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Transcranial direct-current stimulation over the motor cortex in patients suffering from anxiety and depression related to rheumatoid arthritis: Study protocol for a randomized, double-blind, placebo-controlled trial

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ABSTRACT

Rheumatoid arthritis is up to three times more prevalent in women. It is often associated with anxiety and depression, comorbidities causing psychic suffering and potentiating pain perception. It is also related to a higher risk of suicide among diagnosed patients. The high rates of discontinuation of conventional pharmacological treatments are the predominant factor in the search for new therapeutic approaches for the treatment of anxiety and depression. Transcranial direct-current stimulation (tDCS) is a promising, safe and low-cost technique that is very associative with other therapies. When applied to the primary motor cortex (M1) it can induce long-term changes in the synaptic level leading to the improvement of neuroplasticity. The primary aim of this study is to evaluate the effect of tDCS on the symptoms of anxiety and depression. The secondary aim is to evaluate the interference of tDCS on the inflammatory profile, cardiac autonomic behavior and quality of life of patients with rheumatoid arthritis. This is a randomized, double-blind, placebo-controlled clinical trial. The intervention consists of 10 consecutive sessions (once a day) applying tDCS with a 2mA current for 20 minutes. The electrode assembly on the scalp is in accordance with the International Electroencephalogram System 10–20 (EEG) and the anodal electrode is placed over the area of the primary motor cortex (M1 - C3 or C4) and the cathodal electrode on the supraorbital contralateral area (SO - Fp1 or Fp2). The analysis of continuous variables will be described by mean and standard deviation for parametric data and median and interquartile interval for nonparametric data. The evaluation of the effect of tDCS on the inflammatory profile, heart rate variability and quality of life will be obtained by the ANOVA two-way test. tDCS is expected to have a greater effect on reducing anxiety and depression symptoms compared to the placebo, being able to decrease inflammation and improve the quality of life of volunteers.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovitis of the joints and damage to the cartilage and soft tissues around it (Watad et al., 2017). Patients not only complain of physical symptoms, but also experience psychological distress. The variable course of the disease complicates the planning of daily activities with uncertainties surrounding the disease that cause anxiety and depression (Soósová et al., 2017).

The coexistence of immuno-mediated inflammatory diseases with depression has been recognized for a long time. Data illustrating the intimate associations between peripheral and cerebral immune responses raise the possibility of shared pathophysiological mechanisms. These associations include the negative effects of pro-inflammatory cytokines on monoaminergic neurotransmission, neurotrophic factors, and synaptic plasticity measurements (Nerurkar et al., 2018).

According to Ng et al. (2019), mood disorders increase perceived pain and worsen functional status. Complementing this a study by Sturgeon et al. (2016), described a vicious cycle between RA and psychiatric illness, in which emotional distress may be due to an underlying

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physiological stressor, such as inflammation, while sustained inflammation is detrimental to physical function, further aggravating emotional distress (Jing Ng & Huang, 2019).

In a critical observation and necessary discussion, Ironside et al. (2019) highlight that psychotropic drugs can cause dependence and adverse effects, impacting on quality of life. Non-pharmacological approaches using electrical stimulation of the cortex have been proposed as an alternative (Moisset & Lefaucheur, 2018). According to Pelletier and Cicchetti (2015) transcranial direct current stimulation (tDCS) is a safe, well-tolerated, low-cost, easy-to-administer technique and its potential use in the routine of clinical practice has become popular. tDCS has been tested to treat aspects of stroke, multiple sclerosis, Parkinson's, schizophrenia and depression (Fregni et al., 2012). Treatment involves the use of a weak electrical current (approximately 2mA) applied to a specific brain region through two or more electrodes (Brunoni et al., 2011; Bikson et al., 2012), which induces changes at a subthreshold level and modulates the potential of the neuronal membrane when one neuron receives input from another (Antal & Herrmann, 2016). tDCS can induce long-term changes in the synaptic level through mechanisms that resemble long-term potentiation (LTP) and long-term depression (LTD) for anodal and cathodal stimulation, respectively, leading to the improvement of neuroplasticity (George et al., 2002; Rossi et al., 2009; Pacheco-Barrios et al., 2020).

