UNIVERSITY OF PADOVA

Department of General Psychology

Master Degree in Cognitive Neuroscience and Clinical Neuropsychology

Final dissertation:

The effect of mood in modulating prefrontal transcranial Direct Current Stimulation (tDCS) cognitive outcomes: A systematic review and meta-analysis

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Academic Year 2021/2022

ABSTRACT

In recent years, several studies in cognitive neuroscience investigated the impact of prefrontal transcranial Direct Current Stimulation (tDCS) on executive functioning. However, the mixed results obtained so far suggest the need for meta-analytic approaches and meta-regression methods, aimed to both synthesize outcomes across studies and potentially identify the reasons for their variability. The present work aimed to test the hypothesis of mood as a possible moderating factor in the effect of prefrontal tDCS on executive functions. This hypothesis stems from the evidence showing that the region targeted by tDCS studies on executive functions, i.e. the dorsolateral prefrontal cortex (dlPFC), is also involved in mood and emotional regulation. Hence, our hypothesis suggests that dlPFC is the shared neural underpinnings of the circuits of mood and executive functioning, and that mood influences the performance of cognitive tasks. Mood disturbances are often linked to cognitive deficits, and there is some evidence in research that suggests that mood states could influence cognitive performance. Moreover, different models attempt to explain how mood modulates cognition, for example by making some contents more available or by triggering different process strategies during cognitive tasks. To test this hypothesis, a systematic review and meta-analysis have been conducted by selecting anodal tDCS studies targeting the dlPFC. The included articles were 19 within-group, sham-controlled and single-session experiments. Every article included at least a mood measurement at baseline and a cognitive task performed after or during stimulation. In this study, both clinical and healthy populations were included. Results discarded mood as a modulating factor of cognitive performance in dlPFC-tDCS. Furthermore, tDCS led to no effect on cognitive outcomes. In conclusion, our analysis adds to the literature by supporting the evidence for a lack of relevant effect of dlPFC-tDCS on bettering cognitive performance, as well as ruling out the mood as a potential factor that explains the variety of findings.

The effect of mood in modulating prefrontal transcranial Direct Current Stimulation (tDCS) cognitive outcomes: A systematic review and meta-analysis

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CHAPTER 1

Prefrontal tDCS and cognitive enhancement: state of the art

1.1 transcranial Direct Current Stimulation: definition and basic principles

Among the so-called Noninvasive Brain Stimulation (NIBS) techniques, transcranial Direct Current Stimulation (tDCS) falls into the category of transcranial Electric Stimulation (tES). As with any other tES, tDCS is a neuromodulatory intervention that involves the usage of a low-voltage applied to the scalp through electrodes that results in changes to the permeability of the cellular membrane. In tDCS, the delivered current is sustained and direct, with a constant polarity going from the anode to the cathode. This type of stimulation is too weak to generate action potentials at the level of the transmembrane neuronal potential, therefore it remains subthreshold and induces small changes by increasing or decreasing the likelihood of a neuronal response (Wagner, Fregni, et al., 2007). Since tDCS does not produce any activity but it modulates it, it is purely considered a neuromodulatory tool.

This type of technique differentiates itself from the other most commonly employed NIBS, the Transcranial Magnetic Stimulation (TMS), for the source of neuromodulation and type of effect at the neuronal level, as TMS modulation stems from the application of a magnetic field on the scalp that alters the excitability of neurons, depolarizing them, hence producing an action potential. The two different mechanisms which follow the application of tDCS and of TMS are shown in Figure 1: the polarization of the membrane potential following tDCS, and the excitation and production of action potential following TMS. Thus, TMS is a device used not only in neuromodulation but also in neurostimulation.

Instead, the main aim of tDCS is just to provoke alterations to the ongoing activity of neurons. Following this type of modulation, multiple changes and mechanisms of action are detected at both focal and more distant levels.

What can be said of the local effects of tDCS is that it alters the electrical and synaptic activity of neurons by shifting the resting membrane potential. The direction of these changes, however, follows no general rule, since the effects of the stimulation depend on many different factors. An important factor is the state of activity of the targeted neurons: if active, it results in an effect on the firing rate

of the neuron; in not active, it results in a shift of the membrane potential (Knotkova et al., 2019; Lefaucheur et al., 2016).

Another factor is the electrode montage and the consequent polarity of the electrode applied to the targeted area. Evidence has revealed a clear influence

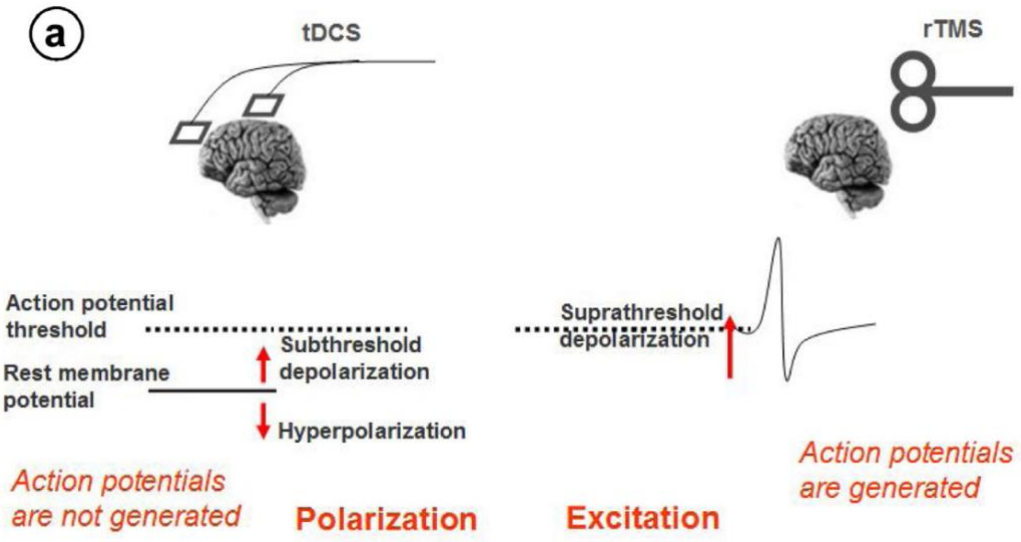

Figure 1. The different mechanisms that take place in the transmembrane neuronal potential when applying tDCS (on the left) and rTMS (on the right). (Lefaucheur and Wendling, 2019).

of polarity on the motor cortex, where anodal tDCS is linked to excitatory effects, and cathodal tDCS results in inhibitory effects (Nitsche and Paulus, 2000). This pattern, however, seems to be limited to the stimulation of the motor areas, since the homogeneity of results ceases when applying the same observation to the stimulation of other cortical areas (Lefaucheur et al., 2016).

Additionally, the orientation of axons and dendrites with respect to the electric field is relevant too: in an experiment conducted in 2004, Bikson and his colleagues found that while the soma of a pyramidal cell in the hippocampus was depolarized by an anodal current, the dendrites of the same neuron were hyper-polarized by the same current (Bikson et al., 2004; see also Knotkova et al., 2019).

Therefore, to better understand the variability in the effects of tDCS, as well as to investigate beyond its focal impact, research has recently set up studies in which tDCS has been paired with electroencephalogram (EEG) and neuroimaging.

Such studies form a body of evidence of changes in distant network connectivity following focal tDCS stimulation (Liew et al., 2014), investigated with the help of tools such as EEG, fMRI, and MEG.

For example, a tDCS study paired with EEG has found increased intrahemispheric connectivity and increased connectivity patterns in motor regions when administered anodal tDCS on left M1 during a motor task on healthy subjects (Polania et al., 2011a). Although such results are largely found in studies on motor areas, the effect is not limited only to said regions. For instance, another study investigated connectivity with fMRI following left dlPFC stimulation while subjects were at rest, and an increase in the connectivity patterns between prefrontal and parietal areas was found (Peña-Gómez et al., 2012).

If on one hand, the presence of these distant effects has been consistently found, on the other, the pattern of these alterations in connectivity is hard to predict due to the variability among the findings. Since various factors have a great influence on the outcomes such as the type of task or montage and could account for this heterogeneity, further research on this topic is needed.

Nonetheless, what can be undoubtedly concluded is that DC stimulation induces alterations at both focal areas and connected but more distant areas, and both at a local neuronal as well as a functional connectivity level.

1.2 tDCS: protocols and setup

As represented in Figure 2, the typical tDCS setup involves the application of at least two electrodes of 25 squared cm (Moreno-Duarte et al., 2014): the anode, from which the current enters the body, and the cathode, from which the current exits (Knotkova et al., 2019). In the tDCS setup, the polarity of each of these two electrodes never changes. The current flowing between the two is constant and low-intensity, ranging from 0,5 to 2 mA (Wagner, Valero-Cabre, et al., 2007) and applied for a time usually varying between 10 and 20 minutes (Nitsche et al., 2008).

Depending on where they are positioned with respect to the target area, the electrodes will take on the role of the working electrode or of the reference electrode, and the typology of stimulation will be anodal or cathodal according to which electrode is positioned above the target area.

It should be clarified, however, that placing an electrode above the part of the scalp corresponding to the location of the area of interest does not mean that the stimulation is specifically targeting said area (Moreno-Duarte et al., 2014). Indeed, tDCS and the other tES have a low spatial resolution, and that is due to the fact that electric current tends to spread where there is low resistance: when it meets the cranial bone, it tends to propagate unevenly and in a poorly controlled manner. In addition, there are some factors that can aggravate the problem. For instance, tDCS usually does not make use of a neuronavigation tool for the placement of electrodes. Moreover, the electrodes that are typically applied are big, thus not producing a focal modulation.

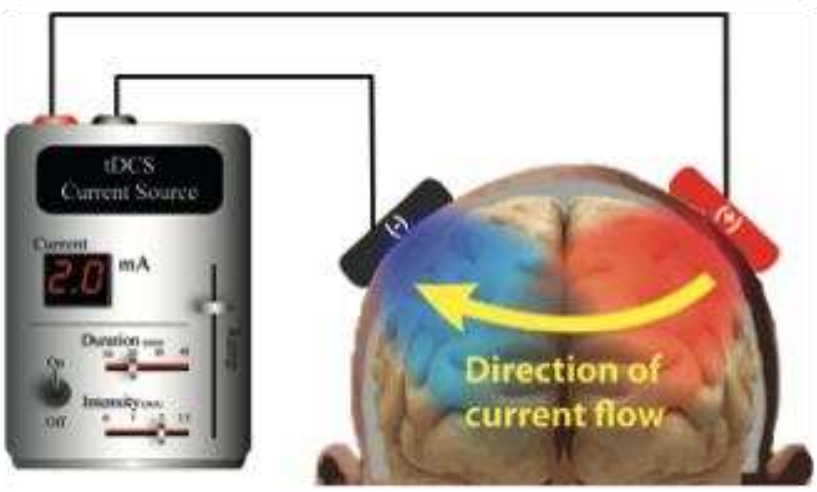

Figure 2. tDCS parameters: intensity (mA), duration, and direction. The current in tDCS flows from the anode (+) to the cathode (-). (Moreno-Duarte et al., 2014).

In order to improve the spatial resolution of tDCS, stimulation systems have recently been developed in which the usage of multiple smaller electrodes – whose size is usually around less than 5 squared cm- has been implemented. These tDCS montages are defined as High Definition tDCS (HD-tDCS) and result in a much more focal electrical field than the conventional tDCS montage. To do so, HD-tDCS is characterized by the application of multiple electrodes, which reduces the dispersion of the electric field. For example, in the HD montage that has been mostly studied, the HD-tDCS 4 x 1 ring montage, there are five electrodes arranged in one central active electrode surrounded by four electrodes opposed in polarity. Since there are many small electrodes so close to one

another, not only is the focality of cortical stimulation increased, but also the intensity of the stimulation itself. The current flow is, in fact, contained in the space of the ring. In Figure 3, conventional tDCS and HD-tDCS 4 x 1 montages are compared. As can be seen, the focality and the intensity of the stimulation montage are higher in the HD-tDCS.

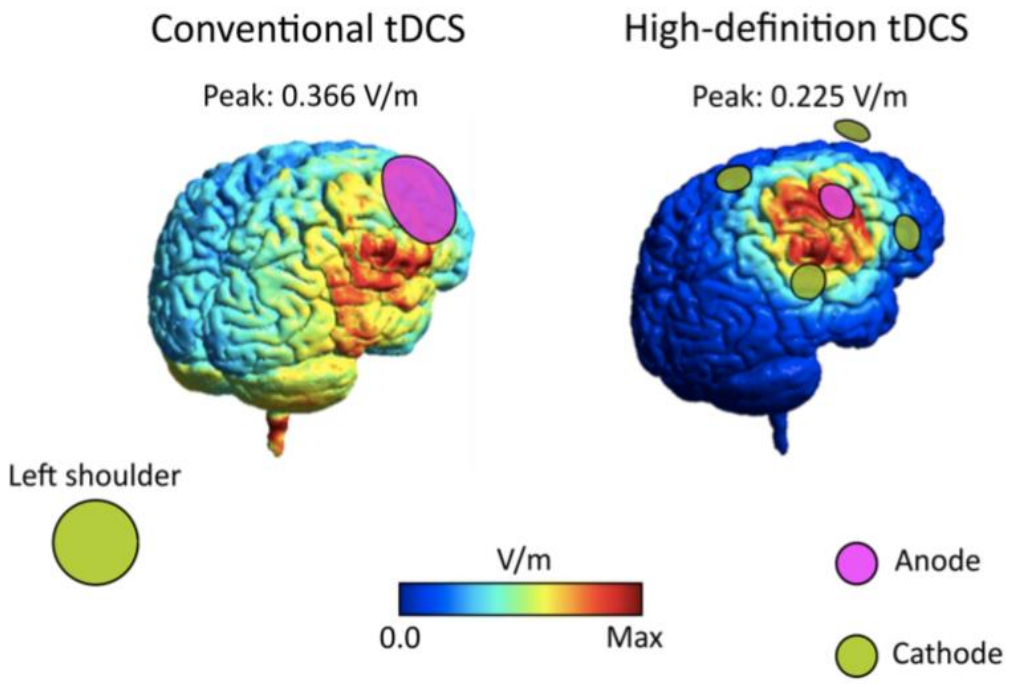

Figure 3. The comparison between the conventional tDCS montage with two electrodes (on the left) and the HD-tDCS 4 x 1 ring montage (on the right). In this image, electric field models are shown, simulated with SimNIBS. (Masina et al. 2021)

Since in our meta-analysis we selected studies with a conventional tDCS montage, the focus will be on this type of stimulation from now on.

