RESEARCH PROTOCOL

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Project Name: "Transcranial direct current stimulation (tDCS) on the dorsolateral prefrontal cortexas adjuvant therapy to cognitive stimulation in working memory, cognitive functioning, P300 cognitive evoked potentials and academic performance in medical students with depressive symptomatology: clinical, cognitive and electrophysiological markers".

Non-invasive brain stimulation mainly comprises transcranial direct current stimulation (tDCS) as well as transcranial magnetic stimulation (TMS). tDCS has a very good safety and tolerability profile (compared to transcranial magnetic stimulation) and at low cost (Ankri et al., 2020; Bogdanov et al., 2016; Carvalho et al, 2021; Chan et al., 2021). Major depressive disorder (MDD) is a major public health problem, adversely affecting cognition, with cognitive deficits affecting information processing speed, attention, memory, executive function, and working memory. In addition, cognitive deficits associated with MDD do not resolve after successful treatment of depressive symptoms. In one study, 94% of individuals with MDD and cognitive deficits at the start of treatment retained these deficits one year later, despite achieving clinical remission. Long- term maintenance of antidepressants does not prevent cognition decline, despite maintaining recovery from depression (Brunoni and Vanderhasselt, 2014; Ke et al., 2019; Mancuso et al., 2016). Cognitive stimulation, has shown the potential to produce broad benefits primarily in working memory (Richmond et al., 2014; Au et al., 2016; Figeys et al., 2021; Ciechanski and Kirton, 2017; Ruf et al., 2017; Talsma et al., 2017). The (tDCS), cognitive functioning (Brunoni and Vanderhasselt, 2014; Richmond et al., 2014; Ciechanski and Kirton, 2017; Hsu et al., 2015; Nelson et al., 2016; Zhang et al., 2021) and working memory in neuropsychiatric populations (Caulfield et al., 2020; Luque-Casado et al., 2019; Salehinejad et al., 2020; Wischnewski et al., 2021). Anodal tDCS increases task-related CPFdl activation (Stagg et al., 2013; Weber et al., 2014). Furthermore, anodal tDCS on CPFdl has been shown to facilitate working memory processes (Friehs et al., 2019; Katsoulaki et al., 2017; Schommartz et al., 2021; Wittkuhn et al., 2018), making tDCS a promising tool for the amelioration of depression- induced working memory impairment in a population with a high prevalence of depression. and/or stress, such as medical school students

The research question: Is Cognitive Stimulation (CS) + active tDCS in CPFdl more effective compared to CS + sham tDCS in improving scores on tests of working memory, cognitive functioning, P300 cognitive evoked potentials and academic performance in medical students with depressive symptomatology?

Aims: To evaluate the effect of active CE + tDCS in CPFdl to improve scores on working memory tests, cognitive functioning, P300 cognitive evoked potentials and academic performance in medical students with depressive symptomatology vs simulated CE+ tDCS.

Materials and Methods: This is a single-blind, comparative (cognitive stimulation + active tDCS vs. cognitive stimulation + simulated tDCS), randomized, longitudinal and prolective clinical trial. Analysis: A descriptive analysis of demographic and clinical characteristics will be performed with frequencies and percentages for categorical variables and with means and standard deviations for dimensional variables. Mean comparison tests (t-tests), analysis of variance (ANOVA) and correlation tests. Significance level $p \leq 0.05$.

THEORETICAL FRAMEWORK

Transcranial direct current stimulation is a method of brain stimulation that involves passing a current (1 to 2 mA) through the cortex using at least two electrodes. Transcranial direct current stimulation (tDCS) is one of the most studied techniques in noninvasive neuromodulation. With a very good safety profile and low cost, it has been widely used to modulate cognition and behavior in both experimental and clinical settings (Coffman et al., 2014; Fregni et al., 2021; Guidetti et al., 2021). A growing body of literature, including randomized controlled trials, reports clinical benefits of tDCS for many psychiatric symptoms, such as depression, anxiety, psychosis, addiction, and cognitive functions (Dedoncker et al., 2016; Huang et al., 2021; Sagliano et al., 2019; Yamada et al., 2021). However, only a few studies have investigated the brain mechanism underlying the effects of tDCS on cognitive processing, especially through electrophysiological markers, such as P3 (Mendes et al., 2021). tDCS has considerable potential as a treatment because of its relative cost, portability, safety, and ease of use compared to other neuromodulation methods. Early studies evaluated the effects of tDCS on the motor cortex; however, more recent research has also focused on its effects on the dorsolateral prefrontal cortex (dorsolateral prefrontal cortex (DLPFC), particularly for treating psychiatric disorders and modulating cognitive performance.

Side effects such as itching, burning sensation or headache are common, but generally mild and without long-term impact. Therefore, tDCS compares favorably with other therapeutic approaches such as antidepressants or transcranial magnetic simulation (TMS).

Physiology tDCS

Transcranial direct current stimulation involves subthreshold modulation of neuronal membrane potentials, stimulation that is too weak to induce neuronal activity independently of afferent input from other sources, but sufficient to alter both excitability and spontaneous activity of neurons.

tDCS is based on the application of a direct DC current through two electrodes with different polarities: the anode and the cathode. The modulation of cortical excitability is polarity dependent. The concept is that anodic stimulation leads to subthreshold neuronal depolarization that increases the probability of spontaneous neuronal firing, while the cathode has the opposite hyperpolarizing effect (Stagg and Nitsche, 2011). Furthermore, tDCS-induced aftereffects occur through neuroplastic changes at the molecular level, at N-methyl-D-aspartate (NMDA) and brain-derived neurotrophic factor (BDNF) receptors, i.e., through the induction of long-term potentiation (LTP) and long-term depression (LTD) (Chan et al., 2021; Frase et al., 2021; Reinhart et al., 2017).

Neuroplastic modulation not only depends on tDCS polarity, but also on other stimulation parameters (e.g., current density, stimulation duration). Recent studies showed that the dose-response relationship follows a nonlinear inverted U-shaped function (Batsikadze et al., 2013; Goldsworthy & Hordacre., 2017). In addition, the resting neuronal state also appears to be relevant for understanding the neurophysiological impact of tDCS. For example, recent studies showed that the effects of tDCS depend on the timing of stimulation, task difficulty, or ongoing neural activity (Fertonani & Miniussi, 2017).

tDCS principles

tDCS devices use a battery and function as a constant current stimulator with a maximum output in the milliampere range. Typical tDCS sessions use 0.5 to 2 mA. The tDCS devices are still under investigation and are not yet FDA approved for any clinical purpose. The standard tDCS configuration

uses a target and a reference electrode (Thair et al., 2017). However, multiple electrode arrays have been developed (Huang & Parra, 2019). The location of the active electrodes (anodal or cathodal) is based on pre-existing knowledge of the underlying abnormal neurophysiological mechanism in each disease or functional area to be improved in healthy volunteers.

Generally, the EEG 10/20 system convention is used to determine the location of the electrodes. There are several types of scalp electrodes, the size and geometry varying from needles (15 μm2) (San-Juan et al., 2011), concentric ring electrodes (Villamar et al., 2013) or conductive rubber electrodes enclosed in a perforated sponge (25 and 35 cm2 [5 × 5 cm and 5 × 7 cm]) using saline or conductive paste or gel to enhance the conductivity of the electrical stimulus (Nitsche et al., 2008). More recently, dry electrodes have been used (Jiang et al., 2019). After finding the stimulation site and skin preparation, elastic or rubber straps should be placed around the circumference of the head to attach the electrodes and prevent movement during stimulation.

Newer tDCS devices are able to incorporate EEG recordings simultaneously (Faria et al., 2012), (Schestatsky et al., 2013) or are compatible with fMRI (Esmaeilpour et al., 2019). For details of step-by-step guidance on how to perform a tDCS treatment, we recommend consulting the published reviews (Thair et al., 2017), (Villamar et al., 2013), (Schestatsky et al., 2013). Current density (dependent on current strength and electrode size), stimulus duration, electric field orientation (related to electrode position and polarity) and number of sessions are important in determining the effect of tDCS (Farahani et al., 2021; Lu et al., 2019).

