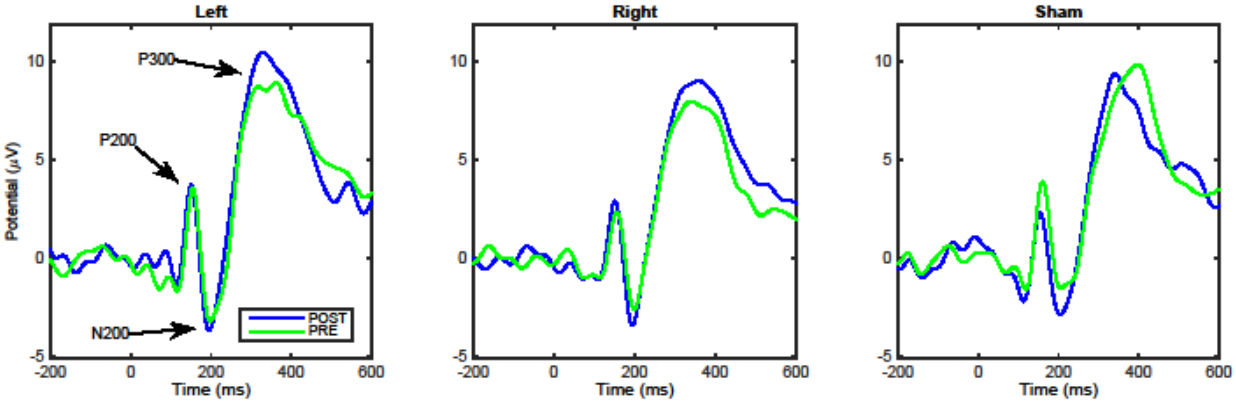


Figure 8: Event-related potentials of No-go trials time-locked to stop signal showing increased amplitude of P300 after left stimulation. Grand average waveforms correspond to the average of F3, Fz and F4 positions.

Frontal ERPs of trials with incorrect responses

Figure 9 depicts ERPs of No-go trials time-locked to incorrect responses. Although we can visually observe a tendency towards a Pe amplitude increase after left stimulation, there were no statistically significant changes for left or right stimulation compared to sham, both for ERN and Pe.

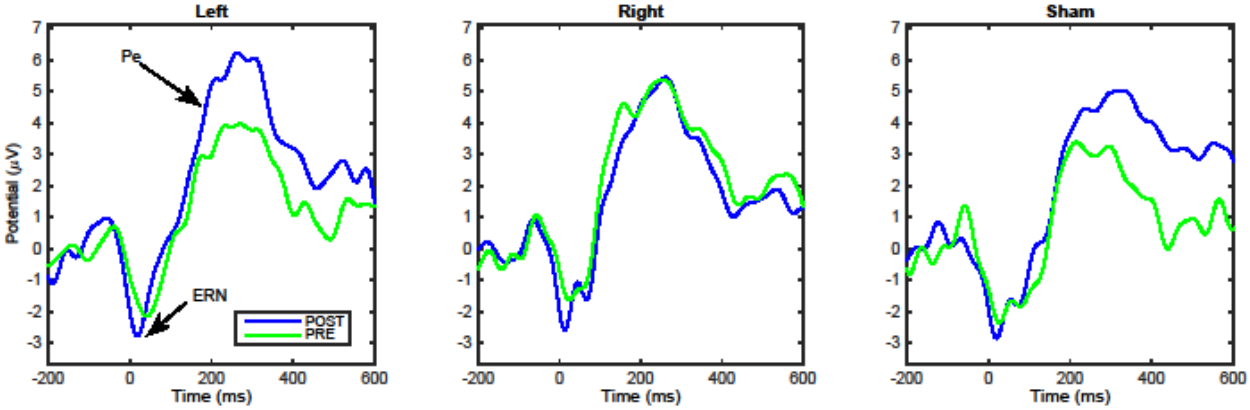


Figure 9: Event-related potentials of incorrect No-go trials responses showing ERN and Pe.

Adverse events

In the current study, we observed mostly mild and transient adverse events like tingling and itching, burning sensation, headaches, scalp pain and sleepiness collected from 18 of the 21 volunteers. Table 2 shows the number of volunteers that experienced adverse effects and the respective intensities.

Table 2 - Frequency of subjects that experienced adverse effects in all sessions and respective intensity

Sensation	Number of subjects (%) (n=18)	Intensity		
		Mild n (%)	Moderate n (%)	Severe n (%)
Headache	3 (17%)	1 (6%)	2 (11%)	0 (0%)
Neck pain	1 (6%)	1 (6%)	2 (0%)	0 (0%)
Scalp pain	3 (17%)	2 (11%)	0 (0%)	1 (6%)
Tingling	7 (39%)	6 (33%)	0 (0%)	1 (6%)
Itching	7 (39%)	5 (28%)	1 (6%)	1 (6%)
Burning	4 (22%)	3 (17%)	0 (0%)	1 (6%)
Skin redness	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sleepiness	3 (17%)	2 (11%)	0 (0%)	1 (6%)
Concentration	2 (11%)	1 (6%)	1 (6%)	0 (0%)
Mood change	2 (11%)	2 (11%)	0 (0%)	0 (0%)

DISCUSSION

In this study, we have evaluated the cognitive control effects of anodal tDCS to the left or right DLPFC comparing to sham as well as the neurophysiological (ERPs) modulation in healthy subjects. We found that left more than right anodal tDCS over the DLPFC improved accuracy in Go trials. The reason for the greater improvement after left-sided tDCS may be because the left hemisphere is the domain of simple motor movements like finger tapping(42). At the same time, we showed that right more than left-tDCS increased Go RT (proactive inhibition) and that right-tDCS increased P200 amplitude of the average waveforms of prefrontal channels. The purpose of proactive inhibition is to prevent anticipated responses, and it requires attention. P200 is an ERP associated with attention, and the right hemisphere is known to be dominant for this function (43, 44). Also, neuroimage studies have shown increased blood flow in the right prefrontal cortex during preparatory attention and proactive inhibition(45). Therefore, left-tDCS increased the number of correct answers in Go trials while right-tDCS modulated attention and proactive inhibition. Meaning that tDCS facilitation was lateralized according to the dominant hemisphere for each function.

Concerning No-go trials, our study did not show significant differences in behavioral measures (accuracy and SSRT). However, after tDCS stimulation over left DLPFC, there was

a significant increase in P300 amplitude, which is related to motor inhibition. This increase could mean that left anodal tDCS modulated NoGo-P300, but this was not enough to translate into a behavioral change. Additionally, the inexistence of improvement in SSRT is in agreement with the absence of changes in N200, known as the inhibitory control ERP that appears in No-go trials. Since the No-go trials consist of 20% of the total number of trials, questioning whether the lack of significant results is due to the lower amount of trials is expected. However, other studies with similar numbers of Go and No-go trials showed significant changes in motor inhibition with tDCS modulation over other targets like pre-SMA and rIFG(17, 19, 46). Importantly, tDCS demonstrated to be safe and well-tolerated. All the complaints of higher intensity adverse effects were from the same volunteer and may have been due to individual susceptibility. Even so, adverse effects were transient and did not cause an interruption in stimulation or drop-out.

Our results are in accordance with Mansouri et al. that evaluated the effect in SST of anodal tDCS over the left DLPFC and found no changes in SSRT and increased Go-RT(24). Moreover, partially following a study that compared anodal tDCS of the right IFG and DLPFC and found shorter SSRT only after right IFG stimulation and no significant changes in Go RT in any of the targets(22). Though, we would expect an increase of Go-RT after anodal tDCS over the right DLPFC. An explanation could be the combination of low current intensity with less focality, since they applied 1.5 mA, for 20 min with a 16 cm^2 sponge while in our study we applied 2 mA, for 30 min with a 3.14 cm^2 electrode and in Mansouri et al. Go-RT increased with 1 mA, for 10 min and 7.5 cm^2 sponge.

Accordingly, all six studies that evaluated anodal tDCS over the right IFG and 2 of the three studies over pre-SMA showed decreased SSRT(17-22, 46, 47). Also, one study found decreased SSRT after anodal tDCS over the right PFC (intersection point between the lines T4-Fz and F8-Cz) which is a premotor area. Beyond that, they used a 25 cm^2 sponge electrode and might have stimulated surrounding brain areas like right IFG, which has a response inhibition function(25). It is worth noting that due to neuroimage study's findings of right IFG activation in cognitive control, all tDCS studies that evaluated the role of IFG in response inhibition modulated only the right hemisphere. Therefore, the tDCS modulation of the left IFG has not been studied (48).

Neuroimaging studies have consistently shown activation of pre-SMA and IFG in SST with greater activation in NoGo trials versus Go trials as well as increased effective connectivity between these two brain areas during successful response inhibition in NoGo trials(49) and identified different roles in response inhibition of each of these brain areas(50).

The IFG would be responsible for detecting the stop signal and the pre-SMA to execute the motor inhibition(51, 52).

In this way, right and left DLPFC do not seem to be directly related to inhibitory response. This lack of relationship raises a question since brain imaging studies had consistently reported that the DLPFC is recruited in cognitive control tasks. Regarding the cognitive control network, some authors proposed that DLPFC have inhibitory function while others reported non-inhibitory functions or task-related functions(53, 54). This diversity of findings may be related to the anatomical and functional heterogeneity of this cortex region. Considering the cytoarchitecture, DLPFC comprises the Brodmann areas 9 and 46 (BA9/46) (23).

Moreover, studies have identified that the DLPFC have sub-regions with varied functions, like executive functions, attention and motor control, among others (16, 53, 54). A dual role of the right DLPFC has been identified, in which the posterior sub-region would be associated with working memory and action execution and the anterior sub-region to attention and action inhibition(23). This study merged data of the BrainMap project and of four studies that evaluated DLPFC activation sites with four different control tasks. They concluded that each sub-region of the right DLPFC would be part of different brain networks(23). Another research group identified 13 sub-regions of the DLPFC according to neuroanatomical and functional similarities using multi-modal magnetic resonance images of the Human Connectome Project (HCP)(55).

Besides that, tasks may need a small number of cognitive processes that rapidly alternate. The DLPFC coordinates functions, and the accomplishment of a task requires executive functions to process the stimulus, select the response, switch tasks, interrupt and restart execution(56). Besides, studies using images that rely on blood flow changes such as PET or fMRI have limitations to precisely locate the brain area responsible for specific functions because the timing resolution of cognitive processes surpasses the current recording timing precision of these techniques(57). On the other hand, ERPs provide temporal resolution but with limited spatial resolution (39). In this way, the combination of both functional neuroimaging and EEG allow a better temporo-spatial relationship.

Therefore, linking our results with the existing literature, we can infer that the Go and NoGo trials activate different brain territories, which implicates different pathways and functions. These pathways interact with one another and are likely to share brain activation regions. The activation of the Go pathway by the tDCS modulation over the DLPFC strengthens the connections between nodes required by the cognitive functions needed for the Go trials. Consequently, the NoGo trials pathway would have to overcome the reinforced

sustained motor response to Go stimuli to cancel the ongoing motor movement. Thus, the fast motor inhibition would depend on the hyperdirect pathway while the execution of the voluntary movements triggered by the Go trials would depend on the basal ganglia (BG) direct pathway. A deeper understanding of the neuromechanisms of the motor control network has been investigated by studies using deep brain stimulation (DBS), functional neuroimage and EEG.

Finally, the long-term effect of tDCS modulation is not well known yet. One study that applied four consecutive tDCS sessions with SST training in healthy subjects observed that the improvement in behavioral performance was not sustained one day after discontinuation of stimulation (19). Upcoming studies should evaluate whether a higher number of tDCS sessions promotes long-lasting effect as well as assess ideal stimulation parameters. Future studies should also associate brain modulation, EEG and brain imaging to better understand neuro and pathophysiology with spatial-temporal and *time*-frequency views.

Limitations

This study was carried out in a population with a high educational level which showed high baseline behavioral parameters. Indeed, the effects of tDCS modulation on a population with a lower educational level may be more prominent. Each tDCS condition was applied only once. Therefore it is not possible to evaluate long-lasting effects. In addition, the results can be task-related. Finally, the limited number of EEG channels used in this study also constitutes a limitation that should be addressed in future studies by increasing the number of channels to have a better spatial resolution.