1.2 tDCS and cognitive enhancement

A topic that has been especially investigated in tDCS research is how it can impact cognitive functions and cognitive tasks performance. In fact, a broad branch of research has stemmed from the use of this technique since the brain stimulation occurring from tDCS not only modifies neuronal activity but has also been shown to induce subsequent changes in brain functioning (Knotkova et al., 2019; Lefaucheur and Wendling, 2019).

tDCS seems to be particularly interesting for neuropsychological research, given the promising results coming from those studies testing the relationship between tDCS and cognitive processes (Fregni et al., 2005; Monti et al., 2008; Coffman, Clark, and Parasuraman, 2014; Looi et al., 2016; DeDoncker et al., 2016). Indeed, a tool to ameliorate cognitive functions would be a major breakthrough considering that cognitive functioning accounts for the majority of the human mind, as it is a general term that underlies many other processes. It includes "cold" cognitive functions, such as memory, attention, language, decision making, and learning, and "hot" ones, like emotion processing, emotional prosody, and empathy. It refers to higher-level functions of the brain that affect every aspect of human life. A comprehensive definition of cognition has been given by Leon, Arendt and Levin: "Cognition comprises the sensory and other information- processing mechanisms an organism has for becoming familiar with, valuing, and interacting productively with features of its environment [exploring, exploiting, evading] in order to meet existential needs, the most basic of which are survival/persistence, growth/ thriving, and reproduction" (Leon, Arendt, and Levin, 2021).

Moreover, a technique that provides cognitive enhancement would also be significantly relevant for many neurological and psychiatric disorders which present impaired or altered cognition, such as stroke, Alzheimer's and Parkinson's disease, depression, bipolar disorder, schizophrenia, and substance abuse disorders.

Research has thus begun to focus on the use of tDCS as a tool to enhance brain functioning, both for cognitive enhancement and betterment of performance (Coffman, Clark, and Parasuraman, 2014) and as a clinical treatment for disorders with cognitive symptoms (Lefaucheur et al., 2016). Furthermore, tDCS also represents a potential method to investigate the cause-and-effect relationship between a certain neural structure and cognitive functions. Improvements in healthy subjects have been observed in the form of potentiation

of learning and memory, as well as enhancement in working memory, attention, and perception (Coffman, Clark, and Parasuraman, 2014). Here are some of the findings obtained by studies on healthy subjects.

Antal and his team applied a 10-minute tDCS stimulation during the learning phase of a visuomotor coordination task. The targeted areas were the middle temporal area, the primary contralateral motor area, and the primary visual cortex. They found that the accuracy of the tracking task increased when the left middle temporal area was stimulated using anodal tDCS (Antal et al., 2004a). This study is relevant because it shows how tDCS can improve implicit memory, and motor learning specifically. Another study, by Kincses et al., revealed the efficacy of anodal stimulation of the prefrontal cortex in implicit probability learning. Subjects performed a probabilistic classification learning in which they had to determine whether a combination of stimuli predicts a particular weather condition or not. To do so, they were presented with repeated stimuli combinations associated with different percentages to different weather conditions: through repetition, they could learn the implicit rule. Anodal stimulation resulted in facilitating probability learning when the left prefrontal cortex was targeted (Kincses et al., 2003).

However, it is not only implicit learning that benefits from DC. Clark et al. applied a 30 min anodal tDCS over the right inferior frontal and right parietal cortex to test explicit learning. In detail, they had to learn to detect concealed objects through feedback in the concealed object learning paradigm. Before the task, the subject would undergo a training period and for the whole learning phase, the stimulation was on. The result was an improved performance during, immediately after, and one hour after tDCS administration over the right inferior frontal cortex (Clark et al., 2011).

A more recent study tested the effects of combining tDCS and cognitive mathematics training to see if it would add improvements to the ones following the cognitive training alone. The targeted areas were the bilateral dorsolateral Prefrontal Cortex (dlPFC) and the stimulation further improved training performance immediately and after two months, as well as transferring to working memory performance as well (Looi et al., 2016).

Leaving learning aside, different experiments showed an enhancement in working memory performance following the stimulation of the prefrontal cortex (Fregni et al., 2005; Boggio et al., 2006; Andrews et al., 2011). The same

happened in different experiments investigating attention networks. Coffman et al. (2012) used the Attention Network Task (ANT) delivering tDCS on the inferior frontal cortex during the training phase. Alerting is one of the three components of attention (alerting, orienting, and executive attention) and its scores were significantly greater following the 30 minutes stimulation (Coffman et al., 2012b). Sparing et al. (2009) applied tDCS -anodal, cathodal, or sham- on the left or right posterior parietal cortex. Offline subjects would perform a visual detection task. Anodal tDCS in healthy subjects increased detection accuracy, as well as decreased reaction times, proving the facilitating effect of anodal tDCS on attention processes (Sparing et al., 2009a).

Moreover, further data on attention enhancement come from Yadollahpour, Asl, and Rashidi, who reviewed 10 studies on tDCS and attention improvement in healthy subjects (Yadollahpour, Asl, and Rashidi, 2017). The target areas of these studies were the dlPFC, right parietal, and right inferior frontal gyrus, and the average stimulation lasted between 15-30 minutes, with a current intensity ranging between 1 and 2 mA. The majority of these studies have resulted in long-lasting beneficial effects on attention, suggesting that tDCS could be considered a booster tool for attentional processes (Yadollahpour, Asl, and Rashidi, 2017).

For what concerns language enhancement, in Sparing et al. (2008) anodal and cathodal tDCS was administered over the left posterior perisylvian region (PPR). They tested the impact of tDCS on language processing by presenting a visual picture naming task to subjects that had to complete it both online and offline. The study revealed that subjects improved their performance, i.e. it shortened the naming latencies, compared to sham (Sparing et al., 2008).

In regard to the effects of tDCS on cognitive symptoms in neurological patients, there is some evidence for the amelioration of cognition in these populations. For example, Parkinson's disease patients reported beneficial long-term effects on non-motor symptoms, such as executive functions, after a two-week tDCS session (Doruk et al., 2014). Improvements were also reported in aphasic patients, in a study in which chronic non-fluent aphasic patients were administered tDCS over the left frontotemporal areas and showed increased accuracy at the picture naming task after cathodal stimulation with respect to sham and anodal stimulation (Monti et al., 2008).

tDCS showed beneficial effects also in people with depression, whose mood increased after repeated sessions stimulating the left dlPFC (Boggio et al.,

2008a; Loo et al., 2012), and people with schizophrenia, who reportedly experienced reduced auditory verbal hallucination (Brunelin et al., 2012a; Mondino et al., 2015) and overall improvement in the score at SANS (Scale for the Assessment of Negative Symptoms) and PANSS (Positive and Negative Syndrome Scale) (Palm et al., 2016b) after left dlPFC stimulation.

In conclusion, even if there is a great variety of results concerning the effects of low-intensity DC stimulation, there is substantial enough evidence that suggests the benefits of tDCS in enhancing cognition.

1.2.1 Prefrontal tDCS and executive functions

Among the different structures and areas of the cortex, the target area relevant to our meta-analysis is the dlPFC, thus the focus will be on this specific region from now on. Besides, dlPFC has been especially investigated in the field of non-invasive brain stimulation with respect to the other portions of the prefrontal cortex. This is due to the location of this portion of the cortex, which is easily reachable from the scalp. Given that tDCS stimulates the cortex but doesn't reach structures located deeper in the brain (Thair et al., 2017), the proximity of dlPFC to the scalp makes it one of the most suitable structures to investigate the effects of tDCS.

Valuable information on the dorsolateral circuit and the cognitive functions that it underpins come from clinical neuropsychological investigations. In fact, as a result of dorsolateral lesions or disruption of the dorsolateral circuit, a typical clinical picture called dysexecutive syndrome has been observed. This syndrome presents alterations of the normal executive functioning, which leads to perseveration, organization deficit, working memory deficit, impairments in planning and action execution, worsening of verbal performance, and a decrease in sustained and selective attention (Szczepanski and Knight, 2014; Reber and Tranel, 2019). One of the most supported roles of dlPFC is its involvement in the top-down control of human behavior, which allows flexibility in goal-oriented actions so that one's behavior aligns with one's intentions. Since flexible behavior is opposed to automatic responses, inhibition of fixed behavior is required to allow for such dynamic behavior. While top-down control enables the ability of task switching, the lack of it results in perseverations of learned or automatic responses. Perseveration is a common symptom resulting from lesions to other parts of the cortex. However, when this is the case, the impairment is limited to a

specific sensory domain, while when it follows an injury affecting the dlPFC specifically, perseveration is generalized to all cognitive processes, independently from the modality. Another deficit resulting from alterations to the dlPFC is related to the planning and the adoption of different strategies aimed at the execution of a task, particularly widespread as it underlies and involves many other cognitive functions (Làdavas and Berti, 2014, chapter 9).

For example, working memory is impaired in dlPFC patients, meaning that they present deficits in the manipulation and monitoring of that information held in memory to perform a certain task (Tsuchida and Fellows, 2009; Barbey, Koenigs, and Grafman, 2012). A study on lesions to the Brodmann areas (BA) 9 and 46 - namely the dlPFC- reported impairments in the Letter–Number Sequencing test (adapted by Wechsler, 1945) and the Spatial Span Backward test (adapted by Wechsler, 1945) with respect to the control group. Both of these tests required the manipulation of the content in working memory, verbal and auditory in the former and non-verbal and spatial in the latter. Hence, the authors suggested that dlPFC, especially the left side, is necessary for information manipulation in working memory (Barbey et al., 2013).

Top-down attention is another process that is undermined by damage to the dorsolateral circuit. In an ERPs study, lesions to dlPFC led to top-down attention and working memory deficits, as patients showed an electrophysiological decrease in neural activity in the ipsilesional visual cortex (Voytek et al., 2010).

Another study confirming the role of dlPFC in attention is Chao and Knight's lesion study (1998) where dlPFC patients had impairments in inhibiting auditory distractors during a delayed-match-to-sample task. They also showed a greater primary auditory ERP to the distractors than controls in correspondence with the increased interference effects that followed the distracting sounds, supporting the hypothesis that dlPFC is crucial to gating unnecessary information and endogenous attention (Chao and Knight, 1998).

Problem-solving is another function majorly impacted by alterations to the dlPFC. Lesions in this portion of the cortex are often linked to a decreased ability to face complex situations that require behavioral organization, and their resulting behavior is chaotic and disorganized. This deficit shows up when the patient is required to select simple behavioral schemes, and organize them in a new way, such as in the Tower of London test (Shallice, 1988a) or the Tower of Hanoi test (Lucas, 1883).

Overall, all the presented deficits that follow alterations in the functioning of dlPFC can be gathered and described by the same umbrella term: executive functioning. In fact, a large body of evidence in research allocates the role of the coordinator of the executive functioning to the dlPFC. For these reasons, prefrontal tDCS, in particular dlPFC tDCS, is studied in relation to executive functions and performance at cognitive tasks.

The connection and the relevance of dlPFC stimulation in cognitive performance have been supported by many studies reporting significant effects (DeDoncker et al., 2016; Hoy et al., 2013; Berryhill and Jones, 2012; Papazova et al., 2018). On the other hand, many others resulted in little to no effect, even when the experimental designs were the same. In fact, Sarkis et al. (2014) conducted a review on the effects of prefrontal tDCS on executive functioning in studies up to 2014 and concluded that there is a lack of consistency among studies, especially in the one where clinical populations were involved. He stated that not only the findings and the study protocols present in the current research were extremely variable, but some results were even contradicted each other. In his work, he included studies that applied stimulation on the site F3 or F4 of the EEG 10-20 international system, corresponding to the location of the left and right dlPFC. The population of the included studies was both clinical and healthy (Sarkis et al., 2014).

Here follows a brief summary of some conflicting articles - coming from both Sarkis' review (2014) and more recent research - about prefrontal tDCS and executive functions.