Mechanism of action of tDCS

Clinical and animal studies have provided insight into the mechanisms underlying the acute and long-term effects of tDCS (Alvarez-Alvarado et al., 2021; Nitsche et al., 2005; Nitsche et al., 2008). In particular, anodal stimulation was shown to increase cortical excitability, whereas cathodal stimulation decreased it (Nitsche and Paulus, 2001; Priori et al., 1998). The acute effects are due to the primary polarization mechanism that induces changes in ionic concentrations (Na+, Ca+, K+, Cl-), alteration of acid-base balance and changes in transmembrane proteins by synaptic (Priori et al., 1998) and non-synaptic (Ardolino et al., 2005) mechanisms.

Pharmacological studies have shown that the long-term effects are due to mainly affecting N-methyl-d-aspartate (NMDA) receptors and the GABAergic system (Liebetanz, 2002; Nitsche et al., 2004). The tDCS also interferes with brain excitability by modulating intracortical and corticospinal neurons acting pre- and postsynaptically (Nitsche et al., 2005; Fritsch et al., 2010; Ardolino et al., 2005) involving several major neurotransmitters such as glutamate, ɤ-aminobutyric acid, serotonin, dopamine, norepinephrine, and acetylcholine (McLaren, Nissim and Woods, 2018). Repetitive tDCS induces cell migration, as well as cell orientation (growth cone direction), differentiation and metabolism, the responses to which vary between cell types, sustainable responses in the form of plasticity similar to long-term potentiation (LTP) or long-term depression (LTD) (McCaig et al., 2005), through activation of the tropomyosin receptor kinase B (TrkB), the main receptor for BDNF (Fritsch et al., 2010).

Several electrode assembly and waveform factors (including shape, pulse width, polarity, polarity, frequency, current duration and amplitude, as well as number and frequency of sessions) influence the direct and remote effects of tDCS (Bikson et al., 2019). Using mathematical models and in vivo

recordings from primates and humans at multiple depths, it was found that 1 mA tDCS resulted in a median field of 0.2 and 0.4 V/m respectively (Opitz et al., 2016) and in humans during tDCS between 0.05-0.5 volt/meter for 1 mA and 0.8 V/m for 2 mA tDCS have been measured (Opitz et al., 2016; Huang et al., 2017; Vöröslakos et al., 2018). Recently, voltage changes at the subthalamic level have been reported in humans (Chhatbar et al., 2018). While physiological effects have been found in vitro for electric fields as low as 0.2 volt/meter (Reato et al., 2010).

Finally, tDCS influences several different tissues (vessels or connective tissue) and pathophysiological mechanisms (inflammation, cell migration, vascular motility) (Pelletier & Cicchetti, 2014), (Merzagora et al., 2010).

Transcranial direct current stimulation of the dorsolateral prefrontal cortex.

Over the past two decades, neuromodulation using transcranial direct current stimulation (tDCS) has been shown to alter cortical activity and, consequently, human behavior (Polania et al., 2018). When using tDCS, a direct electrical current is applied resulting in a low-amplitude electric field that is induced in the brain noninvasively. By targeting brain regions corresponding to specific cognitive functions, tDCS has the potential to alter behavioral performance (Kuo et al., 2014). Importantly, modeling studies that have simulated tDCS electric field distribution highlighted the influence of electrode mounting and brain anatomy on the affected brain regions (Miranda et al., 2013; Opitz et al., 2015). Therefore, for tDCS to alter performance, it is necessary to use a setup that appropriately targets the cortical regions underlying a specific behavior.

One cognitive domain that has been extensively studied is the effect of tDCS on working memory (WM). This is crucially involved in several cognitive functions, including language comprehension, decision making, learning and reasoning (Baddeley, 1992). In addition, MT deficits are observed in neuropsychiatric disorders, including major depressive disorder, schizophrenia, and obsessive-compulsive disorder (Gold et al., 2019; Heinzel et al., 2018).

The dorsolateral prefrontal cortex (DLPFC) is part of the prefrontal cortex, which is subdivided into dorsolateral (i.e., DLPFC), medial (anterior cingulate) and orbitofrontal regions. The literature suggests that the medial and orbitofrontal areas are more involved in emotional/motivational aspects while the dorsolateral regions are involved in more cognitive/metacognitive aspects. More specifically, the CPFdl has been shown to be particularly involved in executive and complex behaviors and the literature supports that it plays a role in (1) manipulation of information in working memory and in (2) planning processes. Whereas the different contributions of left vs. Right CPFdl has been controversial and has even been proposed to be gender-based, some evidence tends to suggest that left CPFdl contributes more to working memory processing, whereas right CPFdl is more involved in processing beyond the scope of working memory, such as goal-directed behavior or decision making.

In recent decades, a great deal of research has attempted to find methods to increase the performance of individuals, with special emphasis on executive functions. One of the neuromodulation methods that has received special attention is transcranial direct current stimulation (tDCS). Two electrodes are placed on the scalp in a specific region of interest. Subsequently, a weak electrical current is run from the positively charged cathode to the negatively charged anode, and cortical excitability is observed to increase near the anodic electrode, whereas a decrease is observed with cathodic stimulation29. Stimulation of the dorsolateral prefrontal cortex (dorsolateral prefrontal cortex (DLPFC) has been reported to improve performance during working memory tasks. Interestingly, the effects of tDCS on performance appear to be maintained after stimulation is terminated. Research on tDCS is currently receiving a lot of attention, with studies investigating motor rehabilitation, motor

learning and cognitive trainings.

Alteration of cortical activity by transcranial direct current stimulation (tDCS) has been found to improve working memory (WM) performance. Simulations in 69 studies targeting the left prefrontal cortex showed that the strength of the tDCS electric field in the dorsolateral inferior prefrontal cortex (Brodmann area 45/47) was most strongly related to improved MT performance. This region explained 7.8% of the variance, equivalent to a medium effect. A similar region was identified when correlating MT performance and electric field strength from right prefrontal tDCS studies (n = 18).

Transcranial direct current stimulation in major depressive disorder.

When used for the treatment of unipolar depression, the anode is placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right, supraorbital or extracephalic DLPFC. The rationale for this setup comes from studies that developed the prefrontal asymmetry theory of depression, which states that right prefrontal activity is greater than left prefrontal activity in depressed patients and from clinical trials with rTMS using facilitatory stimulation over the left CPFdl and inhibitory stimulation over the right CPFdl.

Most stimulation protocols for major depression are performed with the same time and position parameters (20 min, bifrontal setup). Some research further explored the possible parameters that can be used. For example, one study found that combining sertraline with stimulation for 30 min was associated with a better response than a combined stimulation for 20 min. Another study by Martin et al. found that an extracephalic electrode position in a group of patients who did not respond adequately to bifrontal stimulation resulted in a better antidepressant effect. They also demonstrated that weekly or twice weekly maintenance sessions induced remission rates of 80% after 3 months and 50% after 6 months.

In several clinical trials, tDCS was found to efficiently reduce clinical symptoms of major depression. Fregni et al. were the first to conduct a double-blind, placebo-controlled study with 20 min 1 mA anodic stimulation over the left CPFdl for 5 days, which resulted in significant symptom improvement. Meta-analyses of randomized clinical trials showed significantly stronger improvement in depression scores as well as higher response and remission rates in the active tDCS group compared to sham tDCS.

BACKGROUND

Cognitive training, such as working memory (WM) training, has demonstrated the potential to produce broad benefits in cognitive functionality (Richmond et al., 2014; Au et al., 2016; Choe et al., 2016; Stephens & Berryhill, 2016; Ciechanski & Kirton, 2017; Ruf et al., 2017; Talsma et al., 2017). As a fundamental and essential cognitive skill, working memory supports complex thinking, but has limited capacity. Therefore, working memory training interventions have become popular as a means to potentially improve working memory-related cognitive skills for those in need (Au et al., 2016).

