Universidade do Minho
Escola de Psicologia

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Electrophysiological and neuromodulatory correlates of waiting impulsivity

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Electrophysiological and neuromodulatory correlates of waiting impulsivity

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e da
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Statement of Integrity

I hereby declare have conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

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Correlatos eletrofisiológicos e neuromodulatórios da impulsividade de espera

Resumo

A impulsividade de espera é a capacidade de esperar para realizar uma ação associada a uma recompensa. Uma maneira de estudar a dinâmica cerebral durante os processos de impulsividade é analisando os potenciais relacionados a eventos (PRE) através da atividade contínua do EEG, como a P3 (ou P300). Assim, o primeiro estudo desta tese teve como objetivo avaliar se a técnica de estimulação transcraniana por corrente contínua (ETCC) era capaz de modular a amplitude e a latência de P3 durante tarefas cognitivas. Uma meta-análise com 23 estudos mostrou que a ETCC frontal aumentou a amplitude do P3 parietal durante as tarefas *oddball* e *n-back*. Este estudo sugeriu que a P3 eliciada em áreas parietais pode ser modulada através da aplicação de ETCC em áreas frontais.

O segundo estudo pretendeu validar o efeito anterior na amplitude de P3 e na atividade oscilatória inerente durante a impulsividade de espera. Assim, 40 participantes realizaram duas sessões separadas de ETCC ativa e simulada sobre a circunvolução frontal inferior direita (CFId) durante um paradigma de respostas prematuras. Os resultados mostraram um efeito diferencial em comparação com o estudo 1, ou seja, a ETCC frontal diminuiu a amplitude do P3-alvo e a potência delta inerente em comparação com a ETCC simulada. Da mesma forma, a ETCC ativa também reduziu a amplitude do P3-also (ou seja, outro PRE induzido durante a impulsividade de espera), mas sem nenhum efeito significativo na atividade oscilatória evocada.

Por fim, considerando os resultados divergentes anteriores, o estudo 3 pretendeu avaliar a viabilidade de individualizar a estimulação transcraniana por corrente alternada (ETCA) ao componente P3 endógeno. Para isso, uma configuração de ETCA-EEG permitindo a sincronização da frequência e fase de ETCA com P3 foi aplicada a 12 voluntários saudáveis durante duas sessões (ativo vs sham). A sessão de tACS ativa revelou um aumento significativo na amplitude do alvo-P3 em comparação com o sham, embora não tenham sido observadas diferenças significativas no poder oscilatório.

Este mostrou que a P3 é um marcador útil para combinar com diferentes técnicas de estimulação elétrica transcraniana (EET). Os resultados sugerem um efeito diferencial da ETCC no componente P3 e na atividade oscilatória inerente, dependendo dos requisitos da tarefa (por exemplo, processamento "frio" *versus* "quente"). Por outro lado, a sincronização da ETCA com a atividade endógena levou a um aumento da amplitude da P3. No geral, este trabalho melhorou a nossa compreensão sobre como as intervenções EET indexadas a marcadores de EEG podem ser úteis para modular a impulsividade de espera.

Keywords: Delta; Impulsividade de Espera; P3; tDCS; tACS

Electrophysiological and neuromodulatory correlates of waiting impulsivity

Abstract

Waiting impulsivity is the ability to wait to perform a rewarded action. One way to study the brain dynamics during impulsive processes is by analyzing the event-related potentials in the ongoing EEG-activity, such as the P3 (or P300). For that, the first study of this thesis pretended to evaluate if transcranial Direct Current Stimulation (tDCS) technique was capable to modulate P3 amplitude and latency during cognitive tasks. A meta-analysis with 23 studies has shown that frontal tDCS increased the parietal P3 amplitude during oddball and n-back tasks. This study suggested that P3 elicited in parietal areas can be modulated through the application of tDCS in frontal areas.

At next, the second study pretended to validate the previous effect in P3 amplitude and inherent oscillatory activity during waiting impulsivity. Hence, 40 participants performed two separate sessions of active and *sham* tDCS over the right Inferior Frontal Gyrus (rIFG) during a premature response paradigm. Results have shown a differential effect in comparison with study 1, namely, frontal tDCS decreased the target-P3 amplitude and inherent delta power in comparison with *sham*. Likewise, active tDCS also reduced cue-P3 amplitude (i.e., another ERP elicited during waiting impulsivity), but without any significant effect in the evoked-oscillatory activity.

At last, considering the previous divergent results, study 3 pretended to evaluate the feasibility of individualizing transcranial Alternating Current Stimulation (tACS) to the endogenous P3. For that, a tACS-EEG setup allowing the synchronization of the frequency and phase of tACS with P3 was applied to 12 healthy volunteers during two sessions (active vs *sham*). The active tACS session revealed a significant increase in target-P3 amplitude in comparison with *sham*, although no significant differences were observed in the oscillatory power.

The current work showed that P3 is a useful marker to combine with different transcranial Electric Stimulation techniques (tES). These findings suggest a differential effect of tDCS in P3 component and inherent oscillatory activity depending on the task requirements (e.g., cold vs hot processing). On the other hand, the synchronization of tACS with the endogenous activity led to an enhancement of P3 amplitude. Overall, this work improved our understanding about how tES interventions indexed to EEG markers can be useful to modulate waiting impulsivity.

Keywords: Delta; P3; tDCS; tACS; Waiting Impulsivity

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Abbreviations

ADHD	Attention-deficit/Hyperactivity Disorder
BIS	Barratt Impulsiveness Scale
BDI-II	Beck's Depression Inventory-II
BDs	Binge Drinkers
BDNF	Brain-derived Neurotrophic Factor
CEICVS	Comissão de Ética para a Investigação em Ciências da Vida e da Saúde
CI	Confidence Interval
CPRT	Cued Premature Response task
DASS	Depression Anxiety Stress Scales
dB	Decibel
EHI	Edinburgh Handedness Inventory
EEG	Electroencephalogram
ERP	Event-related Potential
ERO	Event-related Oscillations
FFT	Fast Fourier Transform
GNG	Go/No-Go
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HD-tDCS	High-Definition Transcranial Direct Current Stimulation
ICA	Independent Component Analysis
iTBS	intermittent Theta Burst Stimulation
ITPC	Inter-Trial Phase Coherence
lDLPFC	Left Dorsolateral Prefrontal Cortex
LC-NE	Locus Coeruleus-Norepinephrine
LTD	Long-term Depression
LTP	Long-term Potentiation
MPFC	Mesial Prefrontal Cortex
MCQ-27	Monetary Choice Questionnaire – 27
MID	Monetary Incentive Delay
NIBS	Non-invasive Brain Stimulation
NMDA	N-methyl-D-aspartate

PFC	Prefrontal Cortex
PCA	Principal Component Analysis
PCC	Posterior Cingulate Cortex
PTSD	Post-traumatic Stress Disorder
PSD	Power Spectral Density
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trials
ROI	Regions of Interest
rTMS	Repetitive Transcranial Magnetic Stimulation
RT	Response Time
rDLPFC	Right Dorsolateral Prefrontal Cortex
rIFG	Right Inferior Frontal Gyrus
S-UPPS	Short-Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency
STDP	Spike-timing Dependent Plasticity
SD	Standard Deviation
SMD	Standard Mean Difference
S-R	Stimulus-Response
SSD	Stop-Signal Delay
SSRTT	Stop Signal Reaction Time task
STN	Subthalamic Nucleus
SM	Supplementary Materials
SMA	Supplementary Motor Area
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
tES	Transcranial Electrical Stimulation
VAS	Visual Analogue Scale
WM	Working Memory

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Thesis Overview

The current thesis pretends to address the electrophysiological and neuromodulatory correlates of waiting impulsivity. This is of particular interest given that exacerbated waiting impulsivity has been observed in several clinical conditions (e.g., addiction and Attention-deficit/Hyperactivity disorders). Likewise, deficits in the ability to wait are associated with abnormal patterns in electrophysiological (EEG) activity such as in the P3 component. Therefore, taking into consideration the association between the P3, impulsive processes, and clinical symptomatology, the current thesis pretended to address how the transcranial Electrical Stimulation (tES) techniques might impact EEG markers of waiting impulsivity.

Therefore, in order to address our goal, the current chapter introduces the theoretical concepts and revision of recent studies about waiting impulsivity, EEG markers (i.e., P3 and delta/theta oscillations), and tES techniques (i.e., tDCS and tACS). The Chapters 2, 3, and 4 comprise the studies conducted during this thesis. Specifically, the first study (Chapter 2) pretends to evaluate the transcranial Direct Current Stimulation (tDCS) effects in the P3 amplitude and latency during oddball, n-back, Go/No-Go, and emotional processing. At next, in Chapter 3, the previous tDCS effects are tested in light of a premature response paradigm. The fourth chapter aims the optimization of the effects detected in the previous chapters through the application of transcranial Alternating Current Stimulation (tACS) based on the endogenous activity of each participant. At last, the findings observed in the three studies of the thesis are discussed accordingly to the most recent literature of the field in Chapter 5. Additionally, in the fifth chapter limitations and future directions are discussed, as well a brief conclusion of the present work.

Overall, the chapters in this thesis pretend to study the modulatory effects of tES techniques in electrophysiological surrogate markers of cognitive processing, specifically the P3 and underlying EROs. Our findings will allow a better understanding of the use of tES techniques in cognition and behavior, while the neuronal activity behind those modulations is unveiled. Therefore, our studies can provide important insight into applied research with clinical populations associated with abnormalities in EEG activity.

CHAPTER 1

General Introduction

1.1. Waiting Impulsivity

Waiting impulsivity is the ability underlying waiting for gratification or withholding from performing an action (Robbins & Dalley, 2017). This ability has been thought to be a predictor of the development of addiction (Belin et al., 2008), as well a consequence of drug consumption (Voon et al., 2014). Furthermore, the inability to wait may end up in more proneness for premature responses, which have been shown to be increased in several clinical populations, such as Attention-deficit/Hyperactivity disorder (ADHD; Van Dessel et al., 2018), alcohol use disorder (Morris et al., 2016), binge drinkers (Sanchez-Roige et al., 2014), methamphetamine use disorder and recreational cannabis users (Voon et al., 2014).

In order to assess waiting impulsivity, two main methods have been suggested as ways of measuring it, namely the impulsive choice by the delay discounting and the impulsive action by premature responses (Robbins & Dalley, 2017). The former implies a choice between smaller-and-immediate or larger-and-delayed rewards, whilst the latter relies on the ability of holding on before performing an action associated with a reward (Dalley et al., 2011). Both processes are dissociable at behavioral and neuronal levels, given that impulsive action is related to response inhibition, whilst impulsive choice is mostly ruled by reward processing (Reynolds et al., 2006). This translates in waiting impulsivity to rely on 'cold' processes with less influence of affective and cognitive processing (i.e., premature response) and 'hot' processes with affective charge implying limbic circuitries (i.e., delay discounting) (Dalley & Robbins, 2017; Winstanley et al., 2006).

On the other hand, both processes seem to be partially overlapped at a behavioral and neuronal level in animal studies. Specifically, a study with rodents showed that premature responses and delay discounting were strongly associated (Robinson et al., 2009). However, this association was not observed in studies with humans, thus suggesting different neuronal circuitries between premature responding and delay discounting (Voon et al., 2014). Regarding the neuronal substrates, subjects that prefer larger-and-delayed rewards show higher activations in the ventral striatum, mesial prefrontal cortex (MPFC), and posterior cingulate cortical (PCC) (Ballard & Knutson, 2009). On the other hand, premature responding have shown an inverse relation with activations in the ventral striatum, ventromedial prefrontal cortex and subthalamic nucleus (Morris et al., 2016). Hence, ventral striatum is suggested to be a crucial subcortical region in both impulsive choice and action from waiting impulsivity (Dalley et al., 2011).

Moreover, proactive inhibitory processes were also suggested to play an important role in preventing premature responses (Los, 2013; Voon, 2014). This notion is explained by the fact that

proactive inhibition requires an action stoppage before the execution of response, whilst reactive inhibition requires that an already ongoing action to be stopped (Aron, 2011). Although both processes rely on the rIFG, they share different neuronal circuits. Specifically, proactive inhibition is associated with an indirect pathway between rIFG and striatum, whereas reactive has been related with a hyperdirect pathway from the rIFG towards the subthalamic nucleus (Aron, 2011; Jahfari et al., 2011). Likewise, there is some evidence of different cortico-striatal substrates between the act of waiting and stopping. Specifically, waiting relies on neuronal areas that are crucial in reward processing, such as the ventral striatum (i.e., nucleus accumbens) and ventromedial prefrontal cortex, whereas stopping is associated with motor areas, namely, dorsal striatum (i.e., caudate nucleus and the putamen), pre-

Supplementary Motor Area and right Inferior Frontal Gyrus (rIFG) (Dalley et al., 2011). Nonetheless, proactive inhibition and premature responding rely on the subcortical relay structure subthalamic nucleus (STN) involved in motor control (Ballanger et al., 2009; Morris et al., 2016).

Overall, premature responding is evaluated as an impulsive action within the waiting impulsivity realm. The waiting impulsive action is suggested to share common features with other impulsive subprocesses. For instance, impulsive action can also be evaluated as a stopping act, and waiting impulsivity can be also evaluated from the perspective of impulsive choice (see Table 1). Nevertheless, the inter-dependency between these impulsive subprocesses is still not clear, and as such further evidence is required. In this sense, the use of electroencephalography and transcranial electrical stimulation can prove to be invaluable in this pursuit of further evidence.

Table 1

Computerized tasks to measure the different subprocesses within impulsivity. Table based on Robbins and Dalley (2017)

Waiting/Stopping	Choice/Action	Task	Reference
Waiting Impulsivity	Impulsive Choice	Delay Discounting task	Ballard & Knutson, 2009
Waiting Impulsivity	Impulsive Action	4/5-Choice Serial Reaction Time task	Morris et al., 2016, Sanchez-Roige et al., 2014, Voon et al., 2014
Stopping Impulsivity	Impulsive Action	Go/No-Go task	Los, 2013
		Stop-Signal Reaction Time task	Morris et al., 2016, Sanchez-Roige et al., 2014,

1.2. P3 & Delta/Theta

Event-related potentials (ERP) are a widely used technique to measure the brain response towards a specific stimulus (Luck & Kappenman, 2011). Since the advent of cognitive sciences, ERPs have been of utmost importance because they allowed the understanding of mental operations underlying a specific output (Sutton et al., 1965). ERPs are measured by averaging the electrical activity collected by the electroencephalogram (EEG) during cognitive tasks. This allow for several cognitive processes to be studied, based on different waveforms, latencies and even in different brain regions. For instance, early ERPs in primary cortices are associated with sensory processing, whilst late ERPs in frontoparietal regions are implied in cognitive functioning (Herrmann & Knight, 2001).

One of the cognitive ERPs is the P3 (or P300), a positive waveform that peaks between 250 – 600 ms after the onset of a stimulus at centroparietal regions (Polich, 2007). This waveform is elicited

by several cognitive tasks in which there is an unexpected onset, and requires averaging through multiple trials (Polich, 2007). Consequently, the P3 ERP component has been observed during oddball paradigms (Polich, 2007), as well as in other tasks such as the n-back (Nikolin et al., 2018), the GNG (Huster et al., 2013), among others (Luck et al., 2000). Despite the fact that there is no consensus about the functional meaning of this component, main theories rely on processing capacity (Kok, 2001), memory storage (Polich, 2007), context updating (Donchin & Coles, 1988), closure of cognitive process (Desmedt & Debecker, 1979), and reactivation of stimulus-response (S-R) link (Verleger et al., 2014). Considering the whole evidence about frequency and relevance effects from oddball and signal detection task, Verleger (2020) concluded that the S-R link reactivation and the closure hypothesis are the models, which show at better fit with the literature. Nevertheless, the work by Verleger (2020) did not consider evidence from n-back and GNG tasks. Likewise, there is not much evidence about P3 during waiting impulsive processes.

Some studies explored how P3 is modulated by the reward anticipation in the Monetary Incentive Delay (MID) task. This paradigm pretends to address the anticipatory and consummatory processing of rewards, even though the premature responses are not evaluated per se. Specifically, MID is comprised of a cue that has a predictive value towards the valence of the rewards (i.e., potential gain, loss, or neutral), which is followed by a target stimulus demanding a behavioral action (Broyd et al., 2012). This allows the elicitation of P3 in centroparietal areas after the onset of both the cue, as well as the target. The cue-P3 is thought to reflect the motivated attention towards the subsequent target, whilst the target-P3 is the response to the relevant-stimulus that will influence the monetary gains or losses (Angus et al., 2017). However, the data concerning the modulation of P3 amplitude during MID is mixed. Particularly, the cue-P3 is increased during trials that predict either rewards (Broyd et al., 2012), losses (in schizophrenia subjects; Vignapiano et al., 2016), or even both (Angus et al., 2017; Novak & Foti, 2015; Vignapiano et al., 2016), when compared to neutral trials. The amplitude of the cue-P3 amplitude was higher for reward in comparison with loss trials (Angus et al., 2017; Pfabigan et al., 2014). However, the target-P3 amplitude increased during reward and losses when compared to neutral trials (Broyd et al., 2012). Therefore, although cue-P3 amplitude seems to be more sensitive to the valence of the trial in comparison with target-P3, both components seem to be susceptible to motivational processes underlying winning or losing.

Furthermore, the P3 ERP component also represents a response in the time-frequency domain. Oscillatory activity (i.e., time-frequency) is thought to be a mechanism of generation of ERPs, which is labeled as Event-Related Oscillations (ERO) (Herrmann et al., 2014). Two models were proposed to explain ERP generation through the oscillatory activity, namely the additive (or evoked) power model and

the phase-reset. The additive model states that the transient oscillatory activity observed during ERPs is a brain response independent of the ongoing neuronal activity (Schroeder et al., 1995). On the other hand, the phase reset hypothesis postulates that ERPs are generated by the phase reset of ongoing brain oscillations, thus suggesting a dependence on the oscillatory background activity (Klimesch et al., 2007). Hence, this hypothesis proposes that oscillatory activity does not necessarily increase from 0 to 2π successively, but some events might reset the phase for a specific value. Nonetheless, most of the evidence has been pointing out that both phenomena are likely to occur in parallel (Fuentemilla et al., 2006; Min et al., 2007; Mishra et al., 2012; Sauseng et al., 2007). In the specific case of P3, a burst of lower-frequency activity in the delta (0.5 – 4 Hz) and theta (4 – 7 Hz) bands are observed during the same time-window (Demiralp et al., 2001). Regardless of the task related differences in the P3 ERP component, this transient delta/theta ERO activity seems to be present in oddball (Demiralp et al., 2001), GNG (Huster et al., 2020), and reward anticipation tasks (Pornpattananangkul & Nusslock, 2016).

Hence, P3 is widely thought to reflect the reactivation of S-R link and working memory processes (Polich, 2007; Verleger, 2020), even though these models do not consider evidence from inhibitory control and waiting impulsivity paradigms (Angus et al., 2017; Huster et al., 2013). In the specific case of waiting impulsivity, P3 has been used as a potential probe for motivated attention towards an upcoming target and subsequent gain/loss (Angus et al., 2017).

1.3. Transcranial Electrical Stimulation Techniques: tDCS and tACS

Transcranial electrical stimulation (tES) techniques have been extensively used to study cognition in recent years. Despite the fact, that most tES techniques differ in the mechanism by which their effects are produced, their effects are due to the modulation of neuronal activity through the application of electrical currents through the scalp (Fertonani & Miniussi, 2017).

The most studied tES is named transcranial Direct Current Stimulation (tDCS). tDCS consists of applying a weak direct current over the scalp (Nitsche & Paulus, 2000). The stimulation is performed through two (or more) electrodes with distinct polarities, namely the positive pole called anode and the negative named cathode, which results in a modulation of the membrane potential of neurons in a polarity-specific manner (Stagg & Nitsche, 2011). Particularly, the cortical region below the anode is thought to be depolarized, suggesting that those neurons are more likely to fire. On the other hand, the cathode is suggested to have the opposite effects, which will result in a decrease of the rate of firing (Nitsche et al., 2008). Likewise, tDCS delivers a unidirectional DC current through the cortex. Specifically,

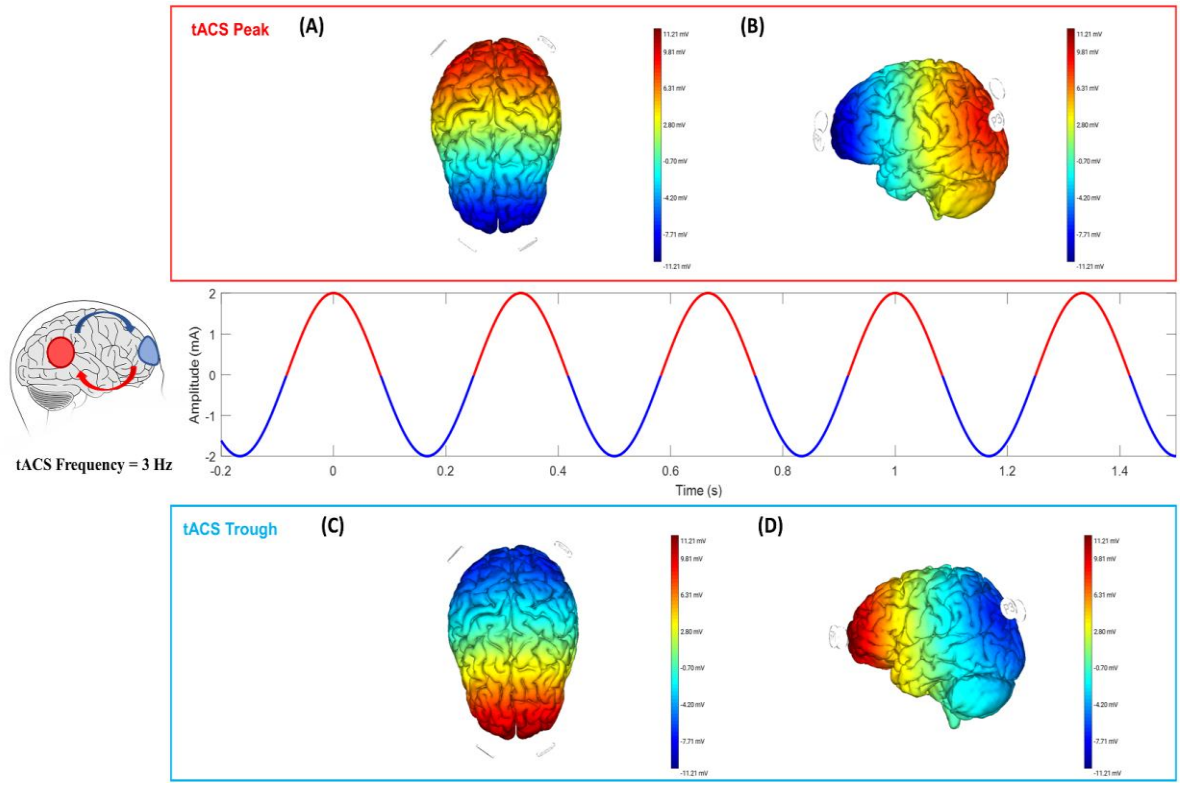
the anode creates an inward current and the cathode an outward producing a positive and negative electric field respectively (Jackson et al., 2016). Furthermore, the neuroplastic tDCS aftereffects observed in the synaptic strengthening also are dependent on the polarity of the stimulation (Nitsche & Paulus, 2000), probably through long-term potentiation (LTP) for anodal and long-term depression (LTD) processes for cathodal tDCS (Monte-Silva et al., 2013).

However, the effects of tDCS on neurophysiological and behavioral markers are not so straightforward, indeed they are non-linear, given that these tDCS effects are dependent on the stimulation parameters and on the ongoing neuronal activity (Fertonani & Miniussi, 2017). For instance, the intensity of tDCS is not necessarily correlated with its neurophysiological impact, as several studies showed a non-linear inverted U-shaped function between intensity and response (Batsikadze et al., 2013; Goldsworthy & Hordacre, 2017). Moreover, the ongoing neuronal activity also assumes a crucial feature in the tDCS impact. Several studies demonstrated that the task performance associated with different neuronal excitability modulated differently the effects of tDCS (Benwell et al., 2015; Bortoletto et al., 2015). And the same is true for cognitive load. For instance, tDCS coupled with high load working memory (WM) training was more efficient than when coupled with low load training (Gill et al., 2015). This level of activity (either in rest, or in active state) seems to be an important factor for further optimize the effects of tDCS.

Transcranial Alternating Current Stimulation (tACS) is another non-invasive technique, in which a low amplitude sinusoidal current is applied on the scalp (Kanai et al., 2008). The rhythmic waveform of the electrical current implies that the two electrodes (or more) do not have a fixed polarity, instead they will act as anode or cathode interchangeably during the cycle of tACS oscillation. For instance, in the first half cycle, one electrode acts as anode and another as cathode, whilst in the next half cycle their roles are inverted (see Figure 1). Therefore, the membrane potential is depolarized and hyperpolarized accordingly, with the frequency from tACS allowing the entrainment of the endogenous oscillatory activity (Antal & Herrmann, 2016). The entrainment of oscillatory activity is explained by the Arnold tongue phenomenon, namely higher tACS amplitudes are able to modulate a higher range of frequencies (Vossen et al., 2015). Thus, considering that the tACS induced effects in the membrane potential are of a low-amplitude, the match between the frequency of tACS and the one from endogenous activity is essential for successful entraining (Frohlich & Townsend, 2021).

Figure 1

The tACS sinusoidal waveform has a distinct effect in the current field depending on the phase of the current. The peak of the sinusoidal current correspond to the maximum magnitude of the current flow (A,B), whilst the tACS trough represents the minimum magnitude (C,D). The rhythmic current allows the constant interchange between anodal and cathodal stimulation according to the frequency of tACS. The electric field maps were computed in the NIC 2.0 software (Neuroelectrics, Barcelona, Spain).



This tACS-induced entrainment phenomenon, was already observed in several frequency bands, namely, delta (Marshall et al., 2006), theta (Pahor & Jaušovec, 2018), alpha (Helfrich et al., 2014; Zaehle et al., 2010), and gamma (Voss et al., 2014). However, the findings are far from being consensual. For instance, instead of an tACS induced entrainment phenomenon, a disruption in delta (Wischnewski & Schutter, 2017) and theta activity (Wischnewski et al., 2016) were reported in the literature. It is important to highlight that the efficacy of tACS relies on the match between the phase of stimulation and the ongoing oscillatory activity, as derived from computer simulations performed by Kutchko and Fröhlich (2013). Therefore, an anti-phasic mismatch between tACS and neuronal oscillations might lead to a perturbation in the phase-reset of ERP and its ERO (Popp et al., 2019). Additionally, the spike-timing dependent plasticity (STDP) model also suggest that synaptic changes induced by tACS occur depending on the timing of the neuronal firing. In particular, the aftereffects of tACS can lead to LTP when pre-synaptic

events occur before post-synaptic, whilst LTD can be induced if post-synaptic events occur before pre-synaptic ones (Zaehle et al., 2010). Hence, STDP model suggests that tACS leads to synaptic strengthening in neuronal frequencies equal or slightly superior to tACS frequency, whereas a synaptic weakening is observed when neuronal frequencies are lower than tACS (Vogeti et al., 2022). Overall, the success of entraining oscillations relies on the synchronization of phase and frequency between tACS and the targeted neuronal activity (Riddle & Frohlich, 2021).

Furthermore, both techniques also have been associated with behavioral gains in different cognitive domains. Meta-analysis on tDCS literature suggested an increased performance during response inhibition (Schroeder et al., 2020) and working memory paradigms (Brunoni & Vanderhasselt, 2014). Likewise, a meta-analysis of tACS studies showed a similar result regarding the cognitive functioning, although each process was not analyzed independently (Schutter & Wischnewski, 2016). For that, Klink and colleagues (2020) did a systematic review and showed different modulatory effects relying on the frequency of stimulation, namely an improvement of working memory and response inhibition after theta tACS. On the other hand, delta tACS is less reported in the literature and its effects on executive functioning are still unknown (Klink et al., 2020).

Thus, depending on the intended neuromodulatory output, two main tES can be applied in the scalp: tDCS and tACS. The main difference between both is the electrical current waveform, which is constant in the former and sinusoidal in the latter (Antal & Herrmann, 2016). tDCS has been proposed to modulate cortical excitability, whereas tACS is able to modulate cortical oscillations. Hence, even though tDCS and tACS have distinct mechanisms of action in the brain, both are suggested to induce LTP or LTD (Vogeti et al., 2022). As such, both techniques are not only capable to modulate brain activity, but also to improve cognitive functions such as the inhibitory control, working memory, and attention (Coffman et al., 2014; Klink et al., 2020).

1.4. Objectives and Hypotheses

The relationship between P3 waveform characteristics and several neuropsychiatric disorders, together with the efficacy of tES in modulating P3, highlights the importance of a deeper understanding of the impact of tES in electrophysiological markers. Specifically, this work assesses the effect of tDCS and tACS on P3 and ERO during a waiting impulsivity task. Moreover, this dissertation also aims to assess how tES modulates the number of premature responses, which contribute for the advancement of

psychological science, as well as for its applications, namely because waiting impulsivity is strongly associated with addiction and ADHD conditions.

Therefore, there are three studies in this dissertation:

i. The first study (Chapter 2) aims at understanding how tDCS modulates P3 amplitude and latency in several cognitive tasks, namely in a oddball, n-back, Go/No-Go (GNG), and emotional processing paradigms. For that, a systematic review and a meta-analysis were performed.

ii. The second study (Chapter 3) addresses the effect of tDCS over the rIFG in the P3 amplitude and ERO during a waiting impulsivity paradigm. An increase in the amplitude of P3 during the active tDCS in comparison with the sham session was expected. Likewise, the increase of P3 amplitude is hypothesized to be combined with an increase in ERO, specifically in delta and theta bands, as well as a reduction in the number of premature responses.

iii. The third study (Chapter 4) aims to understand if tACS frequency tailoring based on the P3 latency and ERO frequency is a feasible method to modulate P3 amplitude. It is hypothesized that the frequency and temporal synchronization between tACS and endogenous P3 related activity will increase P3 amplitude and enhance ERO.

1.5. References

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CHAPTER 2

Modulation of the cognitive event-related potential P3 by transcranial Direct Current Stimulation: systematic review and meta-analysis

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2.1. Abstract

Transcranial direct current stimulation (tDCS) has been widely used to modulate cognition and behavior. However, only a few studies have been probing the brain mechanism underlying the effects of tDCS on cognitive processing, especially throughout electrophysiological markers, such as the P3. This meta-analysis assessed the effects of tDCS in P3 amplitude and latency during an oddball, n-back, and Go/No-Go tasks, as well as during emotional processing. A total of 36 studies were identified, but only 23 were included in the quantitative analysis. The results show that the parietal P3 amplitude increased during oddball and n-back tasks, mostly after anodal stimulation over the left dorsolateral prefrontal cortex ($p = 0.018$, SMD = 0.4) and right inferior frontal gyrus ($p < 0.001$, SMD = 0.669) respectively. These findings suggest the potential usefulness of the parietal P3 ERP as a marker of tDCS-induced effects during task performance. Nonetheless, this study had a low number of studies and the presence of considerable risk of bias, highlighting issues to be addressed in the future.

Keywords: Event-related potential P3 P300 tDCS Cognition Working memory Attention Inhibitory control

2.2. Introduction

Transcranial direct current stimulation (tDCS) is one of the most studied techniques in non-invasive neuromodulation. With a very good safety profile and low cost, tDCS has been used to modulate cognition in both experimental and clinical settings (Coffman et al., 2014; Fregni et al., 2020). tDCS relies on the application of a weak direct current through two electrodes with different polarities – the anode and the cathode. The cortical excitability modulation depends on the polarity. The concept is that anodal stimulation leads to a subthreshold neuronal depolarization augmenting the likelihood of spontaneous neuronal firing, whilst the cathode has the opposite hyperpolarization effect (Stagg and Nitsche, 2011). Additionally, tDCS induced after-effects occur through neuroplastic changes at molecular level, e.g. in the N-methyl-D-aspartate (NMDA) receptors and brain-derived neurotrophic factor (BDNF), namely by inducing long-term potentiation (LTP) and long-term depression (LTD) (Chan et al., 2021; Monte-Silva et al., 2013). The neuroplastic modulation is not only dependent on tDCS polarity, but it is also contingent on other stimulation parameters (e.g., current density, stimulation duration). Recent studies showed that the dose-response relationship follows a non-linear inverted U-shaped function (Batsikadze et al., 2013; Goldsworthy and Hordacre, 2017). Moreover, resting neuronal state seems also to be relevant for understanding the neurophysiological impact of tDCS. For instance, recent studies showed that tDCS effects are dependent on the timing of stimulation, task difficulty, or ongoing neuronal activity (Fertonani and Miniussi, 2017).

tDCS has been widely studied 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-reporting) to assess the effectiveness of tDCS, without a clear explanation of the underlying mechanisms responsible for its effects. The understanding of the mechanisms underlying brain activity and the impact of tDCS on those networks is especially important in cognition, in which task performance, although important, is only correlated with brain functioning.

The P3 (or P300) is one of the most studied event-related potentials (ERP) (Sutton et al., 1965). This positive component peaks with a latency around 300 – 400 ms after the stimulus onset in any sensory modality, and is thought to underlie attention and working memory processes (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 and Wang, 2019), attention-deficit/hyperactivity disorder (ADHD; Kaiser et al., 2020), bipolar disorder (Wada et al., 2019), post-

traumatic stress disorder (PTSD; Johnson et al., 2013), and psychopathy and antisocial behavior (Pasion et al., 2018).

Often referred in the literature as a single component, P3 can be divided in two additional subcomponents: P3a and P3b. P3a signals an attentional and orientation processes (P3a) occurring after the exposure of an unpredictable stimulus (e.g., a distracter or a novel stimulus in a three-stimulus oddball paradigm) and it is elicited in the frontocentral brain region (Friedman et al., 2001). This subcomponent might be a neuronal representation of attentional allocation and orientation to something unexpected (Simons et al., 2001; Spencer et al., 2001). The amplitude and latency of P3a are modulated by the 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 novelty and/or salience of the stimulus decreases in repeated presentations, especially with short interstimulus intervals (Rushby and Barry, 2009). On the other hand, P3b is elicited in parieto-temporal region approximately 60-80 ms after the P3a during a standard oddball paradigm, specifically after an infrequent stimulus (i.e., target) that is intermingled in a series of frequent stimuli (i.e., non-target). Participants are instructed to respond to a target stimulus (e.g., press a button or count the number of targets), whilst they need 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 maintained on the WM, suggesting a role in processing task-relevant information and subsequent memory storage (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 and Kessler, 2019).

However, the oddball task is not the only task in which the P3 component can be elicited. For instance, the memory operations reflected by P3 are also observed during n-back tasks, mostly after the exposure of a target stimulus that matches the stimulus displayed *n* trials before (Saliasi et al., 2013). In sum, P3b is thought to reflect the comparison between the present stimulus and the information already stored (i.e., categorization of task-relevant information), while the P3 elicited in n-back is more strongly related with the memory storage of the current stimulus (i.e., update WM) to successfully perform the upcoming comparisons (Polich, 2007). The amplitude of the component is related to the allocation of the neuronal resources and the cognitive processing, while the latency is associated with the time required to evaluate the stimulus, which suggests that reduced P3 amplitude with longer latencies indicates poorer and delayed operations relative to the task-relevant stimulus.

Additionally, P3 is also elicited during tasks requiring the inhibition of a forthcoming response, such as the Go/No-Go (GNG) task and the Stop Signal Reaction Time task (SSRT). Both paradigms require

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

P3 is also very sensitive to the emotional-motivational value of the stimuli. For instance, P3 amplitude increased after emotionally laden stimuli when compared with a stimulus with a neutral emotional meaning (Hajcak et al., 2010) or after the exposure of drug-related pictures in subjects with addiction problems (Dunning et al., 2011). Moreover a study using P3 as a workload probe showed that videos with high levels of emotional arousal (e.g., horror or erotic) have strong interference in the P3 amplitude during an oddball paradigm when compared with videos with lower arousal (Carvalho et al., 2011). These findings suggest that P3 is also responsive to the salience of the stimulus, which might reflect the motivational purposes in the allocation of attentional resources as well (Boggio et al., 2009; Nakamura-Palacios et al., 2012).

Overall, P3 has been used frequently as an index of attention and working memory underlying several cognitive processes and can be used to assess the impact on cognitive functioning of several neuromodulatory interventions on the brain. In this sense, it is important to study its usefulness as mechanistic biomarker of the effects of tDCS in cognition. Thus, this systematic review and meta-analysis assess the effect of tDCS on the distinct P3 components elicited during cognitive processing. For this, the current study analyzed P3 amplitude and latency in four main sections/paradigms: Oddball paradigm, N-back tasks, GNG task, and Emotional Processing.

2.3. Methods

The systematic review with meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009) and the Cochrane Handbook for Systematic Reviews (Higgins, 2021)

2.3.1 Literature Search and Study Selection

We searched in MEDLINE/PUBMED, EMBASE, Cochrane Central, Web of science, and Central, using a two-staged approach to increasing selection sensitivity. In the first stage, we used general controlled and uncontrolled search terms for "non-invasive brain stimulation," and "electroencephalography," or "event-related potential." The complete search strategy is available at the Table SM.1 in Supplementary Materials. The accuracy of the search formula was confirmed by cross-verification with the results of previous systematic reviews on the topic (Horvath et al., 2015; Kim et al., 2018). The last search was performed on March 11, 2020. Additionally, we reviewed the bibliographic references of the included studies and previous systematic and narrative reviews on the topic. The screening phase was performed by two researchers independently in the Covidence web-based platform (Kellermeyer et al., 2018), where potential disagreements were resolved by a third researcher.

We performed a two-stage study selection process. The inclusion criteria for the first stage were: i) randomized or counterbalanced experiment (pseudorandomized) sham-controlled trials, ii) studies assessing the effects of Non-invasive brain stimulation (including tDCS), iii) studies reporting any EEG-related variable, and iv) studies including healthy subjects and clinical populations. No restrictions by language or publication date. We excluded other publication types (conference proceedings, abstracts, or reviews) and other studies design (non-randomized studies or observational studies). The screening on this step was based on the abstract of each study.

In the second stage, we selected a specific set of studies from the highly sensitive identified studies and the screening was based on the full-text article. The inclusion criteria for this stage were:

i. Randomized controlled trials (RCT, e.g., parallel-groups, crossover designs, pilot studies) and quasi-experimental trials (e.g., pseudo-randomized) were included.
ii. EEG was performed during the engagement in tasks involving cognitive processes, such as inhibitory control, working memory, attentional processing, or cue-reactivity paradigms.
iii. Application of tDCS during or before the EEG collection comprising active and sham conditions.
iv. P3 was analyzed during one of the aforementioned tasks and analyzed with the aim to compare active tDCS with a sham condition.

v. Studies including healthy or clinical population.

In the case of multiple publications related to one cohort, we included the most updated report. We did not exclude studies because of language or publication date. Moreover, before the screening phase, the reviewers screened titles and abstracts from one random sample of 100 search results to ensure an inter-rater agreement of at least 90%. The Cohen's kappa was estimated as a measure of the inter-rater reliability assessment (McHugh, 2012). The mean inter-rater agreement and kappa estimators were 94% and 90% respectively (see Table SM.2 in Supplementary Materials for more details).

2.3.2 Data extraction

The relevant information was extracted from the second-stage included studies, namely, first author, year of publication, mean, and standard deviation of P3 amplitude and latency post or during tDCS, number of subjects analyzed (i.e., excluding outliers or subjects with noisy EEG data), EEG electrode(s), brain region of stimulation (i.e., anode and cathode location), tDCS parameters (i.e., intensity, density, and duration), number of sessions (e.g., single or multi-session), population (e.g., healthy subjects or with clinical diagnostic), computerized cognitive task that elicited P3, target probability and stimulus modality in the computerized task, (e.g., auditory, visual), and study design (e.g., crossover, parallel). In studies lacking the required statistical information to estimate effect size in the text or tables, however with the information available on the graphs, the Web Plot Digitizer was used to extract those data (Rohatgi, 2017). In case of the inexistence of the required statistical information in any format, an email was sent to the corresponding author requesting the intended information. Furthermore, considering that P3 is a component more prominent in frontal and parietal regions (Polich, 2007), the amplitude and the latency of P3 were extracted from the Fz and Pz electrodes when available. Otherwise, the regions of interest (ROI) analyzed in the studies are considered to extract the data, namely P3 on parietal and frontal areas (Table SM.9 in Supplementary Materials). Therefore, the meta-analysis of P3 was performed independently for frontal and parietal areas since they represent the main regions of interest with distinct functional significances. Additionally, the GNG subsection is also divided by type of trial (i.e., No-Go and Go trials).

2.3.3. Statistical analysis

All the analysis was conducted using R (R Development Core Team, 2018; R Version 4.0.3) using the *metafor* package (Viechtbauer, 2010; metafor Version 2.4-0, released on 19-03-2020).

2.3.3.1. Pooled effect estimates and subgroup analysis. A random-effect model was performed due to the expected high level of heterogeneity, assuming that the true effect size among the studies might not be identical (Borenstein et al., 2010). The effect size was calculated by subtracting sham P3 values from the active tDCS condition measured during/after tDCS. The standard mean difference (SMD) between both tDCS conditions, namely the effect size of the intervention relatively to its variability, was calculated following the unbiased method of Hedges' g (Hedges, 1981). Thus, the pooled effect estimates were analyzed independently for anodal and cathodal tDCS due to its potential antagonistic effects (Cochrane, 2019). The subgroup analysis were performed accordingly to the tDCS polarity and brain region of stimulation (e.g., left dorsolateral prefrontal cortex - lDLPFC, right Inferior Frontal Gyrus - rIFG). These analyses were performed only when there were the effect estimates from at least two studies. Furthermore, the I2 index was performed to assess heterogeneity (Higgins and Thompson, 2002).