CONCLUSION

This study showed that DLPFC is not implicated in response inhibition in SST, but especially with proactive inhibition in Go trials. Also, anodal tDCS over DLPFC could modulate this cognitive function in both hemispheres. In sum, a single session of anodal tDCS over the left DLPFC (F3) modulated accuracy more effectively than over the right (F4) in healthy subjects. While selective attention and proactive inhibition increased significantly more over the right DLPFC. No significant changes in motor response inhibition were observed with tDCS modulation over right or left DLPFC. The ERPs provide neurophysiological support for these findings. In general, tDCS significantly enhanced the capabilities of the stimulated brain area according to the respective dominant brain hemisphere and the cognitive functions

required by the task. Therefore, tDCS significantly enhanced the capabilities of the stimulated brain area according to the respective dominant cerebral hemisphere as well as the cognitive functions required by the task.

Accordingly, these results may help to better understand the cognitive control network dynamics during the SST, in which two pathways are activated, one involving DLPFC that would be responsible for the non-inhibitory functions required by the Go Trials, while another including IFG would be responsible for the response inhibition in NoGo trails. Future studies should evaluate cognitive processes associating brain modulation, functional Magnetic Resonance Imaging (fMRI) and multi-channel EEG to define in more detail the time course of neural network activities and possible therapeutic implications.

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Supplemental material

Figure S1 – POST-PRE-difference of P200 amplitude according to tDCS condition (Go trials)

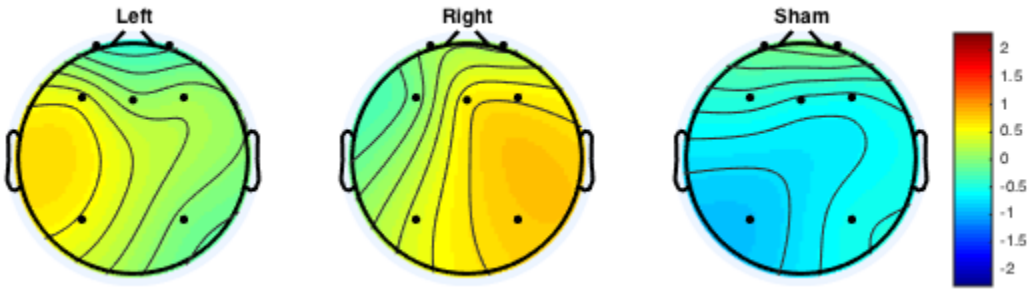
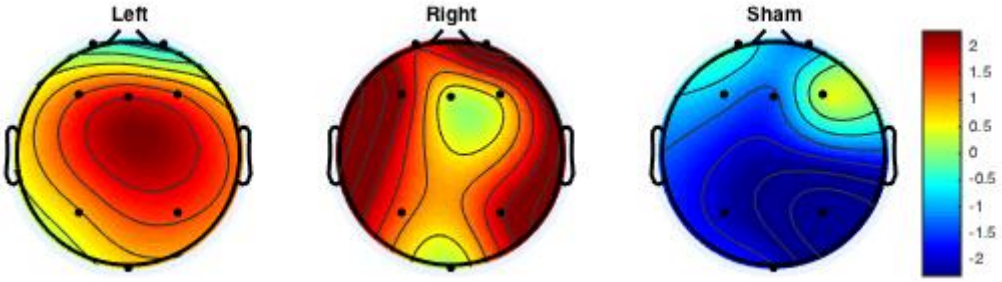


Figure S2 -POST-PRE-difference of P300 amplitude according to tDCS condition (No-go trials)



2.2 - Artigo 2

Efficacy and Cognitive Effects of Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder in Elderly

Abstract

Background: Elderly patients with MDD usually have failed to respond to several antidepressant trials and need an alternative treatment. TMS showed efficacy in MDD but has been poorly studied in patients with 60 years-of-age or more. Besides that, cognitive deficits are common in depressed patients. Importantly, cognitive impairment may not enhance despite mood improvement.

Objective: The objectives of this study were to investigate the efficacy of high-frequency (10 Hz) rTMS over the DMPFC in the treatment of moderate to severe MDD in the elderly and to assess the effects of rTMS on cognition of neuropsychological tests.

Methods: In this open-label study, patients underwent 30 sessions of 10 Hz rTMS, over the DMPFC. They responded questionnaires to measure depression and anxiety at baseline and post-treatment as well as neuropsychological tests.

Results: There was a significant improvement in depression and anxiety. Processing speed imporved regardless of treatment response.

Conclusions: This study showed efficacy of rTMS over the DMPFC in the elderly with TRD. The rTMS protocol applied also demonstrated safety and good tolerability. The literature supports the cognitive enhancement not related to mood improvement.

Keywords: Transcranial magnetic stimulation, Major depressive disorder, Aging, Treatment-resistant depression, Cognition

Introduction

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders in the elderly, with a prevalence of 20-39%(1). MDD is a public health problem with biological, psychological, and socioeconomic causes that significantly compromise the activities of daily living (ADL), and quality of life of patients, their families and caregivers(2-4). MDD is a chronic and recurrent disease in which 70-90% of patients who present a second depressive episode will present new episodes throughout their lives while the response rate progressively decreases with each new antidepressant trial(3, 5). As the first depressive episode often begins around 25 years of age, an elderly subject with MDD usually has a chronic and refractory condition, with a long-term evolution and two or more failures to antidepressant trials of different pharmacologic classes, which is considered treatment-resistant depression (TRD)(6).

In addition, the persistence of cognitive deficits even in patients that remitted after psychopharmacologic and psychotherapeutic treatments is a challenge in MDD management(1, 4, 7). This lack of cognitive improvement may be because psychotropic drugs substrates have weak specificity with cognitive targets. The executive function circuits involve cortical, subcortical and cerebellar nodes and the prefrontal cortex (PFC) is a central hub. The target-directed mechanism of action of TMS makes it a promising treatment and more specific than the brain pharmacological medications(8).

Therefore, the high rate of patients with TRD (30%) and the permanence of dysexecutive syndrome show the need for new treatments. Repetitive Transcranial Magnetic Stimulation (rTMS) is a therapeutic option. rTMS is a non-invasive, safe, well-tolerated method, with no need for anesthesia(9). In this treatment, the coil positioned on the scalp according to a selected brain target generates a magnetic field that depolarizes the neurons, to restore the balance of the neural networks(10).

rTMS has been widely studied as a treatment for MDD and is approved by several regulatory agencies like the FDA(10, 11). However, few studies have included elderly patients(12). Elderly subjects have clinical and neuroanatomical specificities due to the presence of cerebral atrophy, a higher number of clinical and neuropsychiatric comorbidities and a reduction in drug tolerance(13). Cerebral atrophy increases the distance between the coil and the cerebral cortex, but the findings on its effect on the intensity of the magnetic field are mixed(14, 15). Additionally, age and refractoriness to previous treatments are negative predictors of response(16). Electroconvulsive therapy (ECT) continues to be a standard

treatment, but some elderly people may not undergo this treatment because of clinical limitations, because they do not want to, or cannot withstand the adverse events.

To date, there are only four randomized, double-blind controlled trials (RCT) and eight open-label, uncontrolled studies (OL) that evaluated the treatment of depression in the elderly with rTMS(12). The RCTs assessed samples from 20 to 62 patients, divided into two groups, while the OL assessed samples of 11 to 102 MDD patients(13). Frequencies of 1-25 Hz, with 80-100% motor threshold (MT), with 400-2000 pulses/session, were evaluated in 5-30 sessions. All studies applied rTMS over the dorsolateral prefrontal cortex (DLPFC), and all RCTs targeted the left hemisphere. About the brain laterality of OL, 5 applied rTMS over the left hemisphere, one over the right, one compared right and left and one compared right, left and bilateral stimulation. Half of the RCTs and 6 of the OLs showed a benefit of rTMS as a treatment of MDD in the elderly. Overall, the studies showed promising results, although most of them evaluated small samples, included patients with less than 60 years-of-age and used parameters currently considered suboptimal(12). Also, 2 of these studies evaluated vascular depression(15, 17).

These studies show response rates in the elderly ranging from 20-58%, which is lower than in patients between 18-60 years of age(13). Still, it is an interesting result, since these patients have treatment-resistant depression (TRD). One study suggested that older people may need more sessions to achieve response(18).

In relation to cognition, rTMS studies have shown no side effects in memory, language, visuospatial and executive function(9). Nevertheless, studies have not demonstrated expected cognitive enhancement (19). A meta-analysis of 18 randomized, sham-controlled studies that evaluated cognitive improvement of MDD patients that underwent rTMS treatment over DLPFC found no significant differences between active and sham in 8 out of 10 tasks of auditory attention, working memory, processing speed, executive function, verbal learning, and memory(19). The two tasks that showed cognitive improvement were Trail making test parts A and B, which assess respectively sustained attention and divided attention and were not related to mood changes. Two of the 18 studies applied bilateral rTMS and one compared left to right modulatory effects while the others evaluated left-sided rTMS(19). Only one of the 18 studies evaluated elderly patients(20).

Recently, the dorsomedial prefrontal cortex (DMPFC) has also been studied as a rTMS target in patients with psychiatric disorders due to evidence of its activation in MDD from

neuroimage, neuromodulation, and brain connectivity studies(21). The DMPFC is adjacent to the dorsal anterior cingulate (dACC), and studies also have demonstrated activation of dACC when DMPFC is modulated(22). The dACC and anterior insula (AI) are the main hubs of the Salience Network (SN). SN functions include switching between other networks and integrating emotional, sensory and cognitive processes, which are impaired in several psychiatric disorders(23). Therefore, rTMS over DMPFC might modulate cognitive functions other than the ones related to the DLPFC like cognitive control and working memory.

Thus, the efficacy of rTMS as a treatment for MDD and the cognitive effects in elderly patients need to be better studied and define parameters. Thus, the objectives of this study were to investigate the efficacy of high-frequency (10 Hz) rTMS over the DMPFC in the treatment of moderate to severe MDD in the elderly and to assess the effects of rTMS on cognition of neuropsychological tests.

Materials and Methods

Subjects

The sample consisted of 11 male and female elderly patients (61-88 years of age) with current depressive episode in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria, screened in the depression and anxiety outpatient clinic of the Instituto de Psiquiatria do Rio de Janeiro (IPUB/UFRJ)(6). The inclusion criteria were: 1) individuals of both genders, 2) with 60 years of age or over, 3) with current moderate or severe depressive episode that failed to respond to at least one adequate antidepressant trials; 4) the primary diagnosis should be MDD. Comorbidities with anxiety disorders were accepted due to the high number of people who experience both disorders simultaneously(24). The exclusion criteria were: suicidal ideation, psychotic symptoms, history of hypomanic/manic episodes, severe personality disorder, neurological disorders or cognitive impairment, alcohol or substance abuse or dependence, and contraindications to TMS (history of seizure, metallic or cochlear implants, implanted stimulators or pacemaker).

The screening consisted of Mini International Neuropsychiatric Interview 5.0.0 (MINI) to confirm diagnosis and comorbidities, evaluation of cognitive impairment with Mini Mental State Examination (MMSE), clock-drawing test and a verbal fluency test to screen for dementia

as well as laboratory tests to exclude the existence of clinical comorbidities like anemia and thyroid diseases.

The current medications were maintained and had to be in stable doses for at least two months prior to and during the entire rTMS treatment. All patients gave written informed consent, and the Ethics Committee of IPUB/UFRJ approved the study.

Study design and rTMS procedure

In this open-label study, patients underwent 30 weekday sessions of 10 Hz rTMS, over the DMPFC, with trains of 5 seconds and intertrain intervals of 10 seconds and 120% of the visual motor threshold (VMT), in a total of 3000 pulses/sessions in each cerebral hemisphere with a cooled figure of 8 coil. We applied rTMS with the Neuro MS/D device (Neurosoft). The coil was placed on a scalp site determined individually by the heuristic method validated by Mir-Moghtadaei(25). The coil was positioned on the scalp line from nasion to inion, with current flow directed toward the stimulated hemisphere. We determined the visual motor threshold as the minimum intensity capable of twitching the extensor hallucis longus in 5 out of 10 trials.

Outcome measures and response criteria

The primary outcome measure was the change in Hamilton Depression Rating Scale-17 (HAMD-17) scores. Other clinical outcomes of interest were 1) Beck Depression Inventory-II (BDI-II): a self-rating scale for depression and 2) Beck Anxiety Disorder (BAI): a self-rating scale for anxiety. The neuropsychological evaluation consisted of 1) Color trails test (CTT) to assess attention, with a subtest for sustained attention (CT1) and another for divided attention (CT2)(26) and 2) Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)(27); with the subtest 2.1) Processing Speed Index (PSI) to measure visual and motor speed and the 2.2) Working Memory Index (WMI), to evaluate short-term memory, the ability to temporarily retain information in memory, perform some operations or manipulations, and build a result as well as mental manipulation of number operations(28).