Transcranial direct current stimulation (tDCS), which has shown potential to modulate brain excitability and cortical activity by transmitting a weak electrical current to the brain (Chase et al., 2020; Solomons et al., 2020), has been found as a possible way to improve working memory (Mancuso et al., 2016; Talsma et al., 2017; Wang et al., 2019), sustained attention (Nelson et al., 2014), motor learning (Ciechanski & Kirton., 2017), multitasking (Hsu et al., 2015; Nelson et al., 2016) and so on. Therefore, cognitive enhancement by tDCS has attracted increased attention over the last decade. A considerable number of single-session studies using tDCS have revealed potential benefits for improving

participants' performance on working memory tasks. In a particularly noteworthy study by Fregni et al. (2005), anodal tDCS (a-tDCS) applied to the left dorsolateral prefrontal cortex (DLPFC), increased response accuracy of the working memory task performed at the same time as stimulation. However, no significant effect appeared when they applied anodal stimulation to the primary motor cortex and cathodal stimulation to the left CPFdl. These findings indicate that the potentiating effect of tDCS on working memory recall depends on the polarity of stimulation and is specific to the stimulation site (Fregni et al., 2005). Many subsequent studies compared factors such as electrode placement, current density, and stimulation duration that can affect the efficacy of tDCS and found that anodal stimulation of the left prefrontal tended to improve MT performance (Coffman et al., 2014; Richmond et al., 2014; Au et al., 2016; Ruf et al., 2017; Talsma et al., 2017). Neuroimaging studies using EEG and functional near-infrared spectroscopy (fNIRS) have provided evidence that tDCS can alter brain activities (McKendrick et al., 2020; Bergmann et al., 2016; Wörsching et al., 2016; Jones et al., 2017; Bogaard et al., 2019). In addition to studies related to working memory, tDCS has also shown potential to mitigate vigilance decline (Nelson et al., 2014) and improve multitasking performance (Nelson et al., 2016).

Based on the assumption that tDCS has the potential to modulate neuronal excitability and synaptic plasticity (Hummel & Cohen, 2006; Santarnecchi et al., 2015), several studies have explored the effect of tDCS on cognitive training in the last 3 years. A study in a non-human primate model found that tDCS, along with multi-session learning, facilitated associative learning and altered functional connectivity when analyzing behavioral outcomes and local field potential (Krause et al., 2017). In a three-session working memory training study implemented in healthy adults, the advantage of working memory training combined with a-tDCS was not only present immediately after training, but also in the follow-up session up to 9 months after training (Ruf et al., 2017). A-tDCS-related benefits remained stable even up to 1 year after the original intervention in a 7-day tDCS-paired working memory training study in healthy young adults (Au et al., 2016; Katz et al., 2017). Improved cortical efficiency and connectivity was also demonstrated in a study that found significant improvement in working memory capacity through tDCS-paired working memory training in healthy young adults (Jones et al., 2017).

In the study by Ruf et al. (2017), the learning curve was steeper when working memory training was combined with tDCS. In fibromyalgia patients, working memory training paired with a-tDCS significantly increased immediate recall compared to a sham (dos Santos et al., 2018). Improvements from multisession MT training paired with tDCS were also found to transfer to untrained MT tasks (Richmond et al., 2014; Au et al., 2016; Stephens & Berryhill, 2016; Ruf et al., 2016). A recent study in monkeys provided evidence that single-neuron activation rates and network interactions could be modulated by polarity and a dose of tDCS and higher intensity of a-tDCS induced higher activation rates of regularly firing neurons (Bogaard et al., 2019). Although some reviews questioned the efficacy of tDCS, these recently published studies provide further evidence that working memory training combined with tDCS can enhance cognition.

Patients with depression exhibit cognitive deficits in several domains (i.e., psychomotor speed, executive functions, memory, and attention), factors such as severity of depression are related to greater cognitive deficits and lower remission rates, even after antidepressant treatment. These issues highlight the importance of investigating cognitive deficits in major depressive disorder.

At the neural level, the frontal limbic system, which encompasses the CPFDdl, amygdala, anterior cingulate cortex and other brain areas, regulates cognitive and emotional processing; interestingly, there is a double dissociation between behavioral management and disinhibition with these brain areas. Hypoactivity of the CPFdl and hyperactivity of subcortical structures are associated with major

depressive disorder and its cognitive deficits. In addition, two modes of impaired cognitive processing are observed in major depressive disorder, which refer to information processing in the absence or presence of emotional influence, respectively. Non-emotionally and emotionally charged tasks recruit and activate distinct but overlapping neural networks.

tDCS has been studied extensively in clinical trials (Fregni et al., 2020) or cognitive enhancement studies (Coffman et al., 2014). However, most of these studies rely on behavioral or clinical measures (mostly self-reports) to assess the effectiveness of tDCS, without a clear explanation of the underlying mechanisms responsible for its effects. Understanding the mechanisms underlying brain activity and the impact of tDCS on those networks is especially important in cognition, where task performance, although important, only correlates with brain function.

The P3 (or P300) is one of the most studied event-related potentials (ERPs) (Sutton et al., 1965). This positive component peaks at a latency of about 300 to 400 ms after stimulus onset in any sensory modality, and is thought to underlie attentional and working memory processes (Huang et al., 2015; Kok, 2001; Polich, 2007). Deviations in P3 amplitude and latency are associated with cognitive deficits in several neuropsychiatric disorders, such as alcohol use disorder (Hamidovic & Wang, 2019), attention deficit/hyperactivity disorder (Kaiser et al., 2020), bipolar disorder (Wada et al., 2019), post-traumatic stress disorder (Johnstone, et al., 2013), and psychopathy and antisocial behavior (Pasion et al., 2018).

Often referred to in the literature as a single component, P3 can be divided into two additional subcomponents: P3a and P3b. P3a signals an attentional and orienting process (P3a) that occurs after exposure to an unpredictable stimulus (e.g., a distractor or a novel stimulus in a three-stimulus oddball paradigm) and occurs in the frontocentral region of the brain (Friedman et al., 2001). This subcomponent could be a neural representation of attentional allocation and orienting to something unexpected (Simons et al., 2001; Spencer et al., 2001). The amplitude and latency of P3a are modulated by stimulus salience with more relevant stimuli eliciting a larger and faster P3a (Kok, 2001). The amplitude of this component is also modulated by habituation, as the novelty and/or salience of the stimulus decreases on repeated presentations, especially with short intervals between stimuli (Rushby & Barry, 2009). On the other hand, P3b is elicited in the parieto-temporal region approximately 60-80 ms after P3a during a standard oddball paradigm, specifically after an infrequent stimulus (i.e., a target) that is intermixed in a series of frequent (i.e., non-target) stimuli. Participants are instructed to respond to a target stimulus (e.g., pressing a button or counting the number of targets), while they are to ignore the non-target stimulus (Polich, 2007). Low uncertainty in stimulus prediction is necessary to elicit the P3b component and this component occurs when the target does not match the representation held in MT, suggesting a role in task-relevant information processing and subsequent storage in memory (Polich, 2007). P3b is thought to be a neural signature of goal-directed target identification in complex cognitive processes such as goal-directed learning and decision making (Rac Lubashevsky & Kessler, 2019).

However, the eccentric task is not the only task in which the P3 component can be elicited. For example, memory operations reflected by P3 are also observed during n-
subsequent tasks, mainly after exposure to a target stimulus that matches the stimulus displayed n trials earlier (Saliasi et al., 2013). In summary, P3b is thought to reflect the comparison between the current stimulus and already stored information (i.e., categorization of task-relevant information), whereas P3 elicited on n-back is more strongly related to storing the current stimulus in memory. (i.e., updating MT) to successfully perform upcoming comparisons (Polich, 2007). Component amplitude is related to neural resource allocation and cognitive processing, whereas latency is associated with the

time required to evaluate the stimulus, suggesting that reduced P3 amplitude with longer latencies indicates poorer and delayed operations relative to the stimulus. task-relevant stimulus.