2.3.3.2. Influential analysis. The influential analysis was performed using the leave-one-out method. This technique allows the recalculation of the estimates of the meta-analysis by removing one study per recalculation in a total of N-1 times (Viechtbauer and Cheung, 2010). This sensitivity analysis tests the robustness of the detected effects by observing the influence of each comparison in the significant findings.

2.3.3.3. Moderator analysis. The moderator analysis was completed using a univariate regression model. The meta-regression comprised the following moderators: brain region and hemisphere of stimulation, tDCS parameters (i.e., intensity, density, duration), number of sessions (i.e., single or multi-session) population (i.e., healthy and clinical), response requirement, target probability, timing (online/offline), and study design. Nonetheless, not all moderators have been included in every moderator analysis because it was dependent on the heterogeneity of the studies analyzed in each subsection. For instance, if all the studies from a sub-analysis have the same tDCS intensity parameter except in one comparison, this variable was not analyzed. Moreover, the meta-regression was not performed if there were less than 10 comparisons (Thompson and Higgins, 2002).

2.3.3.4. Publication bias. The publication bias was analyzed through funnel plots and Egger's regression test for the asymmetry (Egger et al., 1997). The p-value and the test-statistics (i.e., z-value) from Egger's test were considered to evaluate potential asymmetries. The methods to detect publication bias test the differences between studies, which implies that only one comparison per study must be included. Nonetheless, in this study, all the comparisons were included due to the low number of studies but with a high number of comparisons. Therefore, these analyses were only performed when there were at least 10 comparisons (Sterne et al., 2011).

2.3.4. Risk of Bias

The risk of bias was assessed using the Cochrane Collaboration's risk of bias tool (Higgins et al., 2011). Each study was classified as "high risk", "low risk" or "unclear" in seven criteria, namely (1) random sequence generation, (2) allocation concealment, (3) selective reporting, (4) other sources of bias, (5) participants and (6) raters blinding, and (7) lack of outcome data. The traffic light graphs were plotted using the *robvis* package in R (McGuinness & Higgins, 2020; robvis Version 0.3.0, released on 22-11-2019).

2.3.5. Evidence certainty assessment

We assessed the certainty of our pooled estimates applying the grading of recommendation, assessment, development, and evaluation (GRADE) approach (Balshem et al., 2011). This assessment is based on five domains: study limitations (i.e., risk of bias of the studies included), imprecision (i.e., sample sizes and confidence intervals (CI)), indirectness (generalizability), inconsistency (heterogeneity), and publication bias as stated in the GRADE handbook (Schünemann et al., 2013). The certainty of the evidence was characterized as high, moderate, low, or very low and was described in the Summary of findings table to present the most relevant pooled estimates. We used the web-based platform GRADE online tool (http://gradepro.org).

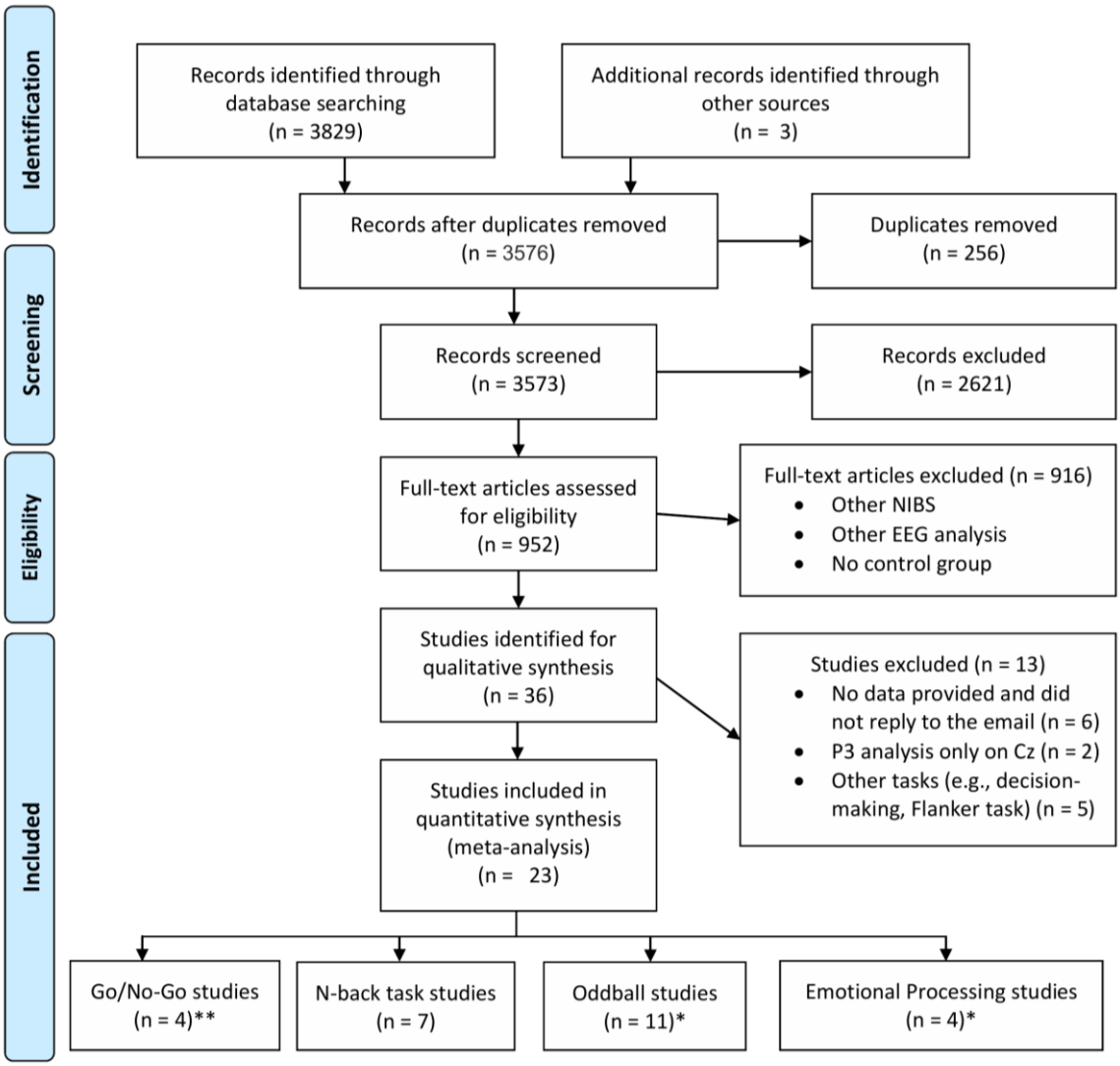
2.4. Results

A total of 23 studies were included, specifically, 4 with GNG, 7 with n-back, 10 with oddball, and 4 with emotional processing. There was one study that evaluated P3 on GNG and in an oddball paradigm and two that used emotional-charge stimuli in the GNG task. Therefore, these studies were included in two sections of analyses accordingly to their characteristics. Two studies that analyzed P3 in an auditory oddball and in GNG were not included because they only reported the data from the electrode site Cz.

Furthermore, six studies did not report sufficient information to estimate the effect size and the corresponding author did not reply to the request via e-mail. We excluded five studies evaluating P3 on other cognitive tasks, such as flanker task, recognition task, naming task, and a decision-making paradigm (Figure 2). The results of the study characteristics, pooled effect estimates, and subgroup analysis are divided into four main analyses, namely in GNG, n-back, oddball, and emotional processing. Finally, we presented the moderator and influential analysis, the publication bias, risk of bias, and evidence certainty assessment.

Figure 2.

*PRISMA flow diagram (*one study analyzed P3 on a GNG task and oddball paradigm; **two studies were included in GNG and emotional processing analysis because P3 was evaluated in an emotional GNG).*



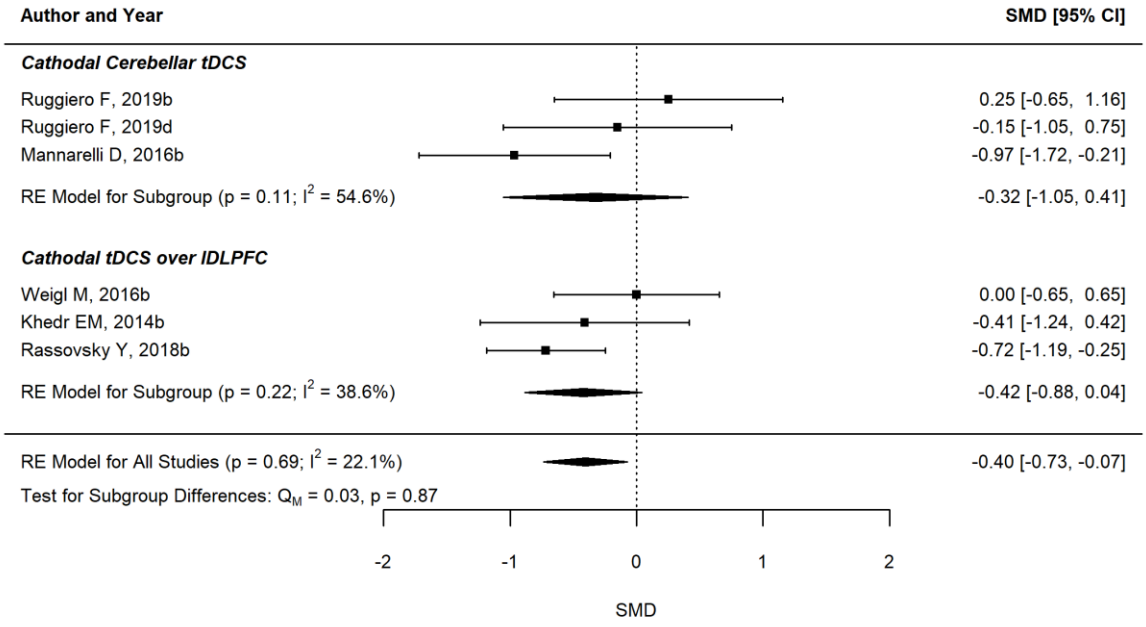
2.4.1. Oddball

2.4.1.1. Study Characteristics. Thirteen studies met the eligibility criteria. However, two studies were excluded because, in one, no relevant data was available directly from the article, and another study only analyzed the P3 in the Cz electrode. Therefore, 11 studies (with 22 comparisons) with a total of 236 participants were analyzed (see Table SM.8 in Supplementary Materials). Seven (out of 11) studies (with 16 comparisons) analyzed the P3 amplitude in the frontal region and nine studies (with 16 comparisons) in the parietal area. In the frontal P3 assessment, the anodal stimulation was performed in seven studies (with 10 comparisons and the cathodal in five studies, with eight comparisons). Considering the studies that analyzed parietal P3 amplitude, all the studies (nine studies with 11 comparisons) studied the effect of anodal stimulation, whilst four of them (with five comparisons) also tested the effects of cathodal tDCS. In line with other tasks, the P3 latency was less frequently analyzed, specifically four studies (with five comparisons) tested anodal and cathodal tDCS in frontal P3, while two studies (with four comparisons) explored the anodal effect and one study (with two comparisons) on parietal P3 (see Table SM.5 in Supplementary Materials). Taking into account the brain region of tDCS, most of the studies targeted to the lDLPFC (six studies with 16 comparisons), others the cerebellum (two studies with six comparisons), rIFG (one study and one comparison), supraorbital area (one study and two comparisons) and motor cortex (one study and one comparison) (see Table SM.6 in Supplementary Materials). Most of the studies performed tDCS before the assessment of P3 (nine studies), whilst only one did it during tDCS and another one assessed the after effects of tDCS on the P3 component. Additionally, the oddball tasks were mostly designed using auditory stimuli (nine out of 11 studies) and only two studies used visual cues (i.e., one employed letters and numbers and another one used human faces). Finally, six studies (with 10 comparisons) explored P3 in healthy subjects and five studies (with eight comparisons) in a clinical population (i.e., three in people with schizophrenia, one in people with multiple sclerosis and Alzheimer's disease).

2.4.1.2. Pooled effect estimates and subgroup analysis. The pooled effect estimated from the seven studies (with 10 comparisons) that analyzed anodal tDCS on the frontal P3 amplitude did not present significant heterogeneity (p = 0.685, I2 = 2.429). Moreover, this set of studies did not show a significant effect on frontal P3 amplitude (p = 0.576, SMD = -0.062, 95% CI [-0.28 0.16]). Further subgroup analysis did not show significant heterogeneity in the studies applying anodal stimulation on cerebellum (p = 0.928, I2 = 0), neither on the lDLPFC (p = 0.385, I2 = 22.448). Nonetheless, both subgroup analysis revealed a non-significant effect of stimulation on the frontal P3 amplitude, namely when using anodal tDCS over the cerebellum (p = 0.668, SMD = -0.104, 95% CI [-0.58 0.37]) or over the lDLPFC (p = 0.839, SMD = -0.029, 95% CI [-0.31 0.25]). Additionally, five studies (with six comparisons) that analyzed the effect of cathodal tDCS in frontal P3 amplitude did not reveal significant heterogeneity (p = 0.18, I2 = 22.141) and showed that cathodal tDCS significantly decreased frontal P3 amplitude (p = 0.017, SMD = -0.404, 95% CI [-0.73 -0.07]) (Figure 3). The subsequent subgroups analysis regarding brain region stimulation did not show significant result in heterogeneity test for cathodal tDCS over the cerebellum (p = 0.109, I2 = 54.612) or over the lDLPFC (p = 0.215, I2 = 38.57). Cathodal stimulation over the cerebellum did not show a significant effect on frontal P3 amplitude (p = 0.383, SMD = -0.325, 95% CI [-1.05 0.41]), whilst a non-significant trend was showed when the cathodal tDCS was delivered over the lDLPFC (p = 0.076, SMD = -0.42, 95% CI [-0.88 0.04]). For frontal P3

Figure 3.

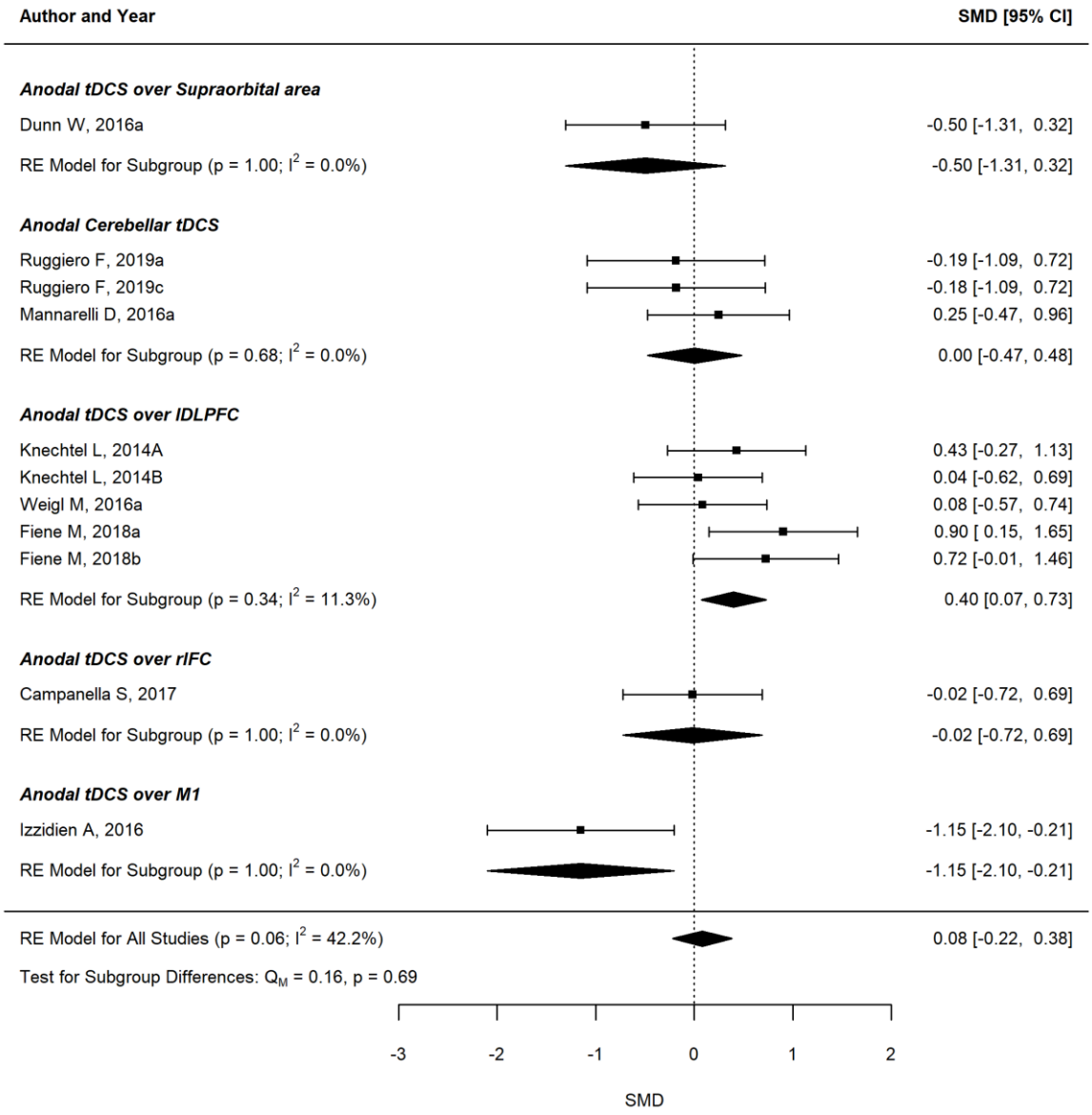
Forest plot with pooled effect estimate and subgroup analysis concerning the cathodal stimulation on frontal P3 amplitude during oddball.



latency, the four studies (with five comparisons), in which anodal stimulation was applied, were significantly heterogeneous ($p < 0.001$, $I^2 = 92.818$). However no significant effects of anodal tDCS in frontal P3 latency were found ($p = 0.47$, SMD = 0.493, 95% CI [-0.84 1.83]). Furthermore, the heterogeneity test in the subgroup analysis revealed a non-significant heterogeneity in anodal cerebellar tDCS ($p = 0.79$, $I^2 = 0$), but a significant heterogeneity in the studies applying anodal stimulation over the lDLPFC ($p < 0.001$, $I^2 = 97.817$). The subgroup analysis probing the effects of anodal tDCS in the frontal P3 latency was non-significant, regardless of the stimulation site ($p = 0.937$, SMD = 0.019, 95% CI [-0.46 0.5] for cerebellum) and ($p = 0.518$, SMD = 1.221, 95% CI [-0.31 4.92] for the lDLPFC). Concerning the same for studies, but for the cathodal stimulation comparisons (five comparisons), a significant heterogeneity was revealed ($p < 0.001$, $I^2 = 91.403$. However, there were no significant effects of cathodal tDCS on the frontal P3 latency ($p = 0.172$, SMD = 0.843, 95% CI [-0.37 2.05]). Subgroup analysis suggested significant heterogeneity in cathodal cerebellar ($p < 0.001$, $I^2 = 93.107$)) and in the lDLPFC tDCS($p = 0.006$, $I^2 = 86.523$). In line with the pooled effect estimate analysis, both subgroups showed no significant effect on the frontal P3 latency, namely with cerebellar ($p = 0.283$, SMD = 1.17, 95% CI [-0.97 3.31]) or the lDLPFC tDCS ($p = 0.465$, SMD = 0.492, 95% CI [-0.88 1.81]). For probing the effects of anodal tDCS in the parietal P3 amplitude, nine studies (with 11 comparisons) were retrieved. There was a non-significant trend regarding heterogeneity ($p = 0.058$, $I^2 = 42.218$) and there was no significant anodal tDCS effect ($p = 0.596$, SMD = 0.081, 95% CI [-0.22 0.38]). Moreover, subgroup analysis did not present significant heterogeneity in studies with anodal tDCS over the cerebellum ($p = 0.68$, $I^2 = 0$) or the lDLPFC ($p = 0.338$, $I^2 = 11.264$). No significant effect of anodal cerebellar tDCS on parietal P3 amplitude was shown ($p = 0.984$, SMD = 0.005, 95% CI [-0.47 0.48]), however there was a significant effect of anodal stimulation over the lDLFPC ($p = 0.018$, SMD = 0.4, 95% CI [0.07 0.73]). The anodal tDCS over the lDLPFC increased the frontal P3 amplitude in comparison with the sham condition (Figure 4). The subgroup analysis of anodal tDCS over supraorbital, rIFG or M1 are not reported because they were comprised by only one study. For cathodal tDCS, the four studies (with five comparisons) did not show significant heterogeneity ($p = 0.857$, $I^2 = 0$) and there was no significant effect of cathodal tDCS in the parietal P3 amplitude ($p = 0.837$, SMD = -0.036, 95% CI [-0.38 0.31]). The subgroup analysis with the cathodal cerebellar tDCS comparisons neither reveal heterogeneity ($p = 0.578$, $I^2 = 0$), nor significant effect of cathodal tDCS ($p = 0.78$, SMD = -0.068, 95% CI [-0.55 0.41]). The subgroup analysis of cathodal

Figure 4.

Forest plot with pooled effect estimate and subgroup analysis concerning the anodal stimulation on parietal P3 amplitude during oddball.



tDCS over the supraorbital region, or the lDLPFC is not reported because there is only one study targeting those regions. Finally, the pooled effect estimate and subgroup analysis was not performed in the parietal P3 latency during oddball due to the lack of data.

2.4.2. N-back tasks

2.4.2.1. Study Characteristics. A total of eight studies met the inclusion criteria, but one of them did not report the required data and the corresponding author did not reply to the data request. So, seven studies (with 20 comparisons) comprising 132 participants were analyzed (see Table SM.8 in Supplementary Materials). Most of the studies (six out of seven with 18 comparisons) analyzed the P3 amplitude in the frontal region, whilst four studies (with 11 comparisons) also assessed it on the parietal area. Concerning anodal polarity, six of them (with 15 comparisons) tested the frontal P3, whilst only four (with eight comparisons) tested anodal tDCS in parietal P3. On the other hand, two of them (with three comparisons) also tested the cathodal stimulation effect in frontal and parietal P3 amplitude. Regarding the P3 latency, only two studies (with seven comparisons) analyzed P3 in the frontal region, and one study (with two comparisons) analyzed P3 in the parietal area (see Table SM.5 in Supplementary Materials).

Every study explored the effect of tDCS on frontal areas, namely over the lDLPFC (five studies out of seven with 15 comparisons assessed frontal P3; and two studies with six comparisons in total, assessed parietal P3) and rIFG (two studies out of seven with three comparisons assessed frontal P3 and five comparisons in parietal P3) (see Table SM.6 in Supplementary Materials). All the studies performed tDCS before assessing the P3 component. Moreover, the study population was different between the included studies, comprising healthy adults (five studies with 15 comparisons), healthy elderly (one study with two comparisons), patients with Alzheimer disease (one study with two comparisons) and children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD; one study with two comparisons). Finally, the P3 was assessed in 0-back and 1-back (three studies with five comparisons), 2-back (five studies with eight comparisons), and 3-back (four studies with seven comparisons).

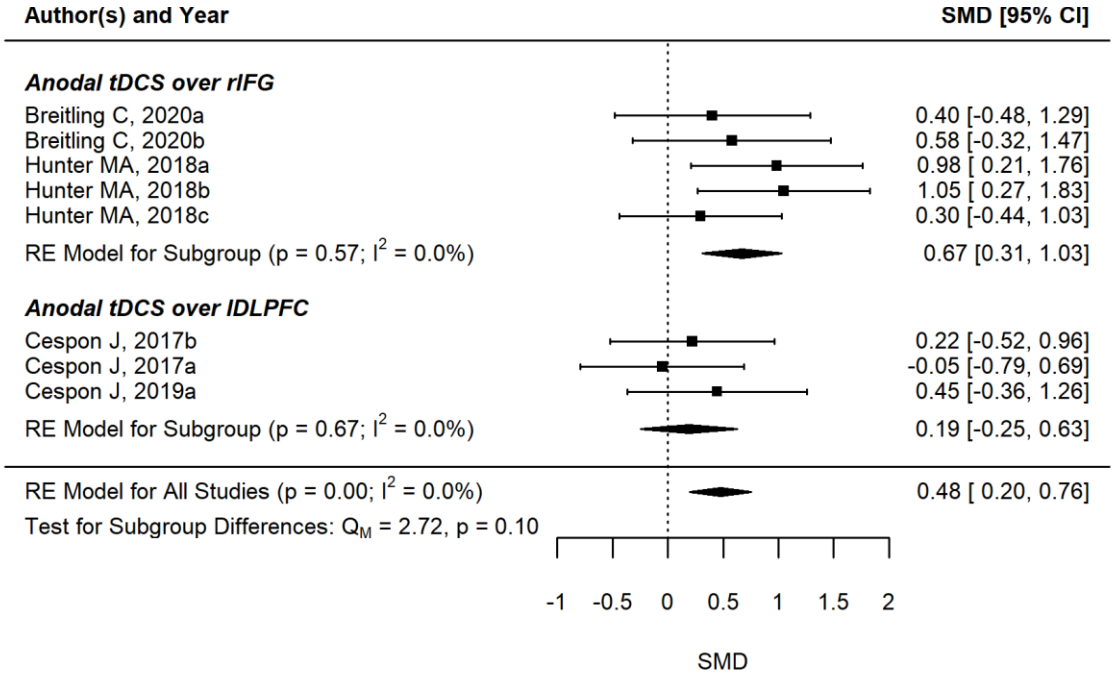
2.4.2.2. Pooled effect estimates and subgroup analysis. The pooled effect estimates of the six studies (and 15 comparisons) with anodal tDCS that incorporated frontal P3 amplitude in their analysis revealed a significant heterogeneity ($p < 0.001$, $I^2 = 70.497$). Considering all the studies, there were no differences between anodal and sham tDCS in frontal P3 amplitude ($p = 0.959$, SMD = 0.008, 95% CI [-0.31 0.33]). The studies with anodal tDCS over the lDLPFC presented a significant heterogeneity ($p = 0.03$, $I^2 = 47.561$). Furthermore, there were no significant effects of anodal tDCS over the lDLPFC in frontal P3 amplitude ($p = 0.169$, SMD = 0.202, 95% CI [-0.09 0.49]). The subgroup analysis of anodal tDCS over rIFG is not reported because only one study analyzed the frontal P3 amplitude. Additionally, both studies that explored the effects of cathodal tDCS over the frontal P3 amplitude did not present significant heterogeneity ($p = 0.368$, $I^2 = 2.664$), but no significant effects were detected ($p = 0.888$, SMD

= -0.032, 95% CI [-0.48 0.41]). Finally, regarding the frontal P3 latency, the two studies (with seven comparisons) did not reveal significant heterogeneity (p = 0.936, I^2 = 0) and no significant effects of anodal tDCS on frontal P3 latency were found (p = 0.201, SMD = -0.173, 95% CI [-0.44 0.09]).

Regarding the P3 evaluated in the parietal region, the four studies (with 8 comparisons) with anodal tDCS analysis did not reveal a significant heterogeneity (p = 0.49, I^2 = 64.786) and there was a significant effect of tDCS on parietal P3 amplitude (p = 0.001, SMD = 0.477, 95% CI [0.2 0.76]). In fact, there is an increase in the P3 amplitude during the performance of the n-back tasks after anodal tDCS (Figure 5). Subgroup analysis performed in the studies that applied anodal tDCS over rIFG did not reveal a significant heterogeneity level (p = 0.572, I^2 = 0) and showed even a significant larger positive mean estimated effect size (p < 0.001, SMD = 0.669, 95% CI [0.31 1.03]). Additionally, subgroup analysis on studies with anodal stimulation over the lDLPFC did not present significant heterogeneity (p = 0.672, I^2 = 47.561), but also did not reveal a significant effect estimate (p = 0.398, SMD = 0.19, 95% CI [-0.25 0.63]). Concerning both studies assessing cathodal tDCS effect, neither significant results in terms of heterogeneity between comparisons was found (p = 0.891, I^2 = 2.664), nor a significant effect on parietal

Figure 5.

Forest plot with pooled effect estimate and subgroup analysis concerning the anodal stimulation on parietal P3 amplitude during n-back.



P3 amplitude (p = 0.939, SMD = -0.017, 95% CI [-0.46 0.42]). Finally, only one study assessed the parietal P3 latency in n-back tasks, which did not allow the analysis to be performed.

2.4.3. Go/No-Go task

2.4.3.1. Study Characteristics. Six studies were eligible according to the aforementioned criteria, nonetheless, in two of them it was not possible to extract the required information and the corresponding author did not reply to our requests. Therefore, four studies (with seven comparisons) comprising 120 participants were analyzed (see Table SM.8 in Supplementary Materials). All the studies used anodal tDCS. Every study analyzed the No-Go P3 amplitude, while only two (out of five) analyzed the No-Go latency. Nonetheless, two of them evaluated the No-Go P3 in the frontal region, whilst the other two in the parietal. Regarding the Go-P3, data was extracted from parietal electrodes, and amplitude was assessed in two studies, and latency in one of them. Most of the studies applied tDCS over frontal areas (three out of four), whilst only one applied tDCS over the motor cortex. Considering the studies of frontal tDCS, the targeted regions were the rIFG, and the right and left DLPFC (see Table SM.6 in Supplementary Materials). All the studies applied tDCS before the EEG recording. Moreover, every study included a sample of healthy adults, but one study included an additional sample of binge drinkers (BDs) and another a sample of elderly subjects. Finally, two studies used emotional-charged stimuli in the GNG, namely alcohol-related and food-related pictures.

2.4.3.2. Pooled effect estimates and subgroup analysis. The pooled effect estimates of the two studies (with one comparison each) which analyzed the No-Go P3 amplitude in frontal areas showed a non-significant trend in heterogeneity (p = 0.087, I^2 = 65.884). No effect of tDCS was revealed in the frontal No-Go P3 (p = 0.866, SMD = -0.086, 95% CI [-1.09 0.92]). On the other hand, two studies (with five comparisons) analyzed the No-Go P3 in parietal electrodes and they did not reveal a significant heterogeneity (p = 0.702, I^2 = 0). Furthermore, there was no significant effect of anodal tDCS on parietal No-Go P3 (p = 0.574, SMD = 0.08, 95% CI [-0.2 0.36]). The No-Go P3 latency was only analyzed in parietal region and the two studies (with five comparisons) did not reveal a significant heterogeneity (p = 0.818, I^2 = 0). Moreover, there was no significant effect of anodal tDCS on parietal No-Go P3 latency (p = 0.854, SMD = 0.026, 95% CI [-0.25 0.3]). Additionally, the two studies (with three comparisons) that assessed the parietal P3 amplitude did not reveal significant heterogeneity (p = 0.336, I^2 = 20.313), but also no significant effect of anodal tDCS effect (p = 0.793, SMD = -0.061, 95% CI [-0.51 0.39]) was detected. Subgroup analysis were not performed due to the lack of data (see Table SM.5 in Supplementary Materials).

2.4.4. Emotional processing

2.4.4.1. Study Characteristics. There were six studies that met the eligibility criteria, although two studies did not report the required data. Hence, four studies (with 12 comparisons) with 87 participants were analyzed (see Table SM.8 in Supplementary Materials). Two (out of four) studies (with three comparisons) analyzed the frontal P3 amplitude, whilst three studies (with eight comparisons) assessed the parietal region. All these studies assessed P3 amplitude with emotional-charged stimuli in different tasks, namely GNG and cue-reactivity paradigms (i.e., two studies each). None of the studies analyzed the P3 latency. All the studies applied tDCS over DLPFC, specifically the anode on the left hemisphere in two studies (with six comparisons) and on the right in another two (with three comparisons) (see Table SM.6 in Supplementary Materials). Moreover, in two studies tDCS was applied before and during EEG recording, while in other two tDCS was applied before. Finally, two studies (with four comparisons) included a group of healthy subjects and three studies (with five comparisons) comprised subjects with addiction conditions, namely BDs, alcoholism, and crack/cocaine dependence.

2.4.4.2. Pooled effect estimates and subgroup analysis. The two studies (with three comparisons) which assessed the frontal P3 amplitude after emotional stimuli in their analysis presented significant heterogeneity ($p < .001$, $I^2 = 92.713$). Additionally, no significant effect of tDCS on frontal P3 amplitude was revealed ($p = 0.506$, SMD = 0.425, 95% CI [-0.83 1.68]). Regarding the parietal P3 amplitude, the three studies (with eight comparisons) revealed significant heterogeneity ($p < .001$, $I^2 = 90.163$), without a significant tDCS effect ($p = 0.706$, SMD = -0.134, 95% CI [-0.83 0.56]). Subgroup analysis with the two studies (with six comparisons) that applied anodal tDCS over the lDLPFC revealed a significant heterogeneity ($p < 0.001$, $I^2 = 90.163$), without a significant effect ($p = 0.706$, SMD = -0.134, 95% CI [-0.83 0.56]). Additionally, excluding the comparison with online anodal tDCS over the lDLPFC with EEG recording, the subgroup analysis still maintained a significant heterogeneity ($p = 0.029$, $I^2 = 54.85$) and without a significant effect in parietal P3 amplitude ($p = 0.249$, SMD = 0.214, 95% CI [-0.15 0.58]). No data about P3 latency was not included in the analysis since this data was not reported in the included studies.

2.4.5. Moderator and Influential Analysis

The moderator analysis was only performed in studies using the n-back (i.e., only in anodal comparisons on frontal P3 amplitude) and oddball tasks (i.e., anodal comparisons on frontal and parietal P3 amplitude). This analysis was not performed in GNG, emotional processing and other comparisons

from the other two cognitive tasks, following the Thompson and Higgins recommendation about the minimum number of studies required to the meta-regression (Thompson and Higgins, 2002). The analysis in studies with n-back and oddball that evaluated the effect of anodal stimulation on frontal P3 amplitude did not reveal any significant moderator effect. These non-significant results are in line with the lack of effects from the pooled effect estimates and subgroup analysis. In the parietal P3 amplitude during oddball paradigms, the univariate meta-regression only revealed a significant moderator effect in duration (p = 0.002, b = 0.093, 95% CI [0.03 0.15]), suggesting that longer intervals of stimulation are related to larger parietal P3 amplitudes.

The leave-one-out method revealed similar results when compared to the pooled effect estimates and subgroup analysis in general. The anodal tDCS effect detected on the pooled effect estimate and subgroup analysis of parietal P3 amplitude in n-back tasks was not changed with the removal of any of the comparisons. Moreover, in oddball paradigms, the enhancement of parietal P3 amplitude after anodal tDCS over the lDLPFC also was maintained in the sensitivity analysis. Additionally, the significant result obtained on cathodal comparisons in frontal P3 amplitude has switched to non-significant when removed only one study (Rassovsky et al., 2018), suggesting that this effect was highly influenced by this study.

2.4.6. Publication Bias

The publication bias analysis was only performed in anodal comparisons on frontal P3 amplitude during n-back and on frontal and parietal P3 amplitude during oddball paradigms (i.e., same requirement of moderator analysis about the minimum comparisons). Thus, comparisons on P3 latency, GNG, emotional processing, and other comparisons from n-back and oddball were not analyzed regarding publication bias (Sterne et al., 2011). In oddball paradigms, frontal P3 amplitude studies do not suggest publication bias in the funnel plot (see Figure SM.13.1 in Supplementary Materials) and in Egger's test (p = 0.158, z = 1.413). Moreover, parietal P3 studies also show some deviations in the funnel plots (see Figure SM.13.2 in Supplementary Materials), namely two studies out of the CI boundaries, one on each side, which was verified in the Egger's test (p = 0.004, z = -1.839). Nonetheless, this result is strongly influenced by one study applying tDCS over M1 and that measured P3 in an oddball speller (Izzidien et al., 2016). At last, the studies with anodal tDCS in n-back tasks that evaluated frontal P3 amplitude suggest a lack of publication bias due to its symmetry in funnel plot, although four studies are out of the CI boundaries (see Figure SM.13.3 in Supplementary Materials) and the non-significant effect in Egger's test (p = 0.32, z = 0.995).

2.4.7. Risk of Bias and Certainty of Evidence

The risk of bias assessed by two researchers was mostly characterized by the absence of information regarding the criteria from the Cochrane Risk of Bias tool (Higgins et al., 2011). The randomization assessment revealed a low risk of selection bias in 16 studies (69.5%), high risk in 5 studies (21.7%), and unclear in two studies (8.6%). The allocation concealment was the criteria less reported on the studies, only one study was labeled as low risk (4.3%), whilst 22 studies did not report any information (95.7%). Therefore, the lack of information in both criteria made it difficult the evaluation of the presence of selection bias in these studies. Moreover, selective reporting was labeled in every study as low risk, because all the studies analyzed the P3 in the tasks that proposed to assess. Regarding participant´s blinding, 15 studies did not evaluate the blinding efficacy of the sham condition (65.2%), while 7 studies were evaluated with low risk in performance bias (30.4%) and only one was labeled as high risk. Otherwise, the rater's blinding was mostly evaluated as low risk totaling 10 studies (43.5% of the studies), eight studies were not clear about the rater's blinding (34.7%), and five studies did not blind the researcher responsible to EEG collection/analysis (21.7%). The attrition bias was low risk in 17 studies (73.9%), unclear in five studies (21.7%), and high risk in one study (4.3%). Finally, the other bias criteria were found in three studies, specifically baseline imbalance in one study, potential contamination bias in two studies. The traffic light plots with the risk of bias assessment per cognitive task in Figure SM.1, SM.2, SM.3, and SM.4 in Supplementary Materials.

The certainty of the included evidence was judged from very low to moderate. Most of the assessed outcomes were graded as very low certainty, only one oddball outcome (frontal P3 amplitude during cathodal stimulation) and one n-back outcome (parietal P3 amplitude during anodal stimulation) were graded as low and moderate certainty, respectively. We started the evaluation from high certainty since we included only randomized and counterbalanced experiments. We downgraded according to the risk of bias of the studies (more than 75% of the studies had an unclear risk of bias on critical domain such as allocation concealment and participant blinding) and due to imprecision (wide confidence interval and small sample sizes), additionally we downgraded two outcomes due to publication bias (see Table SM.7 in Supplementary Materials).

2.5. Discussion

The current study aimed to study the usefulness of the P3 component as a potential neural signature for probing the neuromodulatory effects of tDCS. P3 is an ERP observed in different

neurocognitive processes, such as attentional allocation, WM, response inhibition, and emotional processing. This meta-analysis focused on the assessment of P3 elicitation during three tasks, namely GNG, n-back, and oddball, as well as an additional analysis during emotional processing. Overall, the data suggests that tDCS over frontal region significantly increases parietal P3 amplitude during oddball and n-back tasks. No effects were found for GNG and emotional processing.

2.5.1. Oddball

During oddball paradigms, parietal P3 amplitude was significantly increased after tDCS, but only when anodal tDCS was applied over the lDLPFC (SMD = 0.4). Moreover, a significant decrease in terms of amplitude was detected in frontal P3 after cathodal tDCS (SMD = -0.4), although it was strongly influenced by the results of one study (Rassovsky et al., 2018). Additionally, long duration tDCS was associated with larger effects on parietal P3, even though the intervals from the analyzed studies only ranged from 15 to 27.29 minutes. Moreover, both significant effects were observed in a set of studies comprising healthy and clinical populations, namely schizophrenia and multiple sclerosis (see Table SM.8 in Supplementary Materials). The differential effect of anodal and cathodal tDCS on P3 might be explained by distinct modulations in cortical excitability as suggested by the initial studies testing the physiological effects of tDCS in motor cortex (Stagg and Nitsche, 2011). The depolarization of the neuronal membrane might counteract a regular decrease in P3 amplitude observed in oddball tasks (Fiene et al., 2018), whilst the hyperpolarization might enhance the decrease in P3 amplitude. Nonetheless, the effect on parietal P3 should be interpreted accordingly to its functional significance in the frontoparietal network and the neurobiology behind both subcomponents.

The P3a component in frontal regions during the oddball task has been associated with the attentional allocation and orienting toward salient stimuli (Friedman et al., 2001). Moreover, studies approaching the EEG band powers associated with the P3 showed a predominant theta activity over the frontal cortex (Bernat et al., 2007; Demiralp et al., 2001). In fact, the midfrontal theta oscillation has been associated to attentional and orienting processes (Cavanagh et al., 2012). Additionally, a recent model suggested that the frontal midline theta is associated with the synchronization of other task-relevant brain regions (e.g., parietal areas), which is commonly observed in attention tasks that require conflict detection and memory operations (Cohen, 2014). tDCS has been shown to improve attentional capacity, as illustrated in phasic attention and conflict resolution (Coffman et al., 2012; Miler et al., 2018). However, the effects of tDCS on oscillatory activity synchronization during attention is still unclear. For instance, a study testing the application of anodal tDCS over the medial PFC showed a resting state

increase in the power of theta over the frontal midline region, although these changes were not observed during a sustained attention task (Miller et al., 2015). On the other hand, a study by Spooner and colleagues (2020) tested the effects of bilateral HD-tDCS over the DLPFC and showed that anodal stimulation over the lDLPFC increased theta connectivity between frontal and visual cortices in the contralateral hemisphere. Anodal stimulation over the rDLPFC did not change theta connectivity, although performance in a visual attention task improved in both tDCS conditions (Spooner et al., 2020). Hence, the effect detected of cathodal tDCS over the lDLPFC in P3 might be related to the modulation of frontal mid-line theta. However, there is lack of consistent regarding the mechanisms of action of cathodal stimulation on this oscillatory activity.