Khedr et al. (2017) demonstrated that by applying tDCS in the M1 area of patients with fibromyalgia (a chronic painful syndrome) the application of the actual tDCS protocol (effective stimulation) is more effective in pain relief than the placebo in patients with fibromyalgia with cumulative and long-term effects. Notably, a parallel improvement in endorphin level and depressive symptoms was also observed.

The analgesic effects of stimulation in M1 may induce functional changes in the thalamic and subthalamic nuclei and modulate the affective component of pain (Vaseghi et al., 2014; Tracey, 2010). Another possible explanation for the improvement in mood is the spread of the effect of tDCS from M1 to the dorsolateral prefrontal cortex which is a widely known cortical target for the treatment of depression. tDCS in the M1 region can alter functional connectivity below electrode stimulation regions, as well as spatially distant but structurally connected areas such as the thalamus (Polania et al., 2012) and the dorsolateral prefrontal cortex (Lindenberg et al., 2013; Sehm et al., 2012).

De Andrade et al. (2011) confirmed that the endogenous opioid systems (EOS) are involved in the analgesic effects induced by repetitive Transcranial Magnetic Stimulation (rTMS) of M1, plus, real tDCS also acts on the EOS in a way similar to rTMS (dos Santos et al., 2014). In their study, Khedr et al. (2017) found significant correlation between the change in serum endorphin levels and the changes in different rating scores after tDCS sessions and this may confirm that the increase of β-endorphins after tDCS stimulation is associated with the pain relief and the improvement of depression and anxiety and opioid system is involved in fibromyalgia. The opioid system plays a key role in mediating analgesia and social attachment and may also affect depression given the link between β-endorphins and depression symptoms (Stein et al., 2007; Navines et al., 2008).

The purpose of this manuscript is to present the protocol of tDCS on the M1 area for treatment of anxiety and depression in patients with RA, including details on the scientific methodology, laboratory and statistical analyses in order to provide innovative therapeutic strategies for particular conditions as well as to support reproducibility of results for future research studies.

2. Aims and hypothesis

Knowing the therapeutic potential of tDCS, the aim of this trial is to evaluate its effect over the M1 area on symptoms of anxiety and depression in patients with chronic pain diagnosed with RA and how this reflects on the improvement of their inflammatory profile. The hypotheses are: tDCS in the motor area reduces symptoms of anxiety and depression in patients with chronic pain diagnosed with RA; tDCS decreases inflammation by reducing inflammatory cytokines in patients with chronic pain diagnosed with RA; tDCS increases HRV and increases vagal behavior in patients with anxiety, depression, and chronic pain diagnosed with RA and tDCS improves the quality of life of patients with anxiety, depression and chronic pain diagnosed with RA.

3. Methods

3.1. Design

This is a randomized, double-blind, placebo-controlled, single-center clinical trial (Fig. 1). The study was approved by the Institutional Research Ethical Committee (CAAE 55182422.5.0000.5020) of the Universidade Federal do Amazonas, Brazil. The trial was registered at the Ensaiosclinicos. gov.br, Registry: RBR-2v2k9gg (https://ensaiosclinicos.gov.br/rg/RBR-2v2k9gg/).

Recruitment will be conducted by telephone with patients living in Manaus. Participants will be a minimum of 18 years old at the time of inclusion in the study (Tables 1 and 2), have been diagnosed with RA and present comorbidities of anxiety and depression, and are linked at the rheumatology department of the Hospital Adventista.

3.2. Eligibility

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3.3. Randomization

The randomization list will be generated electronically with a random number of blocks composed of 4–6 participants per block, generated in the statistical software R version 3.6.3 (Project R for statistical computing), using the blockr and package. Participants will be allocated to the intervention groups through software-generated codes. In order to avoid possible errors and confusion, random numbers will be assigned with "I" for intervention and "C" for control. The allocation sequence will be blinded to researchers, research assistants and study participants.