In addition, P3 is also elicited during tasks that require inhibition of a proximal response, such as the Go/No-Go (GNG) task and the stop-signal reaction. Both paradigms require different basal frontal ganglia circuits due to different functional demands on inhibitory processing via proactive (e.g., GNG Task) and reactive (e.g., SSRT; Aron, 2011) inhibition. In GNG tasks, P3 is elicited during "no-go" and "go" trials. The amplitude of "no-go" P3 has been highlighted as an important marker of inhibitory control and often occurs in frontocentral regions during successful inhibition trials (Huster et al., 2013). Thus, this component has been associated with P3a because of their topographic similarities, whereas P3 "go" is observed in parietal regions following a stimulus requiring a motor action (Ruchsow et al., 2008). On the other hand, during SSRT, the P3 component is elicited during "stop" trials that require inhibition of an action that was already initiated. In addition, changes in P3 amplitude have also been shown to reflect inhibitory processes. For example, P3 amplitude has been shown to increase under conditions of high inhibitory load, such as that required by faster response times or a lower stop signal probability (Huster et al., 2013). In addition, a recent meta-analysis also demonstrated the importance of P3 latency for inhibitory processes, showing a strong correlation between early P3 latency (and not amplitude) with successful inhibition in stop trials (Huster et al., 2020).

P3 is also very sensitive to the emotional-motivational value of stimuli. For example, P3 amplitude increased after emotionally charged stimuli compared to a stimulus with a neutral emotional meaning (Hajcak et al., 2010) or after exposure to drug-related images in subjects with addiction problems (Dunning et al., 2011).

In general, P3 has been frequently used as an index of attention and working memory underlying various cognitive processes and can be used to assess the impact on cognitive processes of various neuromodulatory interventions in the brain.

However, research efforts on this topic have been largely correlational, whereas the causal relationship between cortical activity and emotional and nonemotional processing in MDD deserves further investigation. In this context, tDCS is a useful tool for inducing prefrontal cortex activation. TDCS is a noninvasive neuromodulatory technique that employs weak direct currents (0.5-2 mA) to modulate brain activity by regulating the frequency of action potentials activated in the neural network. Several studies have investigated the interaction between tDCS and pharmacological interventions. It has been found that tDCS elicits antidepressant effects similar to those of 20 mg fluoxetine; however, a significant response to tDCS occurred more rapidly than a significant response to medication. In 2013, Brunoni et al. published a study comparing the effect of tDCS, sertraline, and a combination of the two in a clinical trial of 120 patients with major depression. Treatment with tDCS or sertraline alone improved depressive symptomatology. The same research group also conducted the largest clinical trial of tDCS to date. This trial consisted of a non-inferiority study with 245 patients receiving escitalopram, tDCS or placebo. In this case, tDCS failed to show inferiority to escitalopram. Findings that depressed patients show improvement in working memory and affective processing after a session of direct current stimulation over the left CPFDL led to the development of protocols combining tDCS with cognitive tasks to improve cognitive performance and clinical symptoms. An exploratory trial investigated whether tDCS could improve the efficacy of cognitive control therapy. They found that both cognitive control therapy alone and tDCS improved depressive symptoms.

The direct effects of tDCS on stress symptoms have recently been published. Individuals such as healthcare workers, who often suffer from high levels of stress and even burnout, could benefit from

preventive measures. When 1,075 mA tDCS stimulation of the right CPFDL was performed for 6 to 10 min in healthy individuals exposed to acute stress, there was less impairment of working memory compared to sham or cathodal stimulation (Cohen's d = 0.62), demonstrating the potential for prevention of stress-induced mental disorders (Bogdanov and Schwabe, 2016).

On the other hand, patients who already developed stress-related psychiatric symptoms may also benefit from non-invasive brain stimulation. Left anodal CPFDL 1.0mA tDCS has also been shown to improve working memory when applied for 20 minutes once a week for 5 weeks in patients diagnosed with PTSD undergoing cognitive training programs compared to baseline, although the effects varied between subjects and were performance test dependent (Saunders et al., 2015). Another study demonstrated enhanced extinction-related processes in veterans with war-zone-related PTSD when 2.0 mA anodal stimulation was combined for 10 min with fear extinction therapy. tDCS targeting the left ventromedial prefrontal cortex (vmPFC) during extinction-consolidation led to lower skin conductance reactivity compared to tDCS applied during extinction-learning (Cohen's d = 0.38) (Van't Wout et al., 2017).

CPFdl has been the usual cortical target of tDCS to prevent and ameliorate the consequences of psychosocial stress. Carnevali et al. (2020) recently postulated that the effects of tDCS may involve both cognitive control of stress and the autonomic system, involving predominantly parasympathetic (vagal) responses (Carnevali et al., 2020). Further research is needed to determine whether tDCS could prevent the consequences of repeated or persistent exposure to stressful situations, such as in the context of social isolation during a pandemic. Furthermore, the response to 1.0 mA anodal left CPFDL stimulation for 30 min may differ depending on individual anxiety traits (Sarkar et al., 2014), with individuals with high anxiety profiles improving performance on cognitive tests (Cohen's d = 0.82), as, well as a decrease in cortisol levels (Cohen's d = 1.37) compared to sham stimulation, an effect that was not observed in subjects with low anxiety profiles. Therefore, assessing specific psychological traits at baseline could help determine which individuals would benefit most from the effects of tDCS.

PROBLEM STATEMENT

Transcranial direct current stimulation is a safe, noninvasive method of brain stimulation in which a low-voltage electrical current (≤2 ma) is passed between two electrodes on the scalp: the anode (the positive electrode) and the cathode (negative electrode). By modulating the membrane potential of underlying cortical neurons, tDCS can alter brain function. More specifically, stimulation with tdcs can make neurons more (anodic; facilitatory) or less (cathodic; inhibitory) prone to fire action potentials (Kuo & Nitsche, 2012; Nitsche et al., 2008).

tDCS has a very good safety and tolerability profile (compared to transcranial magnetic stimulation) and low cost (Ankri et al., 2020; Bogdanov et al., 2016; Carvalho et al, 2021; Chan et al., 2021). The tDCS is based on the application of a direct DC current across two electrodes with different polarities: the anode and the cathode. The modulation of cortical excitability is polarity dependent. The concept is that anodic stimulation leads to a subthreshold neuronal depolarization that increases the probability of spontaneous neuronal discharge, while the cathode has the opposite hyperpolarizing effect (Stagg and Nitsche, 2011). Therefore, it is considered as a neuromodulation technique because it modifies neural excitability by changes in electrical gradients that modify the membrane potential and, therefore, also the probability of opening ion channels which ultimately implies changes in the probability of action potential discharge and neurotransmitter release. The effects of tDCS may be related to long-term potentiation due to protein synthesis-dependent changes, modulation of cyclic adenosine monophosphate levels, intracellular calcium and molecular-level neuroplastic changes in N-methyl-D-

aspartate (NMDA) and brain-derived neurotrophic factor (BDNF) receptors (Chan et al., 2021). Significant effects of tDCS on motor, visual, somatosensory, vestibular, cognitive and emotional functioning have been reported (Ankri et al., 2020; Berryhill et al., 2018; Bogdanov et al., 2016; Burden, 2021; Carvalho et al, 2021; Chan et al., 2021; Dedoncker., 2016; Wischnewski et al., 2021). Early studies evaluated the effects of tDCS on the motor cortex; although more recent research has also focused on its effects on the dorsolateral prefrontal cortex (DLPFC), particularly for treating psychiatric disorders and modulating cognitive performance. The use of tDCS has initially been expanded by work related to psychiatric disorders; stimulation on the prefrontal cortex has been used for the treatment of psychological disorders such as depression, apathy, insomnia, anxiety, and in the treatment of addiction (Aboulafia-Brakha, 2016; Herrera-Melendez et al., 2020; Kim et al., 2020).

Patients with depression exhibit cognitive deficits in several domains (i.e., psychomotor speed, executive functions, memory, and attention), factors such as severity of depression are related to greater cognitive deficits and lower remission rates, even after antidepressant treatment. These issues highlight the importance of investigating cognitive deficits in major depressive disorder.

At the neural level, the frontal limbic system, which encompasses the CPFdl, amygdala, anterior cingulate cortex and other brain areas, regulates cognitive and emotional processing; interestingly, there is a double dissociation between behavioral management and disinhibition with these brain areas. Hypoactivity of the CPFdl and hyperactivity of subcortical structures are associated with major depressive disorder and its cognitive deficits. In addition, two modes of impaired cognitive processing are observed in major depressive disorder, which refer to information processing in the absence or presence of emotional influence, respectively. Non-emotionally and emotionally charged tasks recruit and activate distinct but overlapping neural networks.