On one hand, multiple experiments have resulted in clear effects of tDCS in altering the ability of the participant in those tasks assessing executive functions. For example, working memory performance has proven to increase after stimulating the left dlPFC. In Hoy et al. (2013), healthy participants underwent three sessions of anodal dlPFC tDCS, receiving randomly either 1 mA active tDCS, 2 mA active tDCS, or sham. An n-back task was performed after each stimulation. Results showed an enhancement in participants' working memory, expressed as a significant decrease in reaction times, particularly in the 1 mA condition (Hoy et al., 2013). In Berryhill and Jones (2012), and amelioration of working memory in healthy older adults followed the application of tDCS of dlPFC. The improvement was selective for the high-education group, where cognitive performance at the verbal 2-back tasks significantly improved after active rather

than sham stimulation (Berryhill and Jones, 2012). Moving to a clinical population sample, people with schizophrenia revealed an increase in working memory performance following stimulation. In this study, patients performed a verbal n-back task at baseline while receiving, randomly, either sham or active anodal tDCS on the left dlPFC. Results demonstrated a better WM accuracy during the active anodal stimulation (Papazova et al., 2018).

On the other hand, other experiments did not share the same findings.

For instance, Motohashi et al. (2013) found no improvement in the performance at the n-back following tDCS on the left dlPFC. In this sham-controlled study, healthy participants underwent 4 days of anodal dlPFC stimulation and, after a washout period, 4 days of sham in a randomized order. They performed cognitive tasks at baseline, at the end of the first 4-days period, and at the end of the experiment. Out of all the cognitive tasks that they had performed, apart from a small enhancement in the visual recognition task, participants reported no effect following tDCS (Motohashi et al., 2013).

Similarly, there is contrasting evidence in attentional performance as well. In Nelson et al. (2014), sustained attention was assessed using a vigilance task. In the meantime, participants received either anodal, cathodal, or sham tDCS on the left dlPFC. Anodal stimulation led to a significant increase in task accuracy (Nelson et al., 2014). In Silva et al. (2017), sham and anodal tDCS on the left dlPFC was delivered in fibromyalgia patients. Attention was assessed through the Attention Network Test (ANT; Fan et al., 2002), and the performance at which improved at two out of three attentional components following active stimulation, namely orienting and alerting (Silva et a., 2017). However, in another sham-controlled study, healthy students received the same stimulation on dlPFC and performed the same ANT task, with very different results. This time active stimulation led to no effect on any of the attentional components (Lema et al., 2021).

The contradiction is not limited to individual articles but is also present in systematic reviews.

For example, the overall performance of executive functions has been reported to be enhanced following tDCS by DeDoncker et al. (2016). In this systematic review and meta-analysis, the authors included 61 within-group studies to attempt to understand the effect of tDCS on dlPFC. The selection criteria consisted of having similar protocols, namely to be single-session articles,

randomized, sham-controlled, and which had F3 or F4 as target sites for the stimulation, the sites associated with dlPFC. The overall population included healthy and neuropsychological samples. In each included article, subjects performed cognitive tasks, that were divided into three categories: memory tasks, attention tasks, and executive functioning tasks. The final analysis reported an overall significant effect following anodal dlPFC stimulation compared to sham and cathodal stimulation. To be more precise, the pattern of effects was different between healthy and neuropsychological subjects. In the former, anodal stimulation led to a significant decrease in reaction times, resulting in faster responses; however, they did not report an increase in accuracy. In the latter, instead, anodal stimulation led to a significant betterment in the accuracy of the tasks, but only a non-significant trend of enhanced response speed was found (DeDoncker et al., 2016). Hence, although the single-session stimulation comported no significant effect on global executive functioning, anodal stimulation did lead to a significant effect.

Similarly, in another meta-analysis, Imburgio and Orr (2018) included 27 articles that were single-session, that targeted F3 or F4 during stimulation, and in which subjects performed cognitive tasks. Executive functioning performance was divided into working memory, inhibition, and set-shifting ability. The analysis resulted in no effect on general executive function. However, a subgroup analysis run by the cognitive domain showed a significant effect on working memory, which increased following anodal dlPFC-tDCS (Imburgio and Orr, 2018).

On the contrary, Horvath et al. (2015) found no effect of tDCS on any neuropsychological measures other than motor evoked potentials, not even in working memory performance. The authors conducted a systematic review of outcome measures of a healthy population. Measures were included if they had been replicated at least twice and from different authors (Horvath et al., 2015).

Another review that exposed the ample variability is Tremblay et al.'s (2014) work. The author included 61 articles in which tDCS stimulation targeted dlPFC - namely the location of electrodes was F3 or F4 - and subjects were involved in cognitive tasks. Results showed great variability and were probably dependent on a wide array of factors. At the same time, anode over left DLPFC led to decreased working memory performance and other executive function performance, as well as increasing working memory and many other executive functions in other studies. The author suggested that variability is due to many

different design factors, but that it could also be accounted for by a variety of individual characteristics (Tremblay et al., 2014).

Overall, this brief overview described the current state of the art on the effect on executive functions of tDCS over the dlPFC. studies on executive functioning. It appears clear that there is a wide heterogeneity among results. This variability highlights the need for additional research, aimed to shed some light on this topic by investigating the reasons for the heterogeneity.

CHAPTER 2
Mood, cognition, and prefrontal tDCS

2.1 dlPFC and mood

As previously discussed, dlPFC is a hub for cognition and, more specifically, for executive functions. However, its roles go beyond that. Indeed, it is also an important area for motivation and emotion regulation. Several studies have in fact demonstrated that dlPFC lesions are often associated with the so-called *pseudodepressive syndrome* concurrent to the most usual *dysexecutive* one. Symptoms consists of a decreased motivation, a general lack of interest in initiating activities, and blunt emotional expression. Hence, following damage to the dlPFC, along with cognitive deficits appear alterations to the emotional sphere, namely abulia, apathy, and lack of initiative (Blumer and Benson, 1975; Szczepanski and Knight, 2014).

For what concerns emotion regulation, evidence from clinical research literature has shown that stimulation of dlPFC has an “antidepressant effect” (Lefaucheur et al., 2016) and that a decrease in its activity is related to an increased depressed mood.

An interesting work by Koenigs and Grafman (2009) has summarized the supporting evidence to the hypothesis stating that the hypoactivity of dlPFC is involved in the development of depression. Neuroimaging studies of patients with depression have revealed a negative correlation between depression levels and dlPFC activity: the more severe is the depression symptoms, the lower the dlPFC activity is (Koenigs and Grafman, 2009).

Evidence coming from tDCS studies confirmed the role of dlPFC on mood and emotion regulation.

The first study that reported an improvement of depressive symptoms following tDCS on the dlPFC dates to 2006 (Fregni et al., 2006). Since then, multiple studies applied repeated anodal tDCS to the dlPFC and obtained improvements in participants' mood levels. According to Lafaucheur’s report, dlPFC tDCS seems to be the most promising and efficient stimulation to reduce depressive symptoms, especially if a 2 mA current is used for at least 20-30 minutes per session (Lafaucheur et al., 2017). For instance, Boggio et al. (2008) applied anodal tDCS on left dlPFC in patients affected by major depressive disorder. In

this sham-controlled study, subjects underwent a ten-session treatment in which tDCS was delivered at 2 mA for 20 minutes daily. Mood levels were assessed with questionnaires, namely the Hamilton Depression Rating Scale (HDRS-21; Hamilton, 1960; Hedlund and Vieweg, 1979) and Beck Depression Inventory (BDI; Beck, et al., 1996), at baseline and 15 days and 30 days after the end of the treatment. The Control group was divided into an active control group, receiving active tDCS on a non-prefrontal site, and a sham one. When compared to both control groups, the dlPFC active group reported significantly higher mood levels after the treatment. Moreover, this result persisted for one month since the end of the treatment (Boggio et al., 2008a).

Another example is a bifrontal tDCS study in which anodal tDCS was applied on the left dlPFC, while cathodal tDCS was applied on the right dlPFC (Brunoni et al., 2013b). Here, patients with major depressive disorder (MDD) received a six-week treatment, consisting of twelve 30-minute sessions. Depression was assessed using Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) at baseline and at week six. Analyses revealed a significant effect of tDCS, when compared to sham, as the changes in MADRS scores were significantly higher in the former. The authors used the same protocol in another sham-controlled experiment in 2014, and the results in MDD patients confirmed the improvement of mood - assessed by the HDRS-21 (Hamilton, 1960; Hedlund and Vieweg, 1979) and BDI (Beck, et al., 1996) - following a 10-session tDCS treatment (Brunoni et al., 2014a).

In 2015, Meron et al. conducted a meta-analysis on the efficacy of tDCS in major depressive episodes. The analysis of 10 randomized controlled trials (RCTs) revealed a significant effect of tDCS in reducing depressive symptoms. Active groups resulted in lower depression rating scale scores compared to sham groups. The authors concluded that an effect of tDCS as a treatment for major depressive episodes is probable (Meron et al., 2015).

Another recent meta-analysis revealed a modest effect of active tDCS compared to sham on mood (Razza et al., 2020). The authors included 23 RCTs in which patients with depressive episodes received left prefrontal anodal tDCS. The primary outcome consisted of the comparison between depression scores at baseline and at end of the treatments. Once again, active groups resulted in more substantial improvements in depression scores with respect to sham (Razza et al., 2020).

In summary, the presented evidence points toward a clear role of the dlPFC in mood regulation, suggesting that hypoactivity of left dlPFC is linked to decreased mood tone, whereas the increased activity correlates with higher mood levels.

2.2 Mood and executive functions

The previous findings allocate a second role to dlPFC: besides being the coordinator of executive functioning, it seems to be also a suitable regulator of mood tone. Hence, the two domains seem to share their neural underpinnings, at least to a certain extent, since dlPFC is a central structure in their functioning. Indeed, mood disorders, not only are associated with emotional and mood tone dysfunctions but also with significant cognitive impairments. In a relevant review, Marvel and Paradiso (2004) reported and discussed the cognitive impairments and alterations that have been associated with some mood disorders, such as unipolar depression and bipolar disorder. The areas of cognition that they noted to be the most impaired in those mood disorders were attention, memory, and executive functions. In regards to the latter, there is a cluster of studies that assessed the executive functioning using cognitive tasks like the Card Sorting Test (WCST; Heaton et al., 1993), the Trail Making Test, Part B (TMT-B; Reitan, 1958), and the Stroop Test (Stroop, 1935), to assess cognitive performance in clinical populations. Compared with healthy controls, patients with bipolar disorder and depression had significantly lower scores, especially during their acute phases (Zubieta et al., 2001; Paradiso et al., 1997; Austin et al., 1992). One of the most interesting findings is that the cognitive symptoms seem to worsen when the depressive or mood symptoms worsen, suggesting a state-dependent dynamic. For example, in McGrath et al. (1997), patients with schizophrenia and patients with bipolar disorder completed the WCST at two different times. Whereas in the first session both their scores resulted extremely impaired compared to the controls, in the second one the mania group showed a significant improvement compared to the schizophrenia group, resulting instead close to the controls' score. Interestingly, the first session of WCST was concurrent with the acute phase of the disorder, while the second one was carried out only after days of clinical care. Therefore, the mood state of the bipolar patients had improved by the second session. This result suggests a correlation between the gravity of mood symptoms and the worsening of executive functioning (McGrath et al., 1997).

In addition, Marvel and Paradiso (2004) reviewed also studies that investigated abnormalities in the brain of patients with mood disorders. Across studies and populations, the structure that was reported to be the most altered – either structurally, functionally, or both – was dlPFC (Marvel and Paradiso; 2004).
Considering also the role of dlPFC in executive functioning, it follows that dlPFC could indeed represent a meeting point between mood and executive functioning, and the two processes are likely to be inherently interconnected.
Therefore, if mood states affect and alter the performance at cognitive tasks, it is possible that they also affect the effect of tDCS on cognitive outcomes.
Throughout the years, many researchers have noticed the relation between mood and cognition; however, the mechanisms that underlie this connection remain still largely unclear. Multiple theories and models have stemmed trying to shed some light. Although they all state and agree that mood levels affect and modulate cognition, the underlying determining process changes greatly.
For example, in regards to mood and memory, according to Bower (1981) and his Associative Network Model, different mood states are linked to different memory representations and the whole of these forms an associative network. When a person is experiencing a certain mood state, such state activates all the associated representations, so that those are more available to be used in the cognitive tasks in which the person is involved. Hence, Bower describes the associative network model of mood states as a form of priming, affective priming. This model cannot be valid for all aspects of cognition, as “colder” and more operative thinking is not likely to access information that has been effectively primed. However, Bower found said effects of mood in the field of memory and judgment making, meaning that his theory could explain a part of the variability in the results obtained on these specific types of cognition (Bower, 1981).
Another interesting model is Forgas’ Affect Infusion Model (AIM) (1995; 2002), which suggests that the likelihood of mood to alter cognition depends on the kind of processing strategies that have been applied to complete the task. Specifically, Forgas states that the more constructive and effortful the process has been, the more mood-affected the cognitive outcome will be (Forgas and Koch; 2013).
There are other models that have focused more on the different types of processing strategies that different moods can trigger. For example, people with a positive mood tend to have a more relaxed and not very effortful approach to

the task, whereas people with a more negative mood tend to be more vigilant and put more effort (Schwarz, 1990).

Another model is Bless and Fiedler's Assimilation-Accommodation Model (2006). According to them, the mood does not act increaing or decreasing motivation, but rather, different mood states facilitate different types of processing strategies. For example, a positive mood would trigger the process of assimilation, and a negative mood would activate the process of accommodation. The former is activated by the sensation of safety and puts more emphasis on the internal structures and previously acquired knowledge of the person when approaching an environment. This promotes the process of the active application of said structures to manipulate and interpret the external environment. Moreover, positive mood promotes also the use of broader, more global, and inclusive strategies when interacting with the world and when acquiring new knowledge. The latter, on the other hand, is activated by the sensation of an unfamiliar situation and direction is quite opposite to assimilation. In fact, the person is more inclined to be vigilant and monitor closely external stimuli, and trust is put more in external stimuli. This model suggests that mood states are adaptive and can all produce positive alterations to cognition by guiding cognition in choosing the best suiting strategy for the situation. In relation to the present meta-analysis, we could expect that people with different mood levels could employ different and opposite strategies, resulting in different performances (Forgas, 2017, Chapter 3).