3.4. Assessments before and after intervention

Before the first intervention session the following will be applied: the mini-mental state examination (MMSE); quality of life assessment (SF-36 Health Survey); application of the visual analog scale for pain (VAS); application of the Beck anxiety inventory (BAI) and Beck depression inventory (BDI); application of Lipp's stress symptom inventory (LSSI); heart rate variability assessment (HRV); blood collection for inflammatory substance scans and saliva collection for stress analysis by quantifying the hormone cortisol. The MMSE and VAS will only be applied before the intervention with electrical stimulation (tDCS), the other assessment instruments will be applied again after the last day of intervention with tDCS.

3.5. Intervention

The intervention will last 20 minutes, and 10 consecutive sessions are stipulated. The tDCS anodic electrode will be connected to the electro stimulator (Microestim focus research, NKL, Santa Catarina, Brazil) which will provide direct current via a pair of sponge electrodes soaked in saline (see Fig. 1).

The assembly of the electrodes on the scalp will comply with the Electroencephalogram International System 10–20 (EEG) being the anodal electrode placed over the area of the primary motor cortex (M1 - C3 or C4) and the cathodal electrode on the supraorbital contralateral area (SO - Fp1 or Fp2) (Fig. 2) depending on the side of the body the volunteers report a major pain perception, which means, the anodal

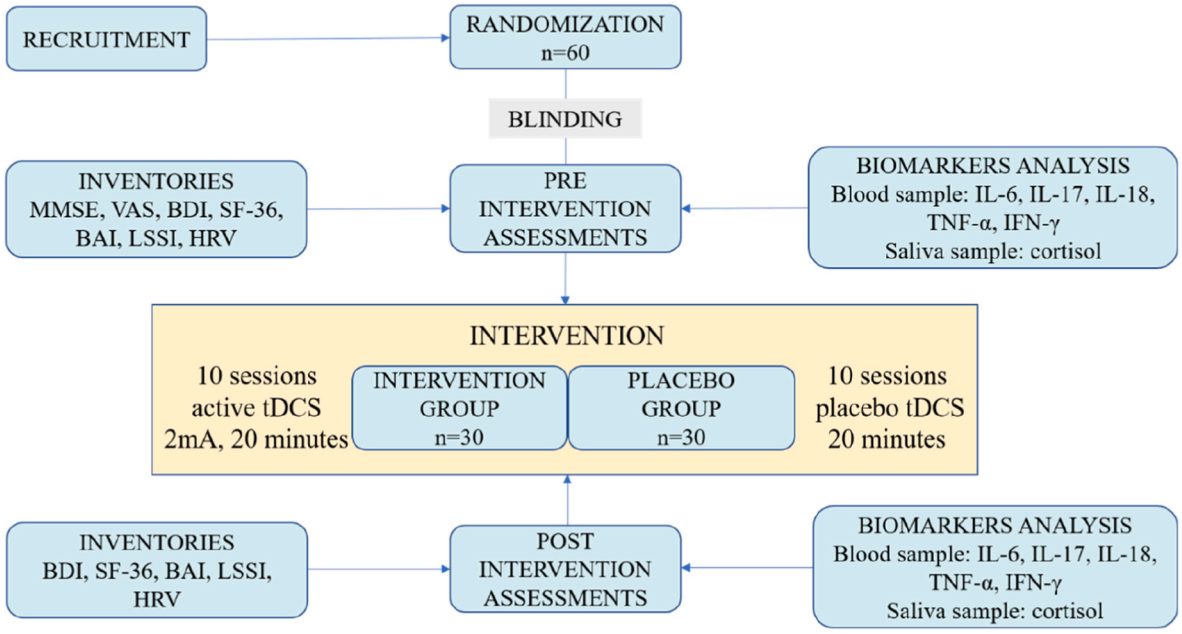

Fig. 1. Overview of the study. Assessments before and after intervention are the same for both Intervention group and Placebo group.

Table 1
Inclusion criteria.

Volunteers will be included in the study if they meet the criteria below
Having chronic pain for a minimum period of 12 weeks
Undergoing clinical treatment with synthetic DMARDs
Presenting pain in intensity under 7 on the visual analog pain scale (VAS)
Anxiety symptoms according to BAI – Beck Anxiety Inventory
Depression according to BDI – Beck Depression Inventory

Table 2
Exclusion criteria.