However, research efforts on this topic have been largely correlational, whereas the causal relationship between cortical activity and emotional and nonemotional processing in MDD deserves further investigation. In this context, tDCS is a useful tool for inducing prefrontal cortex activation. TDCS is a noninvasive neuromodulatory technique that employs weak direct currents (0.5-2 mA) to modulate brain activity by regulating the frequency of action potentials activated in the neural network.

One cognitive domain that has been extensively studied is the effect of tDCS on working memory (WM). Working memory is crucially involved in several cognitive functions, including language comprehension, decision making, learning, and reasoning (Baddeley, 1992). In addition, working memory deficits are observed in neuropsychiatric disorders, including major depressive disorder, schizophrenia, and obsessive-compulsive disorder (Gold et al., 2019; Heinzel et al., 2018).

Cognitive training, such as working memory training, has demonstrated the potential to produce broad benefits for those with special cognitive skill requirements, or for those with cognitive impairments (Richmond et al., 2014; Au et al., 2016; Choe et al., 2016; Stephens & Berryhill, 2016; Ciechanski& Kirton, 2017; Ruf et al., 2017; Talsma et al., 2017). As a fundamental and essential cognitive skill, working memory supports complex thinking. Therefore, working memory training interventions have become popular as a means to potentially improve related cognitive skills (Au et al., 2016).

Cognitive deficits, including working memory impairment, are central features of several neuropsychiatric disorders, which contribute substantially to the burden of disease and remain largely refractory to conventional pharmacological therapies, in particular, depression present cognitive deficits in several domains: psychomotor speed, executive functions, memory and attention (Ciechanski & Kirton, 2017; Coffman et al., 2014; Hsu et al., 2015; Nelson et al., 2016; Richmond et al., 2014; Santarnecchi et al., 2015).

Transcranial direct current stimulation (tDCS), has been found as a possible way to improve

working memory (Richmond et al., 2014), sustained attention (Nelson et al., 2014), motor learning (Ciechanski & Kirton, 2017) and multitasking (Hsu et al., 2015; Nelson et al., 2016). Several studies have reported beneficial effects of tDCS on working memory in both neuropsychiatric populations and healthy individuals. Combinations of neuroimaging and tDCS demonstrated that anodal tDCS increases task-related CPFdl activation (Stagg et al., 2013; Weber et al., 2014). Furthermore, anodal tDCS on CPFdl has been shown to facilitate working memory processes (Fregni et al., 2005; Boggio et al., 2006; Nitsche et al., 2008), making tDCS a promising tool for the amelioration of depression and/or stress-induced working memory impairment.

The present study aims to evaluate the effectiveness of tDCS on the dorsolateral prefrontal cortex (in conjunction with cognitive stimulation) on working memory, cognitive functioning, P300 cognitive evoked potentials, and academic performance of medical school students subjected to significant stressors and with a high prevalence of depression. Similar to single-session working memory enhancement studies, the anode will be placed over the dorsolateral prefrontal cortex and the cathode over the orbitofrontal prefrontal cortex (contralateral above the right eye).

RESEARCH QUESTION

The research question: Is active CE+ tDCS more effective compared to simulated CE+ tDCS in improving scores on tests of working memory, cognitive functioning, P300 cognitive evoked potentials, and academic performance in medical students at UNAM?

CONTRIBUTION OF THE PROJECT TO THE ADVANCEMENT OF KNOWLEDGE IN ITS OWN SUBJECT AND AREA OF EXPERTISE

Non-invasive brain stimulation mainly comprises transcranial direct current stimulation (tDCS) as well as transcranial magnetic stimulation (TMS). tDCS has a very good safety and tolerability profile (compared to transcranial magnetic stimulation) and at low cost (Ankri et al., 2020; Bogdanov et al., 2016; Carvalho et al, 2021; Chan et al., 2021). The tDCS is based on the application of a direct DC current across two electrodes with different polarities: the anode and the cathode. The modulation of cortical excitability is polarity dependent. The concept is that anodic stimulation leads to a subthreshold neuronal depolarization that increases the probability of spontaneous neuronal discharge, while the cathode has the opposite hyperpolarizing effect (Stagg and Nitsche, 2011). Therefore, it is considered as a neuromodulation technique because it modifies neural excitability by changes in electrical gradients that modify the membrane potential and, therefore, also the probability of opening ion channels which ultimately implies changes in the probability of action potential discharge and neurotransmitter release. The effects of tDCS may be related to long-term potentiation due to protein synthesis-dependent changes, modulation of cyclic adenosine monophosphate levels, intracellular calcium and molecular-level neuroplastic changes in N-methyl-D-aspartate (NMDA) and brain-derived neurotrophic factor (BDNF) receptors (Chan et al., 2021). Significant effects of tDCS on motor, visual, somatosensory, vestibular, cognitive and emotional functioning have been reported (Ankri et al., 2020; Berryhill et al., 2018; Bogdanov et al., 2016; Burden, 2021; Carvalho et al, 2021; Chan et al., 2021; Dedoncker., 2016; Wischnewski et al., 2021). The use of tDCS has been expanded, in principle, by work related to psychiatric disorders; stimulation in the prefrontal cortex has been used for the treatment of psychological disorders such as depression, apathy, insomnia, anxiety and in the treatment of addiction (Aboulafia-Brakha, 2016; Herrera-Melendez et al., 2020; Kim et al., 2020).

One cognitive domain that has been extensively studied is the effect of tDCS on working memory

(WM). Working memory is crucially involved in several cognitive functions, including language comprehension, decision making, learning, and reasoning (Baddeley, 1992). In addition, working memory deficits are observed in neuropsychiatric disorders, including major depressive disorder, schizophrenia, and obsessive-compulsive disorder (Gold et al., 2019; Heinzel et al., 2018).

Cognitive stimulation, such as working memory training, has demonstrated the potential to produce broad benefits for those with special cognitive skill requirements, or for those with cognitive impairments (Richmond et al., 2014; Au et al., 2016; Choe et al., 2016; Stephens and Berryhill, 2016; Ciechanski & Kirton, 2017; Ruf et al., 2017; Talsma et al., 2017). As a fundamental and essential cognitive skill, working memory supports complex thinking. Therefore, working memory training interventions have become popular as a means to potentially improve related cognitive skills (Au et al., 2016).

Cognitive deficits, including working memory impairment, are central features of several neuropsychiatric disorders, contributing substantially to the burden of illness and remain largely refractory to conventional pharmacological therapies, in particular, cognitive deficits in several domains are present in depression: executive functions, memory and attention (Andrews et al., 2011; Brunoni and Vanderhasselt, 2014; Ciechanski and Kirton, 2017; Coffman et al., 2014; Hsu et al., 2015; Nelson et al., 2016; Richmond et al., 2014; Santarnecchi et al., 2015).

Depression, stress, and their key mediators such as glucocorticoids and catecholamines, are well known to modulate a wide range of cognitive processes, ranging from attention and cognitive control to social cognition, decision making, learning, and memory (Diamond et al., 2007; Lupien et al., 2007; Lupien et al., 2009; Roozendaal et al., 2009; Schwabe et al., 2012; Schwabe and Wolf, 2013; Sandi and Haller, 2015). Specifically, working memory processes are among the cognitive functions that are most sensitive to the effects of depression, stress, and stress hormones, with most studies reporting persistent impaired working memory even after stress (Diamond et al., 1999; Lupien et al., 1999; Roozendaal et al., 2004; Elzinga and Roelofs, 2005; Schoofs et al., 2009).

Working memory processes are underpinned by a large network of interconnected cortical and subcortical brain regions (Goldman-Rakic, 1987; Fuster, 1997; Rottschy et al., 2012; Sreenivasan et al., 2014), with the dorsolateral prefrontal cortex (dorsolateral prefrontal cortex (dorsolateral prefrontal cortex (dlPFC) playing a pivotal role in this network (Fuster and Alexander, 1971; Jonides et al., 1993; D'Esposito et al., 1995; McCarthy et al., 1996; Barbey et al., 2013). As the CPFdl is one of the most sensitive brain areas (de Kloet et al., 2005; McEwen and Morrison, 2013), neurotransmitters and hormones that are released in response to stressful encounters are thought to negatively regulate CPFdl activity and thus impede working memory performance.