In conclusion, although there is no unified theory, these and many other models have highlighted the role of mood as the moderator of cognitive performance, either by acting on the type of information or the type of process.

CHAPTER 3
Mood and prefrontal transcranial Direct Current Stimulation (tDCS) cognitive outcomes: A systematic review and meta-analysis

3.1 Hypothesis and goal of the study

This meta-analysis stems from the need to shed light on the high variability of the results obtained when assessing the effect of prefrontal tDCS on executive functions. of studies that report no effects of tDCS on executive functions. The hypothesis is that the heterogeneity of cognitive performance at executive functioning tasks in prefrontal tDCS studies can be explained by a moderating factor: mood. Specifically, different mood levels at baseline in the participants of the studies could explain part of the variability in the effects of prefrontal tDCS on cognitive performance.

The goal of this meta-analysis is therefore to evaluate the possible effect of mood as potential modulating factor that could explain the heterogeneity of results that have been obtained to this date by studies assessing the effects of prefrontal tDCS on cognitive performance.

3.2 Methods

3.2.1 Systematic review

The search was conducted on articles published up to November 8t, 2021 and present in the following database: PubMed, ScienceDirect, and PsychINFO.

The keywords that were used in the searches were: “transcranial direct current stimulation” or “direct current stimulation” or “tDCS”, and “DLPFC" or "dorsolateral prefrontal cortex" or “LPFC” or “PFC” or “prefrontal cortex” or “lateral prefrontal cortex”.

The search resulted in a total of 1713 articles, which have been assessed by two independent evaluators. Exclusion criteria were the age of participants – namely, being younger than 18 years old, and studies that did not involve an assessment of mood and executive functioning through cognitive tasks. The stimulation had to be associated, in fact, with at least a cognitive task measuring executive functions - either online or offline - and had to include a mood measurement at baseline.

Regarding the inclusion criteria, tDCS had to target dlPFC, the most suitable structure to investigate mood and executive functioning, as evidence has provided proof of dlPFC to be involved in both domains. Moreover, the stimulation had to be anodal and the location of the anode had to be either on F3 or F4 of the International 10–20 system, as these placements are widely recognized to be the most accurate to reach dlPFC. Those same sites were also targeted in other reviews on the cognitive effects of dlPFC tDCS (Sarkis et al., 2014; Dedoncker et al., 2016) and its effects on mood disorders treatment (Razza et al., 2020). For what concerns the criterion of anodal tDCS, it was decided to consider the possibility that anodal and cathodal tDCS could have differential effects, either presenting different effect directions or even presenting an effect vs no effect, therefore the decision to include only anodal stimulation. The main reasons were that: (1) there is a wider pool of anodal tDCS studies on dlPFC and executive functioning; (2) since there have been found some contrasting results of anodal and cathodal tDCS effects on cognitive tasks, we thought that by choosing only one type of current to target dlPFC we could isolate the direction of the effect more accurately, without the risk of it being nullified by opposing trends. In regards to the type of montage, the included articles presented a unilateral montage, with the active stimulation targeting only one hemisphere.

In addition, studies had to be randomized sham-controlled trials and within-subject. The design had to be crossover and with a single active tDCS session. This choice was taken to reduce the overall variability of the sample of the articles and to compare the results more widely. In fact, the majority of articles in the field of dlPFC tDCS and cognition are single-session, as well as other recent meta-analyses on dlPFC tDCS and cognitive performance that analyzed mostly single-session studies (Horvath et al., 2015; Hill et al., 2016; DeDoncker et al., 2016).

Lastly, the included articles involved subjects coming either from neuropsychological or clinical samples or from healthy ones.

3.2.2 Quality assessment

For quality assessment, each article was checked for blinding and counterbalancing. As only within-subject studies were included, it was checked to see if they were all crossover designed. Indeed, counterbalancing the order of

the stimulation session - meaning that the sequence of stimulation sessions is not the same across participants: some start with sham and the active condition follows, and others have it the other way - prevents within-subjects studies from order-effect bias. Moreover, the selection of the included articles was double-checked, as well as the process of data extraction. In the former, two people went through the entire sample of articles and selected the one to be included independently and blindly. For conflicting articles, a third party helped to sort said discrepancies and make the final selection.

3.2.3 Data extraction

From each article, it was extracted study information, sample information, design information, procedure information, and measures of interest.

For what concerns the characteristics of the sample, it was reported the population type and its eventual diagnosis, the number of the initial sample and the group considered in the final analysis, the gender, and the mean age. Then, the details of the design were extracted: if the study was crossover or parallel designed, and within-group or between-group. For procedure information, the interested was in: the location of the anode and the cathode, the number of active sessions, the duration of the stimulation, and the wash-out period.

The measures of interest were divided into (1) cognitive task and (2) mood assessment, since this two are the primary outcomes of the meta-analysis. For the cognitive outcome, the interest was on the type of task, if it was performed online or offline, the type of cognitive outcome, and the average scores and standard deviations of the active condition and sham condition. To do so, it was often extracted the standard error of the mean and transform it into standard deviation. For the mood assessment, it was extracted the type of mood assessment that had been performed at baseline, the average score of the sample, and the maximal score that could be obtained at said scale.

For several articles, it was needed to contact the authors to get the needed information, as not every article reported the average scores on the cognitive tasks and/or mood assessments. In Fig. 4, it is shown the flow chart of the procedure of the data extraction.

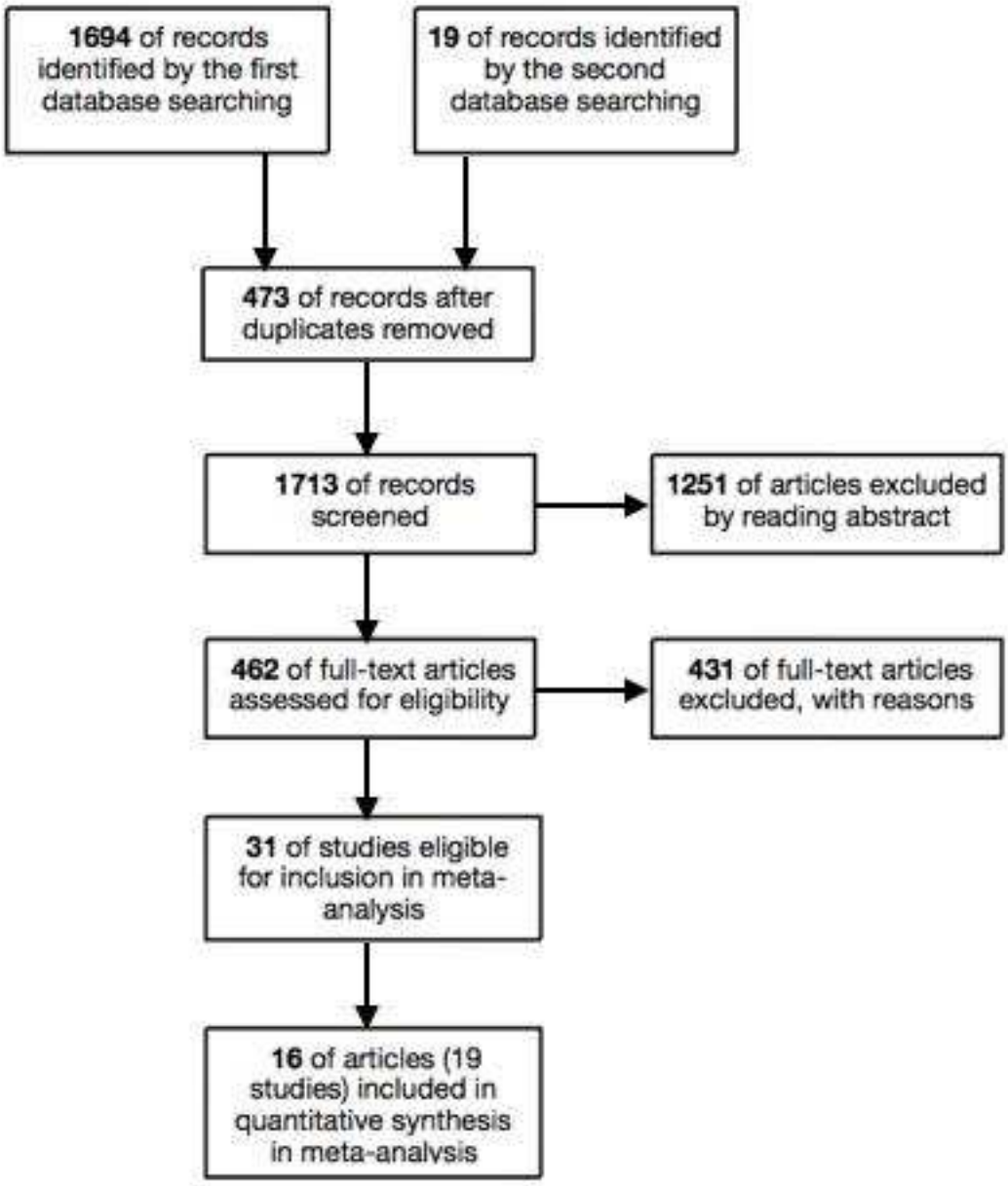

Figure 4. PRISMA flowchart of the database search strategy.

3.2.4 Statistical analysis

The analysis was conducted using R (version 4.1.0) (R Core Team, 2020) and the metafor package (version 3.0.2) (Viechtbauer, 2010). We estimated the effect size for each comparison between the effects of anodal tDCS and the effects of sham tDCS on the cognitive outcomes, namely response times and accuracy.

The calculation of effect size (*yi*) was based on Borenstein and colleagues (2009) that suggested a modality to compute effect size for studies with repeated measures (i.e., in this study, real tDCS and sham tDCS):

$$yi = J\,[(C.m\_real - C.m\_sham) / sd.pooled]$$

where *C.m_real* and *C.m_sham* are respectively the means in the real tDCS condition and sham tDCS condition, *sd.pooled* is the pooled standard deviation, and *J* (sometimes called Hedges' *g*) is a correction factor to avoid the effect *d* has a slight bias, tending to overestimate the absolute value of the effect in small samples (Hedges, 1981).

According to Borenstein and colleagues (2009), the pooled standard deviation is given by:

$$sd.pooled = sqrt\,[(C.sd\_real^2 + C.sd\_sham^2) / 2)]$$

As for *J*, according to the recommendations of Borenstein and colleagues (2009), the formula is:

$$J = 1 - [3 / (4df - 1)]$$

where *df* is the degrees of freedom calculated as (n-1), namely the numerosity of the sample minus 1.

The calculation of estimate variance (*vi*), based on Borenstein and colleagues (2009), is given by:

$$vi = J\,[2\,(1 - r.stim) * (1 / n + yi^2 / (2n)]$$

where *r.stim* is the estimated correlation between the real and sham tDCS conditions (i.e., 0.5).

When multiple outcomes were present in the same study (e.g., more than one measure of accuracy), the composite effect size for the whole study is defined as the mean effect size in that study, with a variance that considers the correlation among the different outcomes (Borenstein et al., 2009, see chapter 24, p.230). The composite effect size is given by:

$$composite\ yi = \frac{1}{m}\left(\sum_{i=1}^{m} yi\right)$$

where *m* is the number of outcomes within a study. The composite variance is given by:

$$composite\ vi = \left(\frac{1}{m}\right)^2 \left(\sum_{i=1}^{m} v_{i_i} + \sum_{i \neq k} \left(r_{ik}\sqrt{vi_i}\sqrt{vi_k}\right)\right)$$

To calculate the composite variance, the correlation between the different outcomes completed by the same sample is needed. However, no study reported this correlation. Thus, *r* = 0.50 was used as reference value in all cases. Meta-analysis results were evaluated in a sensitivity analysis using *r* = 0.50.

In this meta-analysis, the estimated effect size was Cohen's d, whose range varies from 0.01 (very small) to 2.0 (huge).

Heterogeneity, sensitivity analyses, and evaluation of publication bias

To test the heterogeneity of the data, we estimated the *tau-squared* (i.e., τ2) using the restricted maximum-likelihood estimator (Viechtbauer, 2005). We also ran the Q-test for heterogeneity (Cochran, 1954) and the I2 statistic (Higgins & Thompson, 2002).

In addition, to detect the presence of outliers among the sampled articles, we ran the *leave-one-out* method. This sensitivity analysis allowed us to evaluate whether a single article among the included ones produced an influential change in the analysis, a result that would undermine the reliability of the results of the analyses (Viechtbauer & Cheung, 2010).

Finally, we checked for the presence of publication bias using the funnel plot, since publication bias is indicated by asymmetries in the plot. To detect funnel plot asymmetry, we ran the rank correlation test (Begg & Mazumdar, 1994) and the regression test (Sterne & Egger, 2005), using the standard error of the observed outcomes as predictors.

Effects of the potential moderator: mood scores

To investigate the role of the potential moderator (i.e. mood scores) on cognitive performance, we used mixed-effects meta-regression models. The moderators were tested using Wald's chi-suare (Viechtbauer, 2010). We conducted two separate analyses for the effects of the moderator on the first cognitive outcome (i.e. response times) and the second one (i.e. accuracy).