Additionally, the tDCS effects on neurotransmitters might also be present, given that P3a is associated with frontal dopaminergic activity (Polich, 2007). A recent study showed that anodal tDCS over the lDLPFC had a modulatory effect in the contralateral subcortical region involved in dopamine release, namely the ventral striatum (Fonteneau et al., 2018). Moreover, another study tested how these effects might impact cognitive processes, namely attention and WM. Results have also shown an increase of dopamine signaling in the ventral striatum after tDCS, which was associated with enhanced attentional skills, but not WM (Fukai et al., 2019). In the present meta-analysis, no significant effects of anodal frontal tDCS in frontal P3 amplitude and latency were observed, nonetheless, cathodal stimulation in frontal regions showed a marginally significant decrease on frontal P3 amplitude. These findings, in line with the previous studies (Fonteneau et al., 2018; Fukai et al., 2019), suggest an opposite effect between anodal and cathodal on dopamine release . Nonetheless, it is important to emphasize that the current meta-analysis considered any P3 assessment in the frontal electrodes after a novel or target stimulus as frontal P3 due to the lack of data. Additionally, the significant result observed in cathodal stimulation was highly influenced by one study, suggesting the need for further studies to address this result.

P3b in parietal (and temporal) areas has been associated to stimulus categorization and context updating during WM (Polich, 2007). The parietal P3 elicited in oddball paradigms has been associated with the delta band over centroparietal regions and linked to categorization of task-relevant stimuli (Bernat et al., 2007; Cooper et al., 2016). Moreover, the interregional communication of relevant information in the frontoparietal network is crucial during the oddball paradigm, namely with enhanced functional connectivity in theta and delta-band between frontal and parietal areas after a target stimulus requiring categorization and updating of the context (Güntekin and Başar, 2010; Harper et al., 2017). Additionally, a recent model suggested that the frontal midline theta is associated with the synchronization of other task-relevant brain regions (e.g., parietal areas), which is commonly observed in attention tasks requiring

conflict detection and memory operations (Cohen, 2014). Interestingly, the current meta-analysis demonstrated that tDCS over the lDLPFC had an impact on parietal P3 amplitude suggesting an interregional effect of tDCS during the oddball paradigm. These findings are in line with previous studies that observed the modulatory effects of tDCS on midfrontal theta power and its connectivity with others task-relevant brain regions (Miller et al., 2015; Spooner et al., 2020). Hence, these findings are in line with the P3 generation model suggested by Polich (2007), the attention and memory processes are controlled by functional connectivity within the frontoparietal network.

In line with this model, P3b arises from phasic response of the noradrenergic activity of the locus coeruleus-norepinephrine (LC-NE) pathway (Nieuwenhuis et al., 2005), and the resulting release of norepinephrine after target stimulus presentation (although this response is also observed after non-target stimuli in a weaker form). Likewise, P3 co-occurs along with several psychophysiological reactions related with LC-NE activity, such as pupil dilation and heart rate increase (Nieuwenhuis et al., 2011). However, few studies have explored the neuromodulatory effects of tDCS in the LC-NE system. For instance, one study showed an effect of tDCS over the motor cortex in the pupil diameter (i.e., an indirect marker of LC-NE activity) and theta activity on frontal areas during an inhibitory control task (Adelhöfer et al., 2019). Thus, the effect observed in parietal P3 amplitude after anodal stimulation on frontal areas might be related with the LC-NE, given that the noradrenergic fibers initially innervate frontal regions followed by posterior cortical areas (Morrison et al., 1982). Likewise, the modulation of distal LC neurons through PFC stimulation was already observed in animal studies (Aston-Jones et al., 1991). Therefore, the parietal P3 amplitude increase after frontal tDCS might be associated with the LC-NE, nonetheless, the evidence is still very scarce in humans.

Finally, the current meta-analysis also analyzed the cerebellar tDCS effect on frontal and parietal P3 amplitude during oddball. No modulatory effect of tDCS over cerebellum on the P3 component was found. The goal of these studies was to test the cognitive functioning regulation through the strong inhibitory projections of cerebellum to frontal and parietal areas (Kelly and Strick, 2003). Hence, it was hypothesized that cathodal tDCS over the lDLPFC could enhance activity on these task-relevant brain regions. Nonetheless, in this meta-analysis there was a lack of evidence regarding the effects of cerebellar tDCS on P3 during the oddball paradigm, namely only two studies were included in this subgroup analysis (Mannarelli et al., 2016; Ruggiero et al., 2019).

2.5.2. N-back tasks

tDCS modulated differently the P3 amplitude during n-back task in parietal regions, however no effects were found on frontal regions. P3 amplitude increased after active tDCS over frontal areas in comparison with sham (SMD = 0.33), especially when tDCS was applied over the rIFG (SMD = 0.67). The significant effect estimate of frontal tDCS was observed in healthy and clinical populations, specifically Alzheimer's disease and ADHD (see Table SM.8 in Supplementary Materials). This is consistent with what has been found after programs of cognitive training with WM exercises (O'Brien et al., 2013; Tusch et al., 2016). Hence, an enhanced parietal P3 amplitude might be related to better WM processing, as some studies suggest this correlation (e.g., Cespón et al., 2017). This finding is in line with Polich (2007) about the role of P3b in the updating WM, given that behavioral performance increase in n-back were associated with the parietal P3 and not in frontal P3 that is more related to attentional processes.

The P3 dynamics observed within the frontoparietal network during WM tasks after tDCS might be explained by the efficiency of the neuronal processing (Neubauer and Fink, 2009). The optimal cognitive functioning relies on the efficiency of broader neuronal networks, instead of the overactivation of frontal regions. In fact, subjects with higher levels of intelligence present less cortical activation in frontal areas during WM task with moderate difficulty (Nussbaumer et al., 2015). Likewise, elderly performing a WM task shown a larger frontal P3 amplitude and a smaller in parietal region in comparison with young adults, suggesting an ineffective distribution of neuronal resources (Saliasi et al., 2013). On the other hand, the opposite pattern is observed on young adults with better WM skills than elderly, namely a larger P3 amplitude in parietal region and a reduced amplitude in frontal areas (Cespón et al., 2017; van Dinteren et al., 2014). Hence, although the large spatial resolution of EEG might difficult the interpretation about the source of the evoked potential, the increase of parietal P3 amplitude after anodal frontal tDCS might indicate the activation of a broader network involved in the WM processing (i.e., attentional allocation in the frontal regions and categorization of task-relevant events in parietal).

Therefore, studies aiming at the enhancement of WM processing using NIBS techniques targeted the frontoparietal network, given its role in the access, maintenance and manipulation of information. A recent study found a coupling between the phase of frontal midline theta rhythm and gamma oscillatory amplitude on the parietal region during a visuospatial WM task (Berger et al., 2019). In fact, changes on phase-amplitude coupling between frontal theta and parietal gamma activity were observed after four sessions of WM cognitive training coupled with tDCS over frontal and parietal regions associated with WM improvements (Jones et al., 2020). Another study, in which intermittent Theta Burst Stimulation (iTBS) was delivered to the lDLPFC, resulted in an improvement in WM skills coupled with stronger connectivity

of frontoparietal theta and an enhancement of parietal gamma activity (Hoy et al., 2016). A similar effect was found in a study testing tDCS over the lDLPFC in patients with schizophrenia, who shown behavioral gains and an increased synchronization of gamma activity during the task (Hoy et al., 2015). Thus, gamma oscillations assume an important role in WM processes, which intriguingly is co-occurring with the P3 component, in parietal regions after task-relevant stimuli, although both markers might index different mental events (Pitts et al., 2014).

More recently, Riddle and colleagues (2020) explored theta and alpha oscillations using repetitive Transcranial Magnetic Stimulation (rTMS) in the frontal and parietal regions respectively to improve WM processing through an optimal engagement and disengagement of neuronal resources. Results have shown that both entrainments enhanced WM abilities, specifically frontal theta entrainment improved the prioritization of information, whilst parietal alpha assisted the inhibition of irrelevant information (Riddle et al., 2020). These studies propose an inter-dependency between both cortical areas for successful access and maintenance of task-relevant information that can be modulated by NIBS. In line with these findings, the current meta-analysis shows a modulation within the frontoparietal network through an increase in parietal P3 amplitude after the application of tDCS over frontal areas. In fact, a comparable effect was already found using neuroimaging techniques in the frontoparietal network after tDCS over the lDLPFC (Keeser et al., 2011). Moreover, enhanced parietal P3 amplitude might be related with gamma synchronization in parietal areas, given that both are enhanced by NIBS and related to successful WM processing (Berger et al., 2019; Hoy et al., 2016).

2.5.3. Go/No-Go task

tDCS did not show any significant change in P3 amplitude and latency during the no-go and go trials, even though a recent meta-analysis suggested a moderate significant effect of tDCS on the behavioral outcomes of inhibitory response tasks (Schroeder et al., 2020). This subsection of analysis included a very low number of studies and with large heterogeneity among them. For instance, two studies (with four comparisons) assessed the no-go P3 in parietal areas, whereas two other studies (with two comparisons) assessed the effects of no-go trials in the frontal region. This variability led us to analyze the no-go P3 in frontal and parietal areas independently, which resulted in a very low number of comparisons per analysis, which decreased the power of the analysis.

The P3 elicited during no-go trials is thought to be generated in fronto-medial areas and it is highly associated with delta band processes (Huster et al., 2013). The frontal delta activity has been associated with the motivational salience of stimuli, which suggests its importance in the attentional

processes required towards a no-go trial (Knyazev, 2012). Likewise, these electrophysiological markers were also observed during the oddball paradigm, namely the enhancement in the delta band, suggesting similar mental operations related to information processing between both cognitive tasks (Bernat et al., 2007; Demiralp et al., 2001). In fact, delta activity has been associated with other cognitive functions such as attention, perception, and decision-making. Moreover, changes in delta activity have also been associated with several clinical conditions with cognitive deficits, such as, mild cognitive impairment, Alzheimer's disease or schizophrenia, in which delta band activity is decreased (Güntekin and Başar, 2016). Additionally, the frontal midline theta, discussed in the previous cognitive tasks, should be considered as well during response inhibition tasks (Miller et al., 2015). Thus, considering these electrophysiological features and its topography, the no-go P3 is thought to be a variant of the P3a component (Polich, 2007). So, the absence of tDCS effect in no-go P3 is in line with the oddball and n-back findings, given that in these cognitive tasks it was not found any modulation on frontal P3. On the other hand, the go-P3 follows a more posterior topography in comparison with the P3 elicited in no-go trials, which suggests similarities with the P3b component (Huster et al., 2013). Nonetheless, the parietal go-P3 amplitude was not modulated by tDCS, although it is important to highlight the scarceness of data to make this claim (i.e., two studies with a total of three comparisons).

These findings should be cautiously interpreted accordingly to recent models of inhibitory control. Specifically, inhibition is a broad concept that can be divided into several subtypes, such as the proactive and reactive processes. The proactive inhibition aims the inhibition a forthcoming response (i.e., GNG task), whilst reactive inhibition is dependent on an external cue (i.e., SSRT task; Aron, 2011). The rIFG assumes an important role in both processes, although proactive inhibition is related to an indirect pathway that connects the rIFG with the striatum, whilst reactive inhibition has been associated with a hyperdirect pathway from rIFG to subthalamic nucleus (Jahfari et al., 2011). Therefore, anodal tDCS over the rIFG might modulate differently both subtypes of response inhibition. In fact, a recent meta-analysis showed that tDCS enhanced inhibitory control only in the SSRT task (and a marginally significant in GNG) and the effect estimate was larger in the anodal stimulation over rIFG in comparison with other cortical areas (Schroeder et al., 2020). Nevertheless, the effect of anodal tDCS over the rIFG in P3 during GNG were analyzed in only one study out of the four.

2.5.4. Emotional Processing

The tDCS did not affect the P3 amplitude and latency after the presentation of emotionally laden stimuli. This subsection aimed to study the emotional processing that occurred during tasks using

affective-charged stimuli (e.g., food, drugs). Specifically, the frontal P3 component related to orienting and attentional allocations was suggested to be an endogenous marker of stimulus-reactivity. For instance, subjects with patterns of heavy drinking in a social context showed a larger frontal P3 amplitude after the visualization of alcohol-related pictures in comparison with neutral pictures (Herrmann et al., 2001). Therefore, given that the DLPFC assumes an important role in top-down cognitive control, it has been hypothesized that tDCS over that area could reduce the reactivity to salient stimuli (Lapenta et al., 2014; Nakamura-Palacios et al., 2012). Nonetheless, although several studies showed that anodal tDCS over the lDLPFC decreased (Den Uyl et al., 2015) or increased craving levels (Carvalho et al., 2019), the current meta-analysis did not show any modulation of this tDCS montage in frontal or parietal P3 amplitude or latency after affective stimuli.

In line with the previous findings from GNG tasks, this analysis was comprised of a reduced number of studies that share important differences among them. First, the study population was different in the four studies, namely Binge drinkers, people suffering from alcohol use disorder, with crack/cocaine addiction, and healthy controls. This might be a potential confounder in the present meta-analysis, given that the pooled effects were observed on distinct effects of craving and consumption pattern (den Uyl et al., 2018; Den Uyl et al., 2015). Second, two studies analyzed the P3 component in a cue-reactivity task, whilst the other two in a GNG with emotional stimulus. Although the analysis included only the P3 evaluated after the affective stimulus, in the cue-reactivity task participants were only instructed to observe the picture and in the GNG they were required to press a button (or not) depending on the type of trial. Therefore, the cognitive operations required during the GNG task might difficult the interpretation of P3 as a marker of cue-reactivity, especially because task dependent effects of tDCS have been shown.

Overall, the tDCS effect on cue-reactivity P3 still needs further clarification due to the heterogeneous and small set of studies analyzed. The P3 related to emotional processing might be dependent on specificities of the population (e.g., BDs vs alcoholics) and also on the experimental task (e.g., observation vs press a button).

2.5.5. Future Directions

The effects of tDCS on the brain during cognitive processing are still unclear (Chan et al., 2021). The current study showed how tDCS can modulate the cognitive P3 in distinct contexts, but the underlying neurophysiological mechanisms are still unclear. For a better understanding, it is important to test how tDCS can influence the connectivity within frontoparietal network during cognitive processing. In particular, the frontal theta activity is a common marker observed in several cognitive processes that rely

on the PFC and has been associated with the synchronization of other task-related regions (Cohen, 2014). Although recent studies have approached the tDCS effect on frontal theta within the frontoparietal network in resting-state (Jones et al., 2020), the dynamics during cognitive functioning are not fully understood yet. Furthermore, the neurotransmitters dynamics are also an important component to understand the cognitive processing and are strongly associated with the elicitation of P3 (Polich, 2007). Specifically, the phasic activity of the LC-NE has been implicated in the P3 generation along frontoparietal areas (Nieuwenhuis et al., 2005). Several physiological changes related with the LC-NE system occur in parallel with the P3 elicitation, such as an increase in pupil diameter or heart rate (Nieuwenhuis et al., 2011). Nonetheless, there is a lack of evidence regarding the tDCS impact on norepinephrine release observed on these autonomic components during P3 response. Moreover, despite the fact that recent meta-analysis suggests that tDCS impacts cognitive function as assessed by behavior (Brunoni and Vanderhasselt, 2014; Schroeder et al., 2020), it is also true that tDCS affects EEG activity per se. Even though ERPs are very specific, it is not possible from the present results to state that the effects of tDCS on P3 are due to changes in cognition, or in the underlying brain activity. However, this does not change the potential value of using biomarkers to direct interventions, especially because they are highly correlated with cognitive function, and as such may prove to be very useful to understand the mechanisms underlying tDCS effects, or to guide interventions, for instance using closed loop systems (Leite et al., 2017). Correlation between the modulatory effects of tDCS on P3 and direct changes in cognition should be further explored with behavioral data analysis. Finally, the current meta-analysis shows the low number of studies testing the tDCS effect in P3 during GNG task or emotional processing. Even in oddball and n-back task analysis, the set of included studies share a reduced sample sizes and the methodological flaws should be addressed in future studies.

2.5.6. Limitations

The low number of studies in some subsections did not allow all the intended analysis, such as the publication bias and the meta-regression analysis. For instance, the meta-regression was only performed in parietal and frontal P3 amplitude after anodal stimulation during oddball and the parietal P3 amplitude after anodal tDCS in the n-back task (see Table SM.5 in Supplementary Materials). Also, the set of studies included share high variability among them (e.g., tDCS intensity, duration), which can difficult the evaluation of the impact of different parameters of tDCS in P3.

In addition, the current study explored the post-tDCS P3 assessments rather than the difference between baseline and post-intervention, due to the fact that eight of the studies did not assess P3

component before the application of tDCS. If differences towards baseline were to be probed, these studies would ultimately be excluded, further decreasing the statistical power to draw conclusions. Nonetheless, controlling for different baseline levels would be important for an improved analysis of the effects of tDCS on P3, as tDCS effects are dependent on the baseline neuronal state (Dubreuil-Vall et al., 2019; Li et al., 2019). Furthermore, the current meta-analysis included healthy and clinical population, which might increase the variability among results. Although heterogeneity tests and meta-regression did not suggest a differential effect of tDCS on P3 regarding study population, this should be addressed in future studies.

Lastly, neuroimaging data suggest high levels of interindividual variability of the effects of active tDCS when comparing to sham (Wörsching et al., 2017). To the best of our knowledge, no similar study was performed using EEG, nonetheless, the available data from behavioral performance, suggests a non-linear effect of tDCS, which is dependent on multiple factors (e.g., individual differences, baseline, task, intensity, duration, electrode placement, and size). Despite these differences, most of the studies included in this meta-analysis are crossovers (16 out of 23), which might mitigate differences in the tDCS effect between individuals.

2.6. Conclusion

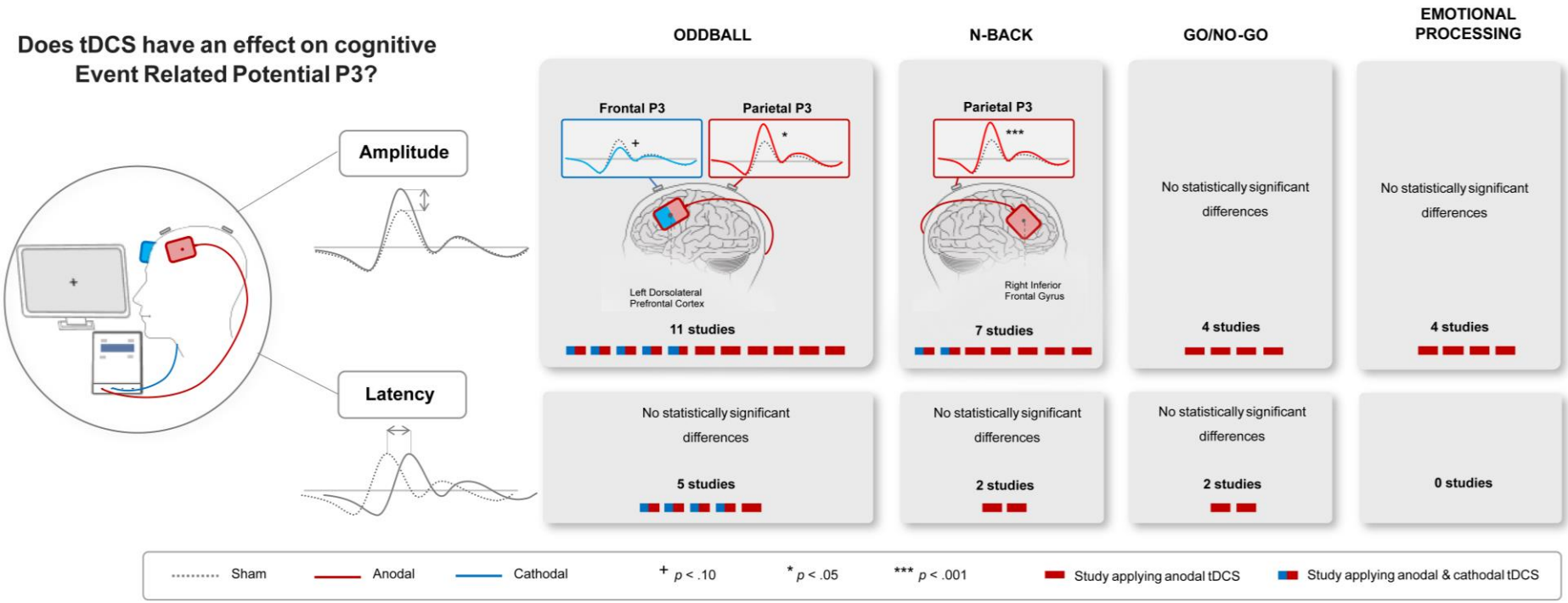
This meta-analysis suggests the usefulness of P3 component to study the neurophysiological effects of tDCS during cognition. Specifically, the current study has shown that tDCS over frontal areas had an impact in P3 amplitude assessed in parietal regions during oddball and n-back tasks (Figure 6). Nonetheless, these effects must be cautiously interpreted due to the low number of studies in this analysis, the low-to-moderate certainty of evidence, and the heterogeneity among them (e.g., study population). Additionally, no tDCS effect was detected in P3 evaluated in the GNG task, after emotionally charged stimulus, or in latency. Even so, the low number of analyzed comparisons and the small sample sizes included in these subsections might undermine the statistical power (Button et al., 2013).

Our findings suggest the broad spatial resolution of tDCS impact, given that the changes were not observed in the brain region of stimulation, but in the task-related brain network. In particular, the connectivity within the frontoparietal network might assume an important role in the neurophysiological effects of frontal anodal tDCS during oddball and n-back tasks, mostly via theta band (Gulbinaite et al., 2014). The frontal midline theta has an important role in several cognitive tasks and it has been associated with the synchronization of other task-relevant brain regions (Cohen, 2014), which can be a mediator of the frontal tDCS impact in other areas (i.e., parietal region). In line with this hypothesis, recent

evidence demonstrated that NIBS techniques are able to modulate not only the cognitive functioning but also its electrophysiological markers in a spatially distributed manner (Hoy et al., 2015; Jones et al., 2020). Therefore, those neuromodulatory effects observed in the oscillatory synchronization might co-occur in parallel with the modulation of P3, namely the increase of parietal P3 amplitude after the application of anodal tDCS over frontal areas.

Figure 6.

Overall effects observed on the meta-analysis of P3 amplitude and latency in each section.



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2.8. Supplementary Materials

Table SM.1

Combinations of the Descriptors Used in our Search strategy

Clinical question		
MEDLINE PubMed	**3/11/2020**	#1 (Electroencephalography[Mesh] OR EEG*[TIAB] OR Electroencephalogram*[TIAB] OR "event-related potential*"[tiab] OR "event related potential*"[tiab] OR "evoked potential*"[tiab] OR "event related desynchronization"[tiab] OR "event related synchronization"[tiab] OR "event-related desynchronization"[tiab] OR "event-related synchronization"[tiab] OR "brain wave*"[tiab]) #2 ("Transcranial Direct Current Stimulation"[Mesh] OR "brain polarization"[tiab] OR "noninvasive brain stimulation"[tiab] OR "non-invasive brain stimulation"[tiab] OR "noninvasive brain stimulation"[tiab] OR "transcranial direct current stimulation"[tiab] OR "trans cranial direct current stimulation"[tiab] OR neuromodulation[tiab] OR NIBS[tiab] OR TDCS[tiab] OR "transcranial electrical stimulation"[tiab] OR "transcranial stimulation"[tiab] OR "Transcranial Magnetic Stimulation"[Mesh] OR "transcranial magnetic stimulation"[tiab] OR TMS[tiab] OR rTMS[tiab] OR "motor cortex stimulation"[tiab] OR MCS[tiab] OR "cranial electrotherapy stimulation"[tiab] OR CES[tiab]) #3 ("Animals"[Mesh] NOT "Humans"[Mesh]) #4 #1 AND #2 NOT #3

The Cochrane Library	**3/11/2020**	#1 (MeSH descriptor: [Electroencephalography] explode all trees OR EEG:ti,ab OR Electroencephalogram*:ti,ab OR "event-related potential*":ti,ab OR "event related potential*":ti,ab OR "evoked potential*":ti,ab OR "event related desynchronization":ti,ab OR "event related synchronization":ti,ab OR "event-related desynchronization":ti,ab OR "event-related synchronization":ti,ab OR "brain wave*":ti,ab) # 2 (MeSH descriptor: [Transcranial Direct Current Stimulation] explode all trees OR "brain polarization":ti,ab OR "noninvasive brain stimulation":ti,ab OR "non-invasive brain stimulation":ti,ab OR "noninvasive brain stimulation":ti,ab OR "transcranial direct current stimulation":ti,ab OR "trans cranial direct current stimulation":ti,ab OR neuromodulation:ti,ab OR NIBS:ti,ab OR TDCS:ti,ab OR "transcranial electrical stimulation":ti,ab OR "transcranial stimulation":ti,ab OR "Transcranial Magnetic Stimulation"[Mesh] OR "transcranial magnetic stimulation":ti,ab OR TMS:ti,ab OR rTMS:ti,ab OR "motor cortex stimulation":ti,ab OR MCS:ti,ab OR "cranial electrotherapy stimulation":ti,ab OR CES:ti,ab) #3 (MeSH descriptor: [animals] explode all trees NOT MeSH descriptor: [humans] explode all trees) #4 #1 AND #2 NOT #3
EMBASE	**3/11/2020**	#1 (Electroencephalography /exp OR EEG:ab,ti OR Electroencephalogram*:ab,ti OR 'event-related potential':ab,ti OR 'event-related potentials':ab,ti OR 'evoked potential':ab,ti

		OR 'evoked potentials':ab,ti OR 'event-related desynchronization':ab,ti OR 'event-related synchronization':ab,ti OR 'brain waves':ab,ti OR 'brain oscillation':ab,ti OR 'brain oscillations':ab,ti OR 'brain wave':ab,ti) #2 ('Transcranial Direct Current Stimulation'/exp OR 'brain polarization':ab,ti OR 'noninvasive brain stimulation':ab,ti OR 'noninvasive brain stimulation':ab,ti OR 'non-invasive brain stimulation':ab,ti OR 'transcranial direct current stimulation':ab,ti OR 'trans cranial direct current stimulation':ab,ti OR neuromodulation:ab,ti OR NIBS:ab,ti OR TDCS:ab,ti OR 'transcranial electrical stimulation':ab,ti OR 'transcranial stimulation':ab,ti OR 'Transcranial Magnetic Stimulation'/exp OR 'transcranial magnetic stimulation':ab,ti OR TMS:ab,ti OR rTMS:ab,ti OR 'motor cortex stimulation':ab,ti OR MCS:ab,ti OR 'cranial electrotherapy stimulation':ab,ti OR CES:ab,ti) #3 ([animals]/lim NOT [humans]/lim) #4 #1 AND #2 NOT #3

Web of Science	**3/11/2020**	TS=(((Electroencephalography OR EEG OR Electroencephalogram* OR "event-related potential*" OR "event-related potential" OR "event-related potentials" OR "evoked potential" OR "evoked potentials"OR "event-related desynchronization" OR "event-related synchronization" OR "brain wave" OR "brain waves" OR "brain oscillation" OR "brain oscillations") AND ("Transcranial Direct Current Stimulation" OR "brain polarization" OR "noninvasive brain stimulation" OR "non-invasive brain stimulation" OR "noninvasive brain stimulation" OR "transcranial direct current stimulation" OR "trans cranial direct current stimulation" OR neuromodulation OR NIBS OR TDCS OR "transcranial electrical stimulation" OR "transcranial stimulation" OR "Transcranial Magnetic Stimulation" OR "transcranial magnetic stimulation" OR TMS OR rTMS OR "motor cortex stimulation" OR MCS OR "cranial electrotherapy stimulation" OR CES)) NOT ("Animals" NOT "Humans"))
Scopus	**3/11/2020**	TITLE-ABS-KEY ((Electroencephalography OR EEG OR. Electroencephalogram* OR "event-related potential*" OR "event related potential*" OR "evoked potential*" OR "event related desynchronization" OR "event related synchronization" OR "event-related desynchronization" OR "event0-related synchronization" OR "brain wave*") AND ("Transcranial Direct Current Stimulation" OR "brain polarization" OR "noninvasive brain stimulation" OR "noninvasive brain stimulation" OR "non-invasive brain stimulation" OR "transcranial direct current stimulation" OR "transcranial direct current stimulation" OR neuromodulation OR nibs OR tdcs OR "transcranial electrical stimulation" OR "transcranial stimulation" OR "Transcranial Magnetic Stimulation" OR "transcranial magnetic stimulation" OR

		tms OR rtms OR "motor cortex stimulation" OR mcs OR "cranial electrotherapy stimulation" OR ces))

Table SM.2

Training of reviewers before titles and abstract screening

Formulas:

- Reviewer agreement: (included by both raters + excluded by both raters)/total
- Chance of inclusion: (Number of included studies/Total, for rater1) * (Number of included studies /Total for rater 2)
- Chance of exclusion: (Number of excluded studies/Total, for rater1) * (Number of excluded studies /Total for rater 2)
- Chance agreement: Chance Yes * Chance No
- Kappa: (Agreement - Chance agreement) / 1 - Chance agreement

On May 2020, we selected a random sample of pre-selected studies from the screening first stage (see section 2.1.). One-hundred references were randomly selected served for training and standardization purposes between the reviewers. The agreement between the reviewers was high (> 0.9).

Training 1 (Agreement: 0.98; Kappa: 0.93)

		Reviewer 1 (KP-B)		
		Included	Excluded	
Reviewer 2 (AJM)	Included	18	0	18
	Excluded	2	80	82
		20	80	100

Training 2 (Agreement: 0.91; Kappa: 0.88)

		Reviewer 1 (KP-B)		
		Included	Excluded	
Reviewer 3 (RM)	Included	11	0	11
	Excluded	9	80	89
		20	80	100

Training 3 (Agreement: 0.93; Kappa: 0.89)

		Reviewer 1 (KP-B)		
		Included	Excluded	
Reviewer 4 (SGL)	Included	13	0	13
	Excluded	7	80	87
		20	80	100

Table SM.3

References of studies included in quantitative synthesis

Studies with Asterisk (*) are present in two subsections

i. Oddball paradigms

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Mannarelli, D., Pauletti, C., de Lucia, M. C., Delle Chiaie, R., Bersani, F. S., Spagnoli, F., Minichino, A., Currà, A., Trompetto, C., & Fattapposta, F. (2016). Effects of cerebellar transcranial direct current stimulation on attentional processing of the stimulus: Evidence from an event-related potentials study. *Neuropsychologia, 84*, 127–135. https://doi.org/10.1016/j.neuropsychologia.2016.02.002

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Ruggiero, F., Ferrucci, R., Bocci, T., Nigro, M., Vergari, M., Marceglia, S., Barbieri, S., & Priori, A. (2019). Spino-cerebellar tDCS modulates N100 components of the P300 event related potential. *Neuropsychologia*, *135*, 107231. https://doi.org/10.1016/j.neuropsychologia.2019.107231

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ii. N-back task

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Table SM.4

Labels of the comparisons in each study

		a	b	c	d
Oddball	Dunn (2016)	anodal	cathodal	-	-
	Fiene (2018)	online	offline	-	-
	Khedr (2014)	anodal	cathodal	-	-
	Knechtel (2014A)	frequency*	duration*	-	-
	Knechtel (2014B)	frequency*	duration*	-	-
	Rassovsky (2018)	anodal	cathodal	-	-
	Ruggiero (2019)	anodal	cathodal	-	-
	Weigl (2016)	anodal	cathodal	-	-
N-back	Breitling (2020)	conventional	HD-tDCS	-	-
	Cespón (2017)	anodal in young	anodal in elderly	cathodal in young	cathodal in elderly
	Cespón (2019)	anodal	cathodal	-	-
	Hill (2019)	only HD-tDCS 2-back	only HD-tDCS 3-back	HD-tDCS w/ task 2-back	HD-tDCS w/ task 3-back
	Hunter (2018)	1-back	2-back	3-back	-
	Keeser (2019)	0-back	1-back	2-back	-
	Nikolin (2018)	1mA	0.034mA	-	-
GNG	Conley (2016)	young adults	elderly w/ tDCS over dominant M1	elderly w/ tDCS over non-dominant M1	-
	Dormal (2020)	binge drinkers	healthy	-	-
Emotional Processing	Nakamura-Palacios (2012)	offline	online	-	-
	Dormal (2020)	binge drinkers in no-go	healthy in no-go	binge drinkers in go	healthy in go

* Labelled as 1 and 2 because the frontal P3 was elicited using deviations on the frequency (a) and duration (b) of the target.

Table SM.5

Number of studies and comparisons per cognitive task and tDCS-polarity.

			P3 Amplitude		P3 Latency	
			Anodal	Cathodal	Anodal	Cathodal
Oddball	Frontal		7 studies (10 comparisons) *	5 studies (6 comparisons)	4 studies (5 comparisons)	4 studies (5 comparisons)
	Parietal		9 studies (11 comparisons) *	4 studies (5 comparisons)	2 studies (4 comparisons)	1 study (2 comparisons)
N-back	Frontal		6 studies (15 comparisons) *	2 studies (3 comparisons)	2 studies (7 comparisons)	n.a.
	Parietal		4 studies (8 comparisons)	2 studies (3 comparisons)	1 study (2 comparisons)	n.a.
GNG	Frontal	No-Go P3	2 studies (2 comparisons)	n.a.	n.a.	n.a.
	Parietal	No-Go P3	2 studies (5 comparisons)	n.a.	2 studies (5 comparisons)	n.a.
		Go-P3	2 studies (3 comparisons)	n.a.	1 study (2 comparisons)	n.a.
Emotional Processing	Frontal		2 studies (6 comparisons)	n.a.	n.a.	n.a.
	Parietal		3 studies (8 comparisons)	n.a.	1 study (2 comparisons)	n.a.

Sections with at least 10 comparisons that were included in the meta-regression and publication bias analysis.

Table SM.6

Number of studies and comparisons per cognitive task and tDCS-location.

\			P3 Amplitude					P3 Latency			
			DLPFC	Cerebellum	rIFG	Motor cortex	Supraorbital	DLPFC	Cerebellum	rIFG	Motor cortex
Oddball	Frontal		5 studies (10 comparisons)	2 studies (6 comparisons)	n.a.	n.a.	n.a.	2 studies (4 comparisons)	2 studies (6 comparisons)	n.a.	n.a.
	Parietal		4 studies (6 comparisons)	2 studies (6 comparisons)	1 study (1 comparison)	1 study (1 comparison)	1 study (2 comparisons)	1 study (2 comparisons)	1 study (4 comparisons)	n.a.	n.a.
N-back	Frontal		5 studies (15 comparisons)	n.a.	2 studies (3 comparisons)	n.a.	n.a.	2 studies (7 comparisons)	n.a.	n.a.	n.a.
	Parietal		2 studies (6 comparisons)	n.a.	2 studies (5 comparisons)	n.a.	n.a.	n.a.	n.a.	1 study (2 comparisons)	n.a.
GNG	Frontal	No-Go P3	1 study (1 comparison)	n.a.	1 study (1 comparison)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Parietal	No-Go P3	1 study (2 comparisons)	n.a.	n.a.	1 study (3 comparisons)	n.a.	1 study (2 comparisons)	n.a.	n.a.	1 study (3 comparisons)
		Go-P3	2 studies (3 comparisons)	n.a.	n.a.	n.a.	n.a.	1 study (2 comparisons)	n.a.	n.a.	n.a.
Emotional Processing	Frontal		2 studies (6 comparisons)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Parietal		3 studies (10 comparisons)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Table SM.7

Summary of Findings.

Active tDCS compared to sham tDCS for the modulation of P3 potential elicited during cognitive processes

Setting: Experimental setting; **Intervention**: active tDCS; **Comparison**: sham tDCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham tDCS	Risk with active tDCS				
Oddball - Anodal stimulation: Frontal P3 amplitude	-	SMD **0.06 SD lower** (0.28 lower to 0.16 higher)	-	318 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of active tDCS on oddball - Anodal stimulation: Frontal P3 amplitude.
Oddball - Cathodal stimulation: Frontal P3 amplitude	-	SMD **0.4 SD lower** (0.73 lower to 0.07 lower)	-	201 (5 RCTs)	⨁⨁◯◯ LOW [a,c]	The evidence suggests active tDCS reduces oddball - Cathodal stimulation: Frontal P3 amplitude.
Oddball - Anodal stimulation: Parietal P3 amplitude	-	SMD **0.08 SD higher** (0.22 lower to 0.38 higher)	-	307 (8 RCTs)	⨁◯◯◯ VERY LOW [a,b,d]	The evidence is very uncertain about the effect of active tDCS on oddball - Anodal stimulation: Parietal P3 amplitude.
Oddball - Cathodal stimulation: Parietal P3 amplitude	-	SMD **0.04 SD lower** (0.38 lower to 0.31 higher)	-	128 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,d]	The evidence is very uncertain about the effect of active tDCS on oddball - Cathodal stimulation: Parietal P3 amplitude.
N-back - Anodal stimulation: Frontal P3 amplitude	-	SMD **0.01 SD higher** (0.31 lower to 0.33 higher)	-	461 (5 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of active tDCS on n-back - Anodal stimulation: Frontal P3 amplitude.
N-back - Anodal stimulation: Parietal P3 amplitude	-	SMD **0.48 SD higher** (0.2 higher to 0.76 higher)	-	207 (5 RCTs)	⨁⨁⨁◯ MODERATE [a]	Active tDCS probably results in an increase in n-back - Anodal stimulation: Parietal P3 amplitude.
No-Go - Anodal stimulation: Frontal P3 amplitude	-	SMD **0.09 SD lower** (1.09 lower to 0.92 higher)	-	49 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of active tDCS on no-Go - Anodal stimulation: Frontal P3 amplitude.
No-Go - Anodal stimulation: Parietal P3 amplitude	-	SMD **0.08 SD higher** (0.2 lower to 0.36 higher)	-	40 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of active tDCS on no-Go - Anodal stimulation: Parietal P3 amplitude.
Go - Anodal stimulation: Parietal P3 amplitude	-	SMD **0.06 SD lower** (0.51 lower to 0.39 higher)	-	98 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of active tDCS on go - Anodal stimulation: Parietal P3 amplitude.
Emotional Processing - Anodal stimulation: Frontal P3 amplitude	-	SMD **0.42 SD higher** (0.83 lower to 1.68 higher)	-	205 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of active tDCS on emotional Processing - Anodal stimulation: Frontal P3 amplitude.
Emotional Processing - Anodal stimulation: Parietal P3 amplitude	-	SMD **0.13 SD lower** (0.83 lower to 0.56 higher)	-	374 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of active tDCS on emotional Processing - Anodal stimulation: Parietal P3 amplitude.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. More than 75% studies reported unclear allocation concealment and participant blinding.

b. The confidence interval is wide and crosses the non-effect value.

c. The upper boundary of the confidence interval is close to the non-effect value.

d. Asymmetrical funnel plot and statistically significant Egger test.

Figure SM.1.

Traffic light plots with risk of bias assessment in oddball paradigms.

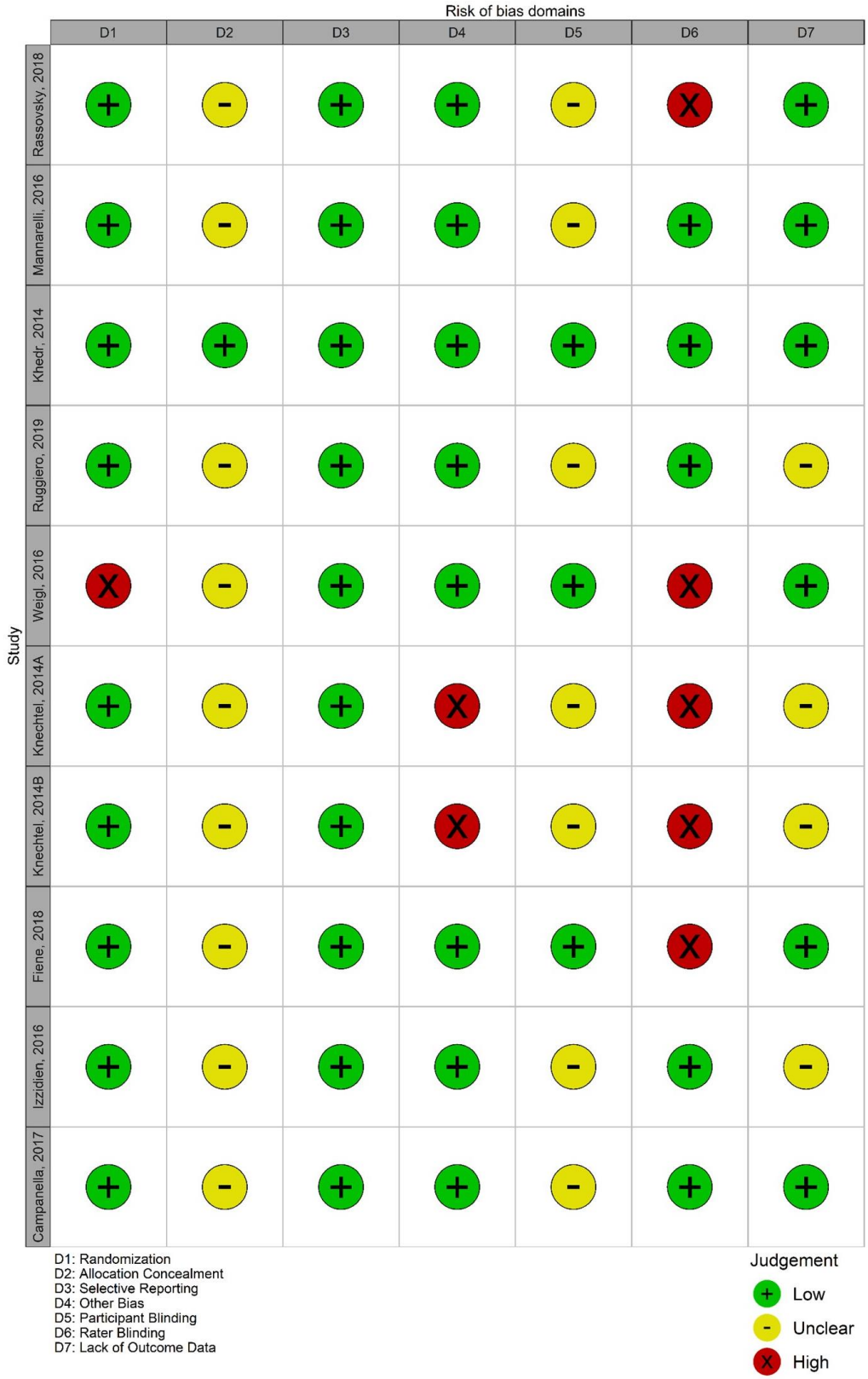


Figure SM.2

Traffic light plots with risk of bias assessment in n-back task.