Combinations of neuroimaging and tDCS demonstrated that anodal tDCS increases task-related CPFdl activation (Stagg et al., 2013; Weber et al., 2014). Furthermore, anodal tDCS on CPFdl has been shown to facilitate working memory processes (Fregni et al., 2005; Boggio et al., 2006; Nitsche et al., 2008), making tDCS a promising tool for the amelioration of depression and/or stress-induced working memory impairment.

The combination of neuropsychological assessment techniques with neurophysiological assessment techniques (PEC) allows the comprehensive evaluation of the cognitive processing being carried out by the subject when performing a given task, enabling real-time monitoring of brain activity contingent to cognitive processing. The combination of the GRADIOR program with the recording of evoked potentials allows us to observe to what extent the different contents of the stimuli determine the subject's performance in cognitive tasks designed for the recording of the P300 potential, thus assessing to what extent the attentional and working memory processes (measured through the waveform) are modulated by the content of the stimulation presented. This type of evaluation has the

added value of identifying which are the contents that cause an optimal performance in the cognitive activity of the subject, thus allowing the creation of rehabilitation programs adapted to the deficits found in the neuropsychological and neurophysiological assessment.

Major depressive disorder (MDD) is a major public health problem, adversely affecting cognition, with cognitive deficits affecting information processing speed, attention, memory, executive function, and working memory. In addition, cognitive deficits associated with MDD do not resolve after successful treatment of depressive symptoms. In one study, 94% of individuals with MDD and cognitive deficits at the start of treatment retained these deficits one year later, despite achieving clinical remission. Long-term maintenance of antidepressants does not prevent cognition decline, despite maintaining recovery from depression (Brunoni and Vanderhasselt, 2014; Ke et al., 2019; Mancuso et al., 2016). The present study aimed to evaluate the effectiveness of multi-session dorsolateral prefrontal cortex stimulation (in conjunction with cognitive stimulation) on working memory and academic performance in medical school students subjected to significant stressors and with a high prevalence of depression. Similar to single-session working memory enhancement studies, the anode will be placed over the dorsolateral prefrontal cortex and the cathode over the orbitofrontal prefrontal cortex (contralateral above the right eye).

HYPOTHESIS

CE + tDCS will be more effective compared to CE + tDCS-placebo or sham in improving scores on tests of working memory, cognitive functioning, P300 cognitive potentials, and academic performance in UNAM medical students with depressive symptoms at 15 treatment sessions (acute phase) and at 4 weeks of maintenance.

OBJECTIVES

To evaluate the effect of CE + tDCS to improve scores on working memory tests, cognitive functioning, P300 cognitive evoked potentials and academic performance in UNAM medical students with depressive symptoms vs simulated CE+ tDCS.

Specific objectives

1. To compare the presence of adverse effects and tolerability of both groups (EC+tDCS and EC+ tDCS- placebo or sham) at 15 treatment sessions (acute phase) and at 4 weeks of maintenance.
2. To describe the association of MEPs amplitude with performance on neurocognition and behavioral symptoms of both groups at 15 treatment sessions (acute phase) and at 4 weeks of maintenance.
3. To describe the association of P300 cognitive evoked potentials with performance in neurocognition and behavioral symptoms of both groups at 15 treatment sessions (acute phase) and at 4 weeks of maintenance.
4. To describe the association of risk factors with performance on neurocognition, behavioral symptoms and MEPs amplitude measure of both groups at 15 treatment sessions (acute phase) and at 4 weeks of maintenance.

RESEARCH STRATEGIES OR METHODS

Methods:

According to the classification of: Alvan Feinstein, this is a clinical trial, single-blind, comparative study (CE + active tDCS vs CE + sham tDCS), randomized, longitudinal and prolective.

The sample size was calculated with the G*Power 3.1 program with an effect size of 0.03 with a formula for factorial ANOVA (between-subjects, within-subjects and interaction effect) with 90%

power, at an alpha of 0.05, with 2 groups and 3 measurements, the final sample would be constituted by a total of 60 participants, which means 30 patients in each analysis group (Jacob Cohen, 1977). The sample will be divided into 2 experimental groups of undergraduates.

1. Group EC + tDCS active = 30
2. Group EC + simulated tDCS =30

Study population:

Selection criteria

Inclusion criteria

1. Age ≥ 18 years old.
2. Vaccinated against SARS-COV2 virus.
3. Students of the Faculty of Medicine of UNAM
4. Fluent in Spanish.
5. Adequate visual and auditory acuity to be able to perform neuropsychological tests and cognitive stimulation.
6. Depressive symptoms with working memory impairment (diagnosed by applying a specific neuropsychological battery).
7. That they are not under antidepressant pharmacological treatment prior to entering the investigation.
8. Good general health without medical illnesses (systemic arterial hypertension, diabetes mellitus, dyslipidemias, infections, thyroid disease, vitamin deficiencies) that do not interfere with the study.
9. Willingness to participate in a scheduled 8-week study and able to attend scheduled evaluations.

Exclusion criteria

1. Any neurological disease that allows suspicion of cognitive failure other than depression, such as Parkinson's disease, multiple infarct dementia, Huntington's disease, hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, history of head injury with loss of alertness.
2. Participants with a history of severe psychiatric disorders according to DSM-5 (bipolar disorder, schizophrenia, chronic depression) or psychotic features, agitation or behavioral problems in the last three months that could lead to difficulties in complying with the protocol.
3. History of psychoactive substance abuse and current alcohol consumption with a pattern of abuse or dependence in the last two years.
4. Participants with alterations in a conventional electroencephalogram (paroxysmal phenomena identified by a neurophysiologist).
5. Participants with pacemakers, intracranial metal objects or history of brain surgery, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body.

Elimination criteria

1. Request to leave the studio.
2. Participants whose clinical condition or laboratory findings require the initiation of complementary treatment with other drugs.

3. The presence of adverse incidents that deteriorate the participant's health (acute confusion, agitation, mania).
4. The presence of exacerbation of neurocognitive or behavioral symptoms during treatment.

Instruments or tools:

-King's Figure (Basal and tracking). This instrument aims to investigate perceptual organization and visual memory in brain-injured individuals. It evaluates memory and perception. Time of Application: The time taken is the time that the copy lasts. It is taken in two stages: copying phase and memory reproduction phase. It uses the following materials: paper, white sheets, colors, pencils. Its application is individual and the time is variable, around 10 minutes. It evaluates perceptual organization and visual memory in individuals with brain injury, by reproducing the memory figure after a period of interference. It assesses the ability to organize and plan strategies for problem solving, as well as their visoconstructive ability. Its application consists of asking the subject examined to copy a complex figure by hand and without time limit and subsequently, without prior warning and without the help of the model, the examinee must reproduce immediately and after 30 minutes again the same figure, in order to assess his capacity for non-verbal material recall. Each unit can earn the subject up to two points. 2 points are given when the drawing is correct in shape and location. 1 point is given when the location or shape of the unit is missed. 0 points are given when it fails to place the location or shape of the unit. Each application is scored on a scale ranging from 0 to 36 points. Score 1⁄2 of an adult =32 points. The memory session is scored in the same manner as the scoring units in the particular areas or details of the figure have been numbered for ease of scoring. A comparison of the scores corresponding to each session will help the clinician determine the presence of visuo-graphic or visuo-memory deficits, as well as their relative severity (Rey, 1996; Rivera et al., 2015).

FAS (Controlled word association test) (Baseline and follow-up). Test that assesses verbal or phonetic fluency, as well as executive functions (cognitive flexibility, strategy, suppression of interference, inhibition of dominant responses), by evaluating the spontaneous pronunciation of words in one minute. The test consists of asking the patient to say as many words as possible, beginning with the letters provided by the evaluator. Normally the letters F, A, S are used, although others such as C, F, L can be used. A high educational level has been related to a better performance in the FAS test. Its use has been validated in numerous studies, showing a difference in the number of words pronounced in patients depending on their age, educational level and comorbidities (Kuslansky et al., 2004; Machado et al., 2009).