Cognitive outcomes

Table 1 reports the average scores and SDs of the cognitive outcomes of each article that we included in the analysis. The two main cognitive outcomes were: Response Times (RT) and Accuracy (Acc). We have considered RT, latencies, completion times, and differential latencies as measurements of response times. We considered accuracy scores, hit rates, average scores, discriminability index, and error rates as measurements of accuracy. Consult Supplementary Materials to see how we considered and calculated every cognitive outcome in the final analysis.

Mood measures

Since most articles had a different type of mood assessment, we needed to find a way to compare the different scores. Therefore, for every sample, we divided its mood score at the particular mood assessment (*score*) by the maximum score obtainable on that mood assessment (*Score max*), and then we multiplied the resulting value by 100.

$$\% \text{ mood score} = \text{Score} / \text{Score max} \times 100$$

For instance, in the BDI-II (Beck Depression Inventory-II) the maximum obtainable score is 63, hence if the sample has an overall score of 6.20, the final score that we use for the analysis is 9.8. For each article, we checked for the direction of the effect of the administered mood measurement, to see if the maximum score represented high levels (i.e. in BDI) or low levels of depressive mood, in which case the score has to be inverted. Lastly, we also checked the minimum score of each mood scale. In fact, not in every assessment, the minimum score was zero, for instance in the Negative Affect Scale of PANAS where the "zero" - i.e. lack of depressive mood - is represented by a score of 10.

In this case, we subtracted 10 from both the score obtained on the mood scale and its maximum score.

$$\% \text{ mood score} = \text{Score } (-10) / \text{Score max } (-10) \times 100$$

Table 1 reports the final mood scores for each experiment, that we obtained by applying the above-mentioned calculation.

Table 1. Cognitive outcomes (average score and standard deviations) and mood scores for each experiment included in the meta-analysis.

Author	Exp	Cognitive outcome	Average score (active)	SD (active)	Average score (sham)	SD (sham)	Mood score in %
Vanderhasselt et al. (2016)	1	CECT (Acc)	Actual Happy: 86.67 Actual Sad: 85.08 Opposite Happy: 83.49 Opposite Sad: 86.14	Actual Happy: 7.03 Actual Sad: 8.50 Opposite Happy: 8.95 Opposite Sad: 7.37	Actual Happy: 88.25 Actual Sad: 85.93 Opposite Happy: 87.41 Opposite Sad: 87.09	Actual Happy: 6.69 Actual Sad: 7.66 Opposite Happy: 5.97 Opposite Sad: 6.31	8.3
	1	CECT (RT)	Actual Happy: 784.79 Actual Sad: 783.59 Opposite Happy: 854.99 Opposite Sad: 816.21 Opposite min Actual: 52.68	Actual Happy: 225.10 Actual Sad: 209.51 Opposite Happy: 244.07 Opposite Sad: 215.48 Opposite min Actual: 80.02	Actual Happy: 768.59 Actual Sad: 829.44 Opposite Happy: 782.37 Opposite Sad: 835.05 Opposite min Actual: 57.85	Actual Happy: 222.39 Actual Sad: 246.05 Opposite Happy: 199.57 Opposite Sad: 222.62 Opposite min Actual: 58.73	8.3
Coussement et al. (2019)	1	PDT (Acc)	Alerting: 31.27 Orienting: 34.53 Executive: 97.61	Alerting: 12.43 Orienting: 16.29 Executive: 23.09	Alerting: 28.42 Orienting: 33.83 Executive: 97.16	Alerting: 8.44 Orienting: 21.79 Executive: 25.67	9.8
Schwippel et al. (2017)	1	Spatial n-back (Acc)	1-back: 1.02 2-back: 1.04 3-back: 1.29	1-back: 0.07 2-back: 0.11 3-back: 0.15	1-back: 1.11 2-back: 1.09 3-back: 1.45	1-back: 007 2-back: 0.05 3-back: 0.19	14.8
	1	Spatial n-back (RT)	1-back: 727.53 2-back: 821.53 3-back: 899.22	1-back: 56.39 2-back: 56.39 3-back: 83.74	1-back: 688.98 2-back: 866.94 3-back: 867.30	1-back: 44.51 2-back: 64.64 3-back: 79.82	14.8
Schwippel et al. (2017)	2	Spatial n-back (Acc)	1-back: 1.07 2-back: 0.89 3-back: 1.15	1-back: 0.05 2-back: 0.05 3-back: 0.15	1-back: 1.11 2-back: 0.9 3-back: 0.93	1-back: 0.04 2-back: 0.06 3-back: 0.12	9.6
	2	Spatial n-back (RT)	1-back: 781.02 2-back: 971.69 3-back: 1026.05	1-back: 67.60 2-back:79.83 3-back: 77.43	1-back: 785.23 2-back: 900.45 3-back: 967.51	1-back: 79.32 2-back: 68.38 3-back: 71.11	9.6
Ferrucci et al. (2011)	1	ER Task (RT)	Negative: 989.00 Positive: 787.94 Neutral: 903.03	Negative: 560.82 Positive: 403.68 Neutral: 461.14	Negative: 1046.88 Positive: 841.19 Neutral: 969.77	Negative: 458.35 Positive: 272.39 Neutral: 442.68	19.7
	1	Visual Attention Task (RT)	295.2	69.24	325.6	103.38	19.7
Heeren et al. (2016)	1	PDT (RT)	social-threat cues: 494.67 non-threat cues: 488.89	social-threat cues: 65.66 non-threat cues: 69.26	social-threat cues: 505.60 non-threat cues: 510.89	social-threat cues: 66.37 non-threat cues: 68.89	21.4
Papazova et al. (2018)	1	N-back (Acc)	1-back: 3.73 2-back: 2.45 3-back: 1.45	1-back: 0.72 2-back: 1.16 3-back: 0.81	1-back: 3.50 2-back: 2.35 3-back: 1.27	1-back: 0.85 2-back: 1.16 3-back: 0.74	12.2
	1	N-back (RT)	712.13 884.42 1100.05	164.66 219.77 293.39	711.83 884.38 974.88	180.33 209.86 292.78	12.2

	1	N-back Hit rate (Acc)	0.93 0.73 0.51	0.09 0.21 0.22	0.88 0.69 0.47	0.14 0.24 0.22	12.2
Papazova et al. (2018)	2	N-back (Acc)	1-back: 3.46 2-back: 2.11 3-back: 1.41	1-back: 1.06 2-back: 0.97 3-back: 0.74	1-back: 3.35 2-back: 1.97 3-back: 1.14	1-back: 1.32 2-back: 1.06 3-back: 0.72	13.8
	2	N-back (RT)	744.42 948.02 1008.39	283.32 329.20 413.73	765.42 886.77 991.47	237.39 234.91 359.37	13.8
	2	N-back Hit rate (Acc)	0.85 0.64 0.43	0.16 0.23 0.23	0.88 0.62 0.47	0.14 0.25 0.22	13.8
Sanchez-Lopez et al. (2018)	1	Attentional disengagement (RT)	disgusted faces: 380 happy faces: 385 sad faces: 380	disgusted faces: 72 happy faces: 81 sad faces: 90	disgusted faces: 408 happy faces: 406 sad faces: 403	disgusted faces: 117 happy faces: 102 sad faces: 80	7.2
	1	Attentional engagement (RT)	disgusted faces: 382 happy faces: 390 sad faces: 383	disgusted faces: 78 happy faces: 94 sad faces: 83	disgusted faces: 425 happy faces: 391 sad faces: 392	disgusted faces: 91 happy faces: 79 sad faces: 94	7.2
Sanchez-Lopez et al. (2018)	2	Attentional disengagement (RT)	disgusted faces: 370 happy faces: 379 sad faces: 339	disgusted faces: 58 happy faces: 76 sad faces: 74	disgusted faces: 330 happy faces: 343 sad faces: 317	disgusted faces: 64 happy faces: 62 sad faces: 49	3.9
	2	Attentional engagement (RT)	disgusted faces: 330 happy faces: 340 sad faces: 369	disgusted faces: 90 happy faces: 54 sad faces: 61	disgusted faces: 351 happy faces: 342 sad faces: 374	disgusted faces: 77 happy faces: 69 sad faces: 85	3.9
Vanderhasselt et al. (2013)	1	IST (RT)	1035.00	285.00	1426.00	444.00	11.2
	1	IST Error rates (Acc)	Emotion: 2.03 Non-Emotion: 2.91	Emotion: 2.19 Non-Emotion: 3.00	Emotion: 2.65 Non-Emotion: 3.78	Emotion: 3.32 Non-Emotion: 4.28	11.2
Keeser et al. (2010)	1	N-back (RT)	0-back: 463.2 1-back: 253.4 2-back: 386.5	0-back: 27.2 1-back: 48.2 2-back: 150.0	0-back: 509.6 1-back: 294.2 2-back: 438.9	0-back: 57.2 1-back: 93.1 2-back: 163.7	3.8
	1	N-back (Acc)	0-back: 0.96 1-back: 0.83 2-back: 0.73	0-back: 0.05 1-back: 0.14 2-back: 0.13	0-back: 0.95 1-back: 0.84 2-back: 0.67	0-back: 0.05 1-back: 0.10 2-back: 0.13	3.8
Eddy et al. (2016)	1	N-back (RT)	1back: 1170 2back: 1343	1back: 376.86 2back: 341.25	1back: 1263 2back: 1307	1back: 357.45 2back: 390.30	31.2
	1	N-back (Acc)	1back: 95.34 2back: 74.84	1back: 7.13 2back: 20.71	1back: 95.34 2back: 70.67	1back: 7.67 2back: 24.02	31.2
	1	Stroop test (RT)	-34.44	23.31	-32.75	16.17	31.2
	1	DOT-A (Acc)	5.05	1.00	4.73	1.07	31.2
Martin et al. (2015)	1	N-back d index (Acc)	2.09	0.74	1.97	0.70	16.8
	1	N-back (RT)	741.00	153.76	742.00	200.23	16.8
Sreeraj et al. (2019)	1	Sternberg's task (Acc)	81.00	15.11	84.06	13.78	4.4
	1	Sternberg's task (RT)	1215.35	649.68	1182.25	586.15	4.4
Nejati et al. (2017)	1	Go/No Go (Acc of No Go)	25.29	1.57	24.16	1.12	44.0
	1	Go/No Go (RT)	0.77	0.38	1.03	0.35	44.0
	1	Tower of Hanoi (RT)	67.20	36.84	110.70	70.62	44.0
	1	BART average pumps (Acc)	34.91	20.79	49.62	16.73	44.0
Chow et al. (2021)	1	Digit Span Forward (Acc)	tDCS only: 11.71 tDCS+music: 11.64	tDCS only: 0.56 tDCS+music: 0.52	sham+music: 11.93	sham+music: 0.67	1.4
	1	Digit Span Backward (Acc)	tDCS only: 8.50 tDCS+music: 9.36	tDCS only: 0.79 tDCS+music: 0.71	sham+music: 8.21	sham+music: 0.78	1.4
Lema et al. (2021)	1	Attention Network Effect (RT)	alerting: 17.25 orienting: 32.31 executive: 100.85	alerting: 38.05 orienting: 33.52 executive: 35.87	alerting: 20.94 orienting: 42.54 executive: 99.17	alerting: 30.34 orienting: 40.01 executive: 41.24	6.3
	1	Attention Network Effect (Acc)	alerting: 97.57 orienting: 98.00 executive: 96.81	alerting: 3.45 orienting: 2.97 executive: 4.18	alerting: 98.00 orienting: 98.18 executive: 97.92	alerting: 3.16 orienting: 2.63 executive: 3.65	6.3
Vanderhasselt et al. (2019)	1	Go/No Go (Acc)	Go w/reward: 0.91 NoGo w/reward: 0.91 Go w/o reward: 0.80 NoGo w/o reward: 0.95	Go w/reward: 0.06 NoGo w/reward: 0.06 Go w/o reward: 0.11 NoGo w/o reward: 0.04	Go w/reward: 0.93 NoGo w/reward: 0.90 Go w/o reward: 0.80 NoGo w/o reward: 0.95	Go w/reward: 0.05 NoGo w/reward: 0.07 Go w/o reward: 0.12 NoGo w/o reward: 0.04	30.0

Abbreviations. CECT = Cued Emotional Control Task; PDT = Probe Discrimination Task; ER = Emotion Recognition; IST = Internal Shift Task; DOT-A = Digit Ordering Test-Adapted; BART = Balloon Analogue Risk Task.

3.3 Results

3.3.1 Selection and inclusion of studies

The first search resulted in 2167 references - 279 of which came from Pubmed, 656 from APA PsychINFO, and 1232 from Science Direct. We reduced the number after the removal of the duplicates, obtaining 1694 articles. To conduct the screening, we used “Rayyan”, a platform that allows blind and independent reading from different viewers. Each article was then screened by three independent readers, each of whom went through all abstracts. After the double screening, we eliminated 1251 articles. The remaining 443 articles were screened full-text and assessed for eligibility. After that, another 336 were excluded due to incompatibility with criteria. For instance, we had to exclude articles without a baseline mood measurement, a sham session, and with different electrode placements from the montage criterion; we also excluded case studies and meta-analyses, as well as texts that were not written in English (2). We then proceeded with the data extraction of the 107 selected articles, dividing them according to their design and number of active sessions, ending up with 40 within-group studies, 62 between-group studies, and 5 mixed studies; of these, 73 included multiple sessions and 34 included single-sessions. We decided to follow DeDoncker’s lead - as he conducted a similar meta-analysis on dlPFC-tDCS in 2016 (DeDoncker et al., 2016)- and opted only for within and single-session studies, obtaining a total of 34 studies from the first search. After the final evaluation, we excluded cathodal dlPFC stimulation and all of those studies that did not report scores. We had to remove some studies since they did not report either mood scores, cognitive outcomes, or standard deviations, and their authors did not respond to the requests of sharing the missing data. The final number of suitable articles was 13.