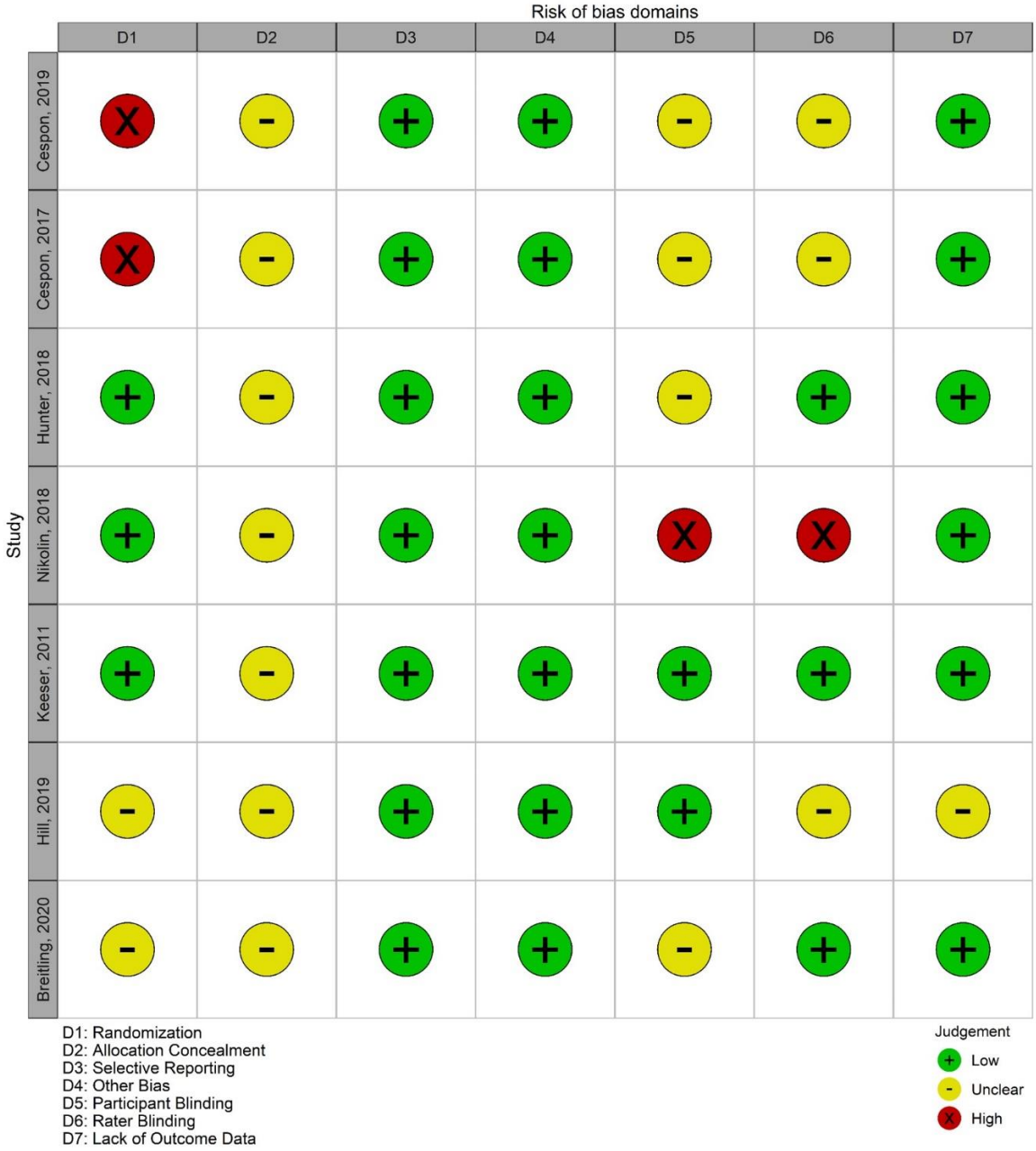


Figure SM.3.

Traffic light plots with risk of bias assessment in GNG tasks.

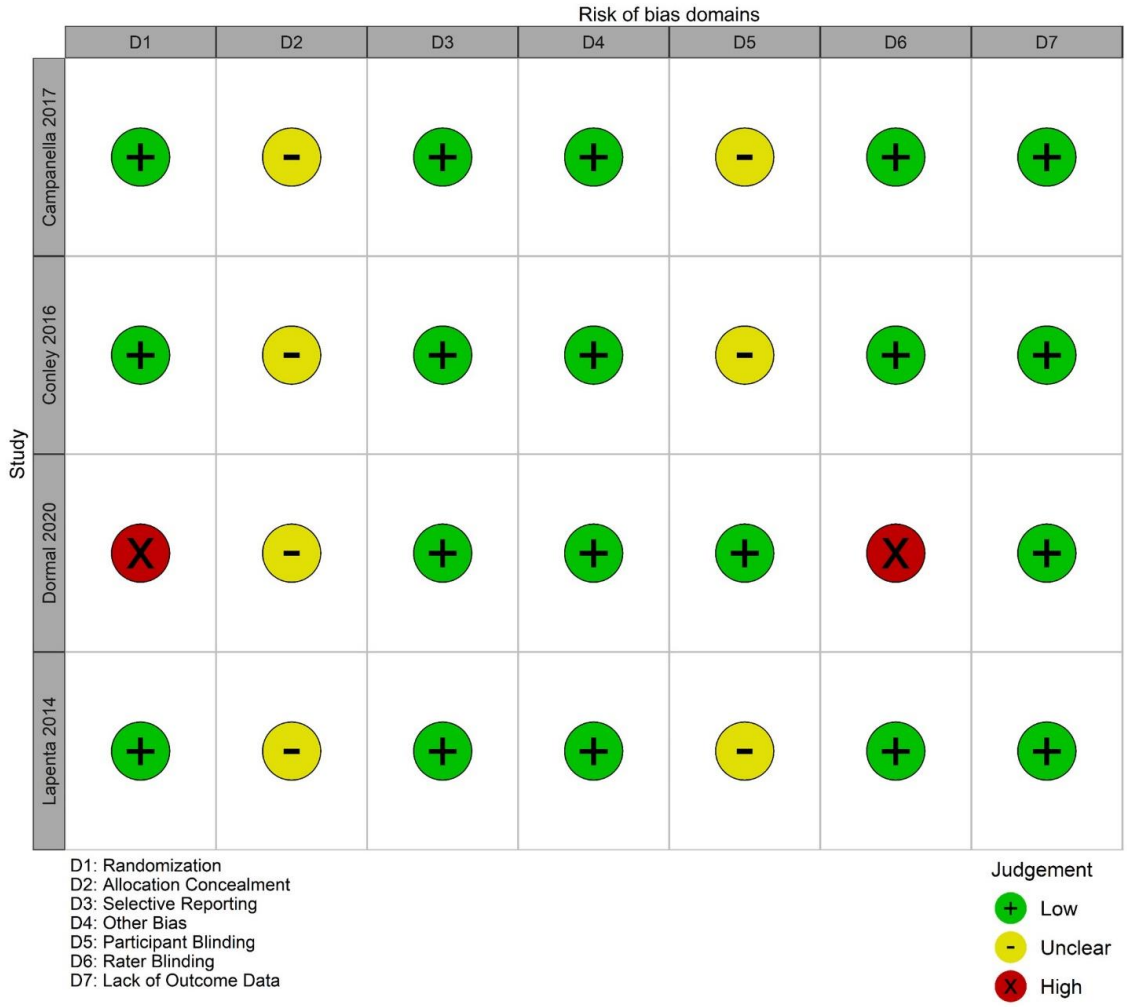


Figure SM.4.

Traffic light plots with risk of bias assessment in emotional processing tasks.

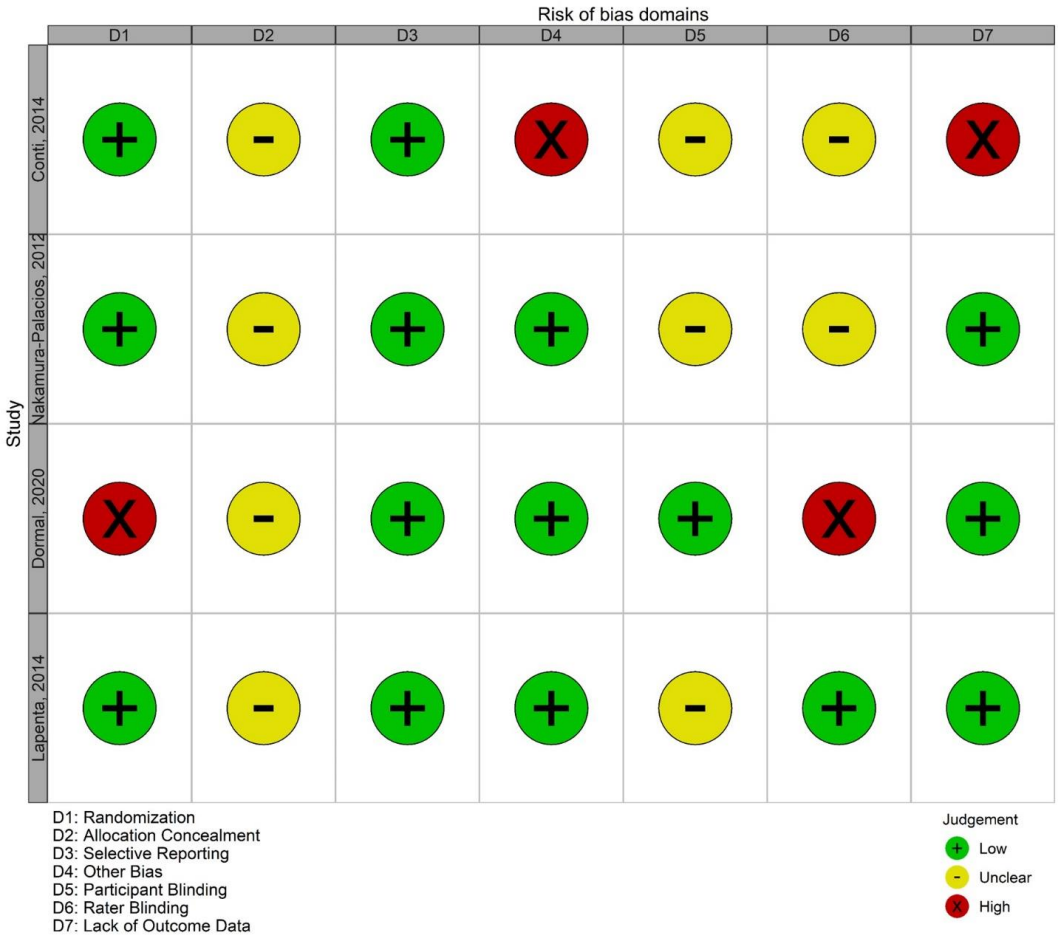


Figure SM.5.

Forest plot with pooled effect estimates and subgroup analysis for frontal P3 amplitude during oddball in anodal stimulation.

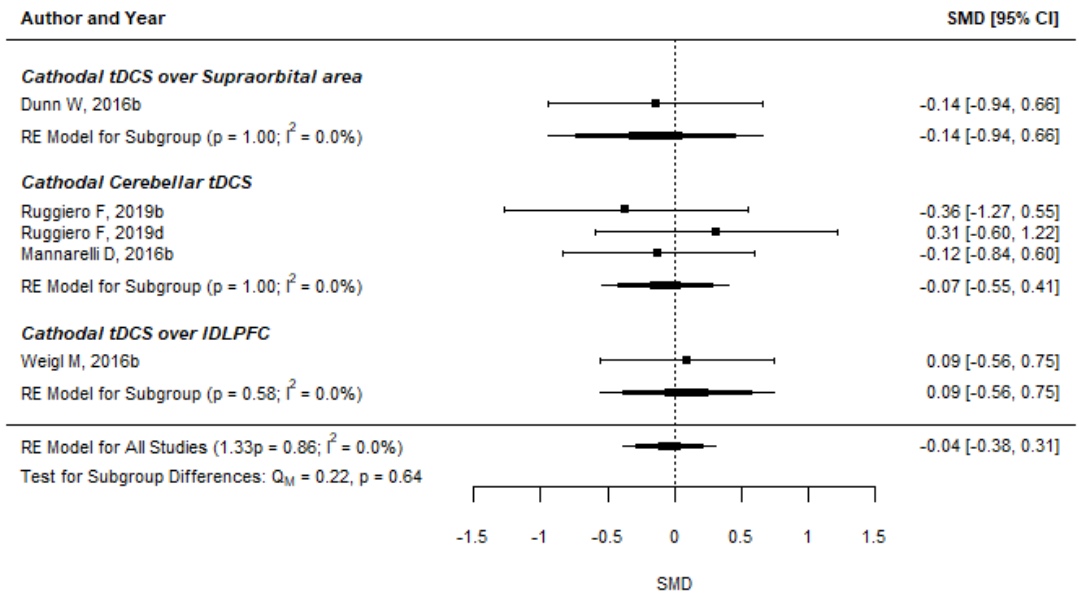


Figure SM.6.

Forest plot with pooled effect estimates and subgroup analysis for parietal P3 amplitude during oddball in cathodal stimulation.

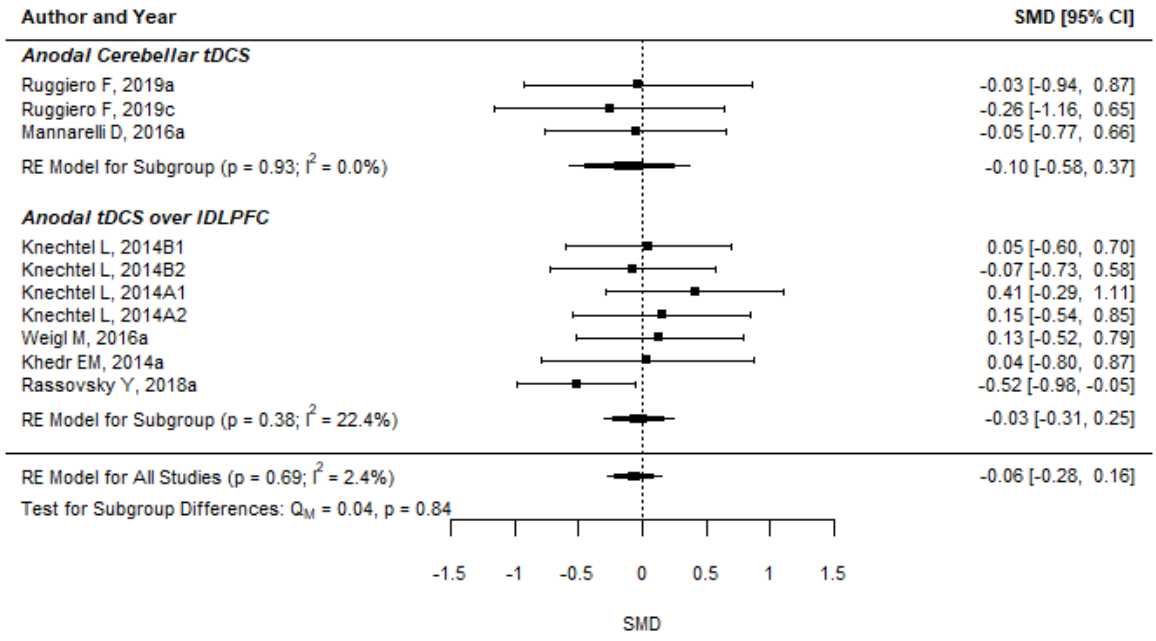


Figure SM.7.

Forest plot with pooled effect estimates and subgroup analysis for frontal P3 amplitude during n-back in anodal stimulation.

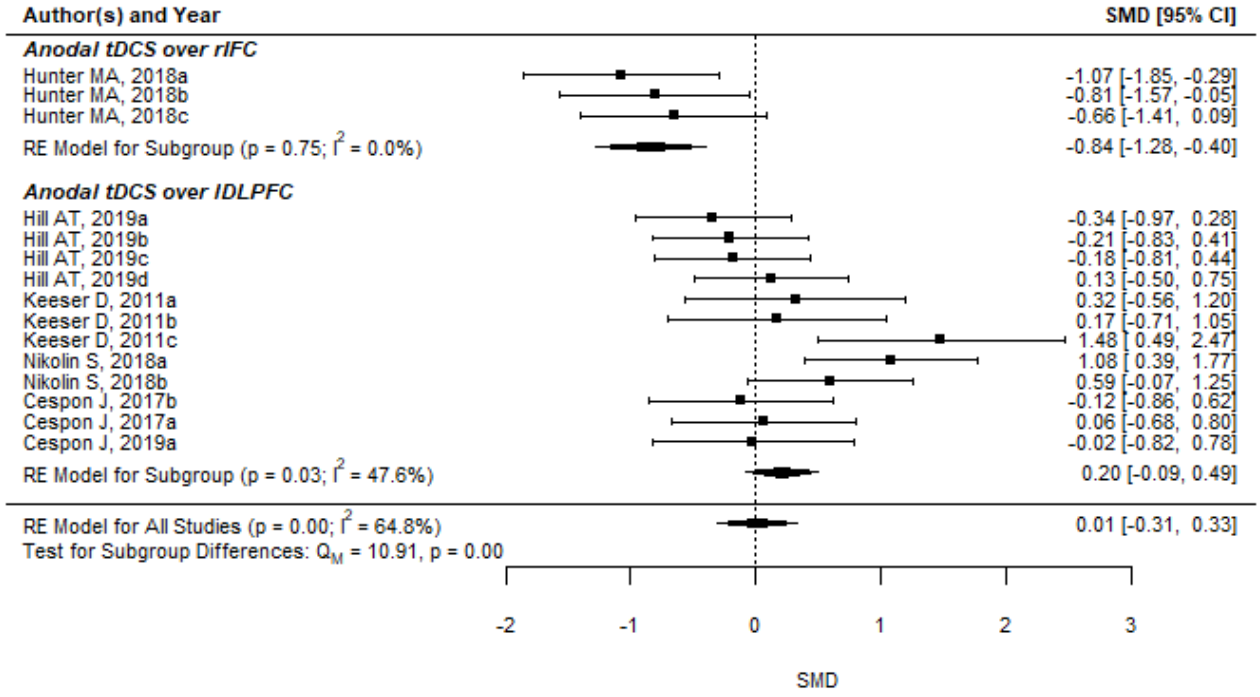


Figure SM.8.

Forest plot with pooled effect estimates and subgroup analysis for frontal No-Go P3 amplitude during GNG in anodal stimulation.

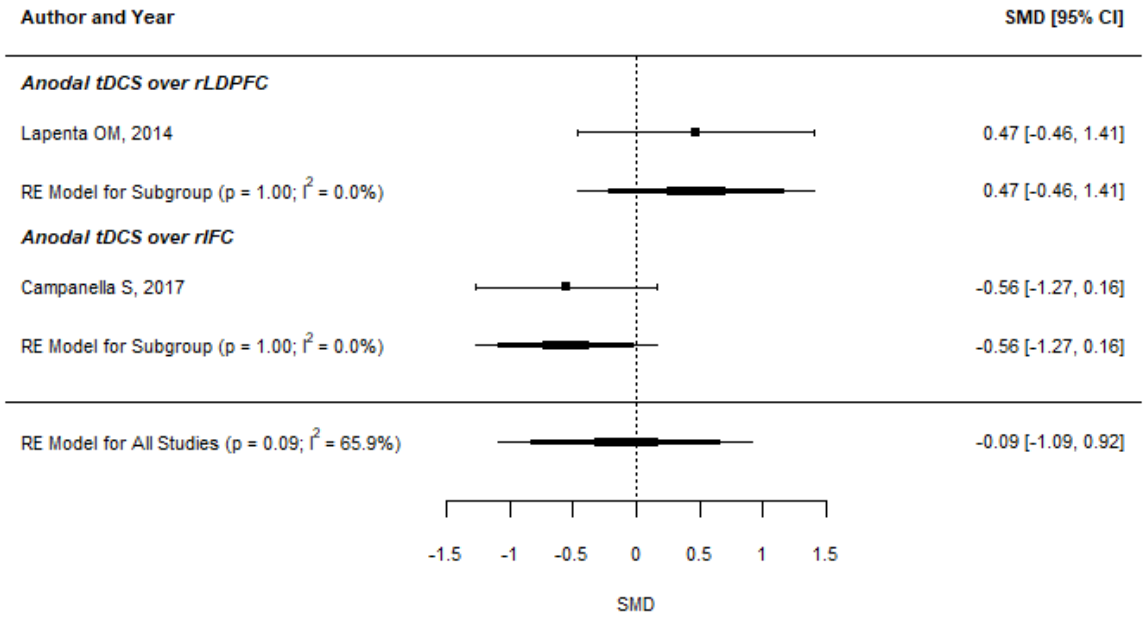


Figure SM.9.

Forest plot with pooled effect estimates and subgroup analysis for parietal No-Go P3 amplitude during GNG in anodal stimulation.

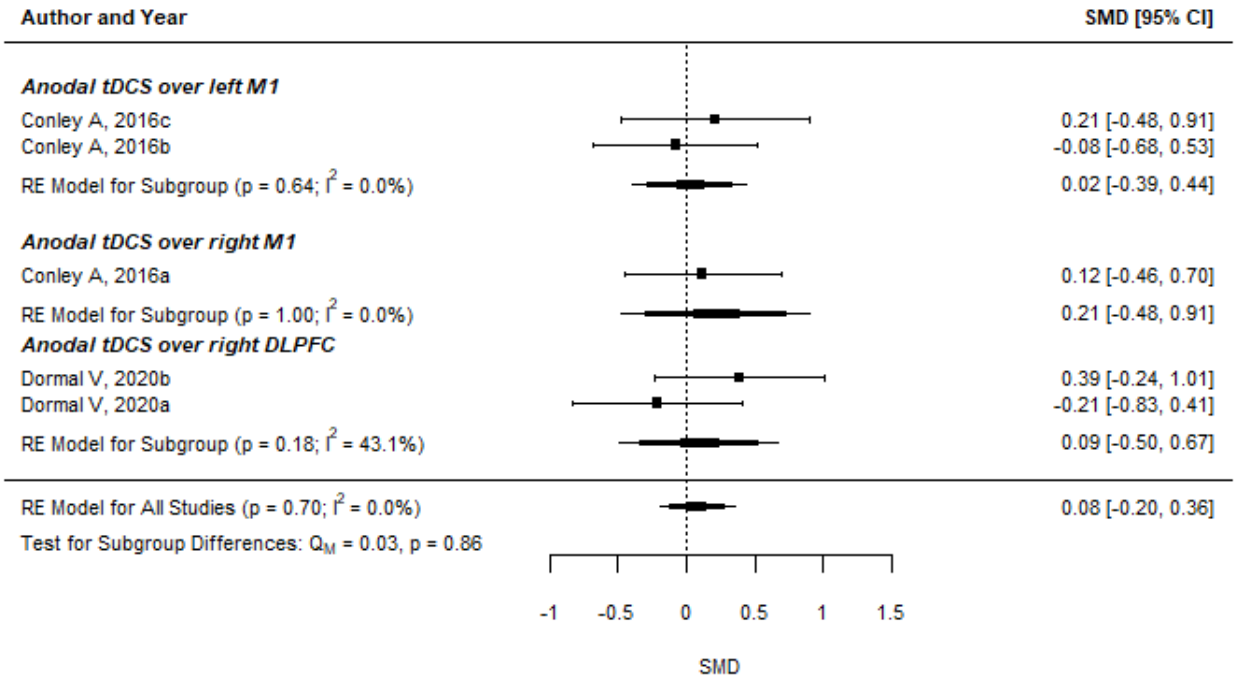


Figure SM.10.

Forest plot with pooled effect estimates and subgroup analysis for parietal Go P3 amplitude during GNG in anodal stimulation.

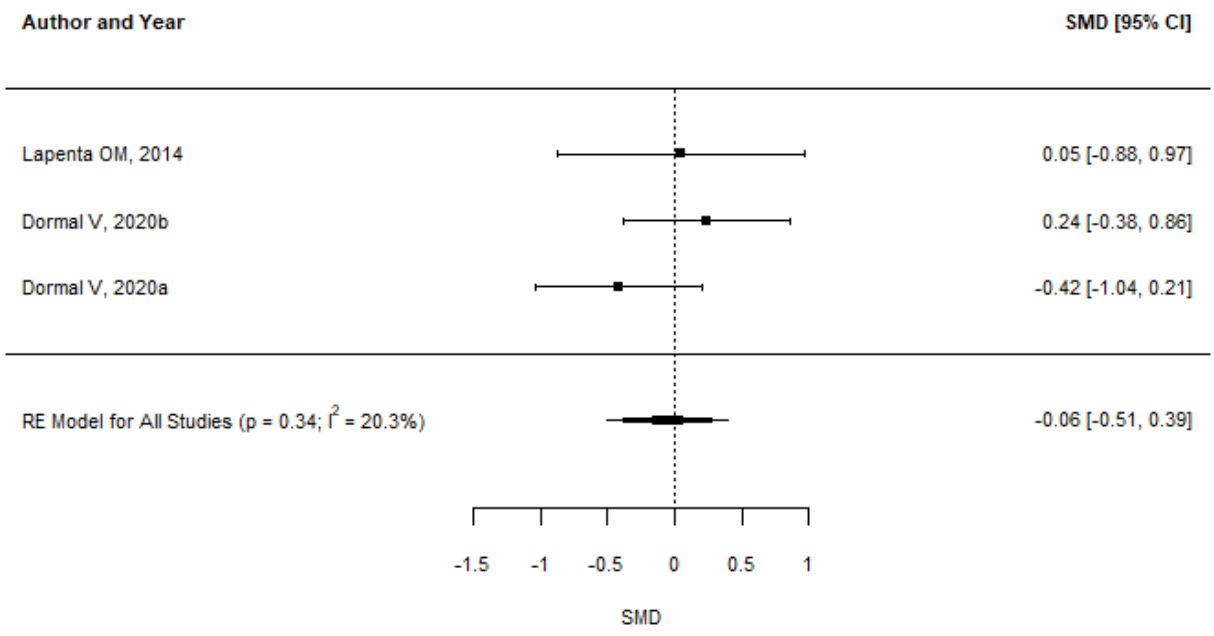


Figure SM.11.

Forest plot with pooled effect estimates and subgroup analysis for frontal P3 amplitude during Emotional Processing in anodal stimulation.

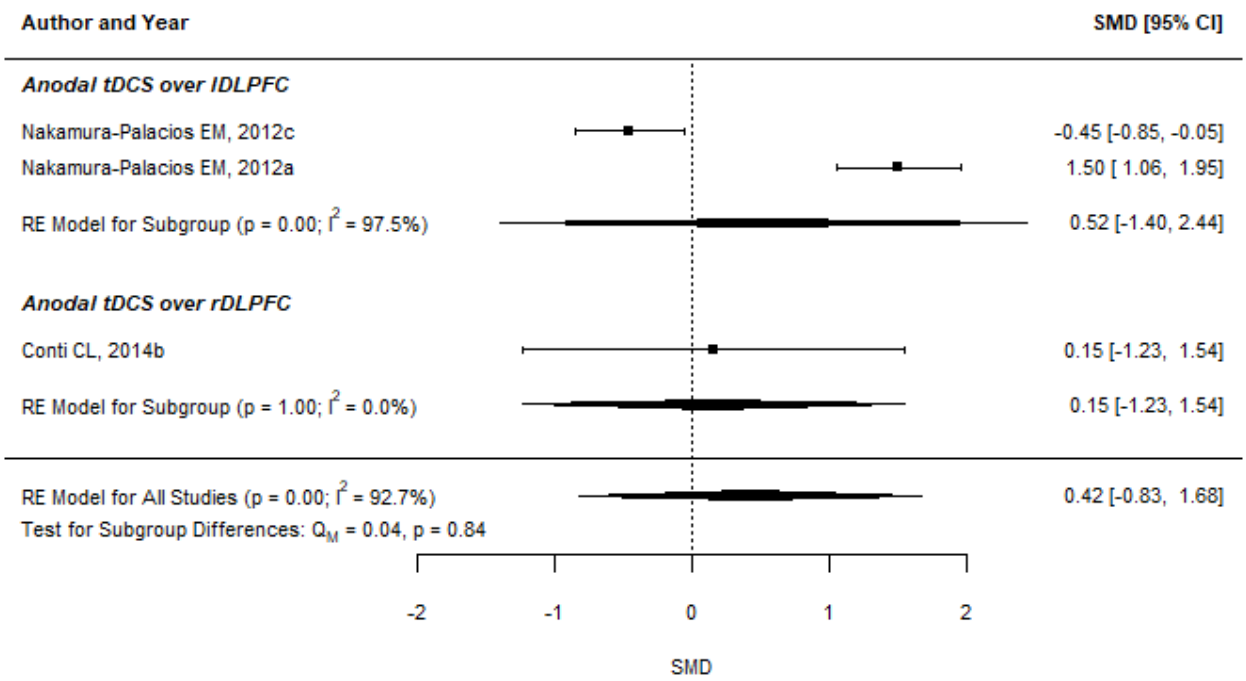


Figure SM.12.

Forest plot with pooled effect estimates and subgroup analysis for parietal P3 amplitude during Emotional Processing in anodal stimulation (only offline comparisons).

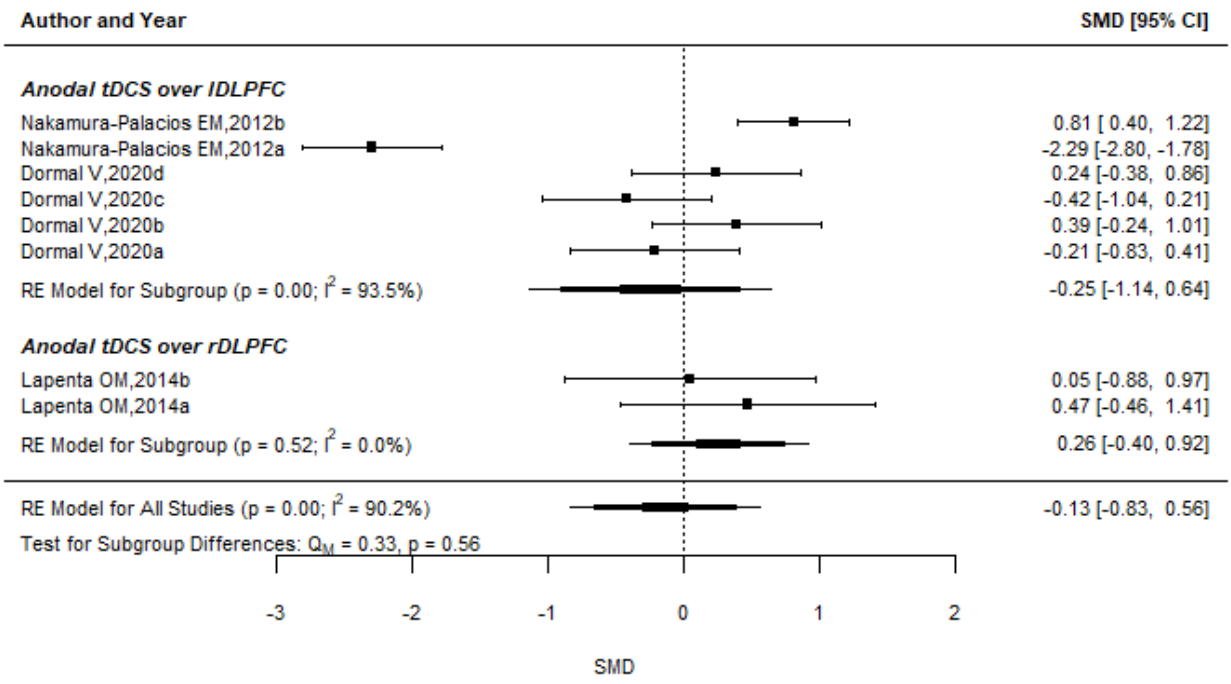


Table SM.8. *Characteristics of the studies considering the cognitive task that elicited P3*

First author (Year)	tDCS group	Control group	Study Design	tDCS intensity (mA)	tDCS density (mA/cm²)	Duration (min)	Active Electrode	Return Electrode	Electrode Size (cm²)	Timing	Number of Sessions	Population
Oddball studies (n = 11)												
Campanella (2017) **	15	16	Between-subjects	2.0	0.08	20	crossing point between T4-Fz and F8-Cz	superior region of the trapezius muscle	25	Offline	1	Healthy
Dunn (2016)	12	12	Between-subjects	1.0	0.028	20	Fp1 & Fp2	right upper arm	35	Offline	1	Schizophrenia
Fiene (2018) *	15	15	Within-subjects	1.5	0.06	~27.29	F3	right shoulder	25 (active) & 35 (return)	Both	1	Multiple Sclerosis
Izzidien (2016)	10	10	Within-subjects	1.5	0.06	15	C3	right supraorbital area	25	Online	1	Healthy
Khedr (2014) *	11 (Anodal) & 12 (Cathodal)	11	Between-subjects	2.0	0.083	25	F3	right supraorbital area	24 (active) & 100 (return)	Offline	10	Alzheimer
Knechtel (2014A)	16	16	Within-subjects	2.0	0.057	20	F3	right supraorbital region	35	Offline	1	Healthy
Knechtel (2014B)	18	18	Within-subjects	2.0	0.057	20	F3	right supraorbital region	35	Offline	1	Schizophrenia
Mannarelli (2016) *	15	15	Within-subjects	2.0	0.08	20	left cerebellar cortex	left deltoid muscle	25	Online	1	Healthy
Rassovsky (2018) *	37	37	Within-subjects	2.0	0.057	20	F3	right supraorbital region	35	Offline	1	Schizophrenia
Ruggiero (2019) *	9	9	Between-subjects	2.0	0.082	20	median line of cerebellum	thoracic spinal cord	35 (active) & 80 (return)	Offline	1	Healthy
Weigl (2016) *	18	18	Within-subjects	1.0	0.029	15	F3	right supraorbital region	35	Offline	1	Healthy
N-back studies (n = 7)												
Breitiling (2020) *	10	10	Within-subjects	0.5 (HD-tDCS) & 1.0 (conventional)	0.029 (conventional)	20	F8	left supraorbital region (conventional)	0.79 (HD-tDCS) & 35 (conventional	Offline	3	ADHD
Cespón (2019) *	12	12	Within-subjects	1.5	0.09	13	F3	right shoulder	16 (active) & 50 (return)	Offline	1	Alzheimer
Cespón (2017) *	14	14	Within-subjects	1.5	0.09	13	F3	right shoulder	16 (active) & 50 (return)	Offline	1	Healthy (young & elderly)
Hill (2019)	20	20	Within-subjects	1.5	0.477 (anode) and 0.119 (each cathode)	15	F3	Fp1, Fz, C3 and F7 (HD-tDCS)	3.14 (HD-tDCS)	Offline	1	Healthy
Hunter (2018)	16	13	Between-subjects	2.0	0.181	30	F10	left lateral upper bicep muscle	11	Offline	~7	Healthy
Keeser (2011)	10	10	Within-subjects	2.0	0.057	20	F3	right supraorbital region	35	Offline	1	Healthy
Nikolin (2018)	18	19	Between-subjects	1.0 & 0.034	0.062 & 0.002	15	F3	F4	16	Offline	1	Healthy
Go/No-Go studies (n = 4)												
Campanella (2017) **	15	16	Between-subjects	2.0	0.08	20	crossing point between T4-Fz and F8-Cz (rIFG)	superior region of the trapezius muscle	25	Offline	1	Healthy
Conley (2016)	23 (healthy) & 37 (elderly)	23 (healthy) & 37 (elderly)	Within-subjects	1.0	0.029	20	C3 (C4 in one subgroup)	right supraorbital region	35	Offline	1	Healthy (young & elderly)
Dormal (2020) **	20	20	Within-subjects	1.5	0.043	20	F3	right supraorbital region	35	Offline	1	Healthy & BDs
Lapenta (2014) **	9	9	Within-subjects	2.0	0.057	20	F4	F3	35	Offline	1	Healthy
Emotional Processing (n = 4)												
Conti (2014)	6	3	Between-subjects	2.0	0.057	20	F4	F3	35	Both	5	Crack/Cocaine addiction
Dormal (2020) **	20	20	Within-subjects	1.5	0.043	20	F3	right supraorbital region	35	Offline	1	Healthy & BDs
Lapenta (2014) **	9	9	Within-subjects	2.0	0.057	20	F4	F3	35	Offline	1	Healthy
Nakamura-Palacios (2012)	49	49	Within-subjects	1.0	0.029	10	F3	contralateral	35	Both	1	Alcoholics

* Studies with anodal and cathodal tDCS comparisons ** Studies present in two subsections.

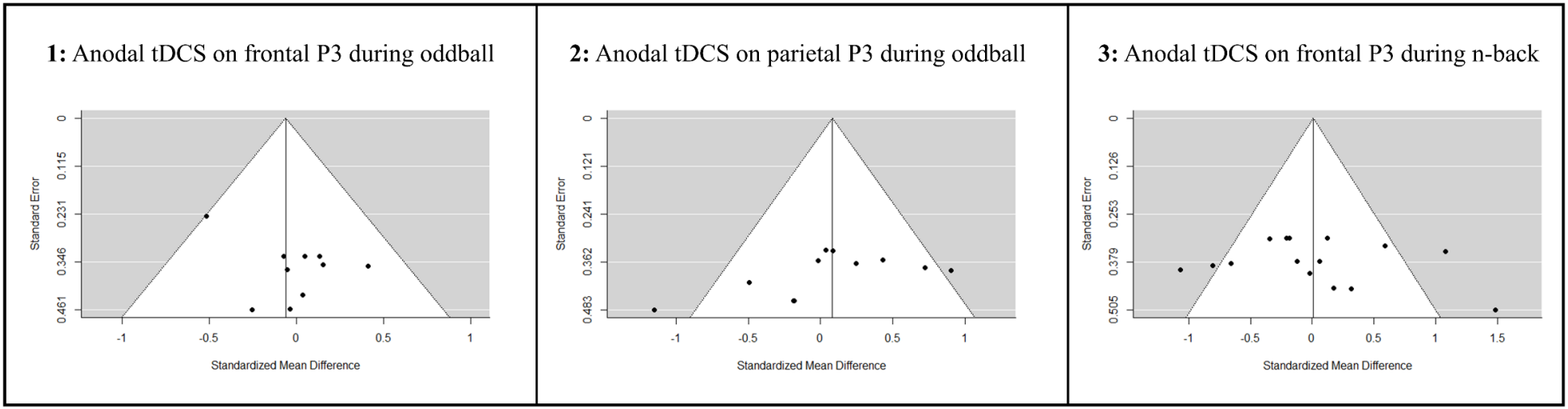
Table SM.9. *Characteristics of the cognitive task and EEG P3 analysis.*

First author (Year)	Cognitive Task	Response Requirement	Stimuli Modality	Target Probability (%)	Frontal P3 Electrode	Parietal P3 Electrode	Frontal P3 Time Window (ms)	Parietal P3 Time Window (ms)
Oddball studies (n = 11)								
Campanella (2017) **	Oddball	Press button	Faces	30	n.a.	Pz	n.a.	300 - 580
Dunn (2016)	Oddball	Press button	Tones	12	n.a.	Pz	n.a.	290 - 400
Fiene (2018) *	Oddball	Press button	Tones	20	n.a.	Pz	n.a.	250 - 450
Izzidien (2016)	Oddball speller	Observation	Letters and Numbers	n.a.	n.a.	Pz	n.a.	270 - 400
Khedr (2014) *	Oddball	Press button	Tones	20	Fz	n.a.	250 – 500	n.a.
Knechtel (2014A)	Oddball	Press button	Tones	10	Fz	Pz	240 – 450	174 - 470
Knechtel (2014B)	Oddball	Press button	Tones	10	Fz	Pz	240 – 450	174 - 470
Mannarelli (2016) *	Oddball	Count the targets	Tones	10	Fz	Pz	250 – 500	250 - 500
Rassovsky (2018) *	Oddball	Press button	Tones	12	n.a.	Pz	n.a.	300-600
Ruggiero (2019) *	Oddball	Count the targets	Tones	25	Fz	Pz	250 – 500	250 - 500
Weigl (2016) *	Oddball	Press button	Tones	10	Fz	Pz	260 – 360	280 - 380
N-back studies (n = 7)								
Breitiling (2020) *	2-back	Press button	Letters	21	n.a.	P4 & P8	n.a.	300 – 450
Cespón (2019) *	1-back	Press button	Letters	25	Frontal cluster***	Parietal cluster***	400 – 700	400 – 700
Cespón (2017) *	2- & 3-back	Press button	Letters	25	Frontal cluster***	Parietal cluster***	350 – 450	350 – 450
Hill (2019)	2- & 3-back	Press button	Letters	25	F1	n.a.	300 – 430	n.a.
Hunter (2018)	1-, 2- & 3-back	Press button	Letters	33	Fz	Pz	300 – 650	300 - 650
Keeser (2011)	0-, 1- & 2-back	Press button	Numbers	?	Fz	-	260 – 400	n.a.
Nikolin (2018)	3-back	Press button	Letters	?	Fz	-	220 – 420	n.a.
Go/No-Go studies (n = 4)								
Campanella (2017) **	GNG	Withhold	Letters	30	Fz	n.a.	300 – 580	n.a.
Conley (2016)	GNG	Withhold	Symbols	30	n.a.	Pz	n.a.	200–500 (young adults); 250–650 (elderly)
Dormal (2020) **	GNG	Withhold	Alcohol-related pictures	33	n.a.	Pz, P3 & P4	n.a.	300 - 500
Lapenta (2014) **	GNG	Withhold	Food pictures	50	Frontal cluster	Parietal cluster	350 – 500	350 - 500
Emotional Processing (n = 4)								
Conti (2014)	CRP	Observation	Crack-related pictures	50	Frontal cluster	n.a.	350 – 600	n.a.
Dormal (2020) **	GNG	Withhold	Alcohol-related pictures	33	n.a.	Pz, P3 & P4	n.a.	300 - 500
Lapenta (2014) **	GNG	Withhold	Food pictures	50	Frontal cluster	Parietal cluster	350 – 500	350 - 500
Nakamura-Palacios (2012)	CRP	Listening	Alcohol-related sounds	100	Fz	Pz	250 – 400	250 – 400

* Studies with anodal and cathodal tDCS comparisons ** Studies present in two subsections. ***Frontal cluster: F4, F8, AF8, FC6, F3, F7, AF7, FC5; Parietal cluster: P4, P8, PO8, CP6, P3, P7, PO7, CP5; CRP: Cue-Reactivity Paradigm

Figure SM.13.