The clinical psychiatric assessments and neuropsychological tests were performed at baseline and post-treatment. Response to treatment was defined as a HAMD-17 score reduction of at least 50%, and remission as a score <7.

Statistical analysis

We analyzed the data of the nine completers. The efficacy of rTMS treatment for depressive and anxious symptoms was determined to compare pre and post-treatment clinical and neuropsychological scores using two-tailed Wilcoxon signed rank test. We analyzed the change in scores between responders and non-responders with the Mann-Whitney test. The significance level was 0.05.

Results

Eleven patients enrolled in the study and 9 completed the rTMS treatment. We excluded one patient due to high VMT, which would require an intensity above the rTMS device limit and another for not complying with the treatment schedule. One patient had previously been treated with TMS and ECT and reported response with TMS and treatment dropout from ECT treatment after four sessions due to adverse events. Another patient had been submitted to a total of 11 ECT sessions. Both denied MDD improvement and reported persistent memory impairment with ECT. The demographic and clinical characteristics of patients are in table 1. There was no influence of any demographic characteristics on treatment outcome.

Table 1 – Demographic and clinical characteristics of the patients

Characteristics	Study population (n=9)
Female gender n (%)	7 (78)
Mean years of education (SD)	13.89 (2.67)
Mean age, years (SD)	68.33 (8,83)
Mean duration of MDD, years (SD)	30.75 (11.42)
Previous ECT treatment n (%)	2 (22.22)
Previous TMS treatment n (%)	1 (11.11)

At the end of the treatment, 44% of the patients responded (4/9), of which, two remitted (22%). There was a significant 52% reduction in HAMD-17 mean scores comparing post- to pre-treatment (table 2). The mean HAMD-17 score at baseline was 20.5 ($\pm$ 4.39) for the responders and 20.8 ($\pm$ 2.64) for non-responders and the mean scores at the end of treatment were, respectively 5.75 ($\pm$ 2.95) and 13.6 ($\pm$ 2.80). Therefore, patients that have not met the criteria to response improved on average 35% (range: 25-47%). The mean scores of BDI-II and

BAI also significantly decreased (table 2). In relation to cognition, only the PSI showed a statistically significant improvement (p = 0.048). The results of the clinical and cognitive outcomes are displayed in tables 2 and 3. The Hedge's *g* (SE) effect size computed from the mean differences of the HAMD-17 is 2.09 (0.64).

Table 2- Clinical and cognitive outcomes

Questionnaires	Mean (SD) (n=9)		Pre-to-post treatment
	pre	post	p-value*[1]
HAMD-17	20.67 (3.74)	10.11 (5.13)	**0.0075**
BDI-II	32.11 (11.58)	14.00 (6.80)	**0.0109**
BAI	24.78 (14.86)	10.67 (7.07)	**0.0089**
WMI	109.33 (12.60)	107.89 (13.57)	0.8586
PSI	112.22 (13.14)	116.56 (14.83)	**0.0484**
CTT1	91.44 (63.24)	82.56 (64.82)	0.1921
CTT2	155.00 (98.13)	148.00 (84.37)	0.4413

*[1] Wilcoxon signed rank test

Tabela 3 – Clinical and cognitive outcomes of responders versus non-responders

Questionnaires	Mean change (SD)	Improvement (%)	Responders x non-responders
HAMD-17 Responders (n=4) Non-responders (n=5)	 -14.75 (4.86) - 7.20 (1.30)	 72.25 35	**0.0127**
BDI-II Responders Non-responders	 -19.25 (14.43) -10.00 (7.62)	 66.7 35.9	0.2207
BAI Responders Non-responders	 -25.5 (13.23) -12.2 (14.92)	 64. 4 47.4	0.3873
PSI Responders Non-responders	 3.5 (7.77) 5 (4.12)	 3.22 6.57	0.9021

*[2] Mann-Whitney test

Safety and tolerability

In this study, there were no severe adverse events. Patients complained of tingling or mild to moderate local pain at the site of the stimulus, headache, and anxiety.

Discussion

This is the first study that evaluated the application of rTMS over the DMPFC to treat elderly patients with TRD. rTMS demonstrated efficacy in elderly patients with TRD and improved processing speed independent of response to treatment. Despite several aspects that generally contribute to non-response like long-term disorder progression and possible cerebral atrophy, there was a significant response rate (44%) among patients. This shows that rTMS is a treatment option for elderly patients with depression without psychotic symptoms, which have not responded or tolerated psychopharmacological treatments. Also, adverse events were mild, showing that rTMS over the DMPFC is safe and well-tolerated in the elderly. Moreover, there were no cognitive adverse events.

HAMD-17 showed a significant difference post to pre-treatment comparing responders to non-responders. However, BDI-II and BAI improvement was independent of response. The reason may be because of the small sample or due to the 35% improvement in non-responders HAMD. Since the patients of these study have TRD, they may have got impressed with the improvement, creating a bias in answering the self-evaluation scales. Besides that, it is possible that some of the non-responders would continue improvement and met response criteria with more rTMS sessions.

Concerning cognition, the improvement of processing speed is probably related to the modulated target. The DMPFC is adjacent to the dACC and frequently co-activated during tasks(22). A good performance in PSI depends on avoiding distraction and graphomotor skills, and dACC functions include attention processing, response selection and motor activity (Weissman 2005, Devinsky 1995). This cognitive outcome is different from the literature of MDD treatment with rTMS over DLPFC, in which selective and sustained attention improved measured by the Trail Making Test (TMT) that is similar to CTT(29). This result seems to be related to DLPFC cognitive functions which includes attention(30, 31).

Our results show that despite possible anatomical brain changes in aging and the lack of brain imaging, rTMS over the DMPFC with a figure-in-8 is feasible and showed positive

outcomes. rTMS application in aging without neuroimage is acceptable because the VMT measurement of the lower extremity is determined over a deeper brain area than the hand MT, and the visualization of the big toe twitching is the proof that the magnetic field is reaching the desired motor area and would probably act in the same way over the DMPFC. The assumption that the MT is the same in all cortical regions of an individual is the standard rule used in TMS treatments with or without neuroimaging. Besides that, diffuse, symmetrical and bilateral cerebral atrophy may not interfere in the outcome since the stipulated MT takes into account these factors so that the motor cortex would have similar cortical changes to the brain target. Therefore, the possibility of loss of rTMS effect would be restricted to patients with prefrontal atrophy. Also, it is possible that the atrophied cortex has increased excitability, requiring lower intensities of rTMS(32), which would compensate for the increase in coil-cortex distance.

Finally, elderly subjects frequently have limitations to commute and need companionship to leave their houses, which worsens with MDD. Therefore, the 30 daily sessions treatment requires commitment and availability of patients and caregivers. Besides that, patients usually do not notice improvement before 15-20 sessions and can discourage treatment. Therefore, accelerated TMS with more daily sessions could be beneficial to speed up recovery and facilitate treatment adherence. Despite that, more studies with larger samples, a control group, and structural and functional neuroimaging should evaluate elderly patients. The protocol used did not present a satisfactory result in the improvement of the anxious symptoms. Therefore, future studies may assess the application of rTMS in another area or combined with another brain region.

Limitations

This study was performed with a small and uncontrolled sample. Therefore, the results should be considered in a weighted way. The impossibility of performing structural neuroimaging did not allow the evaluation of possible cerebral atrophies, as well as the relationship between the distance from the coil to the cortex and the outcome. However, diffuse, bilateral and symmetrical atrophy may not interfere with rTMS dose, since in the MT was determined over a region with similar atrophy.

Conclusion

This study showed efficacy of rTMS over the DMPFC in the elderly with TRD. The rTMS protocol applied also demonstrated safety and good tolerability. rTMS over this newer brain target also improved response selection and processing speed regardless of treatment response. This is in accordance with the literature, which suggests that cognitive improvement is not related to mood improvement. Interestingly, the literature about cognitive enhancement after neuromodulation of DLPFC showed attention improvement, a cognitive domain different from the one that improved in the current study. Therefore, the clinical and cognitive effects of rTMS seem to be related to the selected stimulation target and respective functional anatomical structures.

Lastly, it is necessary to evaluate this rTMS protocol in a randomized, double-blind, sham-controlled study in TRD aging patients. Moreover, performing structural and functional MRI to assess neuroanatomical changes, correlate outcomes with the coil-cortex distance, and the effects on neural networks.

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2.3 - Artigo 3

ARTIGO SUBMETIDO PARA PUBLICAÇÃO

Transcranial Magnetic Stimulation in anxiety and trauma-related disorders: a systematic review and meta-analysis

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Abstract

Background: Transcranial magnetic stimulation (TMS) has been evaluated as an effective treatment option for patients with major depressive disorder. To date, however, limited research has evaluated the capacity of TMS for other neuropsychiatric disorders.

Objective: The objective of this paper is to systematically review the literature that has evaluated TMS as a treatment for anxiety and trauma-related disorders.

Methods: We searched for articles published up to December 2017 in Embase, Medline, and ISI Web of Science databases, in accordance with the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement. Articles (n = 520) evaluating TMS in anxiety and trauma-related disorders were screened and a small subset of these that met eligibility criteria (n = 17) were included in the systematic review, of which 9 evaluated TMS in Posttraumatic stress disorder (PTSD), 4 in Generalized Anxiety Disorder (GAD), 2 in Specific phobia (SP) and 2 in Panic disorder (PD). The meta-analysis was performed with PTSD and GAD since PD and SP had an insufficient number of studies and sample sizes.

Results: Among anxiety and trauma-related disorders, TMS has been most widely studied as a treatment for PTSD. TMS demonstrated large overall treatment effect for both PTSD (ES = -0.88, 95%CI: -1.42, -0.34) and GAD (ES= -2.06, 95%CI: -2.64, -1.48), including applying high-frequency over the right dorsolateral prefrontal cortex. Since few studies have evaluated TMS for SP and PD, few conclusions can be drawn.

Conclusions: Our meta-analysis suggests that TMS may be an effective treatment for GAD and PTSD.

Keywords: transcranial magnetic stimulation; theta-burst; anxiety disorders; posttraumatic stress disorder, meta-analysis, systematic-review.

Highlights

- We performed a systematic review and meta-analysis of PTSD, GAD, PD, and SP.
- TMS presented large effect sizes as a treatment for PTSD and GAD.
- Follow-up studies in GAD showed improvement of the disorder after TMS.
- High-frequency TMS over the right dorsolateral prefrontal cortex (rDLPFC) showed better results for both PTSD and GAD when compared to low-frequency over the rDLPFC or high-frequency over the left DLPFC (lDLPFC).
- Future studies should evaluate maintenance treatment.

Introduction

Transcranial Magnetic Stimulation (TMS) is a safe and effective noninvasive and nonconvulsive neuromodulation therapy cleared by the U.S. Federal Drug Administration for the treatment of major depressive disorder (MDD) since 2008(1), and now part of the standard of care for this condition. Other neurological and psychiatric conditions are being investigated as possible indication for this treatment, including bipolar disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), chronic pain, and Alzheimer`s disease, among others (2-5).

TMS is a biomedical application of Faraday's principle of electromagnetic induction and works by generating strong and rapidly changing electric currents in a circular coil that is placed on the surface of the skull. This primary current generates a magnetic field that travels unimpeded through the hair, soft tissue, skull and *cerebrospinal fluid* (CSF) (i.e., these structures are minimally affected by the magnetic field) until it reached the neurons of the cortex. At this level, the magnetic field converts back into a (secondary) electrical current able to depolarize neurons and force an action potential, which will then travel from synapse to synapse across an entire functional circuit of interest(6). In a parameter-dependent manner, TMS can induce long-lasting plastic changes and either facilitate (long-term potentiation-(LTP)-like effect) or inhibit (long-term depression-(LTD)-like effects) cortical neurons, and so modulate physiological dynamics across brain regions and networks(7). In this context, TMS has the potential to therapeutically modulate aberrant circuit properties across neuropsychiatric conditions and hence be useful as a treatment beyond conditions such as MDD. The standard TMS is called repetitive TMS (rTMS). Later, other forms of TMS have been created to improve

this technique, for example, to reach deeper brain regions (dTMS) or to reduce treatment time like theta-burst stimulation (TBS). Meanwhile, these stimulation methods are still experimental.