In addition, the second search -conducted in November 2021- resulted in 19 more articles (16 from PubMed and 3 from ScienceDirect). However, after a thorough assessment for eligibility, only 3 of them were selected.

In sum, we screened the abstracts of 1713 studies and the full text of a total of 462 articles (443 from the first search and 19 from the second one). After multiple evaluations, the final included articles amounted to 16. Since some of these (3) reported more than one experiment, with different samples and datasets, we considered those as different studies. For this reason, the final number is 19: 16 articles and 19 experiments. The data of the 19 included articles is reported in Table 2.

Table 2 shows the experiments selected for the meta-analysis and their main characteristics. For each study, we report: current intensity of tDCS (mA), current density (the ratio between current intensity and surface of the electrode: mA/cm2), duration of tDCS active session, the type of cognitive task and the type of outcome, whether the task was administered during tDCS (online) or following tDCS (offline), the type of mood assessment, the type of population of sample, the number of participants.

Author	Exp	Anode	Cathode	mA	Current density	Duration (min)	Cognitive outcome	Online Offline	Mood assessment	Condition	N
Vanderhasselt et al. (2016)	1	F4	L SupOr	2	0.06	20	Cued Emotional Control Task (Accuracy)	offline	BDI-II	H	35
	1	F4	L SupOr	2	0.06	20	Cued Emotional Control Task (RT)	offline	BDI-II	H	35
Coussement et al. (2019)	1	F3	L arm	2	0.06	25	Probe Discrimination Task (Latencies)	online	BDI-II	H	20
Schwippel et al. (2017)	1	F4	L delt	1	0.03	21	Spatial n-back (Discriminability index)	online	CDSS	SZ	16
	1	F4	L delt	1	0.03	21	Spatial n-back (RT)	online	CDSS	SZ	16
Schwippel et al. (2017)	2	F4	L delt	2	0.06	21	Spatial n-back (Discriminability index)	online	CDSS	SZ	16
	2	F4	L delt	2	0.06	21	Spatial n-back (RT)	online	CDSS	SZ	16
Ferrucci et al. (2011)	1	F4-Fp2	R delt	2	0.06	20	Emotion Recognition Task (RT)	offline	VAS	H	21
	1	F4-Fp2	R delt	2	0.06	20	Visual Attention Task (RT)	offline	VAS	H	21
Heeren et al. (2016)	1	F3	L arm	2	0.06	25	Probe Discrimination Task (Latencies)	online	BDI-II	SAD	19
Papazova et al. (2018)	1	F3	R delt	1	0.03	21	N-back (Discriminability index)	online	CDSS	SZ	20
	1	F3	R delt	1	0.03	21	N-back (RT)	online	CDSS	SZ	20
	1	F3	R delt	1	0.03	21	N-back (Hit rate)	online	CDSS	SZ	20
Papazova et al. (2018)	2	F3	R delt	2	0.06	21	N-back (Discriminability index)	online	CDSS	SZ	20
	2	F3	R delt	2	0.06	21	N-back (RT)	online	CDSS	SZ	20
	2	F3	R delt	2	0.06	21	N-back (Hit rate)	online	CDSS	SZ	20

Sanchez-Lopez et al. (2018)	1	F3	R SupOr	2	0.06	20	Attentional disengagement (RT)	offline	BDI-II	H	27
	1	F3	R SupOr	2	0.06	20	Attentional engagement (RT)	offline	BDI-II	H	27
Sanchez-Lopez et al. (2018)	2	F4	L SupOr	2	0.06	20	Attentional disengagement (RT)	offline	BDI-II	H	27
	2	F4	L SupOr	2	0.06	20	Attentional engagement (RT)	offline	BDI-II	H	27
Vanderhasselt et al. (2013)	1	F3	R SupOr	2	0.06	20	Internal Shift Task (RT)	offline	PANAS	H	32
	1	F3	R SupOr	2	0.06	20	Internal Shift Task (Error Rates)	offline	PANAS	H	32
Keeser et al. (2010)	1	F3	R SupOr	2	0.06	20	N-back (RT)	offline	PANAS	H	10
	1	F4	R SupOr	2	0.06	21	N-back (Accuracy)	offline	PANAS	H	10
Eddy et al. (2016)	1	F3	Fp2	1.5	0.06	15	N-back (RT)	offline	HADS-Depression	HD	20
	1	F3	Fp2	1.5	0.06	15	N-back (Accuracy)	offline	HADS-Depression	HD	20
	1	F3	Fp2	1.5	0.06	15	Stroop test (Completion Time)	offline	HADS-Depression	HD	20
	1	F3	Fp2	1.5	0.06	15	Digit Ordering Test-Adapted (Accuracy)	offline	HADS-Depression	HD	20
Martin et al. (2015)	1	F3	R arm	2	0.06	30	3-N-back (d index)	online	DAAS-21	BD	15
	1	F3	R arm	2	0.06	30	3-N-back (RT)	online	DAAS-21	BD	15
Sreeraj et al. (2019)	1	F3-Fp1	btw T3-P3	2		20	Sternberg's task (Accuracy)	online	CDSS	SZ	11
	1	F3-Fp1	btw T3-P3	2		20	Sternberg's task (RT)	online	CDSS	SZ	11
Nejati et al. (2017)	1	F3	Fp2	1.5	0.04	20	Go/No Go (Accuracy of No Go)	online	DAAS-21	H	24
	1	F3	Fp2	1.5	0.04	20	Go/No Go (RT)	online	DAAS-21	H	24
	1	F3	Fp2	1.5	0.04	20	Tower of Hanoi (Completion Time)	online	DAAS-21	H	24
	1	F3	Fp2	1.5	0.04	20	Balloon Analogue Risk Task (average pumps)	online	DAAS-21	H	24
	1	F3	Fp2	1.5	0.04	20	Teporal Discounting Task (K value)	online	DAAS-21	H	24
Chow et al. (2021)	1	F3	R SupOr	2	0.06	20	Digit Span (Forward score)	offline	PANAS	H	14
	1	F3	R SupOr	2	0.06	20	Digit Span (Backward score)	offline	PANAS	H	14
Lema et al. (2021)	1	F3	Fp2	2	0.06	20	Attention Network Effect (RT)	online	BDI	H	27
	1	F3	Fp2	2	0.06	20	Attention Network Effect (Accuracy)	online	BDI	H	27
Vanderhasselt et al. (2019)	1	F4	F3	2	0.06	20	Go/No Go (Accuracy)	offline	VAS	hD	37

Abbreviations of "Cathode": L = left; R = right; SupOr = Supraorbital; delt = deltoid. Abbreviations of "Condition": H = healthy; SZ = patients with Schizophrenia; HD = patients with Huntington's Disease; BD = patients with Bipolar Disorder; SAD = patients with Social Anxiety Disorder; hD = heavy Drinkers.

3.3.2 Results

tDCS effects on Response Times

No significant effects of tDCS on Response Times were found (see Figure 5). For anodal tDCS effects on response times, a total of 17 studies were included, comprising a total sample of 360 participants (N = 360). One study, Chow et al. (2021), was not included in this analysis as it reported only an accuracy score.

The observed outcomes ranged from −0.53 to 1.02. Cohen's d, based on the random-effects model, was 0.11 (95% CI: −0.0584 to 0.2760). Therefore, it did not differ significantly from zero (z = 1.2752, p = 0.2022). To identify one or more particularly influential studies that could substantially determine the general effect, we run the *leave1out* function. We conducted the analysis by eliminating every time one of the articles. It resulted that no article was an outlier and had a substantial weight in the final effect (see Table 3).

We then run the Q-Test, which is normally used in meta-analyses to make sure that effect sizes are homogenous. According to the Q-test, the outcomes appear to be heterogeneous (Q(16) = 50.87, p < 0.0001, $\hat{\tau}$ = 0.09, I2 = 72%). This result could reflect the wide variability of the included articles, which not only are different in the kind of cognitive task that they administered, but also in the number and type of population of the samples.

Small studies are more apt to overestimate the effects of treatments (Sterne and Harbord, 2004), hence, we report the funnel plot obtained by the dataset to rule out such possibility. In fact, funnel plots allow for the investigation of said bias, as well as reduce the probability of the publication bias, the presence of which is represented by an asymmetric funnel plot. To rule these possibilities out, we draw a funnel plot that resulted to be symmetric, as neither the rank correlation (p = 0.7765) nor the regression test (p = 0.5347) indicated any significant asymmetry (see Figure 6).

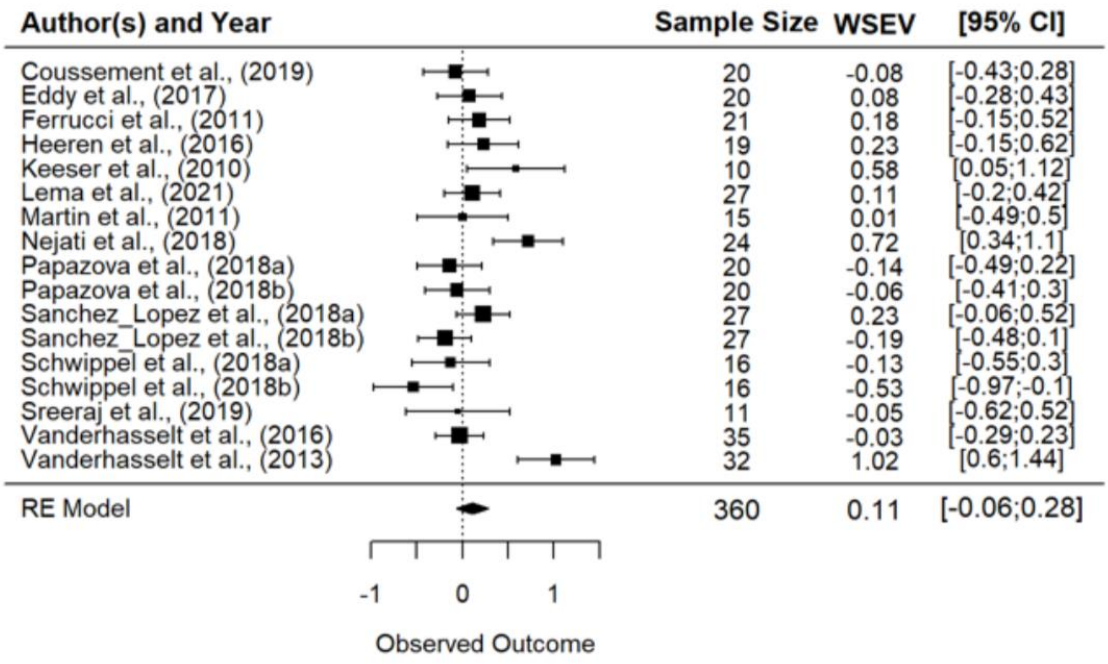

Figure 5. Forest plot showing the effect sizes from the comparison between anodal vs. sham tDCS for response times (RTs). Each square represents the effect size of the study together with 95% confidence level. The size of the symbol (the square) is proportional to the study's weight.

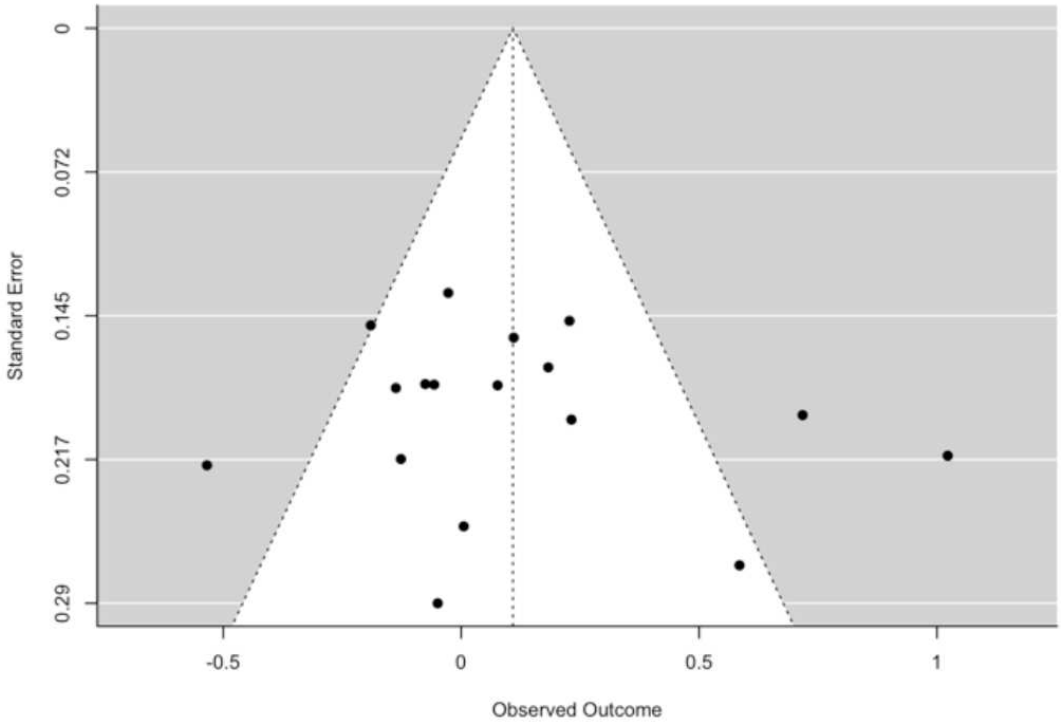

Figure 6. Funnel plot. Each black dot represents one study included in the meta-analysis.