Funnel plots in the analysis with at least 10 comparisons.



CHAPTER 3

Transcranial Direct Current Stimulation decreases P3 amplitude and inherent delta activity during a waiting impulsivity paradigm

3.1. Abstract

Background: The inability to wait for a target before initiating an action (i.e., waiting impulsivity) is one of the main features of addictive behaviors. Current interventions for addiction, such as transcranial Direct Current Stimulation (tDCS) have been suggested to improve this inability. Nonetheless, whereas there is consensus about the role of prefrontal cortex on impulsive behavior, the effects of tDCS in waiting impulsivity and underlying electrophysiological (EEG) markers are still not clear.

Objective: The study aimed to evaluate the effects of neuromodulation over the right inferior frontal gyrus on behavior and EEG markers of reward anticipation (i.e., cue and target-P3 and underlying delta/theta power) during a task designed to elicit premature responses.

Methods: Forty healthy subjects participated in two experimental sessions, where they received active and sham tDCS over the right Inferior Frontal Gyrus (rIFG) with a current intensity of 2 mA for 20 minutes. Participants were asked to perform a premature responding task, while they were receiving tDCS. EEG recording was performed throughout the stimulation period. Participants also performed two control tasks to evaluate transfer effects for delay discounting and motor inhibition abilities.

Results: Active tDCS decreased the cue-P3 and target-P3 amplitudes, as well as delta power during target-P3. While no tDCS effects were found for motor inhibition, active tDCS increased the discounting of future rewards in small values when compared to sham.

Conclusion: These findings suggest a tDCS-induced modulation of the P3 component and underlying oscillatory activity during waiting impulsivity. Moreover, this modulation was also associated with changes in terms of discounting of future rewards. Thus, the current study suggests the usefulness of tDCS in impulsive processes modulation, namely in terms of reward processing and changes in terms of P3 amplitude and inherent delta power.

Keywords: Waiting Impulsivity; Premature responses; tDCS; rIFG; P3; Delta; Theta.

3.2. Introduction

TDCS over the prefrontal areas has already shown promising effects for addiction (Lapenta et al., 2018), craving (Carvalho et al., 2019), and reward responsiveness (Terenzi et al., 2021). Studies using tDCS to target inhibitory processes have been targeting several cortical regions , such as the right inferior frontal gyrus (rIFG) related with response inhibition (Schroeder et al., 2020) or the dorsolateral prefrontal cortex (DLPFC) in order to enhance delay discounting (Mayer et al., 2020). Although both processes are framed within impulsivity (i.e., stopping vs waiting), they differ in their cognitive procedures and neuronal networks. For instance, waiting impulsivity relies on top-down regulation of the prefrontal cortex, involving subcortical structures such as the ventral striatum, amygdala, and hippocampus (Dalley et al., 2011); while stopping requires interactions between the right inferior frontal gyrus (rIFG) and the pre-supplementary motor area (SMA), with the dorsal striatum and the subthalamic nucleus (STN) (Dalley & Robbins, 2017).

Waiting impulsivity can be further divided into two main dimensions, namely the impulsive action measured by premature responses and the impulsive choice assessed in delay discounting tasks. This distinction highlights the role of impulsive action as a 'cold' process, less prone to affective/emotional influences, whilst impulsive choice is thought to be a 'hot' process relying on reward processing (Reynolds et al., 2006). Premature responses have also been associated with proactive stopping evaluated in Go/No-Go (GNG) paradigms, given that inhibitory processes may be prior to response selection (Voon, 2014). On the other hand, reactive inhibition paradigms, such as the Stop Signal Reaction Time task (SSRTT), have not been associated to premature responses, given that the inhibitory processes act after response has started (Morris et al., 2016).

Furthermore, attentional and inhibitory processes have been studied using event-related potentials (ERPs), mainly through the P3 component. P3 is characterized by positive prominent wave at centro-parietal sites with a peak between 250 and 600 ms after the presentation of a task-relevant stimulus (Polich, 2007). P3 can also be elicited when rewards/punishments are anticipated. The anticipatory or cue-P3 is elicited after the cue onset and it has been interpreted as the motivated attention to a subsequent task-relevant stimulus (Pfabigan et al., 2014). The consummatory or target-P3 is the actual response towards the motivational stimulus predicted by the cue (Broyd et al., 2012). These components have been tested in the Monetary Incentive Delay (MID) task, in which participants are rewarded or punished accordingly to the response time towards a cued target stimulus (Broyd et al., 2012). The cue indicates the type of trial (i.e., win or loss), followed by a target (with a jittered interval)

and immediate feedback about performance. Thus, the cue-P3 is elicited following the cue-onset that predicts the incoming target and the type of feedback (i.e., reward/punishment), which has been suggested to represent the motivated attention towards the impending relevant-stimulus (i.e., target) (Glazer et al., 2018). The target-P3 is elicited following the onset of a stimulus implied in the subsequent reward or punishment process. Thus, target-P3 amplitude increases after cues that predict gains or losses (Broyd et al., 2012). However, the specific effects in terms of valence of reward in cue-P3 are not clear (Angus et al., 2017; Broyd et al., 2012; Novak & Foti, 2015; Vignapiano et al., 2016). Specifically, cue-P3 is greater in trials predicting rewards (Broyd et al., 2012), losses (in schizophrenia subjects) (Vignapiano et al., 2016), or both (Angus et al., 2017; Novak & Foti, 2015; Vignapiano et al., 2016) in comparison with neutral trials. Moreover, cue-P3 amplitude was increased in win, when compared to loss trials (Angus et al., 2017; Pfabigan et al., 2014). Overall, both P3 components are enhanced in reward-laden trials suggesting attentional allocation to motivational stimuli (Novak & Foti, 2015).

Assuming that ERPs are representations of specific brain activations in the time domain, they co-occur with the synchronization of oscillatory activity in the time-frequency domain, i.e., the event-related oscillations (ERO) (Herrmann et al., 2014). Regarding the EROs, the P3 elicited during oddball paradigm is accompanied by a transient increase in delta (0.5 – 4 Hz) and theta (4 – 7 Hz) power at the same latency and scalp distribution of P3 (Güntekin & Başar, 2016). These findings suggest that both oscillatory frequencies might represent the mechanism of generation of the P3 component (Demiralp et al., 2001). Also, an increase in parietal delta power after a reward-laden stimulus has been shown, suggesting that the association between P3 and delta might occur also during the anticipation of rewards (Pornpattananangkul & Nusslock, 2016). Nevertheless, this concurrent activity between both EEG markers in parietal regions was not tested yet in MID tasks or other reward processing paradigm.

In a recent meta-analysis about the modulatory effects of tDCS in the P3 component during cognitive tasks, we were able to show an increase in the parietal P3 in attentional and working memory tasks after tDCS to the frontal cortex (Mendes et al., 2022). The effects of tDCS in terms of P3 amplitude elicited during response inhibition were mixed: some studies showed an increase in P3 amplitude (Lapenta et al., 2014), while others a decrease (Cunillera et al., 2016; Verveer et al., 2020).

Even though previous tDCS studies have targeted addictive/impulsive behaviors, the available knowledge about neural correlates of impulsivity highlights the importance of understanding how tDCS impacts cognition, but also the underlying neuronal activity. For instance, a recent study guided tDCS through an online analysis from EEG data collected during the performance of a cognitive task (Leite et al., 2017). This closed-loop methodology aimed to augment the effects of tDCS, but also relied on the

detection of specific neuro-markers of cognition. Therefore, the understanding of the effect of tDCS in cognition, as well as the understanding of the effects of tDCS in EEG markers related to cognition, is of upmost importance for the optimization of the effects. In this sense, the aim of the current study was to assess the effects of tDCS over rIFG in (i) premature responses, and in the (ii) anticipatory and consummatory ERPs and EROs related to waiting impulsivity. For this purpose, we developed a computerized task to test the anticipatory and consummatory neural response towards a salient-stimulus involved in reward-seeking, which was tailored to individual performance. Considering the essential role of rIFG in response inhibition (Aron et al., 2014), we hypothesized that active tDCS over the rIFG would lead to a reduction in the number of premature responses. Moreover, this reduction in the number of premature responses may also show a transfer effect for delay discounting and inhibitory control. Likewise, the behavioral modulation is expected to be combined with an increase of P3 amplitude and consequently delta/theta power.

3.3 Methods.

3.3.1. Participants

A total of 40 healthy volunteers (31 females; mean age: 23.2 ± 3.52) participated in the study. All the participants were right-handed (Edinburgh Handedness Inventory > 40) and without recent history of neurological or psychiatric disorders. Prior to their participation in the experiment, volunteers were assessed using the Beck Depression Inventory II (Beck et al., 1996), Alcohol Use Disorders Identification Test (Saunders et al., 1993), and Drug Use Disorders Identification Test (Hildebrand, 2015) to ensure the absence of depressive symptomatology and the consumption of alcohol/drugs. Moreover, participants who reported medication or psychotropic drugs consumption during the 4 weeks prior to the study were not included. All participants gave their written informed consent preceding their enrollment. The study was in accordance with the Declaration of Helsinki and was approved by the local ethics committee (CEICVS 127/2019).

3.3.2. Study Design

The study comprised two sessions, one with active and another with sham tDCS, which were administered randomly to each participant in a counterbalanced order. Both sessions followed similar procedures, except for the screening, informed consent, and self-report questionnaires that were performed only in the first session. In each session, participants performed the Cued Premature Response Task (CPRT) (Figure 7) during tDCS. EEG data was collected during the entire performance of the CPRT.

Then, participants performed the SSRTT (Band & van Boxtel, 1999) and the Monetary Choice Questionnaire – 27 (MCQ-27) (Kirby et al., 1999) in a counterbalanced order to assess potential far-transfer effects for delay discounting and inhibitory control. At the end of the session, participants filled a blinding questionnaire about the tDCS condition and the side effects of tDCS using a Visual Analog Scale from 0 to 10 (see Table SM.10 and SM.11 in Supplementary Materials).

3.3.3. Cued Premature Response Task

The experimental task was developed to assess premature responding during monetary reinforcement and punishment. For that, CPRT was adapted from the 4-Choice Serial Reaction Time Task (Voon et al., 2016) and the MID (Broyd et al., 2012). Participants were instructed to press the middle button of the E-Prime Chronos response box to start a trial and to release it as fast as possible when the target was displayed on the screen. The target was always preceded by a cue, which informs the participant that the target was about to be displayed. The cue and the target were always displayed with a random onset to minimize expectancy. Specifically, the interval between the trial onset and the cue ranged from 1250 to 1750 ms and the interval between the cue and the target ranged from 500 to 2500 ms (Figure 7.A). However, in the baseline block, these intervals were fixed at 1000 ms.

Participants were instructed to release the button after target, as fast as possible, thus favoring speedier responses instead of more accurate, however slower, responses. Participant's responses were rewarded with virtual money if their responses were faster, punished if their responses were slower, or neither rewarded nor punished if they responded before target onset (i.e., premature responses; Figure 7.B) (Voon et al., 2016). The task comprised one training block with 20 trials and one test block with 180 trials in total. Participants started to perform the test block task after three minutes of the onset of tDCS and the total duration of the task was approximately 15 minutes.

The reinforcement/punishment feedback was individualized to each participant according to the mean and variability of the release time (RT) observed in the last 10 trials of the baseline block (Figure 7.B), namely:

- Very fast responses: the RT was below -0.66 standard deviation (SD) of the baseline RT mean, which was reinforced with virtual 1€. In case of three successful consecutive trials, the feedback increased to 2€ as a reward for the "very fast responses".
- Fast responses: the RT was between -0.66 SD and +0.33 SD of the baseline RT mean and the participant received a virtual 0.5€.

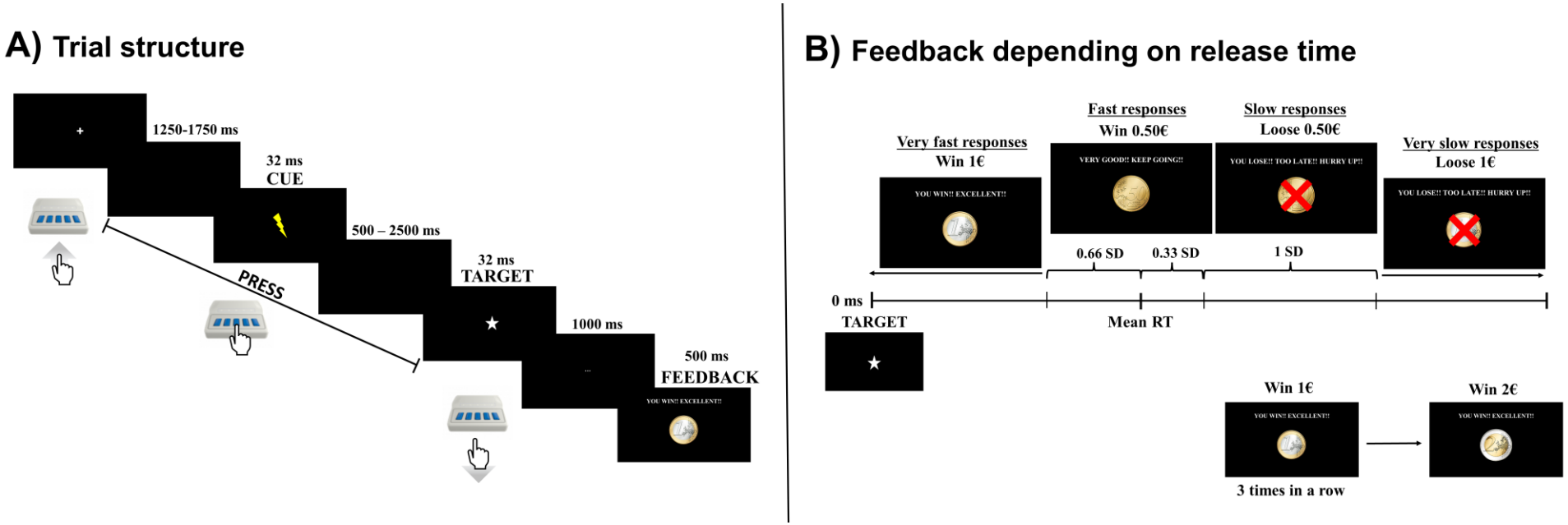
- Slow responses: the RT was between +0.33 SD and +1SD of the baseline RT mean and the participant punishment was the loss of 0.5€.
- Very slow responses: the RT was above +1SD of the baseline RT mean and the participant would lose 1€.
- Premature responses: participant released the button before the target, which was neither reinforced, nor punished, and the feedback was instead "Continue" (i.e., please continue) in the native language.

The interval between the trial onset and the cue were very similar in both sessions, namely a mean of 1499.93 ms and a standard deviation of 9.49 ms in during the active tDCS session, and a mean of 1499.72 ms and a standard deviation of 10.25 ms in sham sessions. Likewise, the interval between the cue and the target had a mean of 1502.39 ms and a standard deviation of 47.16 ms in active sessions, and a mean of 1502.99 ms and a standard deviation of 49.75 ms in sham sessions.

Two participants were removed from the analysis because they did not correctly perform the baseline block and other outliers with values above/below three standard deviations from the mean were eliminated. The behavioral outcomes analyzed were the number of premature responses, the monetary gain/loss, and the RT average.

Figure 7

Overview of the experimental task (A) and the individualized reinforcement/punishment feedback (B).



3.3.4. Control Assignments

3.3.4.1. Stop-Signal Reaction Time Task. The SSRTT is designed to assess the inhibitory control abilities and the version used in the study followed the latest guidelines for appropriate structure of the task (Verbruggen et al., 2019). For this purpose, participants were instructed to respond accordingly to the orientation of an arrow. Specifically, if an arrow was pointing to the left, the participant should press the left button ("Z"); on the other hand, when the arrow was pointing to the right, the participant the participant should press the right button ("M"). Moreover, for stop trials, a red frame around the arrow (i.e., stop-signal) was shown on the screen, which informed participants to withhold any response. The stop-signal appeared after the arrow was displayed with a delay adjusted for each participant following a staircase-tracking algorithm (Band & van Boxtel, 1999). The Stop-Signal Delay (SSD) was set to 250ms at the beginning of each block, which was adjusted after an unsuccessful inhibition (-25 ms) and a successful inhibition (+25 ms). The maximum SSD was 400 ms and the minimum was 0 ms. The goal of this adjustment was to guarantee a p(response|stop-signal) of 0.5. Therefore, participants were instructed to be as faster and accurate as possible, even though they should not wait for the stop-signal to control for the speed-accuracy tradeoff.

The task started with a training block of 24 trials, followed by four experimental blocks with 64 trials each. In each block, there were 75% of go trials (i.e., 48 trials) and 25% of stop trials (i.e., 16 trials). However, the first 6 trials of a block were always a go trial. The task had a total duration of approximately 8 minutes. The outliers were identified following the lenient criteria from Congdon and colleagues (Congdon et al., 2012). The outcomes included in the statistical analysis were accuracy and RT of go trials, p(respond|signal), SSD, and the stop-signal reaction time (SSRT).

3.3.4.2. 27-item Monetary Choice Questionnaires. The MCQ-27 was administered to evaluate the discount rating (i.e., if the participant prefers smaller but immediate rewards, instead of larger but delayed rewards). The questionnaire is composed of 27 questions with two possible answers, namely smaller and immediate or a larger, however, delayed reward (Kirby et al., 1999). The outcomes of the questionnaire are the overall, small, medium, and large k. The overall k represents the steepness of the discounting for all the monetary values (i.e., takes into consideration all the items from the questionnaire), while the small, medium, and large k are specific to the corresponding amounts (i.e., takes into consideration 9 items from the questionnaire per amount). The discount rates (i.e., k) were calculated in an Excel-based spreadsheet scoring tool (Kaplan et al., 2016).

3.3.5. Transcranial Direct Current Stimulation

Participants received both active and sham tDCS in distinct sessions through a Starstim R20 (Neuroelectrics, Barcelona, Spain). For the active tDCS condition, an electric current of 2 mA of intensity for 20 min (with 15 second of ramp up and ramp down) was applied while the participant performed the CPRT. Sham procedure was similar to the active stimulation, however with only a 45 sec duration (with 15 seconds of ramp up and ramp down). 25 cm2 round saline-soaked electrode sponges (~radius of 3 cm, current density: 0.08 mA/cm2) were placed over F8 (active electrode) and posterior to the left mastoid (return electrode) (Breitling et al., 2016). This tDCS montage was chosen, because according to computer modeling, the current densities are higher over the inferior frontal (Breitling et al., 2016). Moreover, the placement of the return electrode on the left mastoid may prevent potential dual effects from other relevant brain areas (Leite et al., 2018).

3.3.6. Electrophysiological acquisition and data analysis

Online EEG data was collected with a Starstim R20 (Neuroelectrics, Barcelona, Spain) using 18 scalps electrodes and one earlobe electrode. Electrophysiological data was offline preprocessed and analyzed using EEGLAB (Delorme & Makeig, 2004). Data was sampled at a rate of 500 Hz and FIR filtered with a bandpass between 0.5 and 40 Hz. The DC offset was removed as the line noise using a notch filter (i.e., 50 Hz). The artifacts in the continuous data were corrected and noisy channels removed using the Artifact Subspace Reconstruction in the clean_rawdata function. The parameters for the identification of noisy channels were the following: flatline with a maximum duration of 5 seconds and correlation between channels below 0.7. EEG data was re-referenced without the pre-identified noisy channels and the rejected channels were interpolated using the spherical spline method (Perrin et al., 1989). An

average of 1.85 channels were rejected (SD = 1.09) in datasets from the active sessions and 1.78 (SD = 0.92) from the sham ones.

The continuous data was segmented in epochs with a total length of four seconds (i.e., 2000 ms prior and post-stimulus onset) centered in the target and cue. The epochs containing premature responses in the 1000ms post-cue onset were excluded. Moreover, due to the time window chosen for the cue-P3, only epochs with at least 800 ms of cue-target interval were selected. The epochs, in which the EEG signal surpassed ±150 μV at non-frontal electrodes were rejected. All the epochs were visually inspected and manually removed in the plot window if artifacts were present. At last, an independent component analysis (ICA) was performed to detect and remove muscle and eye movement artifacts using the ICLabel (Pion-Tonachini et al., 2019).

Seven participants were excluded from the EEG analysis due to: the saturation of the signal during the anodal tDCS session (4 participants), the number of EEG epochs in any condition was lower than 20 trials (2 participants), and one outlier with the difference of P3 amplitude between active and sham condition higher than 3 SD from the mean.

3.3.6.1. Event-Related Potentials. The ERPs analyzed were the cue-P3 and target-P3 in the Pz electrode. The target-P3 and cue-P3 epochs were baselined to the 200 ms pre-stimulus interval. The time-windows selected for each ERP were based on the study by Broyd and colleagues (2012), and the data was averaged following these time-windows: target-P3 was the average amplitude between 250 and 450 ms and the cue-P3 was between 350 and 600 ms.

3.3.6.2. Event-Related Oscillations. The ERO power was analyzed using the Event-Related Spectral Perturbation (ERSP) in EEGLAB function newtimef() (Delorme & Makeig, 2004). An additional analysis was performed regarding the ERO phase, specifically the magnitude of Inter-Trial Phase Coherence (ITPC) (see in Supplementary Materials). For that, a time-frequency decomposition using 3 cycle Morlet wavelets with a frequency resolution of 0.25Hz and temporal resolution of 8 ms was applied. The analyzed frequencies ranged from 1.5Hz to 20Hz for the cue and target epochs. The ERSP baseline normalization followed an unbiased single-trial baseline correction (i.e., full-epoch length single-trial corrections) to minimize the sensitivity to noisy trials (Grandchamp & Delorme, 2011). Therefore, at first, the average activity from the full-epoch length (i.e., μV) was subtracted to each epoch. Subsequently, the spectral power was averaged considering all the trials according to the baseline window (i.e., 1000 ms pre-cue or target). Finally, following the additive model (Grandchamp & Delorme, 2011; Gyurkovics et al., 2021), each epoch was normalized by the previously calculated power spectral average . The ERSP was averaged for delta (1.5 – 4 Hz) and theta (4 – 7 Hz) bands (Demiralp et al., 2001) following the same electrode (i.e., Pz) and time-windows (i.e., target-P3: 250 – 450 ms; cue-P3: 350 – 600 ms) from the ERP analysis (Broyd et al., 2012).

3.3.7. Statistical analysis

The analysis focused on the difference between the active and sham stimulation conditions. Therefore, paired t-tests were performed when the difference between both conditions followed the normal distribution, as assessed by the Shapiro-Wilk test. If there was no normal distribution, Wilcoxon signed rank test on paired samples were performed instead. Holm-Bonferroni correction was also performed in each section of the statistical analysis for multiple comparisons. At last, to probe the association between the number of premature responses and the average release time on the Baseline block, Pearson correlations were performed to evaluate the association between the reward/punishment system in the number of premature responses. The statistical analysis was performed in R (R Development Core Team, 2018; Version 4.0.3).

3.4. Results

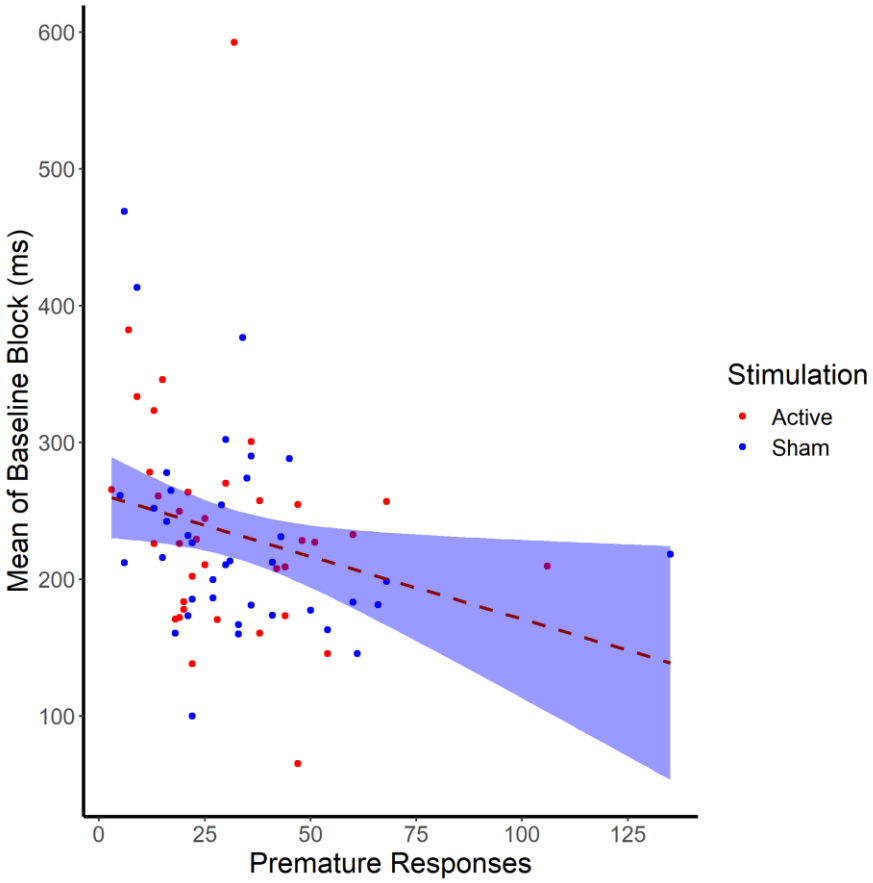
3.4.1. Behavioral analysis

3.4.1.1. Cued Premature Response Task. No significant effects of tDCS were observed in premature responses (t(35) = -0.79, p = 0.438), monetary amount earned (t(37) = 0.78, p = 0.438), and release time (t(37) = -0.87, p = 0.438) (Table 2). However, there was a significant correlation between the number of premature responses and the average release time for the baseline block (R = -0.25, p = 0.028), suggesting that the reward/punishment system was associated with the posterior number of premature responses (Figure 8).

3.4.1.2. Stop Signal Reaction Time Task. The t-tests did not reveal any significant effect, namely in terms of Go trials accuracy (t(30) = -2.11, p = 0.215), Go trials response time (t(30) = 1.09, p = 0.707), p(respond | signal) (t(30) = -0.38, p = 0.71), SSD (t(30) = -0.52, p = 0.71), or SSRT (t(30) = 0.73, p = 0.71) (Table 2).

Figure 8

Correlation between the number of premature responses and the average release time in the baseline block.



3.4.1.3. 27-item Monetary Choice Questionnaires. There was a significant effect in the Small *k* (V(39) = 199, *p* = 0.016), suggesting a higher *k* in small amounts of money for the active tDCS session, when comparing to sham. However, no other were differences due to tDCS were found for the 27-MCQ, namely Overall *k* (V(39) = 344, *p* = 0.12), Medium *k* (V(39) = 134, *p* = 0.12), and Large *k* (V(39) = 223, *p* = 0.12) (Table 2).

3.4.2. EEG analysis

3.4.2.1. Event-related Potentials. The Wilcoxon signed rank test revealed a significant difference between active and sham session for the target-P3 amplitude (V(32) = 106, *p* = 0.003) and the cue-P3 (V(32) = 142, *p* = 0.036). The target and cue-P3 amplitude was significantly lower in active session, when comparing to sham (Figure 9.B and 10.B; Table 3).

3.4.2.2. Event-related Oscillations. During the target-P3 time-window, the event-related synchronization in delta band during target-P3 was significantly higher during sham when comparing with active tDCS (t(32) = -2.29, *p* = 0.03) (Figure 9.C and 10.C). However no differences were found for theta band power (t(32) = -0.66, *p* = 0.805). Regarding the cue-P3 time-window, t-tests did not reveal any significant effect in terms of ERO, namely for delta (t(32) = -0.24, *p* = 0.847) and theta bands (t(32) = -0.19, *p* = 0.847) (Table 3).

Table 2

Descriptive (mean and SD) and inferential statistics (degrees of freedom, t or V, Hedges' g, p-value, and adjusted p-value) for each behavioral outcome

		tDCS		*df*	*t* / V*	*g*	*p-value*	*Adjusted p-value (BH)*
		Active	Sham					
Cued Premature Response Task	Premature Responses	27.78 (14.65)	29.75 (15.77)	35	-0.79	0.13	0.432	0.438
	Monetary Gain/Loss	41.82 (66.10)	31.50 (70.73)	37	0.78	0.15	0.438	0.438
	Release time *(ms)*	240.97 (34.19)	244.89 (42.14)	37	-0.87	0.1	0.388	0.438
Stop-Signal Reaction Time Task	Accuracy Go trials	97.1 (2)	96.2 (3)	30	2.11	0.35	0.043	0.215
	RT Go trials	456.49 (70.32)	443.34 (82.68)	30	1.09	0.17	0.283	0.707
	p(respond | signal)	44 (10)	45 (10)	30	-0.38	0.1	0.710	0.71
	SSD	207.71 (55.89)	212.25 (51.45)	30	-0.52	0.08	0.605	0.71
	SSRT	223.77 (46.38)	215.85 (61.63)	30	0.73	0.15	0.471	0.71
Monetary Choice Questionnaire - 27	Overall *k*	0.016 (0.02)	0.015 (0.03)	39	344*	0.04	0.061	0.12
	Small *k*	0.033 (0.04)	0.024 (0.04)	39	199*	0.23	0.004	0.016
	Medium *k*	0.016 (0.02)	0.015 (0.03)	39	134*	0.04	0.120	0.12
	Large *k*	0.012 (0.02)	0.010 (0.03)	39	223*	0.09	0.106	0.12

Figure 9

Grand average event-related target-P3 at Pz electrode (B) with topographical maps in the time-window of interest (represented in the gray area and dashed lines: 250 – 450 ms), and ERO results at Pz electrode (C) between both tDCS conditions.

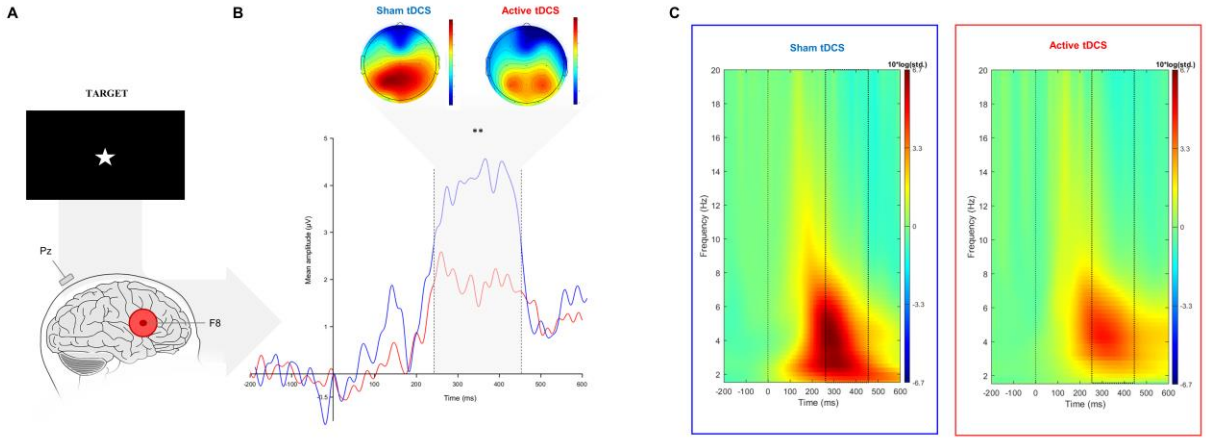


Figure 10

Grand average event-related cue-P3 at Pz electrode (B) with topographical maps in the time-window of interest (represented in the gray area and dashed lines: 350 – 600 ms), and ERO results at Pz electrode (C) between active and sham tDCS.

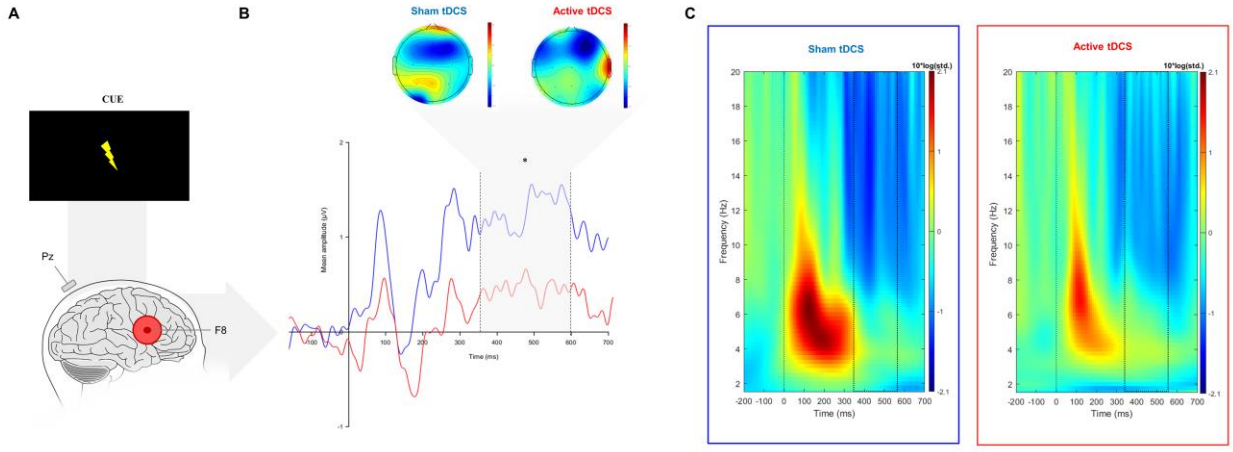


Table 3

Descriptive (mean and SD) and inferential statistics (degrees of freedom, t or V, Hedges' g, p-value, and adjusted p-value) for each EEG outcome

		tDCS		*df*	*t* / V*	*g*	*p-value*	*Adjusted p-value (BH)*
		Active	Sham					
Target-P3 (250 – 450 *ms*)	ERP (μV)	0.99 (5.33)	3.58 (3.14)	32	106*	0.59	0.001	0.003
	Delta (dB)	2.49 (3.18)	5.01 (6.51)	32	-2.29	0.49	0.015	0.03
	Theta (dB)	3.28 (3.44)	3.77 (4.72)	32	-0.66	0.12	0.805	0.805
Cue-P3 (300 – 650 *ms*)	ERP (μV)	0.38 (1.97)	1.39 (1.65)	32	142*	0.56	0.012	0.036
	Delta (dB)	-0.17 (1.06)	-0.11 (1.04)	32	-0.24	0.03	0.808	0.847
	Theta (dB)	-0.12 (0.91)	-0.07 (1.17)	32	-0.19	0.05	0.847	0.847

3.5. Discussion

The current study shows that tDCS over the right inferior frontal gyrus is able to modulate the P3 component and underlying oscillatory activity during a waiting impulsivity task (CPRT). Namely, active tDCS induced a decrease of target and cue-P3 amplitudes. Moreover, the reduction in target-P3 amplitude during active stimulation was combined with a simultaneous reduction in terms of delta power for the same time-window. Regarding behavioral analysis, there was a significantly higher k in the small amounts condition after active tDCS in comparison with sham, thus suggesting a preference for small immediate rewards instead of larger delayed in active tDCS session. However, no modulatory effects of tDCS over rIFG were found in terms of waiting impulsivity and inhibitory control measures (i.e., CPRT and SSRTT respectively).

3.5.1. Electrophysiological correlates

In the present study, anodal tDCS over the rIFG decreased the target-P3 amplitude and underlying oscillatory activity (namely delta power) during a waiting impulsivity task. However, there is a growing body of evidence suggesting that anodal tDCS over frontal areas, is able to increase the P3 amplitude in tasks involving attentional and working memory processes (Mendes et al., 2022). However, the effects of tDCS over frontal regions in the P3 amplitude during inhibitory control paradigms are mixed. While some studies report a decreased (Cunillera et al., 2016; Verveer et al., 2020) P3 amplitude following tDCS, others report an increased P3 amplitude following tDCS (Lapenta et al., 2014). Thus, the differential effects of tDCS on P3 may be related to the functional role of each cognitive task and its underlying neuronal substrates (Mendes et al., 2022).

Furthermore, these findings underpin the relationship between P3 and the delta/theta power at the same time-window observed in several cognitive tasks (Demiralp et al., 2001; Harper et al., 2014) (Inter-Trial Phase Coherence (ITPC) analysis and additional discussion about cue-P3 in Supplementary Materials). In fact, a recent study showed an enhancement of P3 amplitude during a visual oddball paradigm after the entrainment of delta/theta frequency bands through the application of transcranial Alternating Current Stimulation (tACS) (Dallmer-Zerbe et al., 2020). However, theta activity was not modulated concurrently to both cue and target-P3 amplitudes. Surprisingly, it was delta power that was modulated. This may show a potential inter-dependency between both electrophysiological markers and its importance during impulsive behaviors. For instance, a study showed decreased impulsive eating

behavior in rats through a closed-loop system that triggered a responsive neurostimulation in the nucleus accumbens, every time delta activity was excessively increased during reward anticipation (Wu et al., 2018). Likewise, delta power and P3 amplitude in parietal region are also enhanced during the anticipation of rewards when compared to neutral trials (Pornpattananangkul & Nusslock, 2016). This is of particular interest because a positive correlation between the cue-P3 amplitude and the activity in the ventral striatum (including nucleus accumbens) has been showed before (Pfabigan et al., 2014). It is important to highlight that the ventral striatum is a core structure for reward processing and impulsive choice (Pfabigan et al., 2014). Similarly, the neuronal activity observed on the left ventral striatum activity during an inhibitory control task was negatively correlated with the rIFG (Weafer et al., 2019). Thus, this might suggest that tDCS over the rIFG might not only reduce the P3 amplitude and delta power, but also a decrease in terms of ventral striatum activity.

Furthermore, the anticipatory (i.e., cue) and consummatory (i.e., target) P3 in tasks with monetary incentives are strongly related with reward processing. The target-P3 amplitude is greater when preceded by cues that predict either win or loss of monetary compensation, thus suggesting the involvement of the P3 component in reward and punishment processing (Broyd et al., 2012). The involvement of the cue-P3 in this reward and punishment processing is more mixed, as there are studies suggesting an cue-P3 enhancement after reward cues (Angus et al., 2017; Broyd et al., 2012; Pfabigan et al., 2014), loss cues (Vignapiano et al., 2016), or both (Novak & Foti, 2015). For ERO, cues that predict rewards elicited an enhancement of delta power in parietal areas (and cue-P3 amplitude) when compared to neutral cues (Pornpattananangkul & Nusslock, 2016). Although, most of previous studies did not show a significant relation between cue-delta activity and delay discounting, a recent study showed that the increase of evoked delta during a delay discounting task was associated with the choice for larger, however delayed rewards (Guleken et al., 2021). Therefore, the decrease of P3 amplitude and delta activity might indicate a modulation in the impulsive choice identified in our delay discounting results (but not found in CPRT and SSRTT).

3.5.2. Behavioral Outcomes

tDCS over rIFG did not impact the CPRT outcomes, namely, the number of premature responses, release time, and total earned money. These findings suggest that, although previous studies suggested the involvement of the rIFG in inhibitory control (Aron et al., 2014; Cunillera et al., 2016), the rIFG might not be critically involved in waiting impulsivity (Voon, 2014). Specifically, we expected an increase in tonic inhibitory process, which in turn, would result in less premature responses. Our results

did not support this hypothesis. Nonetheless, several reasons might be pointed out to explain the lack of tDCS effects in waiting impulsivity. First, tDCS over rIFG might show greater effect in reactive inhibition than on tonic inhibitory response involved in premature responses. Indeed, a recent meta-analysis exploring the effects of tDCS in both inhibitory processes showed a significantly larger effect size in reactive (e.g., SSRTT) than tonic inhibition (e.g., GNG task) (Schroeder et al., 2020). Therefore, a smaller effect of tDCS over the rIFG could be expected, due to the association between proactive stopping and premature responses (Voon, 2014). Additionally, the rIFG neural circuits involved in both reactive and proactive inhibition follow different pathways. An indirect pathway has been related to proactive inhibition, in which the rIFG connects with the globus pallidus through the dorsal striatum; while reactive inhibition is related with a hyperdirect pathway from the rIFG and pre-SMA to STN by-passing the striatum (Jahfari et al., 2011). Moreover, the increase in terms of premature responses was associated with lower connectivity within structures relevant for motor inhibition, such as the STN and ventral striatum (Morris et al., 2016). Therefore, differences in neural pathways might influence how tDCS affects the rIFG based on the network-dependent activity related to the CPRT (Fertonani & Miniussi, 2017). This is supported by the absence of transfer effects from the waiting impulsivity task to the motor inhibition performance evaluated by the SSRTT. Nonetheless, this hypothesis is not in line with previous literature, given that several studies targeting the same area showed an enhancement of proactive inhibitory processes (Cai et al., 2016; Campanella et al., 2018; Cunillera et al., 2014, 2016; Leite et al., 2018).