The number of studies evaluating the treatment of other psychiatric and neurological disorders with TMS is growing. Nevertheless, few studies discuss TMS as a treatment for anxiety and trauma-related disorders. Anxiety disorders include disorders mostly related to fear and anxiety and related behavioral changes(8). Despite being a key symptom of these disorders, anxiety is a broad concept and occurs with different features in each disorder like the anticipation of future, sudden periods of intense fear with somatic sensations or worry of being judged. The most prevalent Anxiety disorders in adults are Specific phobia (SP), *Social anxiety disorder (SAD)*, generalized anxiety disorder (GAD), panic disorder (PD) and agoraphobia(9). Before DSM-5, post-traumatic stress disorder (PTSD) was also considered an anxiety disorder(10).

The lifetime co-morbidity rates of PTSD with other psychiatric disorders range from 62% to 92% (11). Furthermore, there is evidence that PD, GAD, and PTSD may have a common genetic predisposition(12). Unfortunately, a significant percentage of patients suffering from these disorders show no improvement after several trials with pharmacotherapy and cognitive behavior therapy (CBT)(13). TMS may be an option for disorders and patients sensitive to side effects of psychotropic medications, since adverse events frequently caused by psychotropic medications, like gastrointestinal symptoms, dry mouth, sexual dysfunction, and weight gain, are not expected with TMS (14, 15). The objective of this systematic review is to review and evaluate the existing literature on TMS for treating anxiety disorders and PTSD.

Materials and Methods

Literature review

We searched Embase, PubMed, and ISI Web of Science (up to December 2017) in accordance with the recommendations of the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement(16). The search terms used were (“TMS” OR “Repetitive TMS” OR “Transcranial Magnetic Stimulation” OR “theta-burst”) AND

(“Anxiety Disorders” OR “Social Anxiety” OR “Generalized Anxiety Disorder” OR “Panic disorder” OR “stress disorder, post-traumatic” OR “Social, Phobia” OR “phobic disorder” OR "Phobia, Specific") NOT ("Obsessive-Compulsive Disorder" OR "Anxiety, Separation" OR "Neurocirculatory Asthenia" OR "Neurotic Disorders"). We also examined the reference lists from selected articles in search of papers that could be missing. Only original articles published in English were included. Studies with animals and duplicated references were excluded.

Eligibility criteria and study selection

The eligibility criteria for the inclusion of the study in the present review were: 1) treatment of SP, *SAD*, GAD, PD or PTSD diagnosed according to DSM-IV to DSM-5 or ICD-10 classifications; 2) intervention with any form of TMS with at least 5 sessions (except for SP), because this is the minimum number of sessions to induce plasticity and improve symptoms for long-term, while in SP a short-term effect may be useful since the symptoms are more punctual(17, 18); 3) report of response and remission rates, or score reduction on a validated scale of the investigated disorder and 4) articles written in English. Controlled or open-label studies with- or without randomization and retrospective studies were accepted. Two researchers evaluated titles and abstracts to select potentially eligible articles, full papers were assessed to confirm eligibility whenever necessary, and divergences were solved by consensus.

Quality assessment and data extraction

The assessment of the quality of the studies and risk of bias followed the Cochrane guidelines(19). The pre- and post-treatment data extracted from each study consisted of study design, mean age, number of patients of each treatment-group, TMS parameters (number of sessions, target and localization method, frequency, intensity, total pulses, type of coil), dropouts and reasons, scale scores mean and standard deviation (SD), response and remission rates and period of follow-up. We contacted authors for additional data whenever necessary. We greatly appreciate the contribution of Dr. Watts, Osuch, and Zangen (4, 20, 21).

Quantitative analysis

The analysis was performed with Stata 15. The primary outcome was the improvement of each disorder measured by a validated scale. The effect sizes of the studies were determined by the mean differences of sham versus active TMS of the post to pre-treatment score changes weighted with Hedges’ g with 95% of confidence interval (CI) in a random effect model, which

assumes variability across studies in terms of the effect size. In studies with three treatment groups, the active group with less effect was excluded. Heterogeneity between studies was assessed with the I-square test (I^2). In case of moderate or high heterogeneity ($I^2 > 50\%$) a sensitivity analysis would be carried out to determine the impact of each study on the results and a meta-regression would be performed to evaluate the influence of each TMS parameter at a time. For studies without the SD of the total score of the primary outcome, the largest similar SD found in other studies was repeated, according to the Cochrane Handbook for Systematic Review(22). Publication bias was evaluated by funnel plots of effect size versus standard error and by Egger`s test (23).

The studies were analysed in 4 groups: SP, GAD, PD, and PTSD, since there were no articles about TMS in SAD. Furthermore, the meta-analysis was carried-out only for GAD and PTSD since the other reviewed disorders do not have the minimum amount of studies and sample size needed to perform a meta-analysis.

Results

A total of 643 references were found (165 in Embase, 360 in Medline, 113 in ISI Web of Science and 5 through additional sources). Of those, 123 were duplicate references, and 37 were not in the English language. The remaining 483 references underwent a title and abstract analysis after which 419 were excluded. Finally, 64 articles were recovered for full-text reading. After this process, only 17 articles met the inclusion criteria of articles that assessed TMS as a treatment for anxiety disorders or PTSD (9 PTSD, 4 GAD, 2 SP, and 2 PD) (Table 1). The meta-analysis of SP and PD were not performed because of the small number of studies and sample size.

TMS and Generalized Anxiety Disorder

GAD criteria include excessive anxiety and worry most of the days, for at least six months with social and occupational impairment (8). We identified a total of 4 studies that used TMS to treat GAD, of which two are randomized, double-blind and sham-controlled and two are uncontrolled open-trials (24-27). The rTMS parameters, questionnaires used and method for target identification are in table 2. Three studies applied low-frequency (1 Hz) rTMS over the right DLPFC (rDLPFC), and one of these studies evaluated bilateral rTMS treatment in patients with comorbid GAD and MDD employing 1 Hz over the rDLPFC followed by 10 Hz over the lDLPFC (24, 26, 27). White and Tavakoli (2015) have not reported the intensity,

neither the pulses applied over the lDLPFC(26). One RCT applied 20 Hz, with 110% MT over the rDLPFC (25). Figure 2 shows the weighted effect sizes of the studies.

The overall effect size was -2.06 (95%CI: -2.64, -1.48), widely favouring active rTMS treatment. There was low heterogeneity (I^2=11.6%, p=0.335); therefore the difference between studies is by chance. Possible causes of publication bias were tested with the funnel plot (fig 3), which showed no asymmetry (p=0.705, Egger`s test). Table 2 shows the reported dropouts and the number of dropouts due to side effects.

Both RCT and one uncontrolled open-trial that evaluated the acute effects of rTMS in GAD, followed-up patients after one, three or six months(24, 25, 28). Diefenbach et al. (2016) showed better results after a three-months follow-up than at the end of rTMS treatment. Six out of 9 patients achieved remission compared to three at the end of rTMS. The number of responders remained the same(24). Dilkov et al. (2017), also found an increase in the remission rate of the active group, that reached 100% after 1-month follow-up (25). Bystritsky et al. (2009) reported maintenance of the improvement after a 6-month follow-up without deterioration of questionnaires scores when compared to the end of rTMS treatment (27, 28). These studies show rTMS as a promising treatment for GAD.

Table 1 – Number of included studies per psychiatric disorder and study design

Disorder	Double-blind, randomized, sham-controlled (n)	Single-blind, randomized, sham-controlled (n)	Open-label (n)	Retrospective (n)
PTSD	6	0	1	2
GAD	2	0	2	0
SP	1	1	0	0
PD	2	0	0	0

Figure 1: Flow chart of the search results and studies selected for the review of TMS and traumatic and anxiety disorders

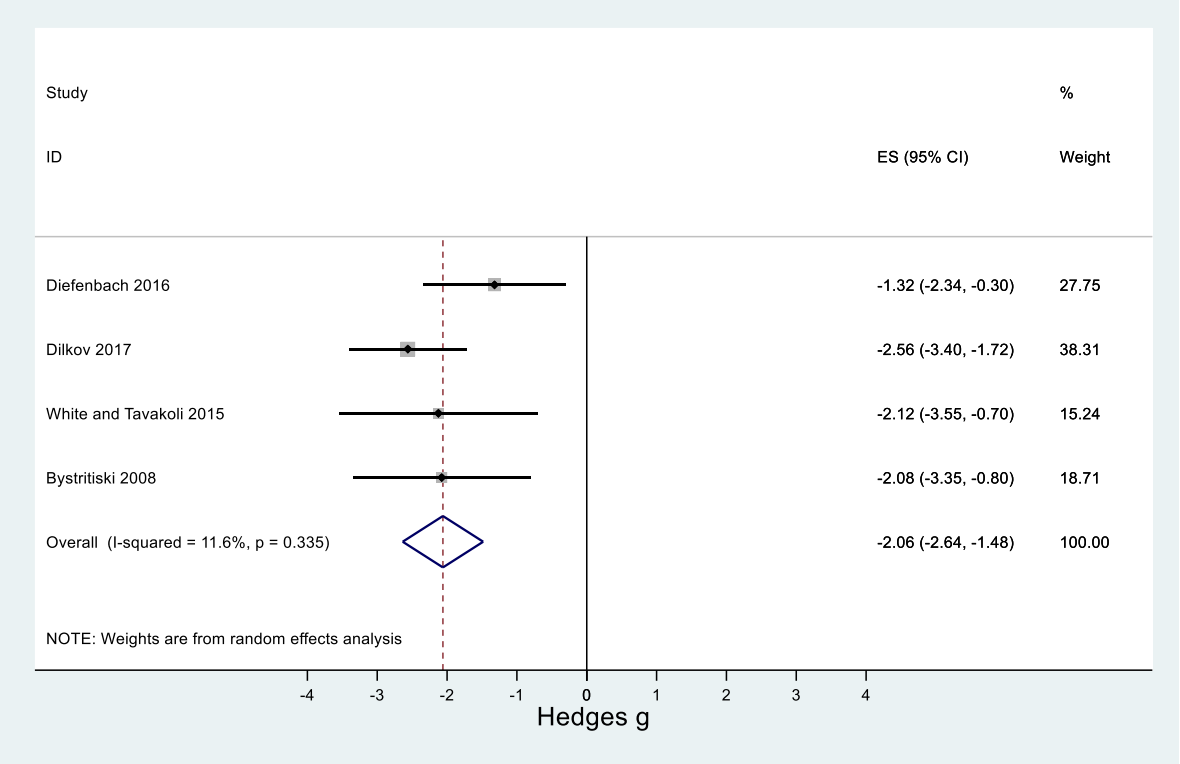

Fig 2 – Forest plot of the 4 studies that evaluated rTMS as a treatment for GAD (2 RCT and 2 uncontrolled open-label studies)

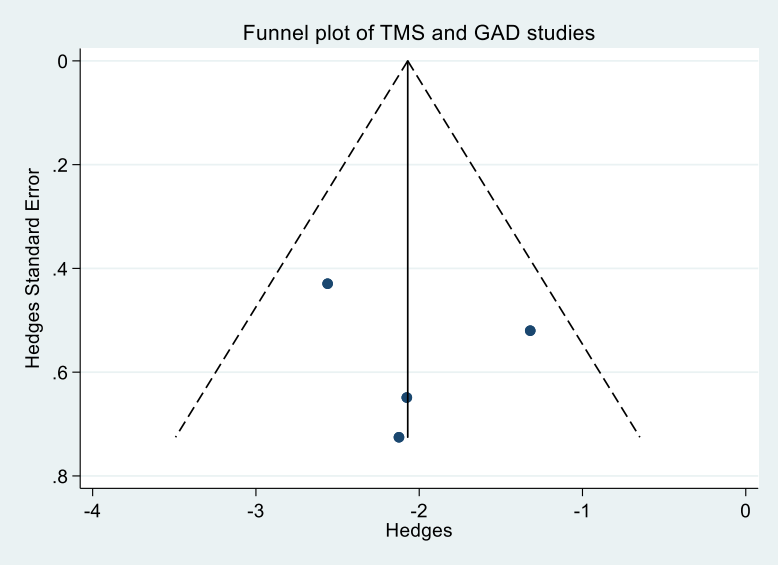

Figure 3 – Funnel plot of the four studies that evaluated rTMS as a treatment for GAD

Table 2 – Therapeutic use of TMS in Generalized Anxiety Disorder

TMS and Specific phobia

Patients with SP suffer from an irrational fear of an object or situation(8). Only two studies evaluated rTMS or inhibitory theta-burst stimulation (iTBS) as a treatment for SP(29, 30). Notzon et al. evaluated the effects of one iTBS session on virtual reality-provoked anxiety in 41 patients with spider phobia and 42 healthy controls randomized to active or sham iTBS, measured by questionnaires of fear of spider (SPQ), anxiety (ASI) and disgust sensitivity (DS) (29). They applied 15 Hz, 80% of the resting motor threshold (RMT), 600 pulses, over the lDLPFC. One session of iTBS showed no improvement. Conversely, iTBS predisposed patients to more anxiety, as measured by heart rate variability(29). However, future studies could evaluate more treatment sessions and different TBS parameters like the number of pulses.