Volunteers will be excluded from the study if they meet the criteria below	
Other autoimmune diseases not related to RA	With a history of illicit drug use/abuse
Who are being treated with biological DMARDs	Presenting neurological, cognitive and motor deficits
Pregnant	Use of pacemakers
Clinical diagnosis of major depressive disorder (>30 in the score according to Beck Depression Inventory – BDI)	Clinical diagnosis of generalized anxiety disorder (>31 in the score according to Beck Anxiety Inventory – BAI)
Decompensated disease (ischemic heart disease, kidney and/or liver diseases)	Underwent craniotomy; with skull implants in the cranial or facial region
With a history of skin diseases	With a history of seizures or epilepsy
Use of high doses of opioids	With cancer diagnosis

electrode will be placed over C3 when the pain related is in the right side of the body and vice versa. Participants will receive 2 mA electrical stimulation. The protocol will have ascent ramp, 20 minutes of electrical stimulus and descent ramp. Patients in the placebo group will undergo the same protocols as the intervention group and will receive a simulation of the stimulation, and only the initial 30 seconds will be active stimulation.

3.6. Clinical monitoring

Clinical monitoring ensures that the conduct of the study complies with the protocols/amendments currently approved and applicable regulations and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed by following specific instructions in the protocols. Details of clinical site monitoring are documented in a clinical monitoring plan (CMP).

Monitoring visits will include, but are not limited to, a review of regulatory files, accountability records, informed consent, medical and laboratory reports, on-site study in intervention storage records, training records, and protocol compliance. Monitors will have access to each study site, participant, study staff and all documentation according to the monitoring plan. Study monitors will meet with researchers to discuss any outstanding issues and documentary issues.

3.7. Sample size

At present there is no data available showing the effectiveness of tDCS to reduce pain in rheumatoid arthritis patients and its impact on their anxiety and depression symptoms. However, Khedr et al. (2017) applying tDCS over the M1 area of fibromyalgia patients observed a link between reduction of pain and reduction of anxiety and depression. That said, our study adopted a little conservative conduct choosing a moderated effect size Cohen's $F = 0.35$, admitting type I error of 5%, sampling power of 80%, two groups and two measurements for the two-way ANOVA model. Accepting sample loss of 20% we set the $n = 60$ patients, each group comprised of 30 volunteers.

3.8. Statistical analysis

The nature of the distribution of variables will be evaluated by the Shapiro-Wilk test. The measures of central tendency and dispersion will be organized and variables with normal distribution will be described in mean and standard deviation, variables with non-normal distribution will be described in median and range of variation. The Levene test will be used to evaluate the homogeneity of the variables. The research models will be an analysis of the mean by the student's t-test (associated with Welch's factor if there is no homogeneity) or the median by the Mann-Whitney test, depending on the distribution of the sample. For analysis of the difference between time and group ANOVA two-way (normal distribution) will be used, or Kruskall-Wallis and Friedman tests (non-normal distribution), and the post hoc tests will be corresponding for each test. The accepted significance level will be $\alpha = 5\%$. The analyses will be made using the Graphpad Prism v.9.2 (Graphpad, CA., USA) and Jamovi v.1.2 (Jamovi Project, Sydney, Australia)