Table 3. Values obtained through the *leave1out* function for response times. The values in each row represent the overall effect of the analysis without counting in the corresponding article.

	estimated	*p value*
Coussement et al. (2019)	0.1213	0.1803
Eddy et al. (2017)	0.1114	0.2230
Ferrucci et al. (2011)	0.1043	0.2539
Heeren et al. (2016)	0.1016	0.2627
Keeser et al. (2010)	0.0859	0.3180
Lema et al. (2021)	0.1092	0.2345
Martin et al. (2011)	0.1146	0.2033
Nejati et al. (2018)	0.0694	0.3846
Papazova et al. (2018a)	0.1251	0.1631
Papazova et al. (2018b)	0.1201	0.1856
Sanchez-Lopez et al. (2018a)	0.1007	0.2709
Sanchez-Lopez et al. (2018b)	0.1304	0.1422
Schwippel et al. (2018a)	0.1228	0.1704
Schwippel et al. (2018b)	0.1438	0.0760
Sreeraj et al. (2019)	0.1163	0.1928
Vanderhasselt et al. (2016)	0.1194	0.1923
Vanderhasselt et al. (2013)	0.0540	0.4272

tDCS effects on Accuracy

No significant effects of tDCS on Accuracy scores emerged (see Figure 7). For anodal tDCS effects on Accuracy, a total of 14 studies were included, comprising a total sample of 297 participants (N = 297). Five experiments - *Coussement et al.* (2019)*, Ferrucci et al.* (2011), *Heeren et al.* (2016), and *Sanchez_Lopez et al.* (2018a; 2018b) - were not included in this analysis since they only reported response time as cognitive outcomes.

The observed outcomes ranged from −0.8875 to 0.7775. Cohen's d, based on the random-effects model, was 0.04 (95% CI: −0.1414 to 0.2234). Therefore, it did not differ significantly from zero (z = 0.4406, p = 0.6595).

To detect any potential outlier, we run the function *leave1out*. However, when removing each article from the analysis, there was no significant difference in the overall effect, meaning that no article represents an outlier (see Table 4). Accuracy scores resulted to be highly heterogeneous as well according to the Q-test (Q(13) = 40.4799, p = 0.0001, $\hat{\tau}$ = 0.0819, I2 = 71%). The funnel plot of the

effect sizes of the accuracy trials resulted once again in a symmetric plot, as neither the rank correlation (p = 1.0000) nor the regression test (p = 0.8992) indicated any significant asymmetry. Hence, no evident publication bias or overestimation of the effect appears to have been detected (see Figure 8).

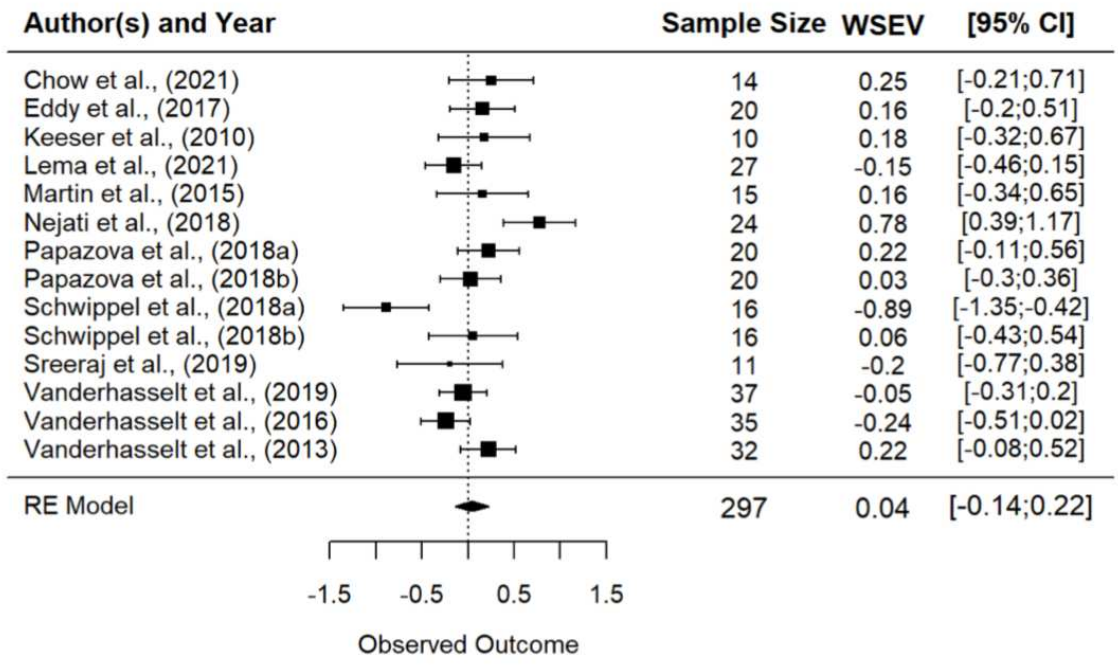

Figure 7. Forest plot showing the effect sizes from the comparison between anodal vs. sham tDCS for accuracy. Each square represents the effect size of the study together with 95% confidence level. The size of the symbol (the square) is proportional to the study's weight.

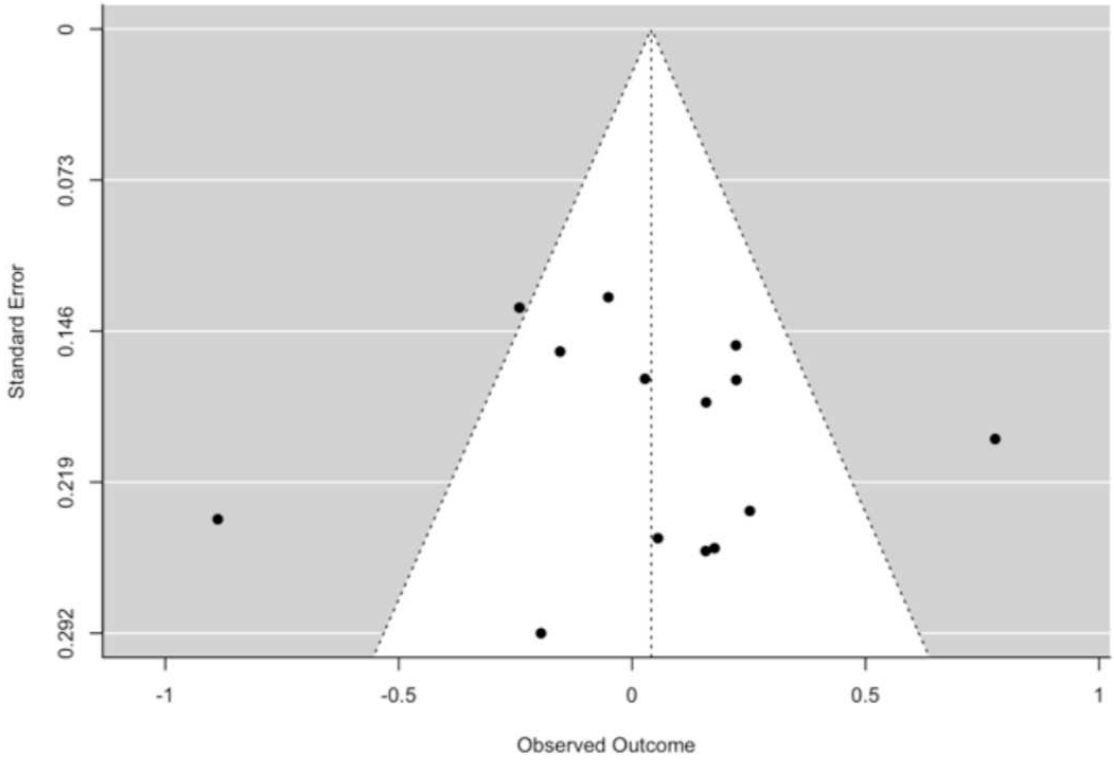

Figure 8. Funnel plot. Each black dot represents one study included in the meta-analysis.

Table 4. Values obtained through the *leave1out* function for Accuracy. The values in each row represent the overall effect of the analysis without counting the corresponding article in.

	estimated	*p value*
Chow et al. (2021)	0.0265	0.7886
Eddy et al. (2017)	0.0313	0.7563
Keeser et al. (2010)	0.0322	0.7457
Lema et al. (2021)	0.0581	0.5615
Martin et al. (2011)	0.0334	0.7364
Nejati et al. (2018)	-0.0146	0.8488
Papazova et al. (2018a)	0.0255	0.7989
Papazova et al. (2018b)	0.0420	0.6797
Schwippel et al. (2018a)	0.0970	0.1957
Schwippel et al. (2018b)	0.0400	0.6890
Sreeraj et al. (2019)	0.0540	0.5805
Vanderhasselt et al. (2019)	0.0495	0.6278
Vanderhasselt et al. (2016)	0.0677	0.4893
Vanderhasselt et al. (2013)	0.0248	0.8051

The effect of Mood on Response Times

The mood had little to no effect on the modulation of the speed of the response times (see Figure 9). A total of 17 studies were included in the analysis. One study, Chow et al. (2021), was not included in this analysis as it reported only an accuracy score. Based on the mixed-effects model, Cohen's d for mood and RTs was 0.01 (95% CI: −0.0038 to 0.0274). Hence, the effect was not significant (z = 1.4860, p = 0.1373).

The Q-test (Q(15) = 43.1204, p = 0.0002, τ̂ = 0.0745, I2 = 68%) showed high levels of heterogeneity.

The test of the moderator was not significant: $\chi 2$ (1) = 2.208, p = 0.137.

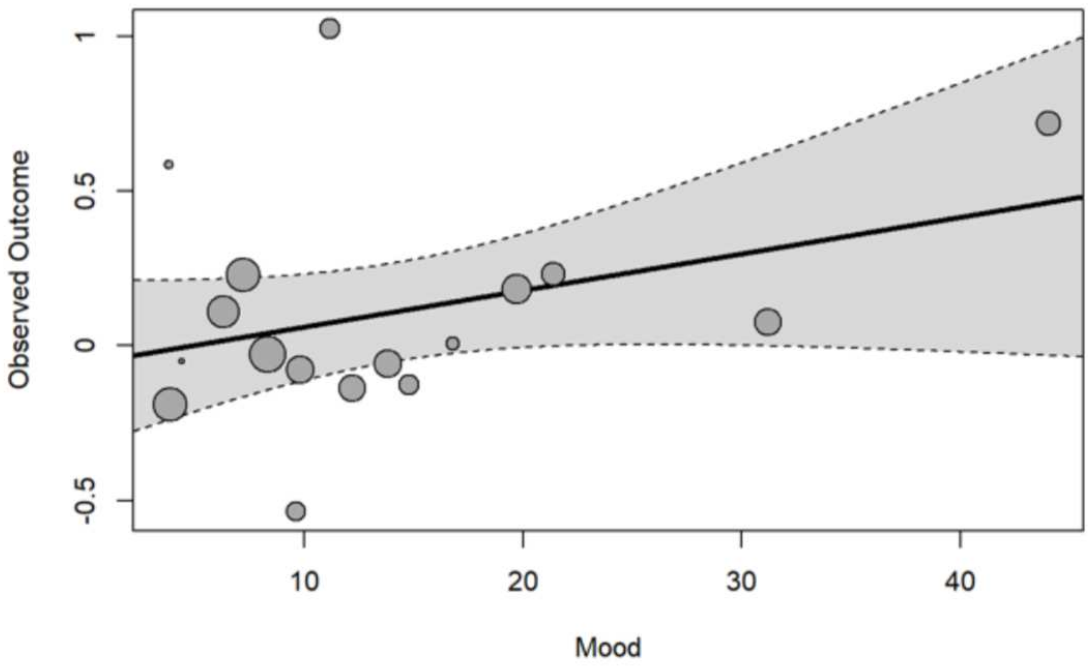

Figure 9. The scatter plot shows the effect of mood on response times (Observed Outcome).

The effect of Mood on Accuracy

The mood had little to no effect on the modulation of accuracy (see Figure 10). The mixed-effects model for mood and accuracy scores, run on the 14 included articles, resulted in a Cohen's d that was 0.01 (95% CI: −0.0028 to 0.0264). The

effect of mood was not significant (z = 1.5802, p = 0.1141). Five experiments - Coussement et al. (2019), Ferrucci et al. (2011), Heeren et al. (2016), and Sanchez_Lopez et al. (2018a; 2018b) - were not included in this analysis since they only reported response time as cognitive outcomes.

For heterogeneity, the Q-test (Q(13) = 33.8529, p = 0.0007, $\hat{\tau}$ = 0.0684, I2 = 66%) reported high scores of heterogeneity.

The test of the moderator was not significant: $\chi 2$ (1) = 2.497, p = 0.114.