Previous studies showed the importance of the ventromedial prefrontal cortex (vmPFC) in fear extinction(30). Since this brain area is too deep to be directly modulated by TMS, a research group used the strategy to indirectly stimulate this region through FPz, according to the electroencephalography (EEG) 10-20 system. Herrmann al. studied the effect of active or sham rTMS applied before a virtual reality exposure to heights in two groups(30). One group comprised 20 individuals diagnosed with acrophobia and the other group 19 healthy subjects. The protocol consisted of two sessions of 20 min of rTMS with 10 Hz at 100% MT, 4 sec on and 26 sec off, with 1560 pulses/session and an interval of 2 weeks. At the end, anxiety (t = 37, 2.33, $p < 0.05$) and avoidance ratings (t = 37, 2.34, $p < 0.05$) decreased when compared to baseline(30).

Table 3 – Therapeutic use of TMS in Specific Phobia

TMS and Panic Disorder

PD is a disorder in which patients experience recurring, unexpected panic attacks, avoid situations that might cause another panic attack, and worry about having additional panic attacks(8). The two double-blind, randomized, sham-controlled trials that evaluated the efficacy of rTMS or iTBS as a treatment of PD used different protocols and obtained mixed results (31-34). One study evaluated the treatment of co-morbid PD and major depressive disorder (MDD) with rTMS (31). This study enrolled 25 patients, randomized to active (n=12) or sham (n=13) rTMS. They applied 1 Hz, at 110% MT, and 1,800 pulses/session, over the

rDLPFC, for four weeks. After the last week of treatment, patients in active rTMS had significant improvement in PD but not depression. This study was followed by four additional weeks of an open-label treatment in which patients in the sham group could undergo active treatment and patients in the active group could receive additional treatment. After this second phase, patients continued to improve from PD and improved from MDD. Subsequently, at a 6-month follow-up, patients showed sustained improvement of both disorders(31).

The other study evaluated whether iTBS associated with psychoeducation sessions could ameliorate clinical symptoms, verbal fluency and brain activity of PD patients (32). This study assessed 44 patients with PD and 23 healthy controls. PD patients were equally randomized to sham or 10 Hz iTBS. Both PD groups underwent 15 weekdays iTBS sessions. All participants completed a verbal fluency task during functional near-infrared spectroscopy (NIRS) and three-weekly group psychoeducation sessions. The healthy controls had not undergone rTMS. In the end, both active and sham rTMS groups showed significant improvement of PD symptoms, without significant difference between groups. There were no improvements in prefrontal hypoactivity or verbal fluency following iTBS(32).

Table 4 – Therapeutic use of TMS in Panic Disorder

TMS and Post-Traumatic Stress Disorder

PTSD is characterized by re-experiencing, avoidance, and hyperarousal clusters of symptoms that may result in significant social or occupational dysfunction(35). The treatment of PTSD with TMS is the most studied in the trauma-related and anxiety disorders, and still, only nine studies were included in this meta-analysis(4, 20, 21, 36-41). Six trials are double-blind, randomized, sham-controlled, and one of these is a crossover. The other three are open-label studies. Only one study evaluated the effect of deep TMS (dTMS)(20), while all others applied rTMS. The details of the study, including protocol parameters and validated questionnaires used are in table 5-8. Figure 4 shows the unbiased weighted estimates of Hedges effect sizes with a random effects model. The overall effect size was -0.88 (95%IC: -1.42, -0.34), which favors TMS and suggests a medium treatment effect. The heterogeneity was low (I^2=49.0%, p=0.047). The funnel plot is symmetric (p=0.992, Egger's test), suggesting that publication bias is unlikely. The reported dropouts and the amount due to side effects are in table 5-8.

Concerning the sample characteristics, two studies assessed combat-related PTSD, and in one of these studies, all patients had a history of substance abuse (39, 40) and four studies evaluated comorbid PTSD and MDD(20, 21, 39, 41). Eight of the nine studies applied 1 to 20Hz rTMS to the r- and/or l- DLPDC. Three of the RCT consisted of 3 treatment groups (20, 36, 38). One study compared 20 Hz rTMS over the r- or lDLPFC to sham, and another compared 1 to 10 Hz over the rDLPFC (36, 38). High-frequency over the rDLPFC showed better results in both studies. The third study compared active and sham deep TMS (dTMS) combined with exposure to images of traumatic and non-traumatic events (20). The response rate of the active-dTMS/traumatic images-group was 44% while in the active-dTMS/non-traumatic images was 12.5% and the sham-dTMS/traumatic images-group was 0% (20).

Three studies reported improvement of all clusters of symptoms, two only of the hyperarousal cluster, one only avoidance and one only re-experiencing cluster (4, 21, 36-38, 40, 41). The two studies that applied rTMS over the lDLPFC in PTSD/MDD patients showed improvement of depressive symptoms(39, 41).

Four studies evaluated patients at follow-up intervals of 14 days, 2 months, or 3 months (4, 36, 38, 39). Three of these studies showed that there was a loss of improvement in PTSD symptoms at follow-up relative to the end of treatment despite improvement from baseline (4, 36, 38). The one other study, which found that patients had improvements in MDD symptoms but not PTSD symptoms post-treatment, also found decreased depressive symptom improvement two months after the end of rTMS treatment (39).

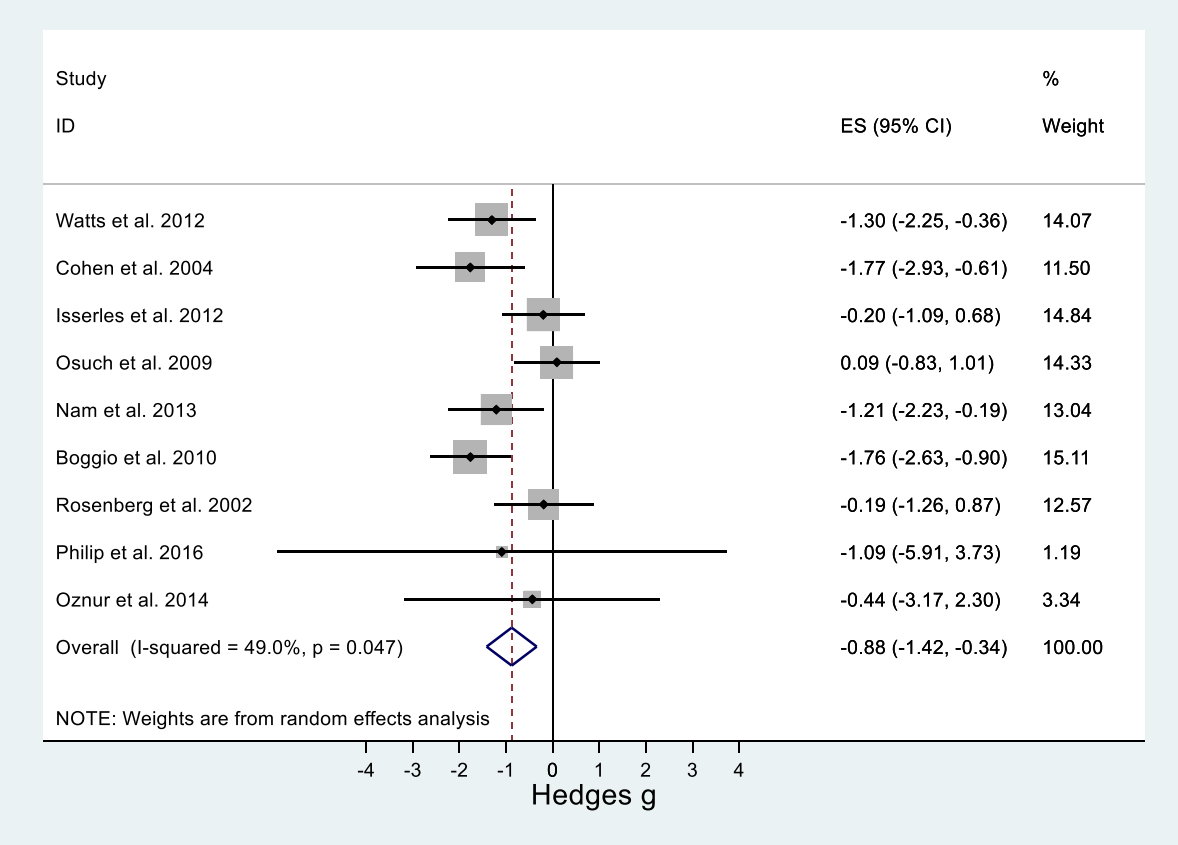

Fig 4 – Forest plot of all 9 PTSD and TMS studies

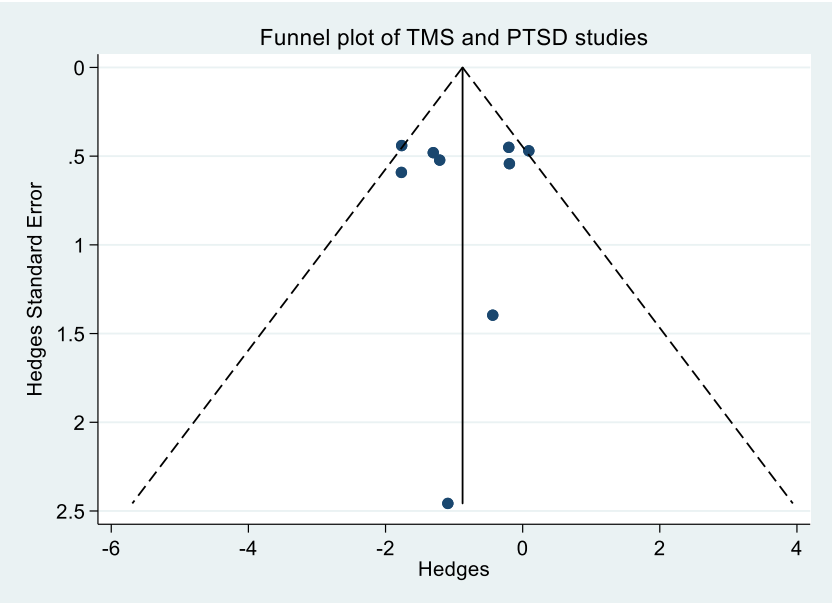

Fig 5 – Forest plot for the meta-analysis of the treatment of PTSD with TMS.

Table 5 – Double-blind, randomized, sham-controlled studies of TMS in PTSD

Table 6 - Double-blind, crossover, sham-controlled studies of TMS in PTSD

Table 7 - Open-label studies of TMS in PTSD

Table 8 – Retrospective studies of TMS in PTSD

Side Effects of TMS

Eleven of the 17 studies (41%) included in this meta-analysis presented adverse events(20, 24, 25, 29-31, 36, 37, 39, 42). Most of the side effects were mild to moderate. However, two studies reported a single generalized tonic-clonic seizure(20, 25). These studies combined higher frequency (20 Hz), a high total number of pulses and intensity above 100% MT. One study applied rTMS over the rDLPFC and the other dTMS over the mPFC (20, 25). Therefore, both studies delivered a high TMS dosage due to a combination of stimulation parameters which may have triggered a seizure in patients with a lower convulsive threshold.

Adverse events in patients that underwent active TMS were headache, neck pain, scalp pain, tingling, sleepiness, facial twitch, and impaired cognition during treatment. A PTSD study reported two patients with manic episodes, one patient in the low-frequency and another in the high-frequency group(36). Few studies reported the adverse events of the sham group separately, which were neck and scalp pain, headache, impaired cognition, dizziness, sleepiness, and discomfort with treatment and the study schedule(20, 24, 31, 37, 38). One PD study reported hearing impairment, mainly in the sham group(31). Adverse events are described in Table 9.

Another critical issue is to evaluate the percentage of patients who dropped out due to adverse events. A quarter of the studies reported the reasons for dropouts: the minority of dropouts were due to adverse events and no studies reported treatment ineffectiveness as a reason for dropouts. The causes of dropouts varied from withdrawal or improvement of the disorder before starting treatment, to impossibility to determine the motor threshold, and technical error(25, 36, 39). Considering studies that evaluated TMS as a treatment for PTSD, one study reported two dropouts, one because of increased anxiety and one due to unease (20) and another reported one dropout in a PTSD sample due to marked headache (39).