Another explanation is that tDCS might increase the proactive inhibition, but without any consequence in terms of premature responding. This dissociation was already observed in literature (Morris et al., 2016; Voon et al., 2014). Waiting and stopping have been suggested to represent distinct constructs within impulsivity(Dalley et al., 2011). They rely on different cortico-striatal connections between the DLPFC and ventral striatum for waiting processes and between the IFG and dorsal striatum for stopping (Dalley & Ersche, 2019; Dalley & Robbins, 2017). Furthermore, the differences between the reward and the punishment systems might undermine our ability to make any conclusions about the effects of tDCS on premature responses, or in other outcomes from CPRT as suggested by the Pearson correlation. Specifically, when it was harder to win money, participants incurred in more premature responses. Furthermore, as the baseline block was performed in the beginning of each section, the system of reward/punishment was also updated in each session (see Limitations and Future Directions).

Moreover, the preference for immediate and smaller rewards observed in the MCQ-27 might be explained by the activation of concurrent neuronal circuitries between waiting impulsive action and delay discounting (Dalley et al., 2011). This is of particular interest given that both processes depend on the

ventral striatum, even though they share different pathways. Specifically, waiting impulsivity relies on the connectivity between the STN with ventral striatum and subgenual cingulate cortex (Morris et al., 2016). Increased magnitudes of delayed rewards were associated with activation of mesolimbic pathways through the ventral striatum, medial prefrontal cortex, and posterior cingulate cortex (Ballard & Knutson, 2009). In line with this, studies have shown an effect of tDCS over the DLPFC in the dopamine release in the ventral striatum (Fonteneau et al., 2018; Fukai et al., 2019), which might explain the transfer effect of tDCS to the delay discounting assessment. Similarly, a neuroimaging study showed that the activity observed in the rIFG was negatively correlated with the activity found in the left ventral striatum (Weafer et al., 2019). Therefore, the application of anodal stimulation over rIFG might result in a lower activation in ventral striatum and consequently increase the k, as assessed by the MCQ-27. Nonetheless, to the best of our knowledge, this study was the first to test the effect of tDCS over rIFG in delay discounting.

In general, the tDCS transfer effects were only observed in terms of impulsive choice (i.e., delay discounting) that partially shares neuronal circuits with waiting impulsive action (Dalley et al., 2011). Therefore, the modulation of the neuronal circuits related with the waiting impulsivity is in line with the tDCS model of the network activity–dependent model (Fertonani & Miniussi, 2017). On the other hand, the lack of transfer effect in the inhibitory control task (i.e., SSRTT) might suggest the dissociation between waiting and stopping impulsivity (Robbins & Dalley, 2017) or between impulsive choice and action (Reynolds et al., 2006).

3.5.3. General Discussion

P3 amplitude has been shown to be significantly enhanced during reward anticipation (Broyd et al., 2012; Novak & Foti, 2015). In particular, P3 elicited during reward cues is positively correlated with the neuronal activation in the ventral striatum evaluated by neuroimaging studies (Pfabigan et al., 2014). Likewise, activity on the ventral striatum was found to be negatively correlated with activity detected on the rIFG during a response inhibition paradigm (Weafer et al., 2019). This cortico-striatal dynamics are of particular interest because lower k was associated with larger activity in the ventral striatum (Ballard & Knutson, 2009). This is in accordance with our EEG and behavioral results, given that tDCS over rIFG decreased the P3 amplitude and increased the choice for immediate rewards, which, in turn, have been associated with reduced activity on ventral striatum (Ballard & Knutson, 2009; Pfabigan et al., 2014). Therefore, there is a possibility that the cortico-striatal interactions might explain the modulation of P3 and small k after tDCS over rIFG.

3.5.4. Limitations and Future Directions

The reward/punishment system was estimated for each session and not for participant, which led to some differences in the mean RT and SD between sessions. This shift might misinterpret the effect of tDCS over the rIFG in the number of premature responses because the urge to prematurely release the button might be influenced by the reward/punishment system. Furthermore, this limitation might also influence the SSRTT because the differential behavioral training (i.e., due to the distinct reward/punishment system) might result in distinct plastic changes induced by tDCS (Fertonani & Miniussi, 2017). This limitation might have a strong impact in terms of behavioral performance and therefore "mask" a potential effect of tDCS in the CPRT outcomes. Additionally, the tDCS effect observed on P3 amplitude and evoked-delta power may not be robust enough to lead to behavioral changes. For instance, during WM paradigms, Cespón and colleagues (Cespón et al., 2017) showed that the increase of P3 amplitude after frontal tDCS was correlated with behavioral gains, while Breitling and colleagues (Breitling et al., 2020) only found an enhancement of P3 amplitude by frontal tDCS, without any behavioral effects. Likewise, similar findings of non-overlapping effects on markers and behavior were showed during functional MRI, in which significant tDCS-induced changes in the BOLD signal, were not accompanied by significant modulation of the behavior (Abellaneda-Pérez et al., 2020). Therefore, a larger sample size should be preferred to evaluate the neuromodulatory effects in CPRT, as well an individualized reward/punishment system per participant (and not per session).

Moreover, the inter-dependency between impulsive subtypes is still not clear within premature response paradigms (Voon, 2014). In fact, most of the evidence was observed from animal studies and does not always match the one found in human studies (Dalley et al., 2011). This highlights the importance of P3 as a potential surrogate marker for the cognitive processing of impulsivity, which can be used for several clinical conditions, such as, alcohol use disorder (Hamidovic & Wang, 2019) and attention-deficit/hyperactivity disorder (ADHD) (Kaiser et al., 2020). Therefore, tDCS and EEG studies are important to understand the neural circuitries underlying, as well as for the development of available interventions related to several clinical conditions (Lapenta et al., 2018).

In addition, applying tDCS to other relevant cortical areas should be addressed in future studies. For instance, tDCS studies aiming the DLPFC have shown modulatory effects in several processes of impulsivity such as delay discounting abilities (Brevet-Aeby et al., 2016). Furthermore, despite the fact that computer modeling of electrical current densities suggests that most of the induced current is over the rIFG, other regions such as the DLPFC may also be stimulated. Thus, future studies should use a premature response paradigm in order to ascertain the relationship between both impulsive sub

processes, as well as to understand specific contributions from different regions of the task related network, such as the DLPFC. On the other hand, other transcranial electrical stimulation techniques, such as tACS (Dallmer-Zerbe et al., 2020), or the application of closed-loop systems (Leite et al., 2017) in impulsive processes should be addressed in the future, given the strengthening of the association between P3 and oscillatory activity suggested by this study. However, although tDCS decreased both the P3 amplitude and delta power after the target, this was not observed after the cue. This finding might raise some questions about the association between cue-P3 and delta/theta power in the time-window suggested by Broyd and colleagues (Broyd et al., 2012). Therefore, cue-P3 should be re-examined according to its functional role and the related oscillatory power during impulsive paradigms.

Finally, in the current study, the cue did not predict the win or loss of money as in the studies previously mentioned (Angus et al., 2017; Broyd et al., 2012; Novak & Foti, 2015; Pfabigan et al., 2014), given that the reward or punishment could occur in each trial depending on the subject's performance (i.e., the only way of not winning/losing virtual money was the premature response). The difference between positive or negative reinforcement should be evaluated in the future to fully understand the dynamics of P3/delta and waiting impulsivity/reward processing.

3.6. Conclusion

Overall, the current study suggests the decrease of anticipatory and consummatory P3 amplitude and underlying oscillatory activity (i.e., decrease of delta power during target-P3) after tDCS over the rIFG. On the other hand, these variations were not accompanied with changes in terms of behavioral outcomes during waiting impulsivity, although a difference in delay discounting ability was detected between active and sham tDCS. These modulatory effects of tDCS are of particular interest due to the association between P3, delta power, and reward processing. Moreover, these findings suggest the usefulness of studying tDCS-induced effects on ERPs and EROs, as surrogate markers of cognitive processes.

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3.8. Supplementary Materials

Table SM.10

VAS of the side effects associated with tDCS in both sessions (Mean and SD).

		Active tDCS			Sham tDCS		
		Pre	Post	Difference	Pre	Post	Difference
Visual Analogue Scale (VAS)	Fatigue	2.55 (1.89)	3.24 (1.89)	0.73 (1.52)	3.13 (2.29)	3.71 (2.29)	0.53 (1.52)
	Anxiety	1.45 (1.53)	0.86 (1.5)	-0.65 (1.25)	1.71 (1.95)	1.13 (1.68)	-0.58 (1.59)
	Sadness	0.68 (1.08)	0.43 (0.88)	-0.25 (0.78)	0.89 (1.31)	0.63 (1.01)	-0.25 (0.71)
	Agitation	1.55 (1.89)	1.41 (2.06)	-0.18 (1.74)	1.97 (2.26)	1.76 (2.09)	-0.2 (1.76)
	Sleepiness	2.13 (2.08)	2.68 (2.46)	0.68 (2.23)	2.13 (2.63)	2.97 (2.65)	0.75 (2.53)
	Itching	0.21 (0.99)	1.7 (2.34)	1.38 (1.98)	0.13 (1.06)	0.79 (1.33)	0.48 (1.6)
	Headache	0.47 (1.15)	0.73 (1.26)	0.23 (0.77)	0.47 (0.88)	0.74 (1.2)	0.25 (0.74)
	Another type of pain	0.29 (1.01)	0.32 (0.86)	0.03 (0.62)	0.24 (0.97)	0.24 (0.86)	0 (0.32)
	Tingling	0 (0)	0.92 (1.89)	0.85 (1.87)	0.03 (0.16)	0.47 (1.11)	0.43 (1.11)
	Metallic taste	0 (0)	0.03 (0.16)	0.03 (0.16)	0.08 (0.47)	0.16 (0.48)	0.08 (0.42)

Table SM.11

Blinding of tDCS in both sessions.

Participant	Active Session		Sham Session	
	Guess	**Confidence**	**Guess**	**Confidence**
1	Active	1	NK	4
2	Active	3	Sham	3
3	Active	1	Active	1
4	Active	4	Sham	2
5	NK	-	Active	2
6	Active	3	NK	-
7	Active	1	Sham	1
8	Active	2	Active	2
9	Active	2	Missing Data	
10	Active	3	Sham	3
11	Active	3	NK	-
12	Sham	2	Sham	4
13	Sham	2	Active	2
14	Sham	3	Active	4
15	Active	4	Active	4
16	Active	3	Sham	4
17	Active	4	Active	4
18	Active	3	Active	3
19	Active	2	Active	2
20	Active	4	Sham	2
21	NK	-	Sham	1
22	NK	-	Active	2
23	Sham	2	Active	3
24	Sham	1	Active	2
25	Sham	2	Active	2
26	Sham	2	Sham	2
27	Active	2	Active	3
28	Sham	1	Sham	2
29	Sham	2	Active	3
30	Active	3	Sham	3
31	Sham	1	Sham	4
32	Active	1	Sham	2
33	Active	3	Active	3
34	Active	3	Active	3
35	NK	-	NK	-
36	NK	-	Sham	4
37	Active	4	Sham	3
38	Sham	1	Active	1
39	NK	-	NK	-
40	Active	2	Sham	2
Correct Guess	57.5		41.03	
Wrong Guess	27.5		46.15	
NK	15		12.82	

Inter-Trial Phase Coherence (ITPC)

The inter-trial phase coherence (ITPC) was calculated given that the delta activity during cue-P3 was not reduced during active tDCS, as opposed to the target-P3. The ITC of delta band during the time-window of cue-P3 was marginally significant higher in sham in comparison with active tDCS ($t(32) = -1.74$, $p = 0.092$; Figure S1). Likewise, this statistically significant effect in delta ITC was also observed in target-P3 ($t(32) = -2.34$, $p = 0.026$; Figure S2). This suggests that active tDCS increases the variability of the phase of delta activity within trials when compared to sham. However, the relation between tDCS and ITC is still not clear, one study has shown a synchronization of theta phase after frontal tDCS (Reinhart et al., 2015), whilst another study did not show any tDCS modulation in ITPC (Miyagishi et al., 2018). The literature is scarce about tDCS effects in ITC, nonetheless, the current findings are in line with the notion that the power and phase of EROs are distinct physiological processes (Burke et al., 2013; Buzsáki & Draguhn, 2004). Specifically, the decrease of cue-P3 amplitude during tDCS might be explained by higher variability in the delta phase caused by tDCS, instead of the decrease in the delta evoked-power (together with phase variability) as occurred in target-P3.

Figure SM.14

The ITPC results of cue-P3 at Pz electrode in the time-window of interest (dashed lines: 350 – 600 ms) between both tDCS conditions.

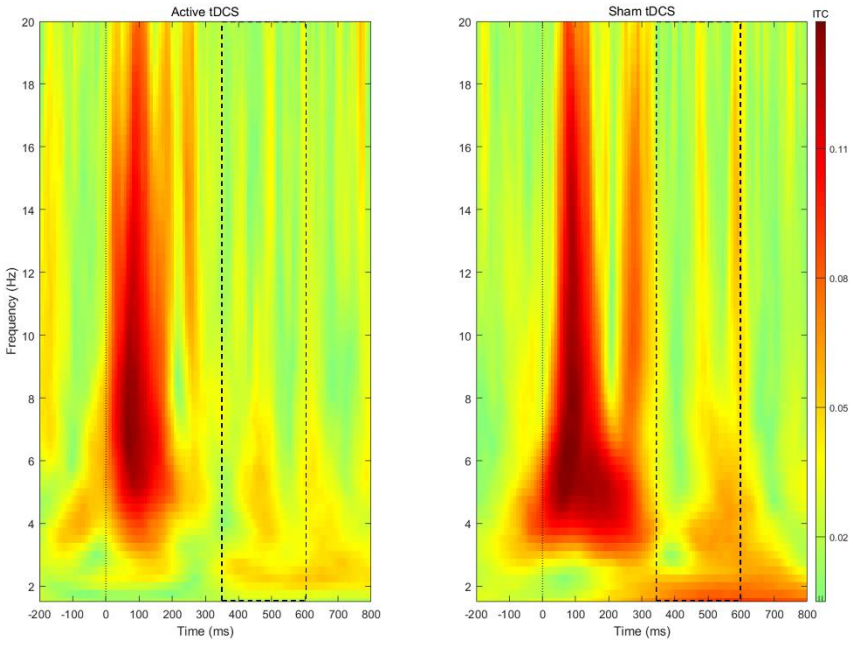
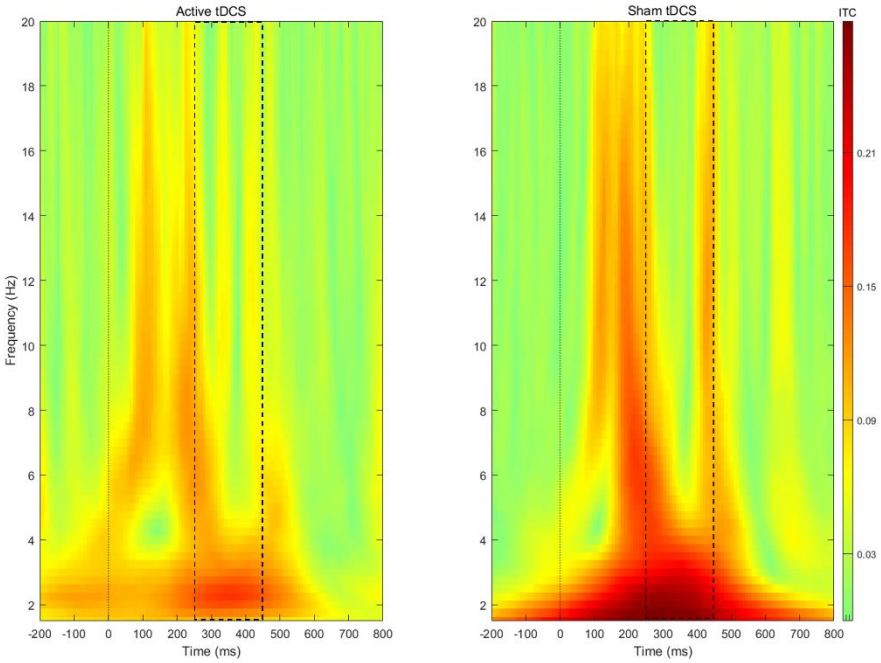


Figure SM.15

The ITPC results of target-P3 at Pz electrode in the time-window of interest (dashed lines: 250 – 450 ms) between both tDCS conditions.



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CHAPTER 4

Tailoring transcranial alternating current stimulation based on endogenous event-related P3 to modulate premature responses: a feasibility study

4.1 Abstract

Background: Transcranial Alternating Current Stimulation (tACS) can be used to enhance endogenous oscillatory activity during sensory and cognitive processes. Likewise, tACS can modulate event-related potentials (ERP) given the temporal overlap with event-related oscillations (ERO). For example, target-P3 elicited during a premature response paradigm is accompanied with an increase in evoked-delta activity. Therefore, tailored tACS might be an important tool to modulate transient electrophysiological activity.

Objective: The aim of this preliminary study was to test the feasibility of individualizing tACS based on individual P3 (latency and frequency) elicited during a cued premature response task. Therefore, tACS frequency was individualized to match target-P3 ERO estimated for each subject. Likewise, the display of the target in the paradigm was temporally adjusted according to the tACS phase and target-P3 latency.

Methods: Twelve healthy volunteers received two sessions of tACS while performing a premature response task. For that, the target-P3 latency and ERO were calculated in a baseline block during the first session to allow a posterior synchronization between the tACS and the endogenous oscillatory activity. The cue and target-P3 amplitudes, delta/theta ERO, and power spectral density (PSD) were evaluated pre and post-tACS blocks.

Results: tACS session significantly increased target-P3 amplitude in comparison with sham session. However, the delta ERO was not significantly modulated by tACS during target-P3. Contrariwise, the evoked-delta during cue-P3 was decreased after tACS. At last, no significant effects were detected in PSD and behavioral outcomes.

Conclusion: Our findings highlight the importance of phase synchronization between tACS parameters and the endogenous oscillatory activity. Specifically, the synchronization between tACS and target-P3 revealed an expected enhancement, whilst a potential mismatch between tACS and cue-P3 might explain the opposite effect. Therefore, the prior identification of P3 and ERO in tACS is highlighted, which can have translational therapeutic implications in clinical populations with alterations in P3.

Keywords: Waiting Impulsivity; Premature responses; tACS; P3; Delta; Theta.

4.2. Introduction

Transcranial Alternating Current Stimulation (tACS) is a non-invasive method that applies a weak electrical current in the scalp at a certain frequency and intensity through two or more electrodes (Herrmann et al., 2013). The sinusoidal current applied over the scalp allows the modulations of endogenous oscillatory activity (Helfrich et al., 2014). The neuromodulatory effects have been observed in vitro (Reato et al., 2010) and in vivo studies (Ali et al., 2013; Johnson et al., 2020). Likewise, recent clinical trials have suggested that repetitive sessions of tACS can induce oscillatory changes that lasts for few weeks (Ahn et al., 2019; Alexander et al., 2019). Therefore, tACS has been proposed as a potential therapeutic tool to modulate abnormal cortical oscillations in clinical conditions (Frohlich & Riddle, 2021). Likewise, tACS has been proposed to modulate event-related potentials (ERP) through the entrainment of the related oscillatory activity. ERP components are observed in parallel with the enhancement of oscillatory activity in a phenomenon called event-related oscillations (ERO) (Herrmann et al., 2014). The difference between both is that ERPs are a neuronal representation in the time domains, whilst the EROs are considered in the time-frequency domain.

One of the most studied ERPs is the P3 component elicited at centroparietal regions and with a peak between 250 – 600 ms after a relevant stimulus (Polich, 2007). The P3 elicited during oddball paradigm is coupled with an increase in delta (0.5 – 4 Hz) and theta (4 – 7 Hz) activity in the same spatial and temporal features of P3 signal (Güntekin & Başar, 2016). Likewise, a recent study has shown the same concomitant activity after a target in a premature response paradigm, suggesting that the relation between delta activity and P3 is present in different cognitive processing (Mendes, Galdo-Álvarez, et al., 2022) . The ERPs elicited in premature response paradigms are important to understand the mechanisms within waiting impulsivity, which is a crucial feature in addiction and Attention-Deficit Hyperactivity Disorder (ADHD) (Dalley & Ersche, 2019; Van Dessel et al., 2019). In particular, target-P3 is elicited after a relevant-stimulus that will result in a reward/punishment (Mendes, Galdo-Álvarez, et al., 2022). On the other hand, cue-P3 is observed after a cue that precedes the target, which is understood to represent the motivational attention towards the upcoming relevant-stimulus (i.e., target) (Broyd et al., 2012). Therefore, it is thought that the modulation of these ERPs is combined with changes in the impulsive processing.

A recent study demonstrated a modulatory effect of tDCS in target and cue-P3 during a premature response paradigm, although no differences were observed in the behavioral outcomes (Mendes, Galdo-Álvarez, et al., 2022). Regarding other cognitive paradigms, a meta-analysis showed that transcranial

Direct Current Stimulation (tDCS) applied in frontal areas is capable of increasing P3 amplitude in parietal sites during oddball and working memory tasks (Mendes, Pacheco-Barrios, et al., 2022). Nonetheless, the effects of tACS on P3 amplitude are still not clear. One between-subject study did not detect significant effects in P3 amplitude and ERO during an oddball paradigm even though the authors tailored the tACS parameters to the oscillatory activity associated to the P3 of each subject (more information about this procedure in Methods) (Popp et al., 2019). On the other hand, another study using a within-subject design in an ADHD sample revealed an increase in P3 amplitude coupled with behavioral improvements after tailored tACS (Dallmer-Zerbe et al., 2020). However, the previous study did not observe significant modulation in the ERO associated with P3 after tACS. Furthermore, a recent study tested the delta and theta tACS effects on P3 amplitude during a decision-making task, although the stimulation parameters were not tuned with ERO and P3 latency from each subject (Wischnewski et al., 2021). The authors observed a significant decrease in P3a and P3b amplitude after theta tACS when compared to sham (Wischnewski et al., 2021). Likewise, another study testing different montages of theta tACS in resting theta power and P3 during working memory has shown inconsistent findings (Pahor & Jaušovec, 2018). The theta tACS applied bilaterally in parietal region and at left fronto-parietal areas resulted in a decrease of resting-state theta band power, whilst no differences were observed in the P3 amplitude. On the other hand, the right fronto-parietal theta tACS did not affect theta power but increased the P3 amplitude during the working memory task (Pahor & Jaušovec, 2018). This study did not match tACS parameters with the endogenous activity and did not test delta tACS as well. Thus, these findings emphasize the need of tuning tACS parameters with the ongoing EEG signal in order to avoid potential anti-phasic effects.

Therefore, the current study evaluates the feasibility and efficacy of tailored-tACS in increasing target-P3 amplitude during a premature response paradigm. Thus, we implemented a tACS-EEG setup tested during an oddball paradigm (Dallmer-Zerbe et al., 2020; Popp et al., 2019), which the ERO associated to the P3 is assessed for each subject in order to apply a tailored-tACS. The match between tACS and the endogenous neuronal activity is extremely important to achieve an optimal modulation of oscillatory activity (Riddle & Frohlich, 2021). Nonetheless, tACS usually aims an entrainment of oscillatory activity with longer duration, however, in this study, it is aimed the entrainment of a transient oscillatory activity. For that, the waiting impulsivity task was adjusted to ensure the overlap between the peak of the sinusoidal tACS and the target-P3 peak. It is hypothesized that tACS will entrain the endogenous brain oscillations associated with P3 and consequently increase the P3 amplitude. Moreover, we do not expect significant changes in ERO of cue-P3 or in the spectral analysis, given that tACS will be synchronized only

with target-P3 ERO. At last, it is expected that the increase of target-P3 amplitude will be coupled with improvements in the waiting impulsivity paradigm.

4.3. Materials & Methods

4.3.1. Participants

Twelve healthy volunteers (7 females; mean age: 25.67 ± 1.97) participated in the study and signed the informed consent before their enrollment in the study. The participants were right-handed, without any history of neurological and psychiatric disorders. Moreover, the study was approved by the local ethics committee (CEICVS 057/2021) and was performed in conformity with the Declaration of Helsinki.

4.3.2. Study design

The study was performed in two sessions with distinct tACS conditions, namely active and sham stimulation. The order of the stimulations was counterbalanced and randomly assigned to the participants. Sessions were separated by at least 48 hours to avoid carryover effects. In the first session, self-report questionnaires were administered to evaluate handedness, impulsive traits, and clinical symptomatology (see Table SM.12 in Supplementary Materials). Additionally, in the first session participants performed a baseline block of the CPRT concomitant with EEG data collection to assess the P3 latency and the ERO associated with P3. Afterwards, three blocks of the waiting impulsivity task were performed, in which the first and the third ones were performed only with EEG (i.e., pre and post-tACS), whilst the second block was performed concomitantly with the tACS (see Figure 11.A). The second session did not include the baseline block; thus, participants only performed the last three experimental blocks (i.e., pre, during, post-tACS). At the end of each session, participants completed a blinding questionnaire to probe for performance bias (see Table SM.13 in Supplementary Materials).

4.3.3. Cued Premature Response Task

The Cued Premature Response Task (CPRT) was programed and executed in E-Prime 3 software (Psychology Software Tools, Pittsburgh, PA) based on the previous study. The baseline block performed only in the first session comprised 10 training trials and 100 experimental trials. Moreover, the following three experimental blocks also comprised 100 experimental trials each. The total duration of each block was approximately 10 minutes, totaling 40 minutes in the first session (i.e., 30 minutes in second session), including several pauses between the experimental blocks. Participants were asked to press a

button in the E-Prime Chronos response box to begin the experiment, and to release it when the target was displayed. The target was always preceded by a cue, which informed the participant that the target is about to be displayed. Participants were instructed to release the key as fast as possible after the target display, in order to favor speedier responses instead of slower responses. In the first and last blocks (i.e., pre and post-tACS), the interval of time between the start of the trial and the cue was a random value between 1000 and 1500 ms, while the interval between the cue and target was a random value between 500 and 2500 ms (see Figure 11.B). On the other hand, the block of CPRT during tACS had a "wait" adjustment dependent on the stimulation parameters that were individually estimated in the EEG online analysis of the baseline block (see Electrophysiological acquisition and data analysis section) (Dallmer-Zerbe et al., 2020). This is of particular interest given that we pretended to entrain oscillatory activity that occur in a specific period after the target, thus, the tACS must match its temporal characteristics (Jones, 2016). In this block, the interval between cue and target was randomly selected between 300 and 2300 ms plus the "waiting" period (see Figure 11.C) to ensure the synchronization between the peak of tACS and the target P3 latency (see Figure S1 and S2 in Supplementary Materials for some examples). This synchronization was controlled in MATLAB (Mathwoks, MA, USA) with the MatNIC package to trigger stimulation by the Starstim R20 (Neuroelectrics, Barcelona, Spain). Each time the stimulation was started, MATLAB sent a UDP trigger to Python console, which, for its turn, sent repetitive TCP triggers to E-Prime 3 every time the tACS was in the phase 0.

4.3.4. Transcranial Alternating Current Stimulation

Both tACS conditions were applied in distinct sessions through the Starstim R20 (Neuroelectrics, Barcelona, Spain). The 25 cm2 round saline-soaked electrode sponges (~radius of 3 cm, current density: 0.08 mA/cm2) were placed in two clusters of two electrodes each, specifically in the parietal areas (i.e., P3 and P4) and supraorbital area (i.e., Fp1 and Fp2) (see Figure 1.D). The clusters delivered alternatingly anodal and cathodal stimulation to ensure the sinusoidal stimulation (Popp et al., 2019). The active tACS delivered a 2 mA (peak-to-peak) electric current for 10 min (with 15 second of ramp up and ramp down) during the CPRT performance. The tACS frequency was individualized for each participant in the range of delta and theta band (1.5 – 7 Hz) according to the ERO detected in the baseline block (check Table S3 in Supplementary materials for individual information). The mean of the stimulation frequency was 3.29 Hz (SD = 1.9 Hz) in line with the previous studies with similar methodology (Dallmer-Zerbe et al., 2020). Sham procedure only delivered 15 seconds of tACS (with 15 seconds of ramp up and ramp down: 45 seconds in total) at the beginning and at the end of the 10 minutes.

4.3.5. Electrophysiological acquisition and data analysis

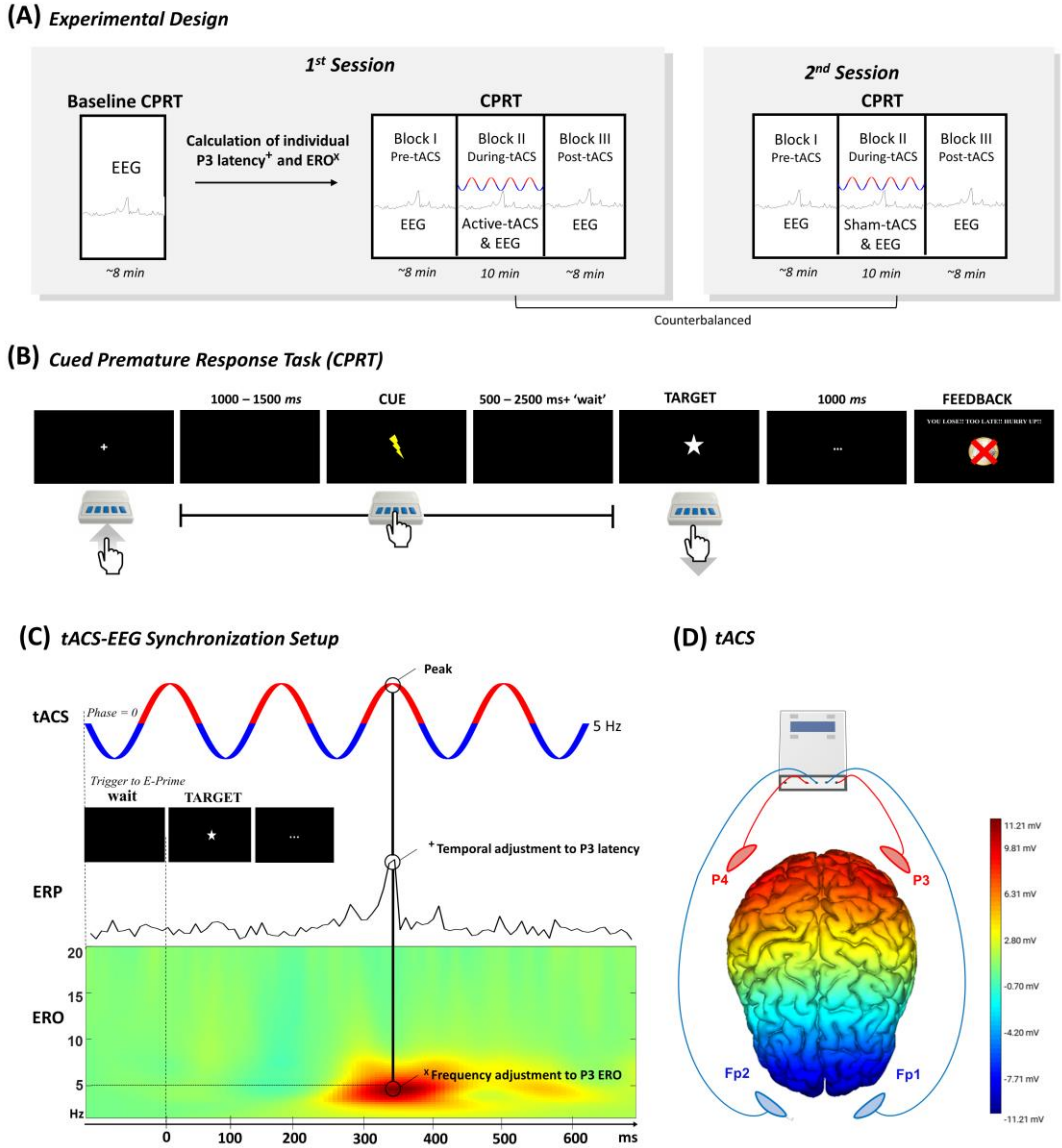
The EEG data collection was performed with the Starstim R20 (Neuroelectrics, Barcelona, Spain). The electrophysiological data were sampled at a rate of 500Hz and posteriorly analyzed in EEGLAB toolbox (Delorme & Makeig, 2004) in two specific times: online and offline analysis. The online analysis aimed the baseline block of the first session, whilst the offline comprehended the remaining EEG data, namely the pre and post-tACS blocks from both sessions.

The analysis started with filtering the EEG data between 0.5 and 40 Hz using a FIR filter and the line noise (i.e., 50 Hz) using a notch filter. The data were posteriorly re-referenced to the average. At next, the continuous data were epoched around the cue and the target with a total duration of four seconds (i.e., 2000 ms before and after the stimulus). Likewise, it was performed a baseline correction considering the 200 ms prior to the target-onset. The cue-epochs with a cue-target interval lower than 800 ms or with a premature response in the initial 1000 ms were removed from the analysis. Moreover, epochs exceeding the ±100 μV in the Cz or Pz during the time-window of interest (i.e., between -200 ms and 600 ms) were also removed. At last, a visual inspection was also performed to detect potential artifacts not removed before. The rejection rate of the epochs was approximately 10% following the recommendations by Delorme and colleagues (2007) (see Table SM.15 in Supplementary Materials).

The offline data analysis was similar to the online plus the artifact removal through the ICA. This step was only performed in the offline analysis given the required computational time and comprehensive examination of each component. The grand average ERPs in the figures were filtered using a 12 Hz low-pass filter. One participant was removed from the data analysis because the post-tACS file of the sham session was corrupted.

Figure 11

Overview of the study design with two distinct sessions (A) and the experimental task to evaluate premature responses (B). The temporal adjustment synchronizing the P3 latency calculated in the baseline block with tACS peak was accomplished with the inclusion of a tailored 'waiting' period before the display of the target in the CPRT (C). On the other hand, the frequency of tACS was calculated based on the P3 ERO, which was the frequency with the maximum dB value within the P3 time-window (C). At last, tACS electrodes were placed in two electrode clusters (i.e., P3 and P4 & Fp1 and Fp2) that were interchangeably anode and cathodes. The electric field map computed in the NIC 2.0 software (Neuroelectrics, Barcelona, Spain) represents the voltage topography distribution when P3 and P4 electrodes deliver cathodal stimulation (D).electrodes deliver anodal stimulation and Fp1 and Fp2



4.3.5.1. Event-Related Potential: P3. The online analysis calculated the target-P3 latency considering the peak on the time window between 250 and 600 ms in the Pz electrode, based in the previous study (Mendes, Galdo-Álvarez, et al., 2022). The target-P3 latency was estimated to allow the conclusion of the online analysis (see ERO subsection). The offline analysis focused on cue and target-P3 amplitude in Pz. The P3 amplitude was calculated with previous time-windows used in literature (Broyd et al., 2012; Mendes, Galdo-Álvarez, et al., 2022), specifically the average amplitude between 250 and 450 ms for the target-P3 and between 350 and 600 ms for the cue-P3.

4.3.5.2. Event-Related Oscillations. The ERO analysis was performed with the EEGLAB function *newtimef()* (Delorme & Makeig, 2004). Specifically, 3 cycle Morlet wavelets were used for the time-frequency decomposition (i.e., frequency resolution = 0.25 Hz; temporal resolution = 8 ms). The baseline normalization was chosen considering the additive model through an unbiased single-trial normalization method (Grandchamp & Delorme, 2011). The normalization method subtracted firstly each epoch by the average activity of the whole epoch. Then, the dB conversion was performed in each epoch considering the baseline period of 1000 ms before the target-onset. In the online analysis, based on Dallmer-Zerbe and colleagues (Dallmer-Zerbe et al., 2020), the dB from the Pz electrode was averaged around ±150 ms the P3 latency for each participants and the maximum value was identified as the P3 ERO and consequently the stimulation frequency to apply (Broyd et al., 2012) (see Figure 11.C). On the other hand, in the offline analysis, the delta (1.5 – 4 Hz) and theta (4 – 7 Hz) bands were averaged in Pz and time-window of cue and target-P3 mentioned before.

4.3.5.3. Power Spectral Analysis. The power spectral density (PSD) was analyzed using the function *spectopo()* from EEGLAB toolbox using the fast Fourier Transform (FFT) (Delorme & Makeig, 2004). The delta and theta band power were estimated for Pz through the Welch method with a Hamming window (i.e., window length: 500 points; FFT length: 500 points). Moreover, it was set an overlap of 20% of the sampling rate (i.e., 100 points) to control the leakage effect caused by epoching. The PSD was performed independently for cue and target-P3 epochs.

4.3.5.4. Additional Analysis. We also performed an EEG analysis tailored to each participant based on Dallmer-Zerbe and colleagues (Dallmer-Zerbe et al., 2020). Specifically, three analyses were done: (i) adjusting to the P3 latency of each participant, (ii) adjusting to the tACS frequency applied to each participant, and (iii) adjusting simultaneously to the P3 latency and tACS frequency. Regarding the temporal adjustment (i), it was analyzed the ERP and ERO with the same procedures, excepting that the time-windows analyzed was the average around ±150 ms to the P3 latency calculated in the online analysis. The temporal adjustment analysis was only performed in target-P3 epochs given that the P3 latency was estimated on target-P3. Likewise, the frequency adjustment (ii) followed the same procedures in ERO and PSD analysis, but, instead of averaging dB in delta and theta bands, it was averaged the dB around ±3 Hz to the tACS frequency of each participant. At last, the adjustment to the time-window and frequency (iii) was a combination of both analyses explained before.

4.3.6. Sample size calculation

The sample size calculation was based in an effect estimate of 1.2 observed in the preliminary within-subject study testing tACS in P3 amplitude (Dallmer-Zerbe et al., 2020). Therefore, the sample size was estimated to find a within-group effect between active and sham tACS in P3 amplitude with a statistical power of 95% and alpha level of 5%. A total of 10 subjects were calculated, but we added 2 subjects to the estimation considering potential differences in relation with the aforementioned study. Thus, the final sample size for this feasibility study was 12 participants. The calculation was performed in G*Power version 3.1.9.7 (Faul et al., 2009).

4.3.7. Statistical analysis

The absolute change was calculated between pre and post-tACS for each session (i.e., active and sham). For that, the values that were observed in the block before tACS were subtracted from the values obtained after tACS. This estimation was performed in every EEG and behavioral outcome. We followed a similar procedure as Dallmer-Zerbe and colleagues (Dallmer-Zerbe et al., 2020). We chose the absolute change because relative change may lead to huge variability when there are very low values in the pre-tACS block. The absolute change observed in active and sham session were tested using paired t-tests if the difference between both tACS conditions followed normality according to the Shapiro-Wilk test. Otherwise, non-parametric analysis was performed, specifically the Wilcoxon signed rank test. The statistics were analyzed in R (R Development Core Team, 2018; R Version 4.0.3).

4.4. Results

4.4.1. Event-related Potentials: P3

The nonparametric analysis revealed a significant difference between the absolute change between active and sham session in target-P3 amplitude (V(10) = 63, p = 0.005), whilst no significant effect were detected in cue-P3 (t(10) = -0.11, p = 0.912). In the additional analysis considering the temporal adjustment around P3 latency to each participant (i), it was also revealed a significant effect in target-P3 amplitude between active and sham tACS (t(10) = 2.84, p = 0.017). The absolute change of target-P3 amplitude was higher in the active session in comparison with sham in both analysis (Figure 12.B; Table 4).

4.4.2. Event-related Oscillations

No significant effects between both sessions were observed in evoked-delta (t(10) = 1.55, p = 0.153) and evoked-theta (t(10) = 0.26, p = 0.797) during target-P3 (Figure 12.C; Table 4). On the other hand, paired t-tests revealed a marginal significant effect in delta activity during cue-P3 (t(10) = -2.06, p = 0.067), but no significant effect was observed in theta (t(10) = -1.54, p = 0.154) (Figure 13.C; Table 5). Furthermore, the additional analysis of the temporal adjustment (i) did not reveal significant differences in delta (t(10) = 1.59, p = 0.142) and in theta (t(10) = 0.79, p = 0.448) between sessions in target-P3. In the frequency adjustment analysis (ii), no significant differences were detected in the adjusted ERO from target-P3 (t(10) = 0.98, p = 0.349), but, it was revealed a significant effect between both tACS session in the adjusted ERO from cue-P3 (t(10) = -2.07, p = 0.032). The active tACS session showed a significant decrease in the adjusted ERO in comparison with sham. At last, the temporal and frequency analysis performed in target-P3 (iii) did not reveal a significant effect on adjusted ERO between active and sham (t(10) = 1.11, p = 0.294).

4.4.3. Power Spectral Analysis

No differences were found in the absolute change between active and sham session in the delta (V(10) = 37, p = 0.765) and theta band (V(10) = 45, p = 0.32) in target-P3 epochs (Figure 12.D; Table 4). Likewise, no significant differences in spectral power of cue-P3 epochs for delta (t(10) = 0.04, p = 0.972) and theta (t(10) = 0.46, p = 0.658) (Figure 13.D; Table 5) were found. At last, regarding the frequency adjustment analysis (ii), there weren´t also significant differences between both sessions in target-P3 (t(10) = 0.73, p = 0.484) and in cue-P3 epochs (t(10) = 0.61, p = 0.556).

Figure 12

Results from EEG analysis of target-P3 at Pz electrode (A), namely the event-related potentials (B) in the time-window of interest (represented in the gray area and dashed lines: 250 – 450 ms), event-related oscillations (C), and power spectral density (D) in Pre and Post-tACS block in both sessions.