Hopkins Verbal Learning Test (Baseline and follow-up). Instrument that evaluates verbal memory. It was designed mainly for its application to older adults and population with neuropsychiatric disorders. It consists of 3 semantic fields, with 4 words each, which are read to the subject on three occasions so that he/she memorizes them. Subsequently, a recognition test is performed in which 12 target words, 12 distractor words, 6 words semantically related to the target words and 6 unrelated words are presented and the patient is asked to identify the previously memorized words. There are 6 equivalent forms of this test, so it is recommended for longitudinal studies, as the development of familiarity with the test is prevented. The Test-Retest correlation is similar to other tests that evaluate verbal memory such as the Wechsler Memory Scale. Its validity has been demonstrated in patients with head trauma, schizophrenia and dementia (Arango-Lasprilla et al., 2015) (Kuslansky, 2004).

Barcelona test (Baseline and follow-up). Neuropsychological test that quantitatively evaluates the patient's cognitive status. In its entirety the test assesses: orientation, language, reading, writing, visual recognition and abstract memory. There are three versions: a complete one with a duration of approximately 3 hours, an abbreviated one, with 45 minutes and aphasia profile.

Electrophysiological measurement

Cognitive evoked potentials:

- Latency p300: time in which the maximum voltage value of the component appears since stimulus presentation. Index of the speed of stimulus processing and classification. It is determined by the speed of neuronal transmission, which depends largely on the degree of myelination of the fibers involved.
- Amplitude p300: voltage of the maximum spike occurring at that latency. Magnitude of the electric field generated at a given time as a result of a specific neuronal activity during information processing of a stimulus; determined by the number of neurons involved in that activation. It involves the quantification of neuronal activity during the comparison of the critical stimulus with the memory trace created by the subject.
- Reaction time: (response time) time elapsed from the presentation of the stimulus until the subject executes the response. It is the time used for the recognition of the stimulus and the response to it.
- Error rate: quantification of the degree of impairment of higher functions.
- Commission error rate: subject's response to frequent stimuli to which he/she should not respond.

- Omission error rate: failure to respond to infrequent stimuli to which it should respond.

- *Oddball paradigm:*

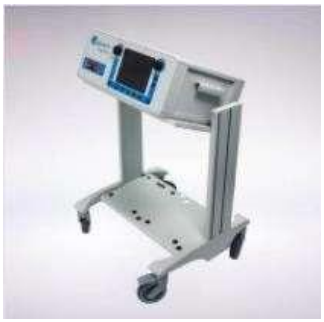
- Auditory Stimuli:
  Non-Significant Stimuli:
  - Frequent: 1000Hz frequency tone with a duration of 70 msg and a probability of occurrence of 80%.
  - Infrequent: 2000Hz frequency tone with the same duration and a 20% probability of occurrence.

  Significant Nonverbal Stimuli:
  - Frequent: telephone ringing of 300msg duration and a probability of occurrence of 80%.
  - Infrequent: bark of 300msg duration and a 20% probability of occurrence. Verbal Significant Stimuli:
    - Frequent: diction of the letter "A" with a duration of 300msg and a probability of occurrence of 80%.
    - Infrequent: diction of the letter "O" with the same duration and a probability of 20%.
- Visual stimuli:
  Non-Significant Stimuli:
  - Frequent: white background and yellow square appears with a display duration of 700 msg. Probability: 80%.
  - Infrequent: white background and red square appears with the same duration on screen. Probability: 20%.
- Significant Nonverbal Stimuli:
  - Frequent: white background and a house appears with a display duration of 700 msg. Probability: 80%.
  - Infrequent: white background and a cow appears on the screen with the same duration. Probability: 20%.
- Verbal Significant Stimuli:
  - Frequent: white background and the letter "R" appears on the screen with a duration of 700 msg. Probability: 80%.
  - Infrequent: white background and the letter "S" appears on the screen with the same duration. Probability: 20%.

The waves recorded at each electrode will be analyzed for frequent and infrequent stimuli in the auditory and visual modality. The latency of the P3 component will be defined as the point of maximum positive amplitude in each area after the exogenous N1-P2-N2 components, with an analysis window between 250

and 450 milliseconds. The amplitude will be measured with respect to the pre-stimulus baseline.

Figure 1. Repetitive transcranial magnetic stimulation equipment.



3. Magnetic stimulator Coil arm 3. 8-shaped coil. B-70

transcranial. MAGPRO R30.

Application of direct current stimulation

Four Sooma™ tDCS version A12 current stimulators will be used. Each device applies a weak, continuous electrical current to the brain. This current modulates brain activity, the anode is able to increase the excitability of the target cortex. Two electrodes are used which are placed on the scalp. The electrodes are connected to the subject through a conductive medium, in this case pads that must be moistened with 0.9% saline solution. A cap is used to hold the electrodes in order to keep them in contact with the participant. The stimulator is portable and battery operated.

The stimulator has a control button, a power switch and an LCD display. On the top of the stimulator there are two insulated, color-coded sockets for the electrode leads. The electrode connected to the red socket becomes the anode and the one in the black socket becomes the cathode. It is recommended to always match the colors of the plug and the electrode cable to ensure the correct polarity of stimulation.

The pair of electrodes with color-coded wires (red and black) and plugs are inserted into the sockets of the stimulator corresponding to the color of the wire. The electrodes should be covered with sponges or pads that allow good contact between the scalp and the electrodes when they are soaked with 0.9% saline solution.

Once the participant has been identified, safe use of the device must be guaranteed, therefore each participant must be examined for contraindications. The stimulator should not be used on persons with metallic devices or objects on or inside the skull, cardiac pacemakers, and eczema or injured skin at the site where the electrodes are to be placed. The effects of electrical current may include heating or malfunctioning of objects and devices containing conductive materials.

The operation of the device is simple, slide it to the on position and once the preparation is completed (place the prepared cap with the electrodes), press the control button to start the measurement of the contact quality between the electrodes and the scalp, "check contact" will appear on the screen until the contact quality measurement value is below"15" and after which the screen will say "press to start", it will not be possible to start if the screen indicates "check contact". The device gives the option to pause or stop the treatment.

As a relevant fact, the equipment is powered by batteries and the battery level is indicated during start-up with a percentage value. Battery replacement should be considered when this percentage reaches 20%. When the battery reaches 0%, the message "replace battery" will be displayed.

Regarding the simulated condition or sham, the equipment has the option inside to program it. It gives the options: Active / sham protocol, by default: ON - enables active stimulation and OFF - enables sham stimulation. The devices will be programmed, such that a few seconds of stimulation are administered at the beginning and end of the programmed time period to mimic the cutaneous perceptions (itching, tingling) that tend to be reported within the first few moments of stimulator on, without being able to modify cortical excitability.

The treatment process will consist of preparing the equipment, placing the current at 2 mA, each session will be programmed for a duration of 30 minutes. Electrodes measuring 25 cm^2 will be placed. The cap should be selected according to size. The size can be estimated based on head diameter: 50 - 54 cm, small (S), 55 - 58 cm, medium (M) and 59 - 62 cm, large (L). Before starting the treatment, it should be ensured that the patient's skin is healthy and that there are no metallic objects such as jewelry, hairpins or glasses near the electrodes. To prepare the equipment, it is always suggested to clean the sponges (pads), the device and the unused accessories. Place the electrode inside the sponge, which should be completely wet with 0.9% saline solution on both sides and from the inside. Squeeze slightly to get rid of the excess saline solution, it is recommended to use 20 ml of the solution for each sponge. The electrodes should then be inserted into the sponge bags and the electrodes and cover placed on the patient's head. It should be ensured that the cloth between the electrodes does not get wet when inserting the electrodes. Current can be diverted through the cloth. Connect the wires to the device: red to red, black to black. Subsequently, the device should be switched on, set the switch to position "I". Start the contact measurement by pressing the control button on the welcome screen. Improve the contact until "OK" appears on the display. It is recommended to press the sponges to

release electrolytes and let the hair dampen for a few minutes. As a precaution, do not start stimulation while pressing the sponges.