Table 9 – Occurrence of adverse events in TMS treatment of anxiety disorders and PTSD

Discussion

This review provides a complete overview of the existing studies that evaluated TMS as a treatment for PTSD or anxiety disorders. Regarding GAD, the overall effect size largely favors TMS treatment. (24-28). The totality of the studies targeted the rDLPFC and one of these studies employed a bilateral stimulation in a sample with comorbid GAD and MDD. The only study that used 20 Hz on the right side (as opposed to the usual 1 Hz) and more than 90% MT, also presented the best response and remission rates and highest effect size(25). This positive outcome may due to the combination of frequency, intensity and total number of pulses.

Interestingly, the same happened with the PTSD studies, in which 20Hz over the rDLPFC showed better outcomes. Therefore, despite the low-frequency being the standard treatment for right-sided TMS, the use of high-frequency seems to be more promising. Nevertheless, it is noteworthy that the higher the frequency and intensity, the more effective and riskier is TMS. Therefore, the safe limits of protocol parameters must be respected to ensure patient safety.

Three GAD studies reported follow-ups from 1 to 6-months. The 6-month follow-up showed sustained improvement and the follow-ups of one and three months, both randomized, double-blind, sham-controlled studies, showed improvement when compared to the end of TMS treatment. In general, these results suggest that rDLPFC rTMS might have anxiolytic activity in GAD and that both high- and low-frequencies work. So, a controlled-trial comparing high- and low-frequency groups would be interesting.

SP is still neglected, so almost no conclusions can be drawn except that treatments with more than one session should be used with intensities of at least 100% MT. Similarly, it is difficult to make assumptions on the use of TMS as a treatment for PD based on two small and heterogeneous trials. However, there are indications that 1Hz over the rDLPFC may work with intensities higher than 100% RMT. Future studies may clarify whether the failure of PD treatment on the left side was due to laterality or to the iTBS technique.

In relation to PTSD, 5 of the 9 selected studies showed substantial treatment effect, one moderate effect and the overall effect size was also large(4, 20, 21, 36-40, 43). The total number

of pulses and the number of sessions demonstrated an impact on treatment outcome and caused heterogeneity. Considering the only four PTSD studies with large effect size and small variability (all of these randomized, sham-controlled trials), there are indications that the rDLPFC is a better target to treat PTSD and anxiety symptoms when compared to the lDLPFC. Two of these four studies applied high-frequency rTMS (10 and 20 Hz) over the rDLPFC and compared with low-frequency over the rDLPFC or high-frequency over the lDLPFC and, in both studies, high-frequency rTMS over the rDLPFC showed greater improvement. (36, 38). This is noteworthy since there is a tendency of applying low-frequency over the rDLPFC.

Comorbidity of PTSD and depression is prevalent, and the association of left-side TMS may be a good option. The only trial with dTMS for PTSD demonstrated efficacy, although with small treatment effect (20). This study is the only that applied stimulation over the mPFC. Therefore, it is essential that further studies assess the efficacy of both dTMS and high-frequency over the rDLPFC. Also, it seems that TMS maintenance would be necessary since the three studies that followed-up patients from 14 days to 3 months already found deterioration of PTSD improvement comparing to the end of treatment (4, 36, 38). However, it is important to note that in PTSD follow-ups, patients presented loss of improvement relative to the end of treatment, despite remaining better when compared to baseline(4, 36, 38, 39). Meanwhile, GAD patients showed improvement in short-term follow-ups when compared to the end of TMS treatment(24, 25, 28).

Considering the studies that reported side effects, TMS seems to be safe and well-tolerated in anxiety disorders and PTSD. However, less than half of the studies in this meta-analysis communicated information about side effects and some only broadly described side effects. Researchers should assess adverse events systematically with a questionnaire and provide the frequency of each adverse event by treatment group. Such a practice would allow for a comparison of adverse events across different treatment conditions and for an evaluation of risk-benefit.

Finally, despite the evolvement of TMS techniques and the constant growth in the number of studies, this technique has been poorly studied in the treatment of anxiety or trauma-related disorders. These disorders can cause significant impairment in the lives of patients, of those who live with them, and in the health system. Therefore, based on the current literature results, TMS should be better studied as an alternative intervention for anxiety and trauma-related disorders so that we can define the best treatment parameters for these conditions. At this point, future studies should consider intensities higher than 100% RMT and, due to the difficulty of obtaining larger samples, multicentric studies should be stimulated.

Limitations

This meta-analysis is limited by few studies with small sample sizes. Moreover, across the reviewed studies, there is a lack of uniformity of study design and how outcomes are measured and reported. This set of factors make it difficult to generalize the results. Furthermore, there may have been language bias since only English studies were included. However, it is possible that this bias would not interfere with the results of the meta-analysis. Finally, the lack of reporting of adverse events limits the evaluation of safety and tolerability.

Conclusion

In summary, there are still limited data on the effectiveness of TMS in anxiety or trauma-related disorders. In general, there are few studies, with small samples and diverse study designs and protocols. Only two studies evaluated TMS as a treatment for SP and PD and none evaluated TMS as a treatment for SAD. The overall effect sizes show that TMS might be an efficacious option for the treatment of patients with PTSD or GAD that failed to respond to at least one adequate trial of standard treatment. Therefore, it is important to have more robust data, longer-term follow-ups, and maintenance treatment studies. Based on the studies that reported side effects, TMS showed safety and tolerability in the treatment of anxiety disorders and PTSD. Nevertheless, authors should describe adverse events in a more objective and detailed way.

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2.4 - Artigo 4

ARTIGO SUBMETIDO PARA PUBLICAÇÃO

Clinical Applications of Transcranial Magnetic Stimulation in Bipolar Disorder

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Abstract

Background: Many patients with bipolar disorder (BD) fail to experience benefit following traditional pharmacotherapy, necessitating alternative treatment options that will enable such patients to achieve remission. Transcranial magnetic stimulation (TMS) is a relatively new, non-invasive neuromodulation technique that involves the application of magnetic pulses on hyperactive or hypoactive cortical brain areas. We evaluated the existing literature on TMS as a treatment for BD across varied mood states.

Methods: We searched Medline for relevant articles using the following search terms: ("TMS" OR "Repetitive TMS" OR "Transcranial Magnetic Stimulation") AND ("Bipolar Disorder" OR "Bipolar Depression" OR "Mania" OR "Hypomania"). We included original data articles published in English that evaluated outcomes in a bipolar sample across depressive, manic, mixed, and maintenance phases of BD.

Results: To date, TMS has been the focus of a limited number of clinical trials in BD. Most research has been conducted in bipolar depression, with several studies suggesting the potential of repetitive TMS for reducing depressive symptoms. Studies of TMS for mania have yielded more mixed findings. Few studies have evaluated TMS in other phases of the bipolar illness. TMS is generally associated with mild side effects though, in a few studies, it has been shown to contribute to a manic switch in previously depressed bipolar patients.

Conclusions: TMS showed mixed outcomes as a treatment for patients with BD who have failed to respond to pharmacological or psychosocial treatment. Future research should more clearly elucidate which TMS protocols may be most effective for a given bipolar patient.

Keywords: Transcranial magnetic stimulation, Bipolar disorder, Bipolar depression, Mania, Maintenance-treatment

Introduction

Pharmacological agents have been effectively applied across all phases of the bipolar illness and, thus, are considered a first-line treatment for bipolar disorder (BD)[1]. However, pharmacotherapy for BD has some notable limitations. Many patients with bipolar disorder fail to respond to adequate pharmacotherapy[2]. For those patients who do experience symptomatic improvements following pharmacological treatment, many are forced to contend with frequent and intolerable side effects that lead to medication non-adherence and/or discontinuation[3, 4]. In addition, several patients with BD suffer from an increased medical burden and clinicians must thus be mindful of interactions among the medications that patients could be taking to manage multiple medical concerns[5, 6]. To that end, the limitations of pharmacotherapy suggest the importance of alternative treatment options that will help patients with BD achieve remission[6].

Transcranial magnetic stimulation (TMS) is a relatively new, non-invasive therapeutic option that involves the application of magnetic pulses on hyperactive or hypoactive cortical brain areas with the aim of restoring the balance in brain networks[7]. To administer TMS, the clinician places an electromagnetic coil on a pre-specified region of the patient's scalp. Magnetic pulses from the coil travel through the skull towards a target cortical area, resulting in neural activation changes. To date, TMS has received the most consistent clinical and research application in treatment-resistant depression[8, 9]. In the past several years, studies have explored the application of TMS in other psychiatric disorders. One initial randomized study in a combined unipolar and bipolar depressed sample evaluated daily TMS over the left prefrontal cortex relative to a sham treatment. Among the TMS treatment responders, 55% had bipolar (as opposed to unipolar) depression[10], supplying early evidence for the benefit of using TMS in a bipolar sample. Since that initial trial, other researchers have evaluated TMS for treating a range of mood symptoms in BD. The aim of this review is to explore the existing literature on the application of TMS across symptomatic and remitted stages of bipolar illness.

Methods

We searched Medline for relevant articles using the following search terms: ("TMS" OR "Repetitive TMS" OR "Transcranial Magnetic Stimulation") AND ("Bipolar Disorder" OR "Bipolar Depression" OR "Mania" OR "Hypomania"). All search fields of the databases were included to maximize inclusivity. The research took place in June 2018 and no time restriction was placed on any of the database searches. Manual searches were also conducted using the reference lists from identified articles.

Eligible studies were original data articles exploring the application of TMS in various stages of a bipolar episode. Articles were not included if they combined unipolar and bipolar samples without separately evaluating outcomes in both disorders. Only articles published in English in peer-reviewed journals were eligible. Single case studies, review papers, and theoretical articles were excluded. Results of the search were compared to exclude repeated references. Following this step, titles and abstracts were assessed to select potentially eligible articles. These articles were read in full to confirm they were relevant for the present review.

Results

TMS in Bipolar Depression

Most studies evaluating the application of TMS in bipolar depression have focused on repetitive transcranial magnetic stimulation (rTMS) which involves repeated magnetic doses at a set intensity level to a specified brain area (tables 1 and 2)[11]. Two seminal rTMS studies in an exclusively bipolar sample yielded mixed results. Dolberg and colleagues conducted a randomized, controlled trial evaluating active, high-frequency, left-sided rTMS (20 sessions) relative to a sham intervention (10 sessions) for bipolar depression (n = 20)[12]. The authors found that the active group had statistically significant improvements in psychiatric outcomes as evaluated by the Hamilton Depression Rating Scale [HDRS][13] and Brief Psychiatric Rating Scale[14] though, of note, improvements were most prominent after the first two weeks of treatment[12]. In a second study, Nahas and colleagues randomly assigned patients (n = 23) with bipolar depression (with two participants in a mixed state; e.g., both depressive and manic) to receive 10 sessions of left prefrontal, high-frequency rTMS or a sham treatment over a two-week period. The prefrontal region was selected for TMS application given data from prior studies which found that consistent stimulation of prefrontal areas yielded mood benefits. Post-treatment, though the treatment was well-tolerated by participants, there were no significant differences between the groups in symptomatic improvements (there was a trend of decreased depressive symptoms favoring the active group)[15]. In this way, subsequent intervention researches are necessary to clarify some important questions remained. First, could rTMS yield a consistently potent response relative to a sham treatment such that modulation of the specific target brain area produced symptomatic improvements (as opposed to the psychological impact of receiving what may or may not have been a neurological treatment)? Moreover, if rTMS is able to consistently yield important mood benefits in BD, is there a defined window for symptomatic improvements? In a subsequent randomized trial, Tamas and colleagues (2007)

randomly assigned participants (n = 5) to receive 8 sessions (4 weeks) of active rTMS or a sham treatment over the right DLPFC. In this study, the sham group consisted of a single participant, a not-insignificant limitation. Participants receiving rTMS demonstrated greater improvements in depressive symptoms (as assessed via the HDRS[13]) relative to those receiving a sham treatment, though the benefits favoring the rTMS group did not emerge until two weeks post-treatment[16], a duration that contrasts with the timeframe for improvements evidenced in the study conducted by Dolberg and colleagues[12]. Ultimately, these data suggest it may be difficult to broadly apply a pre-determined time frame of rTMS treatment or to expect treatment gains within a specific time period. Certain clinical variables may be associated with the need for a longer duration of rTMS treatment in BD (e.g., more than 15 rTMS sessions). Older patients with a longer, more refractory, and more severe bipolar depression may require more rTMS sessions than patients with a shorter, less chronic bipolar depression[17].