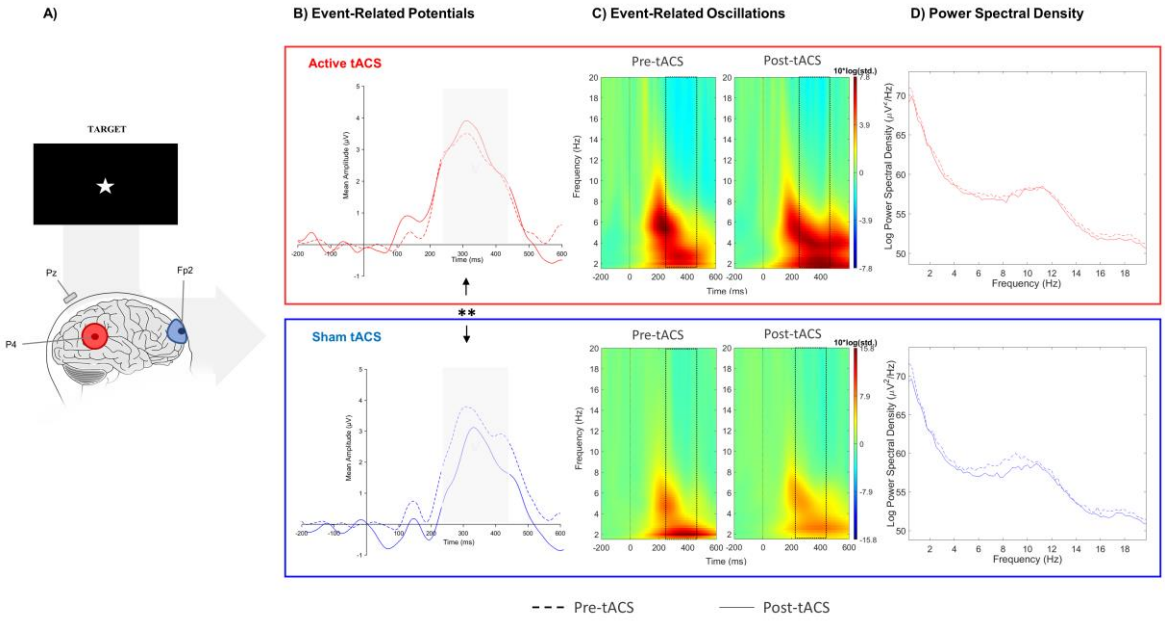


Figure 13

Results from EEG analysis of cue-P3 at Pz electrode (A), namely the event-related potentials (B) in the time-window of interest (represented in the gray area and dashed lines: 350 – 600 ms), event-related oscillations (C), and power spectral density (D) in Pre and Post-tACS block in both sessions.

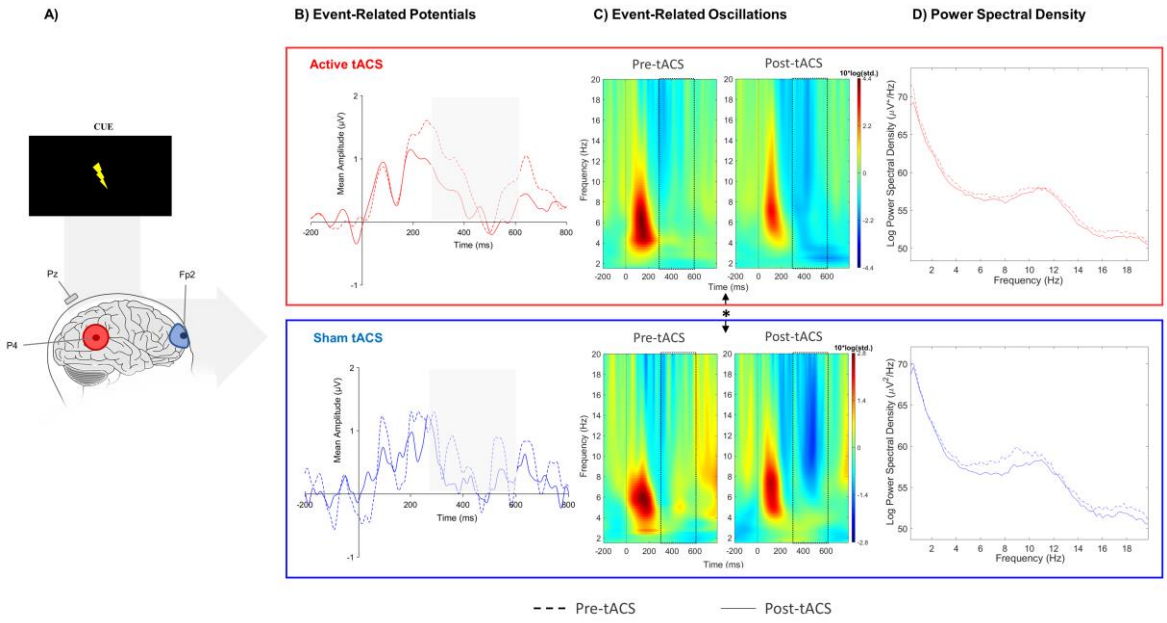


Table 4- *Descriptive (mean and SD) and inferential statistics in ERP, ERO, and PSD analysis for target-P3*

		Active tDCS			Sham tDCS			*t* / V	*p-value*
		Pre	Post	Absolute Change	Pre	Post	Abs. Change		
Target-P3 (250 – 450 *ms*)	ERP (μV)	3.45 (1.63)	3.49 (1.15)	0.04 (1.02)	3.96 (1.17)	2.83 (0.98)	-1.14 (0.96)	63	0.005
	Delta (dB)	5.31 (4.99)	6.62 (3.82)	1.31 (4.16)	8.29 (9.66)	6.26 (3.99)	-2.03 (9.20)	1.55	0.153
	Theta (dB)	3.75 (3.75)	4.58 (3.69)	0.83 (3.61)	3.96 (5.73)	4.47 (4.04)	0.50 (5.53)	0.26	0.797
	Adjusted Frequency (dB)	4.80 (4.01)	5.76 (3.25)	0.96 (3.01)	6.86 (8.48)	5.86 (3.59)	-1.01 (8.14)	0.98	0.349
Target-P3 (Adjusted time: ±150ms around P3 latency)	ERP (μV)	2.86 (1.18)	2.78 (1.16)	-0.09 (0.86)	3.11 (0.89)	2.08 (0.64)	-1.03 (0.95)	2.84	0.017
	Delta (dB)	5.08 (4.56)	6.22 (3.28)	1.14 (3.66)	7.71 (8.58)	5.64 (3.73)	-2.06 (7.75)	1.59	0.142
	Theta (dB)	4.02 (4.01)	5.22 (4.17)	1.20 (3.57)	4.35 (5.76)	4.28 (3.57)	-0.07 (5.44)	0.79	0.448
	Adjusted Frequency (dB)	4.85 (3.60)	6.01 (3.27)	1.16 (3.17)	6.71 (7.77)	5.64 (3.73)	-1.07 (7.33)	1.11	0.294
Spectral Analysis	Delta (dB)	7.62 (2.41)	7.08 (2.34)	-0.54 (2.21)	7.43 (2.27)	6.81 (2.59)	-0.62 (2.27)	37	0.765
	Theta (dB)	0.75 (2.17)	0.43 (1.83)	-0.31 (1.48)	1.24 (3.02)	0.42 (2.21)	-0.82 (2.82)	45	0.32
	Adjusted Frequency (dB)	5.09 (3.53)	4.72 (3.84)	-0.39 (1.71)	5.54 (4.26)	4.22 (4.08)	-1.32 (3.25)	0.73	0.484

Note. Absolute change is the subtraction of Post – Pre

Table 5

Descriptive (mean and SD) and inferential statistics in ERP, ERO, and PSD analysis for cue-P3

		Active tDCS			Sham tDCS			*t* / V	*p-value*
		Pre	Post	Absolute Change	Pre	Post	Abs. Change		
Cue-P3 (350 – 600 *ms*)	ERP (μV)	0.40 (0.58)	0.19 (1.41)	-0.20 (1.52)	0.43 (1.05)	0.29 (0.69)	-0.14 (1.28)	-0.11	0.912
	Delta (dB)	-0.57 (1.19)	-1.19 (1.33)	-0.62 (1.65)	-0.31 (0.95)	0.02 (0.81)	0.33 (1.36)	-2.06	0.067
	Theta (dB)	-0.29 (0.91)	-1.20 (0.63)	-0.91 (0.75)	0.18 (0.93)	-0.34 (1.18)	-0.51 (1.20)	-1.54	0.154
	Adjusted Frequency (dB)	-0.48 (1.13)	-1.05 (0.79)	-0.57 (1.20)	-0.19 (0.82)	-0.14 (0.96)	0.06 (1.31)	-2.07	0.032
Spectral Analysis	Delta (dB)	7.47 (2.76)	7.08 (2.34)	-0.39 (2.50)	7.26 (2.14)	6.81 (2.59)	-0.44 (2.22)	0.04	0.972
	Theta (dB)	0.39 (2.48)	0.43 (1.83)	0.04 (1.79)	0.94 (2.77)	0.42 (2.21)	-0.51 (2.53)	0.46	0.658
	Adjusted Frequency (dB)	4.94 (3.87)	4.72 (4.84)	-0.22 (1.93)	5.26 (4.02)	4.22 (4.08)	-1.04 (3.08)	0.61	0.556

Note. Absolute change is the subtraction of Post – Pre

4.4.4. Behavioral analysis

The paired t-test did not reveal statistically significant effects in the number of premature responses between the absolute change in the active and sham session ($t(11) = -0.51$, $p = 0.615$). Likewise, nonparametric analysis also did not show significant effects in the absolute change of total money earned/loss ($V(11) = 41$, $p = 0.505$) and release time ($V(11) = 41$, $p = 0.91$) between both sessions (Table 6).

4.5. Discussion

This preliminary study tested the feasibility of individualizing tACS based on the individual P3 (latency and frequency) in order to match tACS to the target-P3 ERO estimated for each subject during a premature response paradigm. Specifically, the tailored delta/theta tACS counteracted the expected decrease of target-P3 amplitude along the session (Polich, 1989). In the sham session the amplitude decreased in the post-tACS block, whilst in the active session this decrease was not observed. Nonetheless, it no tACS effects were detected in the ERO analysis during the target-P3 time-window. This is of particular interest given that a decrease of the ERO activity in the active session during cue-P3 was observed. Furthermore, tACS neither result in a broader oscillatory activity modulation as suggested by PSD analysis, nor impacted significantly any behavioral outcome, as assessed in CPRT.

Table 6

Descriptive and inferential statistics for CPRT outcomes

		Active tDCS				Sham tDCS				*t* / V	*p-value*
		Pre	During	Post	Abs. Change	Pre	During	Post	Abs. Change		
Cued Premature Response Task	Premature Responses	17 (11.21)	13.5 (8.94)	16 (10.88)	-1 (7.64)	16.67 (10.96)	15.42 (10.5)	17 (11.39)	0.33 (5.12)	- 0.51	0.615
	Monetary Gain/Loss	21.13 (38.02)	13 (32.51)	17.13 (29.17)	-4 (15.53)	21.54 (30.61)	20.13 (24.79)	16.92 (25.92)	-4.63 (15.72)	41	0.505
	Release time *(ms)*	189.27 (48.67)	203.35 (45.89)	193.51 (61.34)	4.24 (27.69)	192.58 (54.31)	196.3 (49.47)	187.17 (47.91)	-5.4 (36.99)	41	0.91

Note. Absolute change is the subtraction of Post – Pre

Our findings emphasize the need of phase synchronization between the tACS and the endogenous activity. This can be partially explained by the effect known as Arnold tongue which states that the entrainment of neuronal oscillations is achieved with lower intensity stimulation if they share the same frequency and phase (Notbohm et al., 2016). Our results support this notion given that the match of the phase and frequency between tACS and P3 ERO was performed specifically to target-P3, which was successfully increased in the active session. Therefore, this study suggests that tACS effects can be limited to transient activity (i.e., P3), instead of the broad oscillatory activity measured in the PSD. The neuronal oscillations have been recently suggested to be rhythmic bursts instead of sustained oscillations (Jones, 2016; van Ede et al., 2018). Previous studies have already demonstrated that theta tACS is capable of increasing the transient theta activity during cognitive tasks (Hsu et al., 2017; Vosskuhl et al., 2015), whilst no effect was detected in the resting theta activity (Mosbacher et al., 2021; Wischnewski & Schutter, 2017). Thus, higher target-P3 amplitude observed during the active tACS session might be due to the increase of delta/theta bursts after the target, rather than an increase of sustained delta/theta activity (Mendes, Galdo-Álvarez, et al., 2022). Nevertheless, our results failed to detect statistically significant effect in delta activity during target-P3, although descriptive statistics show that target-P3 amplitude and delta activity increased during active session, whilst both decreased in the sham session (see Limitations and Future Directions).

On the other hand, the cue-P3 amplitude was not modulated by tACS. Nonetheless, it was revealed a decrease observed in evoked-delta during cue-P3, which might suggest an anti-phasic effect between the stimulation and the evoked oscillation (see Figure 14.A). The decrease in event-related delta activity during a cognitive task was already observed after the application of delta tACS (Wischnewski & Schutter, 2017). However, the authors of the previous study did not synchronize tACS and oscillatory activity, which can explain the unexpected effect (i.e., decrease of evoked-delta) through the mismatch between both signals (Wischnewski & Schutter, 2017). In line with this, the decrease in delta-activity might also be explained with the spike-timing dependent plasticity (STDP) hypothesis, which suggests that tACS is mostly successful in the oscillatory activity above the stimulation frequency (Vogeti et al., 2022; Zaehle et al., 2010). If the dominant oscillation between two neurons is higher than the stimulation frequency, there is a strengthening of the synapse (i.e., Long-term Potentiation; LTP) because pre-synaptic events occur before the post-synaptic. On the other hand, if stimulation frequency is higher than the ongoing oscillation, it will allow pre-synaptic events to occur after post-synaptic, which decreases the synaptic strength (Long-term Depression; LTD) (Vossen et al., 2015). However, the decrease of delta

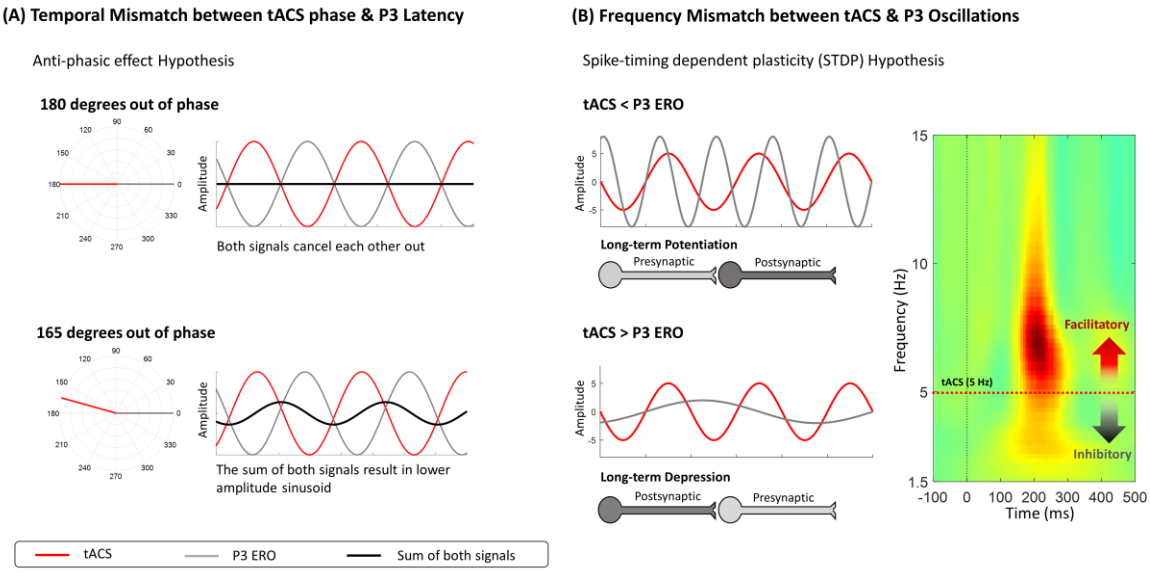
activity in tACS session was only observed in cue-P3 (and not in target-P3), which, according to STDP hypothesis, suggests that the ERO associated with cue-P3 is lower than the target-P3 (see Figure 14.B).

The results from cue and target-P3 suggest that the preceding identification of the frequency in tACS is an effective way to engage the intended oscillatory activity. In fact, this methodology was recently tested in clinic trials with different neuropsychiatric disorders (Huang et al., 2021; Riddle et al., 2021). In order to further explore this, we performed an additional analysis that adjusted the temporal and frequency windows for each subject (see Figure SM.19 in Supplementary Materials). The results obtained were the same than the previous that employed the conventional P3 time-windows and frequency bands. Nonetheless, the effect size observed in the P3 amplitude between both sessions was lower when the time-window was adjusted to the P3 latency of each subject. The temporal adjustment performed might bias the results because tACS is also capable of modulate P3 as already reported in literature (Pahor & Jaušovec, 2018).

At last, the current study tried to address some previous methodological limitations. In online EEG analysis, we had a frequency resolution of 0.25Hz, instead of 0.5Hz by previous studies (Dallmer-Zerbe et al., 2020; Popp et al., 2019). This is of particular interest given that the frequency of tACS is identified during the online analysis, which allows an improvement in stimulation parameters and consequently better modulatory effects. Likewise, both studies mentioned before applied an intensity of 1mA peak-to-peak, whilst we have decided for a peak-to-peak intensity of 2mA. The tACS with lower intensities might not be enough to properly modulate the intended oscillatory activity (Johnson et al., 2020). Furthermore, Popp and colleagues (2019) also pointed the between-subject design as a caveat in tACS studies, thus, we implemented a within-subject design with two sessions to optimize statistical power. At last, regarding behavioral analysis, we maintained the same reward/punishment system in both sessions, given that a recent study has shown that the system was associated with the number of premature responses (Mendes, Galdo-Álvarez, et al., 2022).

Figure 14

Frameworks about mechanisms of action of tACS that might explain the decrease in evoked-delta after tACS, namely the anti-phasic effect (A) and the spike-timing dependent plasticity (STDP) (B)



4.5.1. Limitations and Future Directions

The low number of subjects is the main limitation of this study. The sample size calculation was aimed to detect an effect in P3 amplitude and not in ERO, PSD or behavioral data. However, our results are in line with the study employed in sample size calculation (Dallmer-Zerbe et al., 2020), in particular the increase of P3 amplitude during active session, although no differences were observed in the ERO during the P3 time-window. Interestingly, the descriptive data suggests an increase in ERO during the active tACS session and a decrease in sham (see Table 4; Figure 12), as similarly observed by Dallmer-Zerbe and colleagues (Dallmer-Zerbe et al., 2020).

Moreover, this study tested the offline effect through the absolute change between the blocks performed before and after tACS rather than analyzing the block during tACS (i.e., online effects). The tACS seems to have offline aftereffects with a duration of at least 30 min (Neuling et al., 2013) or 70 min (Kasten et al., 2016). However, other studies suggested that tACS effects are mostly observed online instead of offline (Pozdniakov et al., 2021). Therefore, for an optimization of tACS effects, future studies should address closed-loop stimulations that are dependent on the online endogenous oscillatory activity (Frohlich & Townsend, 2021; Leite et al., 2017).

Finally, the number of premature responses has been shown to be increased in clinical conditions such as ADHD and addiction (Morris et al., 2016; Van Dessel et al., 2019). Therefore, the modulation of P3 during a waiting impulsivity paradigm might be more appropriated for therapeutic use in these impulse-control disorder in comparison with an oddball paradigm (Dallmer-Zerbe et al., 2020). Therefore, future studies should increase the sample size, and to assess these potential effects in participants in which impulsivity control is at deficit, such as people with ADHD or with addictive disorders.

4.6. Conclusion

Our findings suggest the modulation of P3 amplitude through the adjustment of frequency and phase of tACS to the endogenous activity of each subject. Specifically, the tACS counteracted the expected decrease in P3 amplitude observed in the sham session. Nonetheless, tACS did not lead to significant effects in the ERO during the time-window of target-P3, although a significant reduction in evoked-delta was observed in cue-P3. This effect might be explained by the differences in the ERO between both P3 components, as well the tACS synchronization with target-P3 (and not cue-P3). Overall, these results demonstrate that identifying the targeted neuronal activity is essential for the efficacy of tACS. Therefore, the current study highlights tACS as a promising intervention to neuropsychiatric conditions with deficits in P3 component, such as addiction and ADHD.

4.7. References

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4.8. Supplementary Materials

Table SM.12

Sociodemographic characteristics, impulsivity measures and clinical symptomatology per participant.

	Sex	Age	EHI	BIS	S-UPPS	DASS		
						Depression	Anxiety	Stress
Participant 1	F	25	100	49	35	4	4	8
Participant 2	M	28	100	52	33	0	4	6
Participant 3	M	24	100	58	51	8	0	0
Participant 4	M	26	100	58	50	8	0	2
Participant 5	M	22	100	69	48	0	0	0
Participant 6	F	26	100	51	33	0	0	0
Participant 7	F	29	66.67	53	39	2	0	8
Participant 8	F	27	80	58	40	2	0	4
Participant 9	F	27	100	48	25	0	0	0
Participant 10	M	24	89.47	62	30	0	4	2
Participant 11	F	26	57.14	54	36	10	6	12
Participant 12	F	24	86.67	56	36	4	4	10

Table SM.13

Results of the tACS blinding questionnaire per participant.

Participant	Active Session		Sham Session	
	Guess	**Confidence**	**Guess**	**Confidence**
1	Active	4	Active	3
2	Active	2	Placebo	3
3	Placebo	5	Placebo	1
4	Placebo	2	Active	3
5	Placebo	3	Active	4
6	Placebo	2	Placebo	3
7	Placebo	1	Active	0
8	Active	2	Placebo	1
9	Placebo	4	Active	3
10	Active	3	Placebo	3
11	Placebo	2	Active	2
12	Placebo	1	Placebo	4
Correct Guess	28.6		42.9	
Wrong Guess	71.4		57.1	

Legend: 0 – "No confident at all"; 1 – "Slightly confident"; 2 – "Moderately confident"; 3 – "Considerably confident"; 4 – "Extremely confident"

Figure SM.16

Examples of synchronization between the tACS peak and P3 latency in CPRT using E-Prime 3. These scenarios correspond to examples that P3 latency is higher than the time of 1 cycle + $\pi/2$ from tACS frequency.

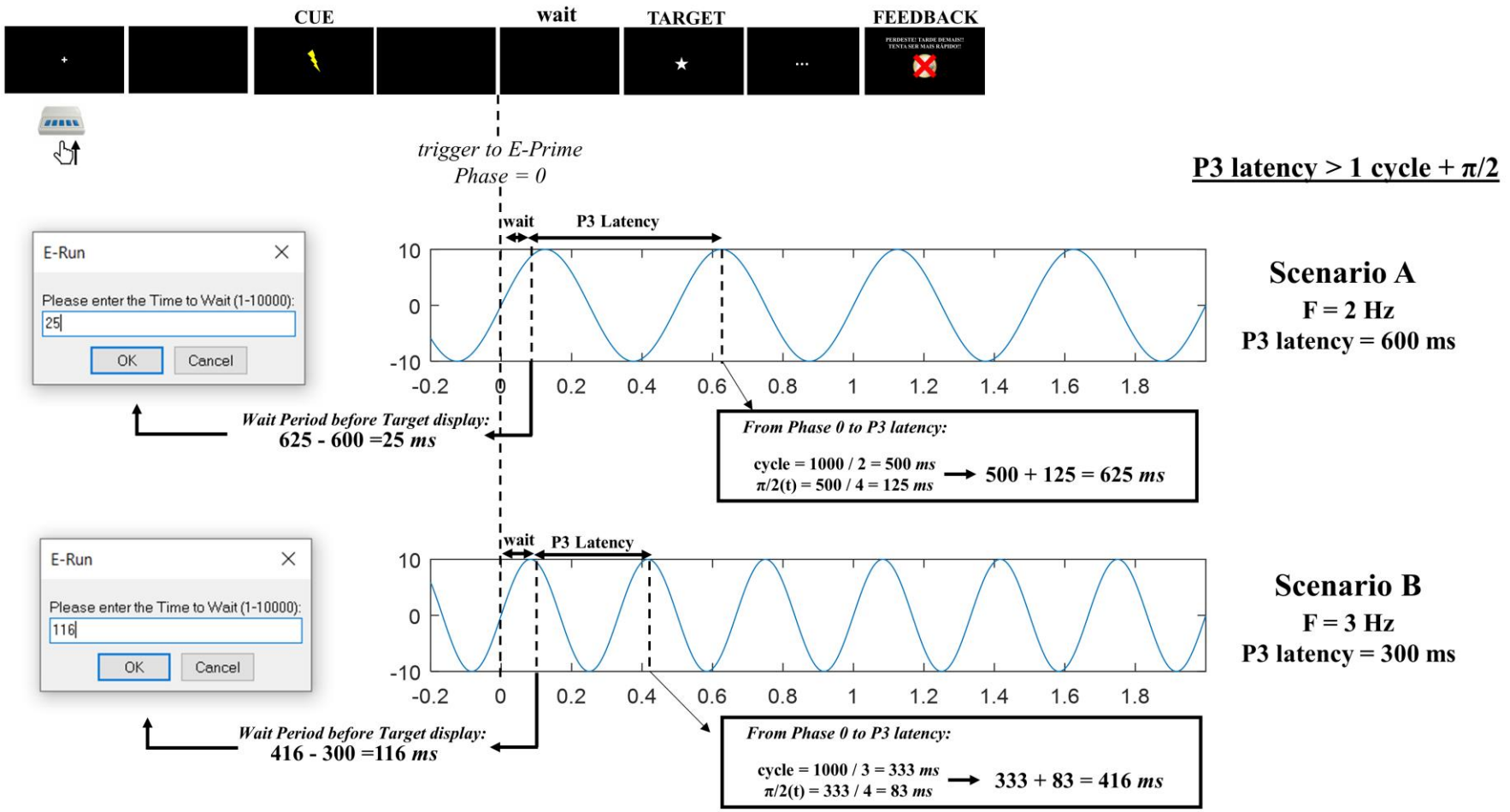


Figure SM.17

Examples of synchronization between the tACS peak and P3 latency in CPRT using E-Prime 3. These scenarios correspond to examples that P3 latency is lower than the time of 1 cycle + $\pi/2$ from tACS frequency, which requires 2 cycles + $\pi/2$ (Scenario C) or 3 cycles + $\pi/2$ (Scenario D) to achieve the match.

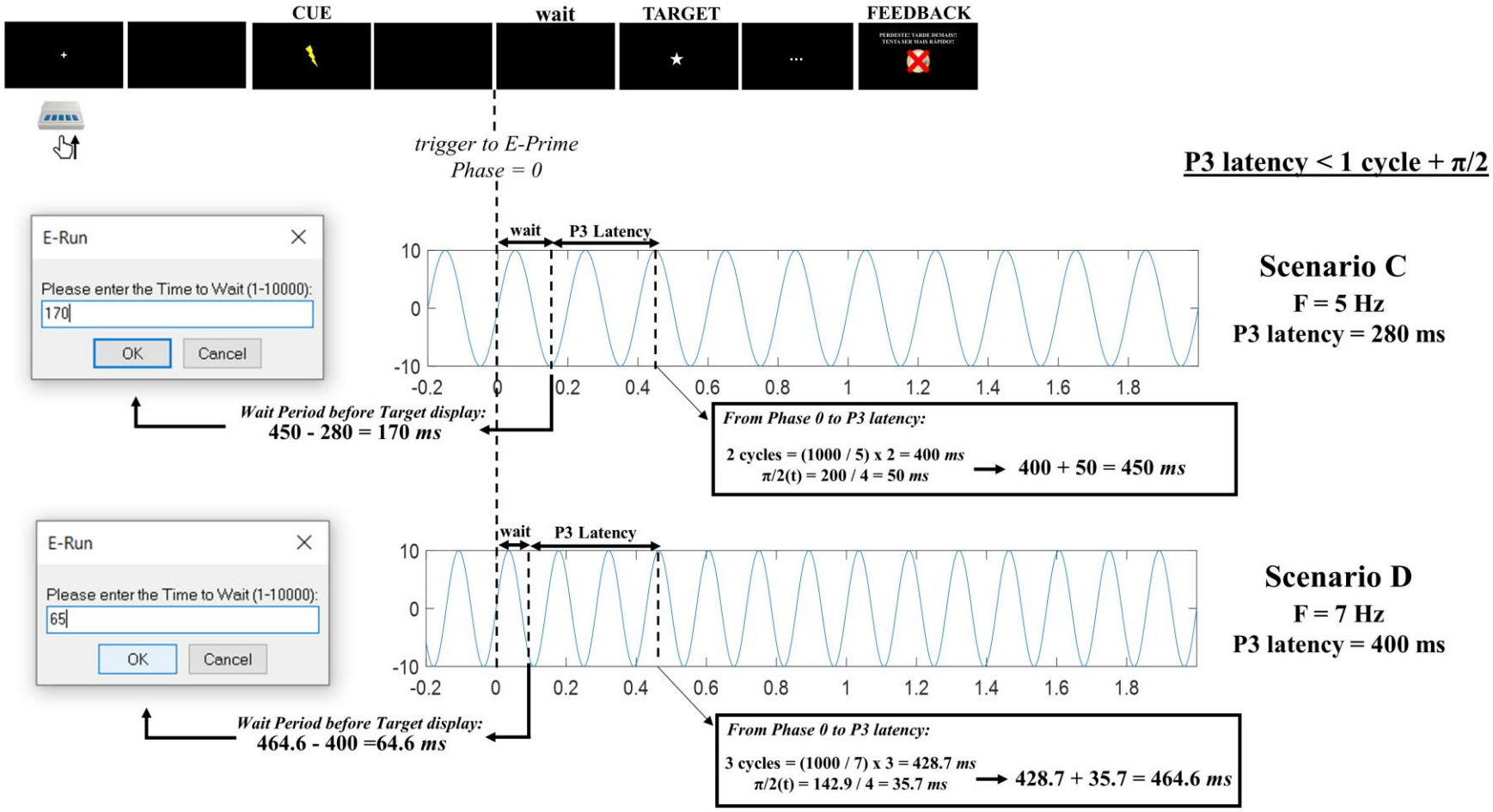


Table SM.14

Online P3 results for subsequent tACS-EEG synchronization and the average/SD RT of the training block

	tACS frequency (Hz)	P3 latency (ms)	"Wait" period (ms)	Mean RT in Training trials (ms)	SD RT in Training trials (ms)
Participant 1	7	280	152.3	200.14	113.8
Participant 2	6	292	217.7	155.6	51.1
Participant 3	2.25	352	203.6	391.4	127.6
Participant 4	2.25	302	253.6	156.9	62.4
Participant 5	1.75	312	402.3	209.5	109.2
Participant 6	2.5	290	210	210.9	57
Participant 7	3	364	52.7	294.1	72.1
Participant 8	2	364	261	160.2	57.4
Participant 9	1.5	302	531.3	288.1	90.6
Participant 10	3	300	116.7	157.1	55.7
Participant 11	2.25	368	187.6	211.9	58.9
Participant 12	6	290	251.7	193.2	35.9

Reinforcement/punishment feedback in CPRT

The reinforcement/punishment feedback pretended to elicit a higher number of premature responses. Therefore, the participant's response was rewarded with virtual money if his/her response was fast, punished if his/her response was slow, or neither rewarded nor punished if they released the button before target onset (i.e., premature response). The feedback was tailored for each participant based on the mean and variability of the response time (RT) observed in the last 10 trials of the baseline block. The mean and variability of the response time (RT) observed in the last 10 trials of the baseline block were considered to estimate the reinforcement/punishment feedback (Figure SM18), specifically:

- Very fast responses: if participant released the button with a RT below -0.66 standard deviation (SD) of the baseline RT mean, participant was reinforced with virtual 1€. Moreover, if any participant earned 1€ three times in a row, the feedback increased to 2€ for "very fast responses".
- Fast responses: if participant released the button with a RT between -0.66 SD and +0.33 SD of the baseline RT mean, participant earned a virtual 0.5€.

- Slow responses: if participant released the button with a RT between +0.33 SD and +1SD of the baseline RT mean, the participant lose virtual 0.5€.
- Very slow responses: if participant released the button with a RT above +1SD of the baseline RT mean, the participant lose virtual 1€.
- Premature responses: if participant released the Chronos button before the target, the feedback was "Continue", in a way that participants were not reinforced nor punished.

Figure SM.18

The tailored reward/punishment system from the CPRT. The feedback was dependent on the mean and SD of the release time from the last 10 trials of the baseline block.

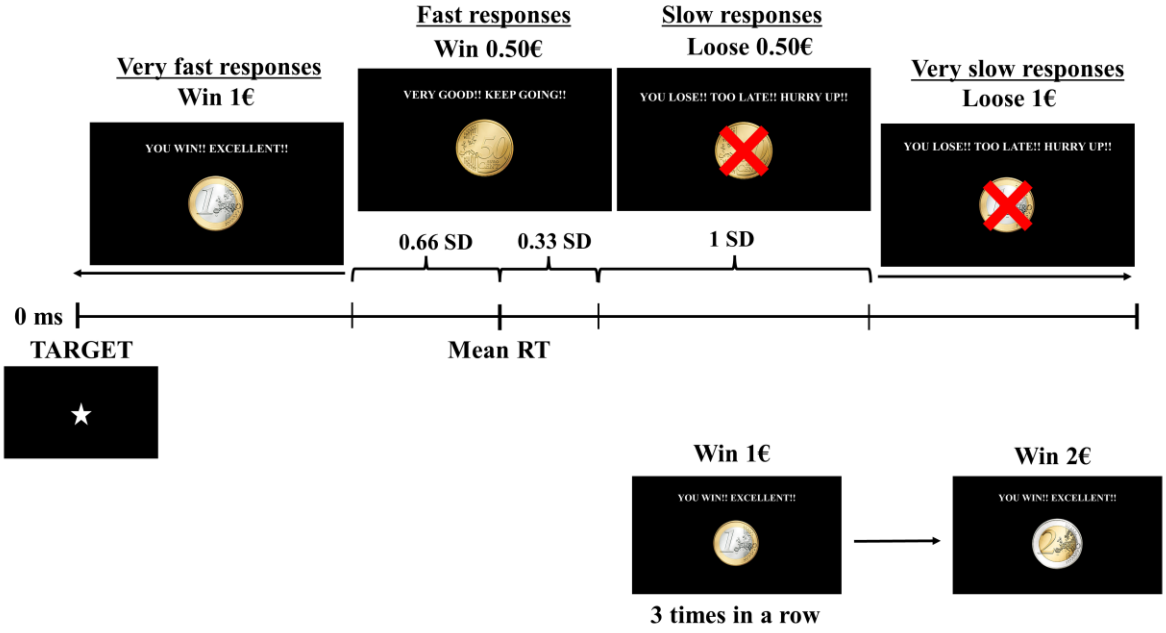


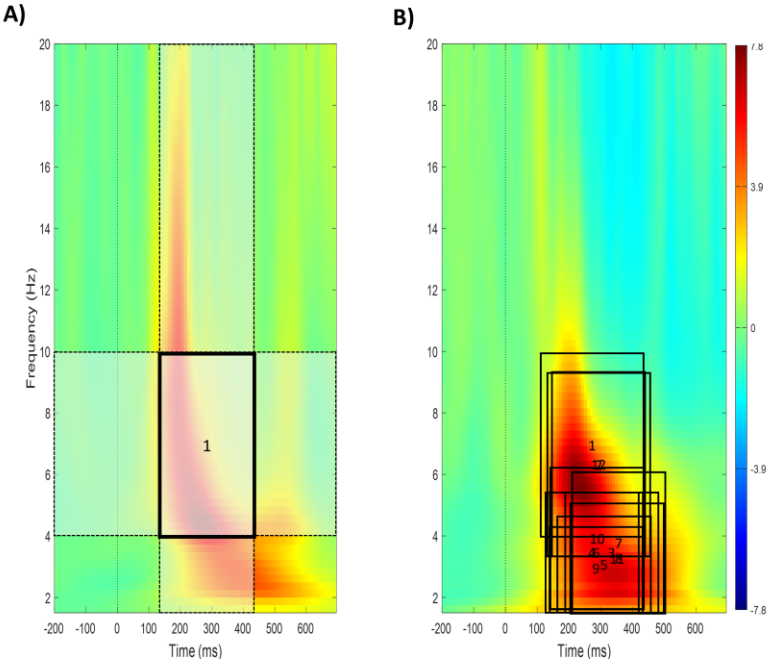
Table SM.15

Total number of epochs in the different steps of the preprocessing of EEG files

		Target-P3				Cue-P3					
		Initial epochs	100 µV	Visual inspection	Rejection Rate (%)	Initial epochs	Premature response	800ms cue-target interval	100 µV	Visual inspection	Rejection Rate (%) *
Active	Pre	82.82	80.36	75.36	9.01	97.36	95.64	83	79.46	72.18	13.04
	Post	83.91	82.27	76.09	9.32	98	95.09	81.27	80.81	74.09	8.83
Sham	Pre	75.27	74.63	70.82	5.91	88	86.18	74.73	74	58.82	21.29
	Post	83.09	82.82	79.09	4.81	96.82	94.73	81.36	81.27	74.27	8.71

Figure SM.19

The additional analysis extracted the ERO power from frequency and temporal windows according to the tACS frequency (± 3 Hz) and the P3 latency (± 150 ms). The first figure (A) represents both windows considering the frequency (4 – 10 Hz) and temporal window (130 – 430 ms) of Participant 1. The second figure (B) represents all the windows used to extract ERO from the 12 participants and the table (C) comprises all the values of the windows.



C)

	tACS frequency ± 3 Hz	P3 latency ± 150 ms
Participant 1	4 – 10	130 - 430
Participant 2	3 – 9	142 - 442
Participant 3	1.5 – 5.25	202 - 502
Participant 4	1.5 – 5.25	152 - 452
Participant 5	1.5 – 4.75	162 - 462
Participant 6	1.5 – 5.5	140 - 440
Participant 7	1.5 - 6	214 - 514
Participant 8	1.5 - 5	214 - 514
Participant 9	1.5 – 4.5	152 - 452
Participant 10	1.5 - 6	150 - 450
Participant 11	1.5 – 5.25	218 - 518
Participant 12	3 - 9	140 - 440

CHAPTER 5

General Discussion

5.1. tDCS in cognitive-P3: effects depending on the cognitive process

Study 1 showed that P3 amplitude increases after frontal tDCS during oddball and n-back tasks. On the other hand, Study 2 showed that tDCS over the rIFG decreased cue and target-P3 amplitude in a premature response paradigm. The opposite effect of tDCS in both studies should be interpreted, having in mind the differences between the cognitive tasks. Specifically, premature response paradigms have been associated with motivational processes and tonic inhibitory control (Voon, 2014), whilst oddball and n-back tasks rely mainly on attentional and working memory operations. Moreover, although activity on the rIFG has been mostly associated with inhibitory control (Aron et al., 2014), this area has also been shown to be positively correlated with reward sensitivity (Fuentes-Claramonte et al., 2016). Thus, the neuromodulatory effects of tDCS over rIFG might be also influenced by the motivational disposition during premature responding, which might also explain the opposite effects in both studies.

Overall, findings from Study 1 and 2 suggest that tDCS might impact differently the P3 component depending on the task requirements. Premature response paradigms rely on hot and cold functioning, such as motivational processes and proactive inhibitory control (Voon, 2014). On the other hand, the modulation of P3 observed during oddball and n-back tasks require distinct cognitive operations based on the frequency and the interval of stimuli. Therefore, these differences might suggest that tDCS effect on P3 depends on the ongoing neuronal network recruited by the task, as well as the level of activation within the network (Fertonani & Miniussi, 2017).

5.2. The relationship between oscillations and P3 in waiting impulsivity

Study 2 and 3 provide evidence about the relationship between the P3 ERP component and EEG activity in the delta range. In Study 2, tDCS over the rIFG decreased target-P3 amplitude and delta power, although the decrease in the cue-P3 amplitude was not correlated with changes in delta/theta bands. Interestingly, Study 3 showed that delta/theta tACS can increase target-P3 amplitude, which strengthens the notion about the inter-dependency of delta/theta and the P3 ERP component.

Changes in delta activity, concurrently with change in the P3 ERP component have been observed during oddball (Demiralp et al., 2001) and GNG tasks (Harper et al., 2014). Specifically, the delta power was mostly enhanced after targets, when comparing with non-targets (Demiralp et al., 2001; Schürmann et al., 1995). These findings were later corroborated by a large sample size study (N = 2068), in which a Principal Component Analysis decomposition was performed (Bernat et al., 2007). Particularly,

the P3 at earlier latencies is associated with higher frequency activity (i.e., theta), which decreases progressively towards lower frequencies (i.e., delta) (Bernat et al., 2007). Likewise, the theta to delta progression during P3 in parietal regions was also observed using the S-transform decomposition, along with an increase in frontal theta activity (Jones et al., 2006). This is of particular interest because recent evidence suggested that P3 and delta activity rely on frontoparietal networks instead of local circuitries (Güntekin & Başar, 2010). These findings might help to further explain the distal tDCS effect in task-related neuronal networks observed in Study 1 and 2.

Moreover, the ERO results from Study 2 and 3 also highlight the notion of oscillatory activity as rhythmic bursts instead of sustained activity (Jones, 2016; van Ede et al., 2018). Brain rhythms might be seen as spontaneous (or sustained in time) in the absence of an external stimulus; or as a transitory activity in response to a stimulus (i.e., evoked or ERO). Both perspectives often result in different functional meanings, highlighting the need for distinguishing between spontaneous and evoked EEG activity (Donoghue et al., 2021). Although spontaneous delta activity is largely reported to be enhanced in clinical populations (Dupuy et al., 2014; Saletu et al., 2010), an opposite effect is observed in transitory delta activity during the P3 time-window (Ergen et al., 2008; Yener et al., 2012, 2013). This view is supported by the fact that pre-stimulus activity has an inverse relationship with the evoked potential (Rahn & Basar, 1993). This inter-dependency might be explained by a resonance phenomenon that blocks a delta response due to the overload of the neuronal network (Başar, 1998).