Figure 3. Direct current stimulation equipment and components

1. Electrodes

2. Sponge or almohailla

3. Electrodes in place inside the cushion.

4. Sponges and electrodes placed inside the cap.

5. Direct current stimulator with electrodes inserted.

6. Complete view of the placement.

The target area to be stimulated will be bilateral stimulation of the dorsolateral prefrontal cortex (DLPFC), placing the anode on the left side (F3) and the cathode on the right side (F4), based on the 10-20 electroencephalography system described below. A total of 15 sessions will be given, providing five sessions per week and then one session per week for 4 weeks.

The equipment to be used in this study is approved by COFEPRIS and additionally, as a safety measure, a checklist of safety measures and adverse effects is used.

Cognitive stimulation application

Cognitive stimulation will require a printed manual and will be carried out in groups of 13 participants, three sessions per week for three weeks (acute) and one session per week for four weeks (maintenance). In the following table, the domains to be stimulated are specified, selected from the U.M.A.N. manual.

DOMAINS	SPECIFIC DOMAINS
Orientation	Space Temporary Staff
Memory	Episodic Visual

	Long-term visual Semantics Visual recognition Job
Attention	Sustained Divided
Language	Expressive (oral) Printed (written) Fluency
Praxias	Constructive
Gnosias	Visual Space
Reasoning	Sequencing
Calculation	Mental
Processing speed	Written Visual

Definition of clinical and neuropsychological improvement or response to treatment.

A positive intervention effect will be considered if there is a change or remains the same in the following dimensions of the previously described instruments and scales

a. **Cognitive:** remain the same or increase by 1 point on the Montreal Cognitive Assessment.
b. **Behavioral:** no decrease in Lawton & Brody Index and Katz Index values, and 1-point decrease in Cummings Neuropsychiatric Inventory (NPI).
c. **Neuropsychological**: increase one standard deviation in T-score of the values obtained for each scale.
d. **Electrophysiological:** increase MEP amplitude from the seventh stimulus onwards *p>0.05
e. **Global:** remain the same or have increased 1 point on the Clinical Global Impression Scale and 1 on the Everyday Life Memory Failure Questionnaire.

General procedure

Students will be recruited through the dissemination of the study at the School of Medicine. In all cases, they must comply with the safety measures to be able to participate and will be evaluated in an initial interview to ensure that they meet the inclusion criteria. In this interview they will be explained in detail what the study consists of, and if they agree to participate and sign the informed consent letter, a time will be agreed upon for the baseline clinical evaluation. Each of the candidates who meet the selection criteria will be verbally invited to participate in the study after explaining the objectives and procedures of the study.

Prior to entry into this research project, the participant will have read and discussed the informed consent document with the principal investigator. Those who agree to participate will be asked to review and sign the informed consent form once all questions have been answered. All participants will be assigned a registration number. They will be given a booklet with information on cognitive stimulation and another on neuromodulatory techniques (rTMS and tDCS).

Subsequently, a clinical interview will be conducted to capture relevant demographic and clinical data, and the clinical and neuropsychological instruments will be applied for diagnostic certainty, which

in turn will count as baseline measurement. The total application of the instruments could be done in one session (3 hours with a 15-minute break). After that, the questionnaire of stimulation safety measures will be applied (see APPENDIX) and the recording of P300 potentials will be carried out with t h e application of the 5 Hz paradigm. The following measurements will be taken at the end of the 15 sessions and at the end of maintenance.

The patient will then be randomly assigned to one of the two tDCS groups and will be given 15 sessions, 5 per week from Monday to Friday and then one per week for 4 weeks. After each session, adverse effects will be asked about and recorded in a questionnaire (see APPENDIX). They will be evaluated at the beginning, at the end of the 15 sessions (three weeks) and four weeks after the end of the study maneuver (the characteristics of each maneuver are described in the methods section corresponding to each stimulation technique). At the same time, all participants will receive three sessions per week of cognitive stimulation using the manual adapted to Mexican Spanish of the UMAM method.

The randomization will be carried out with a list of numbers in Excel that will be in charge of one of the members of the research who will not have contact with the participants.

The applicators of the stimulation techniques will be the same as the assessors and will not remain blind to the maneuver, unlike the students. All applicators will be randomized to form the two groups and the applicator of the techniques will know whether it is the experimental maneuver or the placebo maneuver.

Statistical analysis

A descriptive analysis of the demographic and clinical characteristics will be performed with frequencies and percentages for the categorical variables and with means and standard deviations for the dimensional variables. Repeated measures ANOVA will be used for the dimensional variables under study. The level of statistical significance was set at a $p \leq 0.05$ for all analyses. Clinical, demographic and baseline variables will be tested for differences between groups with X^2 or analysis of variance (ANOVA). If any differences between groups emerged ($p<0.05$), the corresponding variables will be included as covariates in the following analyses.

The groups will be included in a two-measure repeated multivariate analysis of variance (MANOVA) model to examine the direction of changes (time effect) between groups (interaction effect) in terms of the variables to be studied, including cognition, working memory and P300 potentials. A p value of 0.05 will be used as statistically significant for the MANOVA analyses due to the objective of testing the therapeutic efficacy of the intervention.

tDCS+EC reduce Type I error.

Effect sizes of comparisons were estimated using partial eta squared ($\eta p2$) and reference values for interpretation of 0.01 = small, 0.06 = medium, 0.14 = large (COHEN, 1988).

All these analyses will be performed using the Statistical Package for the Social Sciences (SPSS), version 22.

ETHICAL CONSIDERATIONS AND/OR LETTER OF INFORMED CONSENT

This project offers a form of therapeutic intervention both by the application of tDCS and the application of the paradigm with TMS, which correspond to a level of risk higher than the minimum according to the regulation of the general health law on research for health, article 17: those in which the probabilities of affecting the subject are significant, among which radiological studies with microwaves and drug trials are considered, due to the fact that brain stimulation interventions approved by the health authorities (e.g. Food and Drug Administration of the USA and COFEPRIS) are carried out for their use in major depression.

The study was planned in accordance with the principles stipulated in the Declaration of Helsinki. The data generated from the research will be used only for scientific purposes without any other use, thus guaranteeing absolute confidentiality of the data obtained from the participants (WMA Declaration of Helsinki, 2013).

Safety measures will be taken such as ruling out from the beginning the presence of a history of convulsive risk (possible risk in any form of electrical stimulation of the central nervous system), as well as ruling out abnormalities in the excitability of the central nervous system (dysrhythmias, paroxysmal activity, graphoelements suggestive of epileptic activity, etc.), as well as other functional alterations of the central nervous system.

The most commonly reported effects are headache and burning at the application site; however, information will be provided regarding other side effects; in subsequent interviews, the participant will be asked propositional questions regarding possible side effects associated with the use of tDCS or the measurement of P300 cognitive potentials; the participant will also have the telephone numbers to contact the researcher and will be informed about the opening hours of the Continuing Psychiatric Care service of the institution to receive attention in case of any eventuality.

Adverse events that occur in participants will be reported using the format for reporting adverse incidents of medical devices in clinical research, the notification will be made by the principal investigator in accordance with the General Health Law and NOM-240-SSA 1-2012 on the installation and operation of technovigilance following the administrative guide for the integration of the technovigilance report.

With respect to the cognitive stimulation and the clinimetric and neuropsychological measurements to be performed during the protocol, no risk is involved for those who agree to participate in the study. In case of performance anxiety, it will be applied by an experienced clinician who will be with the participants at all times.

Before entering this research project, the participant and his/her family member must read and discuss the informed consent document with the investigator. This document, in turn, must be signed and a copy given to them, while an additional copy will be attached to the research file. Throughout the research, the names of the participants will be omitted from the databases; they will be assigned to a sequential code for statistical analysis.

Participants may withdraw at any time during the course of the research without prejudice to their academic career.

INFRASTRUCTURE

Neuropsychological testing and cognitive rehabilitation: The Department of Psychiatry and Mental Health has a Psychology department. It has experience with the cognitive training program both in groups and individual sessions, will be led by Diana Guízar who will perform the neuropsychological tests and cognitive stimulation.

Non-invasive neuromodulation techniques: Transcranial magnetic stimulation area with MagVenture magnetic stimulators, MagPro R-30 model. They meet international specifications for human use (European Standards and COFEPRIS permit for human application).

There are 4 tDCS equipment, which will be loaned to the concession to carry out this study.

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