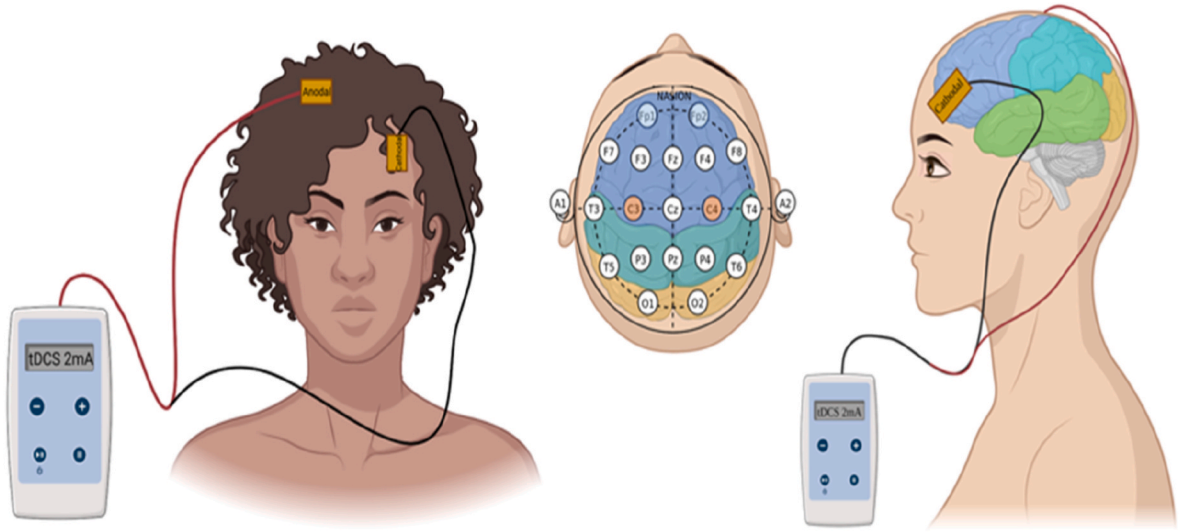

Fig. 2. Electrode montage. Cortical areas stimulated according to 10–20 EEG system depend on the side of the body volunteers report major pain perception – anodal on C3 and cathodal on Fp2 if major pain perceived in the right side and anodal on C4 and cathodal on Fp1 if major pain perceived in the left side. Created with BioRender.com.

programs. In addition, a linear correlation will be made in order to evaluate the relationship between the inflammatory profile and the anxious, depressive and stress states of the volunteers.

3.9. Study organization and funding

This study is supported by: the Graduate Program in Basic and Applied Immunology; Immunology and Flow Cytometry Laboratories of the Institute of Biological Sciences of the Universidade Federal do Amazonas, Brazil, where the analysis of biological samples will be carried out; the Pain, Neuromodulation and Rehabilitation Laboratory (LDNR) of the Health Research Center (CEPES) of the Universidade Federal do Amazonas, where the interventions will be carried out; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Amazonas (FAPEAM). All data interpretations, perceptions and points of view expressed in this article are strictly those of the authors, the cited funders do not take part in research decisions, such as definition of study design, data analysis and choice of journal for submission of this article for publication.

4. Discussion

Considering the vicious cycle between RA and psychiatric disease described by Sturgeon et al. (2016), where inflammation operates as a stressor and aggravates emotional distress, we can identify an amplitude in this relationship (Fig. 3). Stress is understood as a trigger of anxiety and depression, since prolonged external and internal stimuli can function as stressors causing emotional and homeostatic dysregulation as well as a consequent release of pro-inflammatory cytokines and the appearance of symptoms of psychiatric disorders. This emphasizes that anxiety and depression are frequently reported as comorbidities in people diagnosed with RA. In addition, since the characteristic inflammation of RA is the main cause of chronic pain in these patients, who develop anxious conditions and a worsening in the status of inflammation due to the unpredictability of prognosis and loss of functionality with worsening of the disease, another aspect of the complexity of this interaction deserves attention, as we realize that anxiety and depression are potentiating pain perception: the emotional dimension of pain. Finally, but of equal importance, are the findings in the review by Vallerand et al. (2019) where it is reported that in addition to RA being able to trigger depression, depression is a risk factor for RA.

Knowing that these two situations (RA and psychiatric disorders) are closely linked to the HPA Axis (Fig. 4), in which chronic stress causes critical reduction of cortisol causing immune response with the release of pro-inflammatory cytokines, this study intends to examine the effect of tDCS in a high complexity condition and is the first clinical study to propose electrostimulation of the M1 area for the treatment of anxiety and depression linked to RA. The results of this research will be important for a better understanding of the impact of neurostimulation on cortical areas with known distinct functions but that are structurally close. More importantly, the research offers an innovative strategy as an alternative to inefficient conventional treatments, enabling the improvement of the quality of life of the study subjects. In addition, the results will support future studies aimed at the non-pharmacological treatment of psychiatric disorders associated with other inflammatory diseases, as well as helping to elucidate the role of biological markers such as cytokines and glucocorticoids in the course of certain mental diseases in comorbidity with autoimmune diseases.