Since these initial studies, follow-up clinical trials of rTMS in bipolar depression have focused on fine-tuning the precision of administration through a focus on specific variables. Many studies of rTMS in unipolar and bipolar depressed samples have historically incorporated left-sided dorsolateral prefrontal cortex (DLPFC) with high frequency rTMS. Data across several studies suggest particular benefits of this location/frequency combination for depression[12, 15, 18]. Some studies also showed the benefit of rTMS applied at a low frequency over the right DLPFC. Dell'Osso and colleagues evaluated the efficacy of low-frequency rTMS over the right DLPFC in patients (n = 11) with bipolar depression for a duration of 3 weeks[19]. This study was unique in that it combined rTMS with brain navigation, or use of magnetic resonance imaging to precisely target the most relevant cortical region for a given patient. Post-treatment, patients demonstrated significant improvements in symptoms of depression (as assessed via the HDRS [13] and the Montgomery-Asberg Depression Rating Scale [MADRS][20]) and reductions in overall illness severity (as assessed via the Clinical Global Impression scale[CGI][21])[19]. Fewer studies have evaluated the comparative effectiveness of high versus low frequency rTMS of the right versus left DLPFC in the context of a single study. Dell'Osso and colleagues (2015) randomized patients (n = 33) to receive one of three 20-session rTMS protocols over a four-week period: 1) low frequency rTMS over the right DLPFC incorporating pauses at specified points (420 stimuli per session), 2) low frequency rTMS over the right DLPFC at a continuous rate (900 stimuli per session), or 3) high-frequency rTMS over the left DLPFC incorporating pauses at specified points (750 stimuli per session). At post-treatment, patients demonstrated significant reductions in depression and illness severity outcomes (as assessed via the HDRS, MADRS, and CGI) with no significant group differences in treatment

efficacy or tolerability[22]. Thus, these data suggest flexibility in rTMS protocols such that patients may still be able to experience benefits regardless of the frequency or location of the rTMS treatment; a novel finding suggesting that the widely-followed left DLPFC, high-frequency rTMS protocol may not be the only effective option. Moreover, these data may indicate that patients who do not respond to a particular rTMS protocol could benefit from a different protocol (e.g., different frequency and/or cortical target).

More recently, studies have suggested the benefit of sequentially applied bilateral stimulation involving left-sided, low-frequency and right-sided, high-frequency rTMS[18]. As such, Fitzgerald and colleagues evaluated 20 sessions of active sequential bilateral rTMS relative to sham treatment for a four-week period among patients (n = 49) with bipolar depression. Post-treatment, no significant differences were found between the two groups, suggesting that the bilateral approach to rTMS may not be more helpful for treating psychiatric symptoms in BD as the historically applied unilateral approach[18]. However, in a separate study evaluating 20 sessions of bilateral (left DLPFC, high-frequency and right DLPFC, low-frequency) versus unilateral (right-sided DLPFC, low-frequency) rTMS for bipolar depression (n = 30), the proportion of rTMS responders was significantly greater in the bilateral group relative to the unilateral group[23]. This study incorporated a unique outcome measure of beta wave activity (as measured via electroencephalography) on the basis of data suggesting that depression is associated with enhanced beta frequency oscillations in frontal and occipital brain areas[23, 24]. Indeed, post-treatment, the authors found that responders to rTMS had significantly decreased beta frequency oscillation, a finding that highlights a possible biological marker for assessing response to rTMS[23].

Lastly, some studies have incorporated novel technology with the goal of enhancing the efficacy of rTMS protocols. One innovative approach involves modification of the coil used in standard TMS treatment. Many rTMS protocols incorporate a coil that provides restricted depth, thus potentially limiting the capacity of direct stimulation over the relevant cortical region. Some data suggest that a novel H1-coil allows a magnetic field that can enable treatment to occur over a wider area and with greater depth of stimulation. The H1-coil has been the focus of limited study in BD, although one trial in patients with bipolar depression (n = 19) found that 20 sessions of rTMS delivered through an H1-coil over a 4-week period led to significant decrease in HDRS scores[13, 25]. More recently, a modified rTMS approach known as theta burst stimulation (TBS) has been applied to bipolar depression. Data suggests that TBS may exert faster, stronger, and more-lasting effects than traditional rTMS protocols[26, 27]. Beynel and colleagues evaluated three weeks of randomly assigned daily intermittent TBS

[iTBS](involving administration of magnetic pulses in bursts, which is thought to contribute to longer-lasting neural effects) or sham treatment in patients (n = 12) with bipolar depression[27]. This study incorporated an antisaccade task which was completed on the first day of each week before and after iTBS treatment. Patients were placed in a dark room in front of a computer screen and asked to fix their attention on a dot in the center of the screen. During AS trials, patients were instructed to look in specific directions upon exposure to different colored cues. At post-treatment, patients receiving the active iTBS demonstrated improvements in depressed mood (as assessed via the MADRS[20]) with mood improvements correlated with antisaccade task performance; a finding that reflects the potential of the task to be used as a metric of response to TMS treatment. Collectively, data on enhancements to traditional rTMS protocols (e.g., H-coil, iTBS) are promising and reflect future avenues for research.

TMS in Mania

Relative to bipolar depression, TMS has been less extensively studied as a treatment during the manic phase, potentially due to concerns that TMS can induce a manic episode in some patients (refer to the Discussion for findings on manic switches in some bipolar patients following TMS). In addition, whereas most TMS studies in bipolar depression have focused on rTMS, approximately half of the studies in mania have centered on traditional TMS protocols (tables 3). Finally, in studies of TMS for mania, nearly all protocols have targeted the right prefrontal region. This pattern stems from an early clinical trial conducted by Grisaru and colleagues in which manic patients (n = 16) were randomly assigned to 10 sessions of right prefrontal or left prefrontal high-frequency TMS over a two-week period. At post-treatment, patients receiving right prefrontal TMS demonstrated significantly greater improvement in symptoms of mania (as evaluated via the Young Mania Rating Scale[28] and the CGI[21]) relative to patients receiving left prefrontal TMS[29], thus paving the way for future studies of TMS in mania. Of note, the researchers stopped the study early as patients receiving left prefrontal TMS were demonstrating markedly low response to treatment despite being on stable pharmacological treatment[29]. The authors concluded that left-sided TMS may have prevented the action of anti-manic pharmacotherapy[29, 30]. As a follow-up to their initial study, the authors randomly assigned patients (n = 19) to receive 10 sessions of right prefrontal TMS versus sham treatment over the course of two weeks. The authors found no difference between right-sided TMS and sham TMS[30], proposing the possibility that a more intensive treatment protocol is warranted for mania (e.g., greater treatment intensity or length)[30]. One other study explored 8 sessions of right prefrontal rapid TMS in bipolar patients experiencing a manic episode (n = 9)

across a four-week period. Patients experienced improvements in manic symptoms at post-treatment (as evaluated by the Bech-Rafaelsen mania scale[31]); however, this was an open-label trial and thus cannot provide complete insight on the efficacy of a right-sided standard TMS protocol[32].

The remaining studies of TMS in mania applied rTMS protocols. Saba and colleagues conducted a pilot trial of 10-session, high-frequency rTMS over the right DLPFC among patients with current mania (n = 8). After the two-week treatment period, patients demonstrated a significant improvement in manic symptoms (as evaluated via the Mania Assessment Scale and CGI[21])[33]. A subsequent trial randomized patient (n = 41) to receive 10 sessions of high-frequency rTMS over the right DLPFC or a sham treatment. Patients who received the active treatment demonstrated significant improvements in mania (as evaluated via the YMRS[28]) relative to the sham group[34]. However, a follow-up study employing an identical protocol in an adolescent sample found no significant differences in mania outcomes between the active and sham groups[35]. The authors suggest that the discrepant findings between the two studies may be accounted for by metabolic differences between adults and children. Specifically, adult patients with mania may have decreased metabolism on the right side of their brain and increased metabolism on the left side. Thus, in adults, an rTMS protocol over the right DLPFC may help account for these metabolic discrepancies. However, if adolescents do not exhibit this pattern of metabolic activity, they may not be as likely to respond to rTMS over their right DLPFC[35].

To date, only one randomized study has suggested the potential benefit of a TMS protocol over the right DLPFC for mania, with that one study employing an rTMS protocol[34]. It is possible that the repetitive nature of the magnetic pulses in the rTMS protocol yields a particular benefit for mania. However, a subsequent study that replicates the results from this positive trial in an adult sample is warranted to confirm that the failed rTMS trial in the adolescent sample was indeed due to different metabolic patterns in adolescents versus adults and not a broad sign of the treatment's limited efficacy

TMS in Other Illness Stages

A few open-label studies have explored TMS across other phases of the bipolar illness (table 4). Li and colleagues evaluated TMS as a maintenance treatment in patients (n = 7) who had been successfully treated with TMS for their depression in a previously-described study[15]. Patients received weekly maintenance TMS over the left prefrontal cortex for up to one year. Among the study patients, 3 continued with TMS for the full year and did not re-enter an acute

depressive episode during that period [36]. Another study explored 15 sessions of low frequency rTMS over the right DLPFC for patients (n = 40) in a mixed bipolar episode. All patients also received a mood stabilizer as part of the study (e.g., valproate). At post-treatment for depressive symptoms (as assessed via the HDRS[13]), the responder rate was 46%, of which 29% met criteria for full remission. For manic symptoms, the responder rate was 15% with all meeting criteria for full remission[37]. These positive trials suggest that future randomized studies may wish to evaluate TMS as an intervention for bipolar mixed states or as a maintenance option.

Discussion

TMS represents an important, largely understudied avenue of intervention research and clinical care in BD. This review synthesizes data from the few clinical trials that have explored TMS as a treatment for patients with BD across varied mood stages. To date, most research has focused on rTMS for patients in a bipolar depressive episode. Nevertheless, studies are varied in their findings. Five of the eight randomized, controlled trials showed TMS efficacy in bipolar depression and two of these studies with positive outcomes included unipolar and bipolar patients in their samples. Also, the studies compared different rTMS protocols (e.g., high-frequency versus low-frequency, right-sided versus left-sided, bilateral versus unilateral). TMS for mania has been the focus of fewer clinical trials and yielded more inconsistent findings with only one randomized, controlled trial suggesting the benefit of rTMS over a sham treatment[34]. Of note, despite the disparate study outcomes, nearly all the studies of TMS for mania targeted similar right prefrontal cortical regions. The only study of TMS for bipolar mixed states showed promising findings that should be considered with caution for being an open-label uncontrolled design[37]. Likewise, the open-label for maintenance care found positive results but evaluated a sample with bipolar and unipolar patients[36] .

Most clinical trials of TMS in BD are limited by small samples with most studies hovering around (or under) 20 patients. Thus, a challenge for upcoming research in TMS will be to conduct larger-scale studies of TMS in BD with a focus on enhancing knowledge on specific TMS protocols: for instance, in selecting a TMS approach for a given bipolar depressed patient with a specific clinical profile, what protocol will likely be most effective?

Other important considerations are worthy of note. First, in most of these trials, patients were receiving adjunctive pharmacotherapy. Thus, findings from these studies may not be entirely generalizable in that patients with BD have unique and complex medication regimens[38]. Yet, this caveat is not so much a limitation, as a reflection, on these studies' capacity to reflect "real world" bipolar patients who may be interested in pursuing TMS

treatment. Second, across the reviewed studies, patients experienced side effects from TMS treatment, though most of these were described as mild. The most common mild side effects among the studies of TMS for bipolar depression were headaches and insomnia with other side effects including local pain at the site of administration, fatigue, memory difficulties, and dizziness[16, 19, 22]. Most notably, in three bipolar depression studies, patients experienced a switch into a manic episode either during or shortly after treatment[22, 39].

It will be helpful for future studies to more clearly elucidate how clinicians can recognize risk factors for developing mania post-TMS, enabling them to more effectively tailor their treatment for a given patient. Only two studies of TMS for mania noted that patients reported side effects; across these studies, patients experienced pain during their procedure (which went away after session completion), dizziness, anxiety, and a brief headache following treatment[34, 35]. The trial evaluating TMS for a bipolar mixed state reported only minor side effects in a few patients that included headaches, insomnia, and pain at the site of administration[37], whereas the trial that studied TMS as a bipolar maintenance treatment reported no side effects[36]. Ultimately, the overall minor and non-interfering nature of most side effects represents another promising aspect of TMS treatment, potentially facilitating treatment adherence and engagement.

Limitations

Regarding the limitations of this review, there are still few studies published and almost all of them with small sample sizes. Furthermore, there is considerable heterogeneity across studies, especially in relation to the TMS protocols used.