Likewise, other authors suggested that ERPs are generated through the resetting of spontaneous activity (Klimesch et al., 2007), instead of the enhancement of oscillatory activity regardless of the ongoing activity (i.e., additive model) (Schroeder et al., 1995). Both models are observed in parallel in the alpha frequency domain during a visual discrimination task (Min et al., 2007). An increase in pre-stimulus mid- and high-alpha was associated to a desynchronization of post-stimulus mid- and high-alpha (i.e., phase-reset model) and a concurrent enhancement in spontaneous and evoked low-alpha activity (i.e., additive model) (Min et al., 2007). In line with these findings, Mishra and colleagues (2012) evaluated the theta-alpha dynamics during early latency ERPs and showed that the additive model was more appropriated in the theta frequency band (however both models were observed in the alpha band). Another study showed that additive power is mostly observed in the initial trials (i.e., increase in Inter-Trial Phase Coherence (ITPC) and spectral power), whilst the phase resetting occurs as long as the stimulus is repeated (i.e., enhancement of ITPC and no changes in spectral power) (Fuentemilla et al., 2006). In fact, Study 2 showed that tDCS decreased ITPC and evoked-delta activity in target-P3, whilst for cue-P3 there was a marginal significant decrease in ITPC and no changes in ERO. Hence, dynamics between the power and

phase of oscillatory activity might be different between both P3 components (Burke et al., 2013; Buzsáki & Draguhn, 2004) and, consequently, a distinct tDCS effect may be expected. Therefore, although it is acknowledged that P3 relies on spontaneous and evoked delta activity, the mechanisms underlying these signals generation are still not fully understood (please see Limitations and Future Directions).

Additionally, Study 2 and 3 showed differences in terms of the oscillatory activity between cue and target-P3. More specifically, cue-P3 amplitude was not modulated in conjunction with the ERO, as opposed to what happened to target-P3. In Study 2, tDCS decreased the cue-P3 amplitude, but no significant effects were observed in terms of delta and theta activity during the P3 time-window. Likewise, Study 3 demonstrated a modulatory effect of tACS in the cue-P3 ERO, but without any effects in the cue-P3 amplitude. According to the STDP, the endogenous oscillatory activities above the tACS frequency are enhanced, whilst the oscillations below stimulation frequency are expected to be inhibited (Vossen et al., 2015; Zaehle et al., 2010). Therefore, accordingly to this assumption, the ERO associated with cue-P3 might be at a lower frequency band, when comparing to the ones for the target-P3. Another hypothesis that may help to explain these results is the time-window used for the cue-P3 (i.e., 350 – 600ms) (Broyd et al., 2012; Pfabigan et al., 2014). Several time-windows have been analyzed for the cue-P3 during the MID task, namely, 300 and 450ms (Gu et al., 2017), 400 and 550ms (Zhang et al., 2017), and 400 and 600ms (Vignapiano et al., 2016). Additionally, a Principal Component Analysis (PCA) study suggested that the cue-P3 can be divided into two main components, namely a central positivity that peaks at ~270ms and a left parietal positivity, which peaks at ~360ms (Angus et al., 2017). In this sense, it is possible that different time windows may produce different results.

Alternatively, the Stimulus-Response (S-R) activation might help explaining these results in the cue-P3. This theory postulates that P3 acts like a reflex because the waveform is elicited based on the S–R links established by the instructions of the task (Verleger et al., 2014). The authors behind the S-R activation hypothesis claim that this hypothesis fits better with the data available from the literature, when comparison with other models (e.g., memory storage, context updating, priming) (Verleger, 2020). Nonetheless, the aforementioned model does not fit with the functional meaning of cue-P3, given that the cue yields predictive information about a future response, instead of an immediate response (Angus et al., 2017; Glazer et al., 2018). Hence, cue-P3 is thought to be a marker for attentional allocation towards a motivational stimulus (i.e., target), whilst the target-P3 is more associated with the S-R reactivation. However, the literature is not clear about the possible differences between cue and target-P3 during reward processing, especially because those components are not commonly compared with one another (Broyd et al., 2012). Likewise, to the best of our knowledge, comparisons between cue and target-P3 in

the time-frequency domain are almost nonexistent, for instance, one study showed that reward trials showed a larger parietal delta/theta activity between 100 and 500ms after the cue (Pornpattananangkul & Nusslock, 2016), but no results for the target-P3 were presented (see Limitations and Future Directions).

Therefore, considering the findings from Study 1, 2, and 3, the role of delta activity in parietal regions during the P3 component seems to be somewhat consistent. Moreover, the increase in frontal theta (Jones et al., 2006) and the frontoparietal connectivity during P3 waveform (Güntekin & Başar, 2010) may also moderate the effects observed in Study 1 and 2. Similarly, taking into consideration the promising results from Study 3, the tACS induced entrainment of endogenous oscillatory activity might be more efficient when synchronized with transient bursts (i.e., ERP and ERO), rather than with sustained EEG activity (Jones, 2016; van Ede et al., 2018).

5.3. Limitations and Future Directions

The current work shows the modulatory effects of tDCS/tACS on P3 and its underlying oscillatory activity. Nevertheless, our findings showed that tES did not modulate equally the ERPs and EROs, specifically the increase of delta/theta power was not always observed concurrently to cue and target-P3 amplitude. Several hypotheses were discussed previously to support the differential effects, namely, the ERO frequency and time-window associated with P3 might change according to different contexts that elicit P3 (e.g., cue or target). These suggestions should be addressed in future studies to increase our understanding of both P3 components, specifically for premature responding and reward processing.

Likewise, the study of ERPs in the time-frequency domain has been extremely helpful to understand the mechanism underlying the signal generation of ERPs. Nonetheless, the neurophysiological mechanisms that allow the elicitation of P3 are still not clear in these specific tasks. More specifically, the additive model and phase resetting hypothesis should be tested by future studies, in a premature response paradigm (Herrmann et al., 2014). By doing so, these models of ERP generation that have been shown to co-occur during a visual discrimination task in the alpha frequency domain (Min et al., 2007; Mishra et al., 2012), should be analyzed during other types of cognitive processing (i.e., waiting impulsivity) and in a more comprehensive frequency domain (i.e., delta and theta bands). This will further foster our knowledge on how P3 is related with the baseline oscillatory activity, and, consequently, will allow for an optimization of tES parameters accordingly to cognitive process.

Furthermore, Study 2 and 3 used the same cue-target interval, stimuli, and reward/punishment system from CPRT. First and foremost, other intervals between cue and target should be addressed due

to the temporal infrequency effect observed in the oddball paradigm (Verleger, 2020). The CPRT includes trials with considerably different intervals between cue and target (i.e., 500 – 2500 ms). Therefore, the impact of short and long cue-target intervals in target-P3 amplitude should also be considered. Additionally, the inclusion of distracters in forthcoming studies should be referred as well. Previous studies have included distractors to enhance premature responding (Voon et al., 2014), which could increase the task difficulty and decrease target-P3 amplitude (Kok, 2001). At last, both studies employed an adaptation of the reward/punishment system of Voon and colleagues (2014). Taking into account the motivational processes involved in premature responding, the influence of the system of reward/punishment in P3 amplitude should be evaluated.

Another limitation is the small sample sizes included in the Study 1 as well the Study 3, in which 12 participants were enrolled. The studies with small sample size in neurosciences have been criticized due to the lack of statistical power (Button et al., 2013). Hence, findings from both studies should be carefully interpreted as pilot studies. In Study 1, the statistical power limitation might be surpassed by the inclusion of several studies in the analysis. However, GNG and emotional processing analysis only included five studies each. Regarding Study 3, the sample was powered to find a significant effect in P3 amplitude and not in ERO or behavioral outcomes. In conclusion, these results and other effects in ERO and behavior should be evaluated by studies using larger sample sizes. It is important to highlight also that behavior and neural markers are correlative by nature, and as such one does not predict exactly the other.

Finally, the current work clearly showed the ability of tES to modulate P3 and ERO. This is of particular interest considering that several conditions are already known for having specific changes in these markers. For instance, changes in terms of P3 waveform have already been shown in alcohol use disorder (Hamidovic & Wang, 2019), ADHD (Kaiser et al., 2020), Post-traumatic Stress Disorder (PTSD) (Johnson et al., 2013). Diminished evoked-delta activity has also been found in Alzheimer's disease (Yener et al., 2012), Mild Cognitive Impairment (Yener et al., 2013), and schizophrenia (Ergen et al., 2008). And in this sense, this is the major strength of Study 3: the need for an a priori assessment of the intended EEG signal, in order to tailor tACS stimulation. Therefore, future studies should test a closed-loop system that allows an online synchronization between tACS and EEG in order to prevent potential mismatches between P3 and tACS (Frohlich & Townsend, 2021; Leite et al., 2017). Tailoring interventions based on specific individual marker may indeed represent the next step optimization, by allowing for dosage optimization, or simply by reducing the variability of effects across participants.

5.4. Conclusion

The current work showed the usefulness of combining specific EEG markers with different types of tES. Specifically, in Study 1, a meta-analysis suggested the usefulness of P3 amplitude during oddball and n-back tasks for anodal tDCS. On the other hand, Study 2 showed a decrease in cue and target-P3 amplitude coupled with a decrease in evoked-delta activity during tDCS over rIFG during a waiting impulsivity task. Moreover, tDCS increased the waiting impulsivity choice (i.e., increased k in small amounts), whereas no changes were observed in the number of premature responses. Finally, Study 3 highlighted the relationship between P3 and delta/theta activity because P3 amplitude was increased after the tACS entrainment of the P3 ERO. This study showed the importance of synchronizing the tACS with P3 ERO and its phase, in order to allow a successful P3 enhancement. Considering the numerous evidence about deviant EEG activity in neuropsychiatric populations, this thesis provides encouraging evidence about modulatory effects of tES in neuronal activity underlying cognitive processing, which can serve a dual objective: probing the mechanisms underlying cognition, while simultaneously providing valuable knowledge that can be translated to more applied research.

5.5. References

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APPENDIXES

Appendix A. Study 2 Ethical Approval

The Study 2 presented in Chapter 3 in the current thesis was approved by *Comissão de Ética para a Investigação em Ciências da Vida e da Saúde* (CEICVS 127/2019), as shown below.

Universidade do Minho

Conselho de Ética

Comissão de Ética para a Investigação em Ciências da Vida e da Saúde (CEICVS)

Identificação do documento: CEICVS 127/2019

Título do projeto: Predicting and Preventing Failures in Waiting Inhibitory Processing

Equipa de investigação: Augusto José Martins Mendes, aluno de Doutoramento, Centro de Investigação em Psicologia (CIPsi), Escola de Psicologia da Universidade do Minho; Sandra da Conceição Ribeiro de Carvalho (Orientadora), Centro de Investigação em Psicologia, Escola de Psicologia, Universidade do Minho; António Jorge da Costa Leite (Orientador), Universidade Portucalense - Porto

Unidade Orgânica Promotora: Escola de Psicologia da Universidade do Minho

PARECER

De acordo com a documentação apresentada, trata-se de um projeto a desenvolver no âmbito de Tese de Doutoramento em Psicologia na Universidade do Minho.

Trata-se de um estudo que tem como objetivo principal "estudar os correlatos eletrofisiológicos que antecedem e seguem uma resposta prematura e testar o efeito da Estimulação Transcraniana por Corrente Contínua (ETCC) ativa em comparação com a Estimulação placebo (sham) nas respostas prematuras". [" the present study pretends to address the neural electrophysiological markers that may predict and follow a premature response."]

Após verificação e análise dos documentos associados ao processo de pedido de emissão de parecer ético sobre o projeto em apreço, a que reporta sumariamente a respetiva "Grelha de verificação e avaliação ética", considera-se que (i) o processo está devidamente instruído, (ii) a análise dos documentos apresentados sobre o estudo a realizar obedecem às regras de conduta ética e requisitos exigidos para as boas práticas na experimentação com humanos e (iii) estão em conformidade com o Guião para submissão de processos a pedido de Parecer Ético na UMinho.

Face ao exposto, a Comissão de Ética para a Investigação em Ciências da Vida e da Saúde (CEICVS) nada tem a opor à realização do projeto, emitindo o seu parecer favorável, que foi aprovado pelos seus membros.

Braga, 26 de novembro de 2019.

A Presidente da CEICVS

MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO

Assinado de forma digital por MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
Dados: 2019.11.28 09:30:45 Z

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ANÁLISE E JUSTIFICAÇÃO DO PARECER

Relatora: Lucília Nunes

Grelha de verificação e de avaliação ética

(Processo submetido em suporte eletrónico - documentos recebidos assinalados com X e respetiva avaliação ética)

Documentos	**Sim**	**Não**	**Não se aplica**	**Avaliação Técnico-ética**
Requerimento e/ou ofício e/ou pedido de apreciação de projeto [a]	X			Adequado
Informação do Responsável pela Unidade/Diretor de Serviço sobre apoio e/ou enquadramento/cabimento do projeto na Unidade/Serviço em que decorrerá [a]			x	
Protocolo do estudo, incluindo, se aplicável, os instrumentos de recolha de dados e/ou informação para o participante [a]	X			Protocolo do estudo elaborado de acordo com os requisitos e normas éticas de boas práticas em experimentação com humanos.
Curriculum Vitae abreviado do Investigador Responsável [a]	X			
Modelo de Consentimento Informado [a][b][c]	X			Linguagem e conteúdos ajustados
Declaração de Compromisso de Confidencialidade	x			Presente
Informação sobre financiamento para o cumprimento do projeto, incluindo, se aplicável, cabimento/inscrição no orçamento da Unidade/Serviço em que decorrerá e/ou com fonte de financiamento nacional/internacional			x	Financiamento FCT
Requerimento dirigido ao Presidente da CE	X			Presente
Outros: O projeto carecerá de Parecer/Autorização ética local das unidade de saúde onde forem realizados os recrutamentos e/ou obtidos os dados clínicos dos pacientes participantes no estudo de investigação.				

Autorizações e/ou Pareceres de Comissões de Ética			x	
Acordo Financeiro			x	
Apólice de Seguro	x			Participante UMinho (seguro escolar)
Informação do Orientador da Tese sobre apoio e/ou enquadramento do projeto		x		

[a] Documentos obrigatórios de acordo com as normas orientadoras para submissão de processos a apreciar pelo Conselho de Ética da UMinho.
[b] Documentos obrigatórios de acordo com o funcionamento da Comissão de Ética para a Saúde do Hospital de Braga (CESHB).
[c] Documento de Consentimento Informado, Livre e Esclarecido para Participação em Investigação de acordo com a Declaração de Helsínquia[1], a Convenção de Oviedo[2] e o Regulamento Geral de Proteção de Dados (RGPD)[3]. Guião na elaboração do consentimento informado é disponibilizado pela ARSN[4] e através do "Documento CEIC sobre o Regulamento Geral de Proteção de Dados (RGPD) no contexto da Investigação Clínica"[5]. Acessos via:
[1]http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf
[2]http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf
[3]https://eur-lex.europa.eu/legal-content/PT/TXT/?uri=celex%3A32016R0679
[4]http://www.arsnorte.min-saude.pt/consentimento-informado/
[5]http://www.ceic.pt/documents/20727/0/Documento+CEIC+sobre+o+Regulamento+Geral+de+Prote%C3%A7%C3%A3o+de+Dados+%28RGPD%29_publica%C3%A7%C3%A3o/ced81411-5fe4-46f5-a613-c7c716abbb4b

Justificação do Parecer

Trata-se de um projeto de Tese de Doutoramento em Psicologia pela Universidade do Minho, com orientação de Sandra Carvalho e Jorge Leite.

O objetivo principal é "estudar os correlatos eletrofisiológicos que antecedem e seguem uma resposta prematura e testar o efeito da Estimulação Transcraniana por Corrente Contínua (ETCC) ativa em comparação com a Estimulação placebo (sham) nas respostas prematuras". ["the present study pretends to address the neural electrophysiological markers that may predict and follow a premature response."]

Quanto aos participantes - "We plan to enroll 32 healthy volunteers, according to a sample size estimation based in a previous study (Cunillera et al., 2016)." Foi clarificada a forma de recrutamento dos participantes voluntários saudáveis.

O "Consentimento informado" foi ajustado a linguagem acessível a participante, apresentando a informação de forma que seja mais acessível aos participantes.

Documentos recebidos no órgão institucional de ética da UMinho

Foram recebidos os seguintes documentos:

- Protocolo de Investigação

- Requerimento para o parecer da SECVS
- Cronograma do projeto
- Declaração do Centro de Investigação de Psicologia
- CV's dos Investigadores Responsáveis
- Declaração de Responsabilidade e Confidencialidade
- Modelo do consentimento informado
- Cópia dos questionários a utilizar

Considerações/Orientações gerais de natureza formativa

A realização de projetos de investigação deverá ter em consideração as regras de conduta e diretivas de boas práticas no âmbito da investigação clínica com seres humanos. Deverá ser solicitado Parecer e/ou Autorização da entidade onde o projeto será realizado, e deverão ser seguidas as diretivas nacionais e/ou locais, de cada lugar de recolha, como aplicável, incluindo de Unidades Hospitalares e/ou Unidades de Saúde onde será realizado o estudo, e/ou onde serão recolhidas as amostras e/ou dados e/ou aplicados os questionários. Deverá ser seguido o Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho de 27 de abril de 2016, com entrada em vigor em 25 de maio de 2018, que revoga a Diretiva 95/46/CE (Regulamento Geral sobre a Proteção de Dados. O Regulamento (UE) 2016/679 é o novo Regulamento Geral de Proteção de Dados (RGPD) da União Europeia (UE) relativo à proteção das pessoas singulares no que diz respeito ao tratamento de dados pessoais e à livre circulação desses dados, estabelecendo as regras relativas ao tratamento, por uma pessoa, uma empresa ou uma organização, de dados pessoais relativos a pessoas na EU. A Lei 58/2019, publicada em Diário da República n.° 151/2019, Série I de 2019-08-08, assegura a execução, na ordem jurídica nacional, do Regulamento (UE) 2016/679 do Parlamento e do Conselho, de 27 de abril de 2016 (RGPD).

Salienta-se o respeito pelas normas e as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996, Edimburgo 2000, Washington 2002, Tóquio 2004 e Seul 2008), da Directiva 95/46/EC do Parlamento Europeu e do Conselho, das Directrizes Sobre as Boas Práticas Clínicas da EMEA - Agência Europeia do Medicamento (Londres 2000), das Directrizes Éticas Internacionais para a Pesquisa Envolvendo Seres Humanos da Organização Mundial de Saúde (Genebra 2002), das Directrizes Éticas Internacionais para os Estudos Epidemiológicos do Conselho de Organizações Internacionais de Ciências Médicas (Genebra 2009) e da Resolução da Assembleia da República n°1/2001.

Quando aplicável o Consentimento Informado, recomenda-se as normas e/ou documentos-guia da Direção Geral de Saúde e/ou da ARS Norte na elaboração do mesmo. A inclusão dos participantes em qualquer um dos âmbitos de investigação considerados num Projeto de Investigação está subjacente o seu consentimento escrito (Lei n.° 12/2005, de 26 de janeiro; Lei n.° 46/2007, de 24 de agosto). O preenchimento e assinatura do formulário de consentimento informado, livre e esclarecido, deverá ser feito em duplicado, garantindo a privacidade e confidencialidade dos dados pessoais e o direito a recusar/abandonar o estudo sem sofrer qualquer penalização.

Recomenda-se o referencial relativo ao documento CEIC sobre o Regulamento Geral de Proteção de Dados (RGPD) no contexto da Investigação Clínica de 17 de outubro de 2018 que incide sobre procedimentos a adotar para o cumprimento do

estabelecido no RGPD, no contexto da investigação clínica em geral, embora que mais especificamente sobre a informação a constar no Consentimento Informado (CI) relativo a matéria de confidencialidade e proteção de dados, da qual se salientam os aspetos a seguir apresentados:

Quem tem acesso aos dados pessoais[1,2,3]: Os responsáveis do estudo poderão necessitar de dar acesso aos registos médicos e registos do estudo a representantes autorizados. Os dados pessoais e processos clínicos apenas poderão ser consultados pelo Investigador Responsável, autoridades reguladoras nacionais e estrangeiras, e comissões de ética. Quando necessário para o seguimento dos fins do estudo, também podem ser acedidos, através do(a) Investigador(a) Responsável, pelos seus representantes autorizados, especificamente monitores e auditores, mantendo os pressupostos da Lei 21/2014 de 16 de abril, alterada pela Lei 73/2015 de 27 de julho. Nunca será pedido um acesso indiscriminado aos registos clínicos e afins, nem nunca tal acesso será realizado; isto é, será apenas colhida a informação relevante e necessária para este estudo. Neste contexto, todo e qualquer acesso cumprirá com todas as garantias aqui descritas. Os investigadores que trabalham com amostras humanas, ou com a recolha e análise de dados pessoais e/ou médicos/clínicos, estão obrigados a manter sigilo profissional sobre os dados pessoais, e sobre os resultados individuais ou demais, segundo a ética profissional, nunca devendo, por isso, fazer uso dos mesmos a não ser para o fim a que se destinam. Esta obrigação mantém-se em efeito após término do projeto de investigação.

Divulgação ou publicação dos resultados[1,2,3]: Os resultados gerais do estudo poderão ser publicados, respeitando-se todas as garantidas descritas.

Prazo de conservação dos dados[1,2,3]: O prazo será limitado ao mínimo necessário para assegurar o seu devido processamento e análise de forma a cumprir os objetivos do estudo e seguindo a legislação, finda a conclusão da finalidade do estudo, não havendo qualquer transferência de dados pessoais para um país terceiro ou uma organização internacional.[1,2,3] Segue-se o Regulamento Geral de Proteção de Dados (RGPD) (Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho de 27 de abril de 2016 relativo à proteção das pessoas singulares no que diz respeito ao tratamento de dados pessoais e à livre circulação desses dados e que revoga a Diretiva 95/46/CE.), que entrou em vigor a 25 de maio de 2018. A Lei 58/2019, publicada em Diário da República n.º 151/2019, Série I de 2019-08-08, assegura a execução, na ordem jurídica nacional, do Regulamento (UE) 2016/679 do Parlamento e do Conselho, de 27 de abril de 2016 (RGPD).

[1] https://eur-lex.europa.eu/legal-content/PT/TXT/?uri=celex%3A32016R0679

[2]Documento CEIC sobre o Regulamento Geral de Proteção de Dados (RGPD) no contexto da Investigação Clínica" de 17 de outubro de 2018:
http://www.ceic.pt/documents/20727/0/Documento+CEIC+sobre+o+Regulamento+Geral+de+Prote%C3%A7%C3%A3o+de+Dados+%28RGPD%29_publica%C3%A7%C3%A3o/ced81411-5fe4-46f5-a613-c7c716abbb4b

[3] https://dre.pt/home/-/dre/123815982/details/maximized

Nos termos do nº 2 do artigo 35º e da alínea c) do nº 1 do artigo 39º do Regulamento Geral sobre a Proteção de Dados, o tratamento de dados pessoais considera-se autorizado nos seguintes termos:
- O acesso aos ficheiros dos dados do estudo (base de dados do estudo e ficheiro com a chave de pseudonimização) deve ser feito através de *password* robusta;

- A chave da pseudonimização só deve ser conhecida pelo investigador principal e o ficheiro deverá ficar unicamente guardado em computador do serviço onde é realizada a recolha dos dados;
- O IR fica responsável pela garantia da destruição da chave de pseudonimização dos titulares de dados do estudo, findo o prazo estabelecido para a sua conservação (até 3 anos após a conclusão do estudo).

Os participantes não deverão incorrer em qualquer custo acrescido, incluindo pagamento de taxas moderadoras, pela sua participação no projeto. Qualquer meio complementar de diagnóstico que não seja suportado pelo centro hospitalar, e/ou outro, onde for realizado o estudo, como parte da prática clínica corrente no processo de diagnóstico ou tratamento, deverá ser apoiado através de financiamento próprio do estudo.

Se se pretende que o(s) questionário(s) e/ou colheita de dados seja aplicado(s) via contato telefónico, e/ou que o consentimento informado seja verbal, do próprio e do adulto responsável, o guião da entrevista deverá ser fornecido em anexo ao processo. O guião deverá encontrar-se em conformidade com as guidelines fornecidas por Singer & Frankel (1982) (Informed consent procedures in telephone interviews. Am Sociol Rev, 47(3), 416-427), não violando os preceitos da WHO ou CIOMS. O procedimento será aceitável se a investigação não envolver o mínimo risco para os intervenientes, a alteração do processo de consentimento informado não vai prejudicar os direitos e bem-estar dos indivíduos, e sempre que necessário e/ou solicitado, serão fornecidas informações pertinentes adicionais aos indivíduos após a participação e/ou o envio do Consentimento Informado.

Se forem realizadas entrevistas gravadas (vídeo ou áudio) estas deverão ser mantidas durante um tempo limitado à sua transcrição e devida análise e deverão ser subsequentemente destruídas, não sendo utilizadas para outros fins.

Se tiver lugar a recolha de produtos biológicos, esta deverá ter em conta os princípios para obtenção e conservação de material biológico (Art. 18.º) da Lei 12/2005 de 26 de janeiro. O tratamento das informações de saúde recolhidas terá em consideração os princípios aplicáveis aos tratamentos de dados pessoais efetuados no âmbito de Investigação Clínica, definidos pela Comissão Nacional de Proteção de Dados e decorrentes da Deliberação nº 1704/2015.

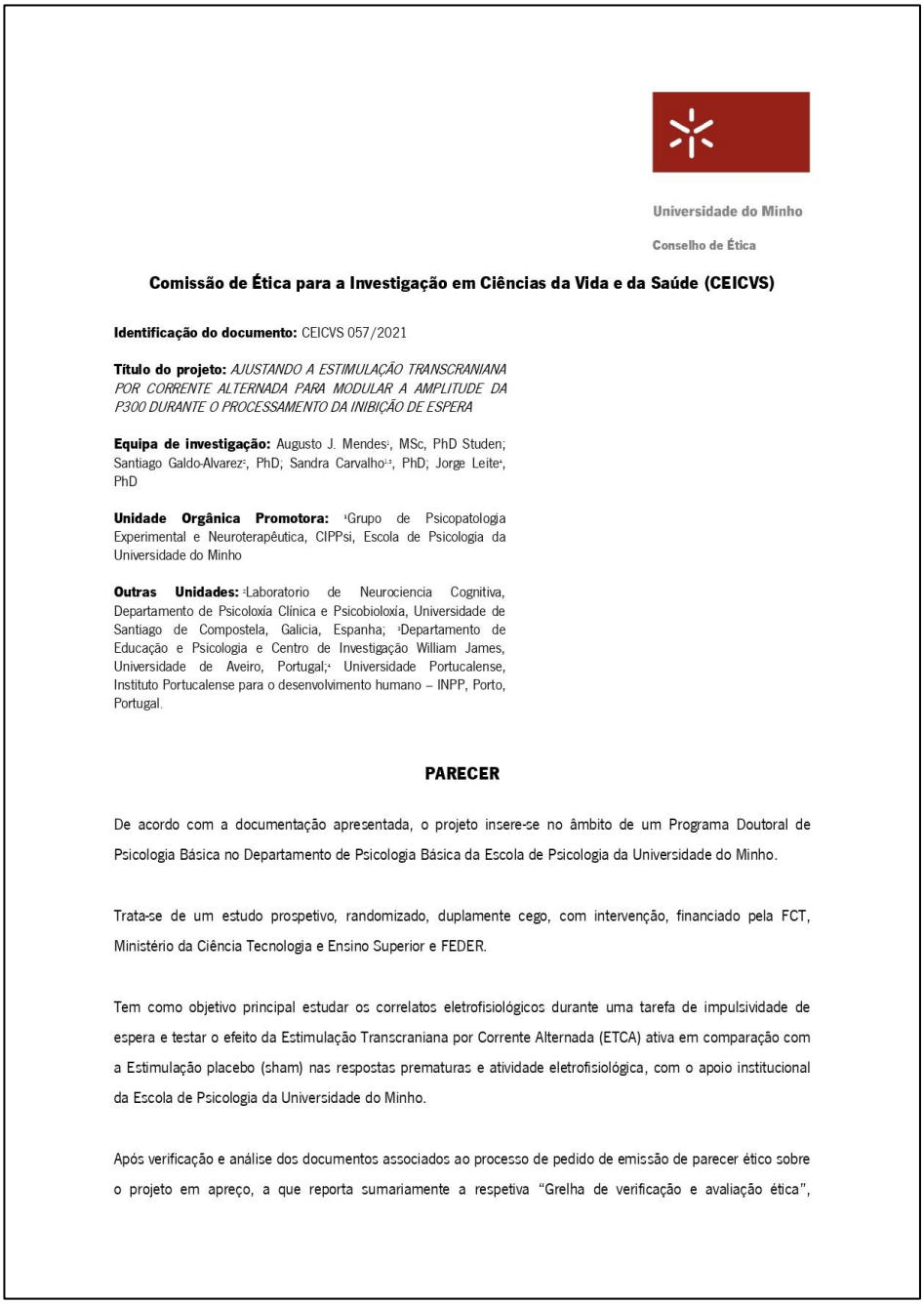
Informações pessoais tratadas não deverão ser identificáveis, mas sim irreversivelmente anonimizadas (Art. 3.º da LPDP), e todos os dados obtidos no âmbito de um Projeto de Investigação estão ao abrigo de medidas técnicas e organizativas adequadas que dão cumprimento ao disposto no Art. 14.º e Art. 15.º da LPDP. Aplica-se ainda o disposto no n.º1 do Art. 17º da LPDP relativamente ao sigilo profissional. Quando não for possível a anonimização dos dados, estes deverão codificados de acordo com uma chave específica, acessível apenas aos investigadores do estudo, e que dificulta a identificabilidade dos participantes, tal como especificado na Deliberação nº 1704/2015 da CNPD e complementado pelo Regulamento Geral de Proteção de Dados (RGPD), com entrada em vigor em 25 de Maio de 2018, e que substitui a atual diretiva e lei de proteção de dados (o Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho. Os dados obtidos deverão ser conservados de forma a permitir a identificação dos seus titulares apenas durante o período necessário para a prossecução das finalidades da recolha ou do tratamento posterior, tal como definido no Art. 5.º, n.º 1, alínea e), da LPDP.

O Modelo de declaração de compromisso e confidencialidade utilizado pelo IR deverá ser seguido e assinado por outros investigadores ou colaboradores na investigação, conforme aplicável, destinado a documentar o seu envolvimento nas garantias de confidencialidade e boas práticas dadas pelo(a) IR. Sempre que necessário, os membros da equipa de investigação deverão assinar uma Declaração de Interesses e Incompatibilidades de acordo com o Decreto-lei n.º 14/2014, de 22 de janeiro.

Neste contexto, assume-se que os investigadores que trabalham com registos ou amostras humanas, ou com a análise de dados, estão obrigados a manter sigilo profissional sobre os dados pessoais e sobre os resultados ou demais obtidos, segundo a ética profissional, nunca devendo, por isso, fazer uso dos mesmos a não ser para o fim a que se destinam. Esta obrigação mantém-se em efeito após término do projeto de investigação.

Appendix B. Study 3 Ethical Approval

The Study 3 presented in Chapter 4 in the current thesis was approved by *Comissão de Ética para a Investigação em Ciências da Vida e da Saúde* (CEICVS 057/2021), as shown below.



Universidade do Minho

Conselho de Ética

Comissão de Ética para a Investigação em Ciências da Vida e da Saúde (CEICVS)

Identificação do documento: CEICVS 057/2021

Título do projeto: *AJUSTANDO A ESTIMULAÇÃO TRANSCRANIANA POR CORRENTE ALTERNADA PARA MODULAR A AMPLITUDE DA P300 DURANTE O PROCESSAMENTO DA INIBIÇÃO DE ESPERA*

Equipa de investigação: Augusto J. Mendes[1], MSc, PhD Studen; Santiago Galdo-Alvarez[2], PhD; Sandra Carvalho[1,3], PhD; Jorge Leite[4], PhD

Unidade Orgânica Promotora: [1]Grupo de Psicopatologia Experimental e Neuroterapêutica, CIPPsi, Escola de Psicologia da Universidade do Minho

Outras Unidades: [2]Laboratorio de Neurociencia Cognitiva, Departamento de Psicoloxía Clínica e Psicobioloxía, Universidade de Santiago de Compostela, Galicia, Espanha; [3]Departamento de Educação e Psicologia e Centro de Investigação William James, Universidade de Aveiro, Portugal;[4] Universidade Portucalense, Instituto Portucalense para o desenvolvimento humano – INPP, Porto, Portugal.

PARECER

De acordo com a documentação apresentada, o projeto insere-se no âmbito de um Programa Doutoral de Psicologia Básica no Departamento de Psicologia Básica da Escola de Psicologia da Universidade do Minho.

Trata-se de um estudo prospetivo, randomizado, duplamente cego, com intervenção, financiado pela FCT, Ministério da Ciência Tecnologia e Ensino Superior e FEDER.

Tem como objetivo principal estudar os correlatos eletrofisiológicos durante uma tarefa de impulsividade de espera e testar o efeito da Estimulação Transcraniana por Corrente Alternada (ETCA) ativa em comparação com a Estimulação placebo (sham) nas respostas prematuras e atividade eletrofisiológica, com o apoio institucional da Escola de Psicologia da Universidade do Minho.

Após verificação e análise dos documentos associados ao processo de pedido de emissão de parecer ético sobre o projeto em apreço, a que reporta sumariamente a respetiva "Grelha de verificação e avaliação ética",

considera-se que (i) o processo está devidamente instruído, (ii) a análise dos documentos apresentados sobre o estudo a realizar obedecem às regras de conduta ética e requisitos exigidos para as boas práticas na experimentação com humanos e (iii) estão em conformidade com o Guião para submissão de processos a pedido de Parecer Ético na UMinho.

Face ao exposto, a Comissão de Ética para a Investigação em Ciências da Vida e da Saúde (CEICVS) nada tem a opor à realização do projeto, emitindo o seu parecer favorável, que foi aprovado por unanimidade dos seus membros.

Braga, 16 de julho de 2021.

A Presidente da CEICVS

(Maria Cecília Lemos Pinto Estrela Leão)

.....

ANÁLISE E JUSTIFICAÇÃO DO PARECER

Relatora: Alexandra Miranda

Grelha de verificação e de avaliação ética

(Processo submetido em suporte eletrónico - documentos recebidos assinalados com X e respetiva avaliação ética)

Documentos	**Sim**	**Não**	**Não se aplica**	**Avaliação Técnico-ética**
Pedido de apreciação de projeto enviado à CEICVS [a]	x			Adequado
Quando aplicável, identificação da Unidade Curricular (UC) no âmbito da qual se insere o projeto (designação do curso, designação da UC e respetivo ano curricular, identificação do/s coordenador/es da UC, nome e número mecanográfico do estudante)	x			Presente
Carta de Apoio/Autorização da(s) Unidade(s) ou Serviço(s) onde decorrerá o projeto [a]	x			Adequada
Quando aplicável, informação do Orientador da Tese sobre apoio e/ou enquadramento do projeto	x			Presente
Protocolo do estudo, incluindo, se aplicável, os instrumentos de recolha de dados e/ou informação para o participante [a]	x			Protocolo do estudo elaborado de acordo com os requisitos e normas éticas de boas práticas em experimentação

				envolvendo humanos.
Curriculum Vitae abreviado do Investigador Responsável e dos membros da equipa e/ou orientadores [c]	x			Presente
Quando aplicável, documento de Consentimento Informado, elaborado e referenciado de acordo com a alínea [c] abaixo indicada	x			Adequado, obedecendo ao enunciado na alínea c) abaixo indicada
Declaração de Compromisso de Confidencialidade (e/ou Termo de Responsabilidade)	x			Adequada
Quando aplicável, informação sobre financiamento para o cumprimento do projeto, incluindo, se aplicável, cabimento/inscrição no orçamento da Unidade/Serviço em que decorrerá e/ou com fonte de financiamento nacional/internacional	x			Presente

[a] Documentos obrigatórios de acordo com as normas orientadoras para submissão de processos a apreciar pelo Conselho de Ética da UMinho.
[b] Documentos obrigatórios de acordo com o funcionamento da Comissão de Ética para a Saúde do Hospital de Braga (CESHB).
[c] Documento de Consentimento Informado, Livre e Esclarecido para Participação em Investigação de acordo com a Declaração de Helsinquia[1], a Convenção de Oviedo[2] e o Regulamento Geral de Proteção de Dados (RGPD)[3]. Guião na elaboração do consentimento informado é disponibilizado pela ARSN[4] e através do "Documento CEIC sobre o Regulamento Geral de Proteção de Dados (RGPD) no contexto da Investigação Clínica"[5].

Acesso aos documentos da alínea c):
[1]http://portal.arsnorte.minsaude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf
[2]http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf
[3]https://eur-lex.europa.eu/legal-content/PT/TXT/?uri=celex%3A32016R0679
[4]http://www.arsnorte.min-saude.pt/consentimento-informado/
[5]http://www.ceic.pt/documents/20727/0/Documento+CEIC+sobre+o+Regulamento+Geral+de+Prote%C3%A7%C3%A3o+de+Dados+%28RGPD%29_publica%C3%A7%C3%A3o/ced81411-5fe4-46f5-a613-c7c716abbb4b
[6]https://dre.pt/home/-/dre/123815982/details/maximized

Justificação do Parecer

Trata-se de um projeto a realizar no âmbito insere-se no âmbito de um Programa Doutoral de Psicologia Básica no Departamento de Psicologia Básica da Escola de Psicologia da Universidade do Minho, com o apoio institucional da última, para a sua realização na Unidade, com duração de 16 meses e com término previsto para dezembro de 2022.

Os Investigadores Responsáveis têm formação académica e experiência solidificada nas áreas de base do projeto.

O objetivo geral do projeto é estudar os correlatos eletrofisiológicos durante uma tarefa de impulsividade de espera e testar o efeito da Estimulação Transcraniana por Corrente Alternada (ETCA) ativa em comparação com a Estimulação placebo (sham) nas respostas prematuras e atividade eletrofisiológica. São objetivos específicos do projeto comparar: i) avaliar a diferença funcional entre pista-P3 e alvo-P3; ii) explorar associações entre traços de impulsividade (avaliada pela Escala de Impulsividade de Barratt e a Escala de Comportamento Impulsivo

UPPS-P), dados eletrofisiológicos (i.e., amplitude de P3 e poder de delta/teta) e marcadores comportamentais (i.e., número de respostas prematuras e tempo de resposta).

Trata-se um estudo prospetivo, randomizado, duplamente cego, com intervenção. A população-alvo são estudantes saudáveis da Universidade do Minho e Universidade Portucalense, recrutados na região de Braga e Porto. Estima-se incluir cerca de 51 participantes. Foram definidos critérios de inclusão e de exclusão.

A seleção de participantes será realizada com recurso a uma triagem *online* inicial, usando um questionário online na plataforma Google Forms, e uma sessão presencial que compreende o preenchimento de questionários clínicos (Expls. Escala de Depressão, Ansiedade e Stress, Escala de Impulsividade, Teste de identificação de perturbação do uso de álcool e outras substâncias...) e a sessão experimental (com colocação dos elétrodos do eletroencefalograma (EEG) e da ETCA de modo a permitir uma estimulação concomitante à recolha de dados do EEG enquanto os participantes realizam a Tarefa de Respostas Prematuras com Pistas (TRPP)). Estima-se que as avaliações durem cerca de 1 hora e 45 minutos. Os questionários a aplicar foram disponibilizados para apreciação.

Após o recrutamento, cada participante será colocado num de três grupos experimentais: i) Placebo & ETCA Ativo sincronizado com Pista-P3 (P&A-P), ii) Placebo & ETCA Ativo sincronizado com Alvo-P3 (P&A-A) e iii) Placebo & Placebo (P&P).

Os dados recolhidos incluem: informações sociodemográficas e informação sobre o estado anímico, e eventual consumo de substâncias, seu padrão e sentimentos associados. Variável, tipo de variável e descrição da mesma foram descritas no protocolo de investigação e foram fornecidos em anexo os Formulários de Recolha de Dados.

O projeto não envolve a colheita de tecidos e/ou células de origem humana. Os participantes serão submetidos a avaliação por Estimulação Trancraniana por Corrente (ETCA), uma técnica não invasiva de estimulação cerebral que se encontra em fase de estudo e que tem sido amplamente utilizada de forma segura em populações saudável e clínica.

Será salvaguardado o anonimato e a confidencialidade do participante (não haverá identificação nominal do titular, sendo aposto um código de participante no estudo).

Todos os dados recolhidos serão anonimizados, será atribuído a cada paciente incluído no estudo um código único no momento da inclusão no estudo. A informação recolhida sobre os participantes será guardada num documento informatizado/armário próprio do estudo fechado, ao cuidado do Investigador Responsável, sendo sua responsabilidade a manutenção da confidencialidade.

Os participantes serão informados dos procedimentos, da garantia de confidencialidade dos dados e do seu direito de desistir em qualquer momento do estudo sem qualquer prejuízo.

Não estão previstos quaisquer abusos de recursos institucionais para a realização do projeto.

Não se declaram existirem conflitos de interesse.

Não se declara a investigação envolver diretamente indivíduos privados do exercício de autonomia (crianças, menores, pessoas com incapacidade temporária ou permanente do exercício de autonomia).

Documentos recebidos no órgão institucional de ética da UMinho

Foram recebidos os seguintes documentos:

- Protocolo de investigação
- Curriculum vitae abreviado dos investigadores responsáveis)
- Parecer do diretor do centro de investigação
- Declaração do orientador no compromisso na orientação e/ou Termo de Responsabilidade
- Modelo de documento de consentimento informado
- Modelo de declaração de compromisso a utilizar pelo(a) IR e por outros investigadores ou colaboradores na investigação destinado a documentar o seu envolvimento nas garantias de confidencialidade e boas praticas dadas pelo(a) IR (Termo de Responsabilidade)
- Cópia dos formulários de recolha de dados a utilizar e/ou enumeração dos dados que serão colhidos
- Curriculum vitae abreviado do aluno