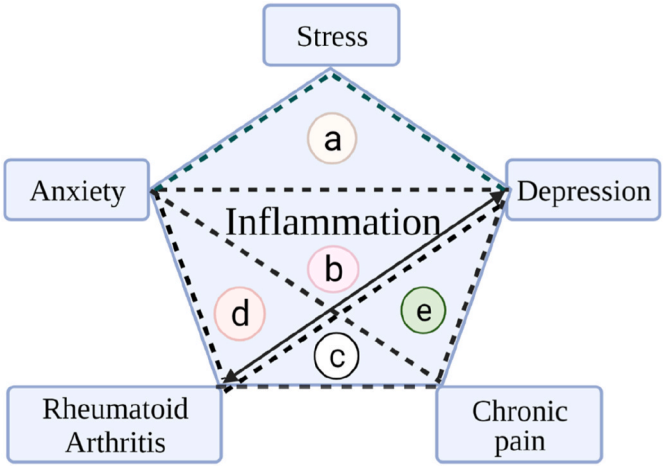

Fig. 3. The extended relationship between mental illness and inflammatory diseases. **a**. Stress, anxiety and depression; **b**. Inflammation has a major role in anxiety and depression; **c**. Inflammation is the source of chronic pain in RA; **d**. Lack of positive prognosis in RA causes high symptoms of anxiety; **e**. anxiety and depression enhance the perceived pain; RA causes depression and depression is a risk factor for RA. Created with BioRender.com.

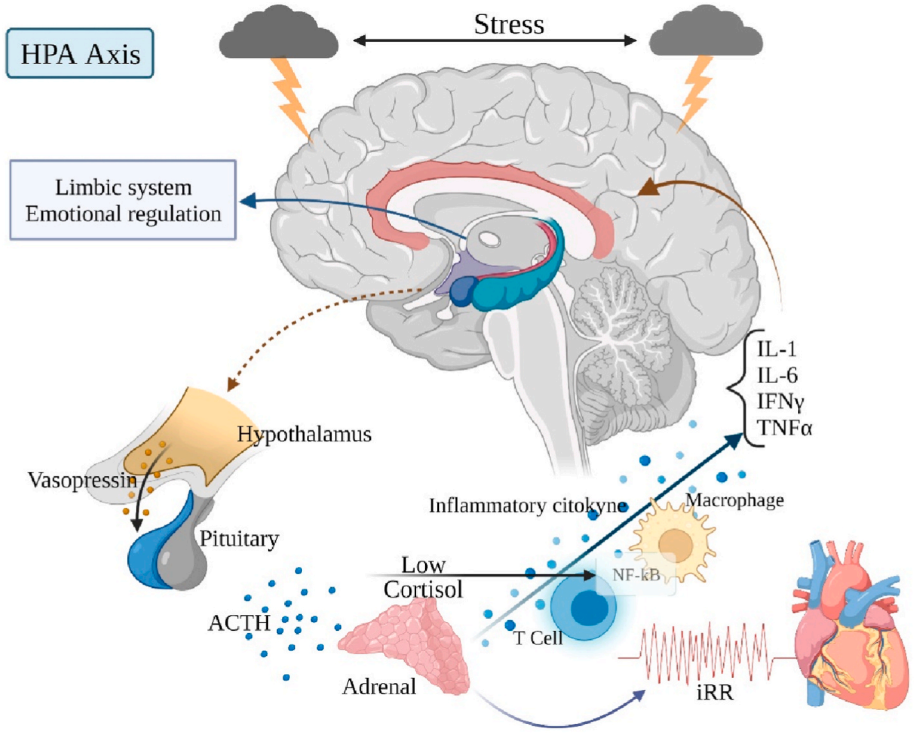

Fig. 4. The HPA Axis. A dynamic system highly influenced by environmental stimuli, especially affective relationships and self-expectations causing immunological response in order to restore the emotional and physiological balance. Created with BioRender.com.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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