Conclusion

Studies have shown mixed results about the treatment of any BD phases with TMS and also have limited power. Therefore, it is not possible to demonstrate the efficacy of TMS in the treatment of bipolar depression or mania or as a maintenance treatment. Nevertheless, TMS seems to be a safe treatment to BD patients since no severe side effects have been reported and the reported adverse events were transient.

Future studies should not include unipolar and bipolar depressive patients in the same group. Also, studies must have larger samples and the design should allow conclusions about the best parameters to be used. Anyway, we need to better understand the efficacy of TMS as a treatment of bipolar depression or mania.

Table 1 – Controlled studies about TMS as a treatment for bipolar depression

Study	Study design	Sample (N)	TMS parameters	Questionnaires	Comparison/objective	Results
Dolberg et al. 2002	Randomized, double-blind, sham controlled trial	20 with bipolar depression	20 sessions rTMS protocol not available	HAMD, GAF, MMSE, PSQI and visual analogue scales	10 patients (20 sessions of rTMS) x 10 patients (10 sessions of sham followed by 20 sessions of rTMS)	Active rTMS > sham; mood improvement after 2 weeks with no benefit of additional 2 weeks
Nahas et al. 2003	Randomized, double-blind, sham controlled trial	23 patients with bipolar depression (19 BDI, 9 BDII, 2 mixed states)	Left rTMS (5 Hz, 110% MT, 8 sec on, 22 sec off, 20 min), 10 sessions	HAMD, YMRS, HAMA, BDI and GAF	Left rTMS (n=11) x sham (n=12)	No difference
Su et al 2005	Randomized, double-blind, sham-controlled trial of add-on rTMS	30 bipolar (n=5) and unipolar depressive patients	20 Hz or 5 Hz Left DLPFC 100% MT, 10 sessions	MINI, HAMD	Add-on 20 Hz (n=10) or 5 Hz (n=10) rTMS in the treatment of unipolar and bipolar depression x sham (n=10)	Active rTMS > sham
Beynel et al. 2014	Randomized, double-blind, sham controlled trial	12 (BDI, BDII and BDIII)	Left DLPFC, 80% MT, 2 sec train of bursts of 3 pulses at 50 Hz, repeated at 200 ms every 10 sec (990 pulses), twice a day 15 sessions	MADRS	Active iTBS (n=5) x sham (n=7)	iTBS = sham
Fitzgerald et al. 2016	Randomized, double blind, sham controlled trial	49 patients with bipolar depression	1 Hz, right DLPFC, 110% MT, single train of 1000 pulses and then 10 Hz, left DLPFC, 110% MT, 20 trains, 5 sec on, 25 sec off (1000 pulses) 20 sessions	MINI, HAMD, YMRS	Active bilateral rTMS x sham	No difference
Tavares et al 2017	Randomized, double blind, sham controlled trial	50 bipolar depressed patients	Left DLPFC 18 Hz 120% MT 2 sec on, 20 sec off 1,980 pulses/session 20 sessions	HAMD	dTMS x sham	Active dTMS > sham at the end of treatment No difference at 1-month follow-up
Dell'Osso et al. 2015	Randomized, blind-rater trial	33 bipolar and unipolar depressed patients	1Hz, right DLPFC, 110% MT, 7 trains of 60 sec on, 60 sec off (420 stimuli/session) (n=10) x 1Hz, right DLPFC, 110% MT,	HAMD, MADRS, CGI-S	High x low frequency rTMS	The 3 treatments showed mood improvement without difference between them.

			continuous, 15 min (900 stimuli/session) (n=13) x 10 Hz, left DLPFC, 80% MT, 15 trains of 5 sec on, 25 sec off (750 stimuli/session) (n=10), 4 weeks			
Kazemi et al. 2016	Randomized, single blind study	30 patients with bipolar depression	1Hz, right DLPFC, 120% MT (n=15) x 1Hz, right DLPFC, 120% MT and 10 Hz, 100% MT (n=15), 20 sessions	BDI, BAI, WHOQOL-BREF	Bilateral x unilateral rTMS	Higher response rates in the bilateral group (80% x 47%) and no difference in remission rates (40% in both groups)

Table 2 – Uncontrolled studies about TMS as a treatment for bipolar depression

Study	Study design	Sample (N)	TMS parameters	Questionnaires	Comparison/objective	Results
Dell'Osso et al. 2009	Uncontrolled clinical trial	11 BDI and BDII with depression	1 Hz, 110% MT, 15 sessions, 300 stimuli/session, Right DLPFC	HAMD, MDRS, CGI	Add-on treatment of rTMS in bipolar depression	Response: 6 of 11 patients, 4 of whom remitted
Harel et al. 2011	Open-label, uncontrolled trial	19 BDI and II	20 Hz, 2 sec on, 20 sec off, (1680 stimuli), 120% MT H1 coil 20 sessions	HAMD, CGI, HAMA, PSQI, CANTAB	Deep TMS with H1-coil as an add-on treatment to psychotropic medication	Response rate: 63.2% and remission rate: 52.6% ($p<0.001$)
Rachid et al. 2017	naturalistic trial	22 bipolar(n=6) and unipolar outpatients with TRD	5 or 10 Hz rTMS left DLPFC 120-130% MT 4 weeks	MADRS CGI-S	5 x 10 Hz rTMS	Response rate: 50% Remission rate: 40.9% No significant differences between the 2 groups.
Krstic et al. 2014	Case report	1	1 Hz, right DLPFC, 110% MT, 5 trains 60 stimuli, 3 min off, 20 min (300 stimuli/session) 10 sessions	HAMD, YMRS	rTMS in unipolar depression	Hypomanic switch

Table 3 – Controlled and uncontrolled studies about TMS as a treatment for mania

Study	Study design	Sample (N)	TMS parameters	Questionnaires	Comparison/objective	Results
Grisaru et al. 1998	Double-blind, controlled trial	16 patients with mania (4 with psychotic mania)	20Hz 2 sec on, 1 min off 80% MT 20 trains/day 10 sessions	Mania scale, PSRS and CGI	Right (n=7) x left DLPFC (n=9) rTMS to treat mania	Right DLPFC > left DLPFC
Kaptsan et al. 2003	Randomized, double blind, sham-controlled trial	19 inpatients (16 with psychotic mania)	20 Hz, 2 sec on, 1 min off, 80% MT, 10 sessions	YMRS, PSRS and CGI	Right DLPFC (n=11) x sham to treat mania	No difference
Praharaj et al. 2009	Randomized, single-blind, sham-controlled study.	41 patients with psychotic mania	Right DLPFC 20 Hz, 110% MT, 20 trains, 2 sec on, 10 sec off, 10 sessions	YMRS CGI	High frequency rapid suprathreshold right DLPFC rTMS x sham in mania	High frequency > sham
Pathak et al. 2015	Randomized, single-blind, sham-controlled trial	26 BDI adolescents	20 Hz Right DLPFC, 110% MT, 20 trains, 2 sec on, 10 sec off 800 pulses/session 10 sessions	YMRS CGI	Add-on treatment over the right DLPFC (n=13) in adolescents with mania x sham (n=13)	No difference
Michael and Erfurth 2004	Open-label, uncontrolled trial	9 (4 with psychotic mania)	20 Hz Right prefrontal cortex, 2 sec on, 60 sec off, 80% MT, 20 trains/session, 4 weeks	BRMAS	Right prefrontal rapid TMS in mania	Rapid TMS may be beneficial.
Saba et al 2004	Open-label, uncontrolled trial	8 BDI with mania (1 with psychotic mania)	10 Hz Right DLPFC 5 trains 15 sec on, 20 sec off 80% MT	MAS CGI	rTMS as add-on therapy in mania	Significant improvement in manic symptoms

Table 4 - Studies about TMS as a maintenance treatment for bipolar

Study	Study design	Sample (N)	TMS parameters	Questionnaires	Comparison/objective	Results
Li et al. 2004	Case series	7 patients with bipolar depression	5 Hz Left prefrontal cortex, 110%MT, 8 sec on, 40 trains (1600 trains/week) Once a week up to 1 year	HAMD	Maintenance rTMS treatment for bipolar depression	3 of 7 patients maintained the improvement. Patients rTMS might be used as an add-on treatment in bipolar depression.
Rapinesi et al 2015	Open-label, randomized, non-sham controlled trial	24 unipolar and bipolar patients	H1 coil dTMS in medial and lateral prefrontal regions, 120% MT, 2 sec on, 20 sec off, 55 18-Hz trains/session, 20 min (1980 stimuli/session), 4 weeks 20 sessions	SCID-I and II, HAMD, YMRS	dTMS maintenance treatment (4 BDI, 4 BDII, 4 MDD) x without dTMS maintenance treatment (4 BDI, 3 BDII, 5 MDD)	The non-maintenance- group worsened after 6 and 12 months x sustained improvement in the maintenance group.

BDI – Bipolar disorder type I, BDII – Bipolar disorder type II, CANTAB- Cambridge Neuropsychological Test Automated Battery, CGI- Clinical Global Impression, dTMS – deep transcranial magnetic stimulation, GAF- Global Assessment of Functioning, HAMA- Hamilton Anxiety Rating scale, HAMD – Hamilton Rating scale for depression, MADRS- Montgomery-Asberg Depression Rating, MAS – mania assessment scale, MAS- Modified Ashworth Scale, MDD – major depressive disorder, MINI- International Neuropsychiatric interview, MMSE- Mini-Mental State Examination, MT – motor threshold, PSQI- Pittsburgh Sleep Quality Index, PSRS- Positive Symptoms Rating Scale, rTMS – repetitive transcranial magnetic stimulation, SCID – Structured Clinical Interview for DSM, sec – seconds, TRD – treatment-resistant depression, YMRS – Young mania rating scale

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3 - CONCLUSÃO

A neuroestimulação é um campo de psiquiatria que está em constante desenvolvimento e permite direcionar o efeito terapêutico para áreas pré-definidas do cérebro relacionadas ao transtorno. Dessa forma, evita-se também efeitos colaterais periféricos. A importância desses tratamentos não farmacológicos consiste em proporcionar melhorias para um grupo de pacientes que já foram submetidos a diversos tratamentos farmacológicos e psicoterápicos e não alcançaram resultados satisfatórios.

Baseado nos estudos apresentados, o ETCC anódico demonstrou capacidade de modular a cognição de voluntários saudáveis. Os resultados ainda são iniciais e os efeitos transitórios. Mas a expectativa é de que os resultados com ETCC em sujeitos saudáveis sejam replicáveis em populações clínicas. Mesmo que alguns ajustes sejam necessários. Além disso, o ETCC contribui para um melhor entendimento da neurofisiologia cerebral, pincipalmente se associado a eletroencefalograma (EEG) e ressonância magnetica funcional.

A Estimulação Magnética transcraniana é amplamente estudada, possuindo aplicabilidade clínica principalmente na depressão. Mesmo assim, há poucos estudos avaliando a eficácia deste tratamento nos idoso. Em nosso estudo, pudemos contribuir com as evidências do tratamento de idosos deprimidos com EMTr em um alvo cerebral ainda não testado nessa população, mostrando eficácia, tolerabilidade e segurança. Dentre a limitada literatura sobre o uso da EMT como tratamento de transtornos ansiosos e trauma-relacionados, a aplicação no Transtorno de Ansiedade Generalizada e Transtorno de estresse pós-traumático mostraram-se promissoras. Ainda assim, não há estudos avaliando a EMT no Transtorno de Ansiedade Social e existem apenas dois estudos para Transtorno do Pânico e dois para Fobia específica. As pesquisas de EMT como tratamento para as diferentes fases do Transtorno Bipolar não mostraram resultados satisfatórios.

De qualquer maneira, os estudos possuem amostras pequenas e são poucos os ensaios randomizados e controlados. Portanto, mais estudos são necessários para avaliar como otimizar os efeitos terapêuticos e mantê-los a longo-prazo.

De forma geral, os tratamentos com EMT e ETCC demonstraram ser uma alternativa segura para pacientes com transtornos psiquiátricos e sujeitos saudáveis. O mecanismo de ação alvo-direcionado amplia as opções terapêuticas e diversifica os mecanismos de ação.

Por fim, a segurança do paciente deve ser prioridade e os benefícios e os riscos devem ser avaliados e discutidos com o paciente antes de introduzir um tratamento de neuroestimulação. Os pacientes devem ser informados sobre os detalhes do tratamento, incluindo eventos adversos. Além de entenderem que esses tratamentos não são garantia de melhora, nem de cura. Portanto, os profissionais envolvidos em tratamentos de neuroestimulação devem seguir as diretrizes de segurança.

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