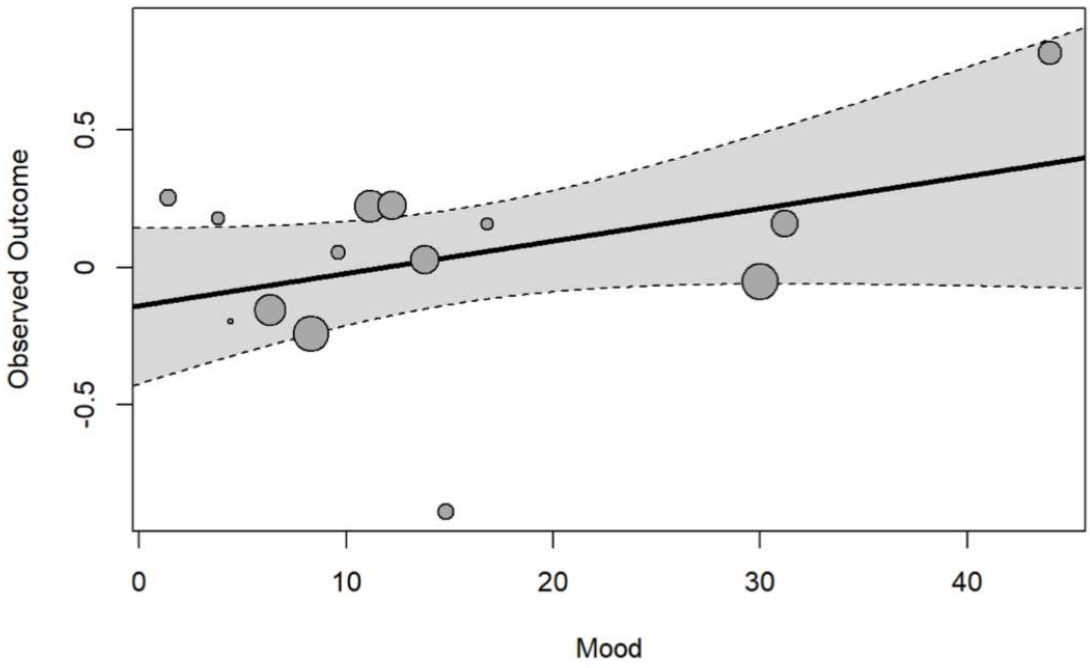

Figure 10. The scatter plot shows the effect of mood on accuracy (Observed Outcome).

CHAPTER 4
Discussion and conclusions

The present meta-analysis aimed to shed some light on the large variability found among study results in the use of tDCS on dlPFC in cognitive tasks. To do so, we conducted a systematic review and meta-analysis including 16 articles, for a total of 19 experimental datasets. The goal was to investigate whether participants' mood levels at baseline could play a role in altering their performance at executive functioning tasks, all while having their dlPFC stimulated through tDCS. The hypothesis that guided the present study was that mood could be a potential moderator of the effects of tDCS on executive functioning, and would hence explain a significant part of the literature findings variability.

To test this hypothesis, the results of 19 sham-controlled, cross-over, single-session, anodal dlPFC tDCS experiments, which reported both cognitive tDCS outcomes and baseline mood assessments were considered. At first, it was used a random-effects model to analyze the effects of anodal dlPFC tDCS on response time and accuracy at executive functioning tasks. Then, we used a mixed-effects model, a meta-regression, to test the effects of mood on the same cognitive outcomes.

The analyses resulted in no significant effect of anodal dlPFC tDCS on executive functioning, as neither the speed nor the accuracy of the response at cognitive tasks improved. Results indicated, in fact, that anodal tDCS did not result in a better performance at the cognitive tasks with respect to the cognitive performance that followed the sham stimulation. Similarly, it did not result in more accurate responses than those following the sham condition.

Moreover, the meta-regression of mood resulted in no significant main effect, showing a lack of significant influence of mood as a moderator of cognitive performance as well, both for response time and accuracy. Contrary to the hypothesis, the baseline mood levels of participants were not found predictive of any alteration of performance at cognitive tasks.

Although the meta-analysis did not confirm the hypothesis, it still represents an important step forward in this research field. Indeed, while plenty of studies investigate the effects of tDCS on the prefrontal cortex in the neuropsychological and clinical psychology fields, very few studies have tried to explain the

uncertainty of these results. Indeed, to our opinion, the main focus of non-invasive brain stimulation research should shift from whether there is an effect of tDCS to why we have such unpredictable results. Specifically, the main question should be which factor among the many contributes to and explains most of the variability. The present meta-analysis collocates itself in said frame. On one hand, the finding that dlPFC tDCS has no significant effect on performance at EF tasks adds a tassel to the pool of studies that found tDCS to be not influential for all executive functions. On the other hand, the meta-regression represents one of the first attempts to clarify the reason behind the mixed results, as well as being a piece of evidence for the lack of a predictive role of mood in the effects of tDCS on cognition. Finding a lack of effect in the meta-regression analysis is useful as it is a contribution toward the said ultimate goal.

However, in order to rule mood levels out definitely as the main predictor, more evidence will be surely needed.

4.1 Limitations and direction of future research

As introduced, a limitation found in this meta-analysis is the significant heterogeneity among the sample of studies, as it is indicated by the extremely high scores on the heterogeneity tests.

Although we had numerous strict criteria and the stimulation protocols were mostly similar, there were different elements that varied across the experiments. Specifically, the cognitive tasks considered, while all linked to the assessment of executive functions, were structured differently from each other. While this is a type of variability common to meta-analysis, it certainly contributed to the overall high score. Secondly, in the current meta-analysis, other sources of variability were represented by the different mood assessments and by the fact that the populations from which the participants' samples were derived were different from each other. In fact, we analyzed healthy participant populations and patient populations together.

Moreover, an additional limitation that must be taken into consideration when interpreting the data is that the sample of included articles was rather small.

At first glance, it may seem that high levels of heterogeneity originated from multiple sources. However, the vast majority of the score can be explained by a single factor, namely the availability of adequate studies currently present in the

research. As previously said, there are not many studies investigating the interrelation between mood and executive functioning in relation to prefrontal tDCS that satisfy all of the criteria, let alone meta-analyses that tried to investigate the variability of findings in this area. For this reason, the sample was small and very heterogeneous.

Overall, it can be concluded that at least another explanation can clarify what led to a lack of effects by mood without having to exclude it as a possible predictor. Due to the scarcity of literature on the subject, the few papers that met the criteria were quite variable. This is evident when referring to the analysis of variability in the result section, where the data obtained a score of 70 percent in heterogeneity, which is extremely high indeed. Therefore, the results could be explained by the nature of the literature research. We can argue that, with so much variability, it is hard to isolate and detect the direction of the effect of the moderator. To check whether this is the case or not, it will be necessary to collect more suitable studies and conduct separate meta-analyses according to the population or types of tasks administered, so that the direction of the effect can be clearer. Indeed, a meta-analysis with a larger sample and a larger pool of studies to choose from could allow for more specific and differentiated analyses, decreasing the degree of heterogeneity across the included articles. Certainly, analyses run isolating a specific population and administering similar cognitive tasks and mood assessments will be more effective in investigating the potential effect of mood levels on cognition. Thus, to resolve the presented limitations and draw more definite conclusions, widening the literature on this topic is necessary.

Future research should focus on the conduct of other prefrontal tDCS studies that integrate both executive functioning tasks and mood assessments, also across a wider variety of populations. Indeed, it is highly probable that different results will be obtained from meta-analyses focused only on healthy participants, with respect to studies considering only clinical samples, such as the ones formed by patients with depression or schizophrenia.

In our opinion, if the research will follow such directions, we could drastically improve the quality of future meta-analyses.

4.2 Conclusions

This systematic review and meta-analysis investigated the variability of the effects of tDCS on the prefrontal cortex on executive functioning, a field of interest in neuropsychological studies. However, it went further, integrating the neuropsychological literature with the psychiatric one. Indeed, the aim was to clarify the relationship between mood levels and tDCS effect on executive functioning, hypothesizing that mood could be framed as potential source of results variability.

Although we found no significant proof of mood as a moderator of tDCS cognitive outcome, more integrative research between mood and cognition must be carried out.

At current times, it is especially important since anxiety and mood disorders have increased, disorders whose symptoms do not fit into either the "neuropsychological" or the "clinical psychology world". They fit both domains, and dlPFC could represent the starting point of integrative future research, as it could be the neural embodiment of that integrative nature between mood and cognition.

Nowadays, we often consider ourselves as cognitive beings whose moods were only side effects that should be controlled, but that should not interfere with our cognition. However, as Forgas and Koch (2013) said, humans are a moody species. I think that our hypothesis can still be valid for future attempts to overcome the compartmentalized, the "either…or" vision of the human mind in order to produce dlPFC-tDCS treatments that are effective and well-rounded.

For all these reasons, the research should point towards the elucidation of the interplay of mood, cognition, and expand the stimulation of dlPFC in the next years, so that the scientific community will collect enough data to draw useful and applicable conclusions.

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SUPPLEMENTARY MATERIAL

This section shows how each cognitive outcome of each article was selected and inserted in the analysis.

1. Chow et al., 2021 (ACC)

Chow_1 (Digit span forward score) and Chow_2 (Digit span backward score) were merged into a single outcome, and a composite ES was calculated (Digit span score).

2. Coussement et al., 2019 (RT)

Single measure (Differential latencies).

3. Eddy et al., 2017 (RT and ACC)

Eddy_1 (Response Time), Eddy_2 (Accuracy), Eddy_3 (Stroop test completion time) and Eddy_4 (DOT Accuracy). Two ES composites are differentiated. The first one considers the measurements in Eddy_1 and Eddy_3, namely RT. The second one considers those in Eddy_2 and Eddy_4, namely ACC.

4. Ferrucci et al., 2011 (RT)

Ferrucci_1 (Response Time of ER) and Ferrucci_2 (RT of visual attention task) were merged into a single outcome, and a composite ES was calculated (Response Time).

NOTE: The mood in Ferrucci et al. is calculated by averaging the score in the real_anodal condition with sham.

5. Heeren et al., 2016 (RT)

Single measure (Differential latencies).

6.Keeser et al., 2010 (RT and ACC)

Keeser et al., 2010_1 (Response Time) and Keeser et al., 2010_2 (Accuracy).

7. Lema et al., 2021 (RT and ACC)

Lema et al., 2021_1 (Response Time) and Lema et al., 2021_2 (Accuracy).

8. Martin et al., 2015 (RT and ACC)

Martin et al., 2015_1 (RT of n-back) and Martin et al., 2015_2 (d index of n-back).

9. Nejati et al., 2018 (RT and ACC)

Nejati_1 (Accuracy of NoGo), Nejati_2 (RT of Go/NoGo), Nejati_3 (Tot time of TOH), Nejati_4 (Average pumps of BART, adjusted value), and Nejati_5 (K value of temporal discounting task). Nejati_5 is excluded because it is neither RT nor ACC. Two composite ES are distinguished. The first one considers measurements in Nejati_2 and Nejati_3, that is RT. The second one considers those in Nejati _1 and Nejati _4, that is ACC.

> NOTE: ES by Nejati_4 was reversed since "low scores of the adjusted value are indicative of low-risk behavior". So, contrary to typical ACC values, the smaller the score of the performance, the better it is.

In **Papazova et al., 2018**, there are two different experiments, hence two different groups. Thus, they are considered as two separate studies: Papazova et al., (2018a) and Papazova et al., (2018b).

> **10. Papazova et al., 2018a (RT and ACC)**
>
> Papazova_2018a_1 (D prime exp1), Papazova_2018a_2 (RT exp1) and Papazova_2018a_3 (Hit rate exp1). Two ES composites are differentiated. The first one considers the measurements in Papazova_2018a_2, namely

RT. The second one considers those in Papazova_2018a_1 e Papazova_2018a_3, namely ACC.

11. Papazova et al., 2018b (RT and ACC)

Papazova_2018b_1 (D prime exp2), Papazova_2018b_2 (RT exp2) e Papazova_2018b_3 (Hit rate exp2). Two ES composites are differentiated. The first one considers the measurements in Papazova_2018b_2, namely RT. The second one considers those in Papazova_2018b_1 e Papazova_3, namely ACC.

In **Sanchez_Lopez et al., 2018**, there are two different experiments, hence two different groups. Thus, they are considered as two separate studies: Sanchez_Lopez et al., (2018a) and Sanchez_Lopez et al., (2018b).

12. Sanchez_Lopez et al., 2018a (RT)

Sanchez_Lopez _2018a_1 (attentional disengagement leftDLPFC) and Sanchez_Lopez _2018a_2 (attentional engagement leftDLPFC) were merged into a single outcome, and a composite ES was calculated (Latency).

13. Sanchez_Lopez et al., 2018b (RT)

Sanchez_Lopez _2018b_1 (attentional disengagement leftDLPFC) and Sanchez_Lopez _2018b_2 (attentional engagement leftDLPFC).) were merged into a single outcome, and a composite ES was calculated (Latency).

In **Schwippel et al., 2017** , there are two different experiments, hence two different groups. Thus, they are considered as two separate studies: Schwippel et al., (2017a) and Schwippel et al., (2017b).

14. Schwippel et al., 2017a (RT and ACC)

Schwippel et al., 2017a_1 (Response Time of n-back) and Schwippel et al., 2017a_2(discriminability)

15. Schwippel et al., 2017b (RT and ACC)

Schwippel et al., 2017b_1 (Response Time of n-back) and Schwippel et al., 2017b_2(discriminability)

16. Sreeraj et al., 2019 (RT and ACC)

Sreeraj et al., 2019_1 (Response Time) and Sreeraj et al., 2019_2 (Accuracy).

17. Vanderhasselt et al., 2019 (ACC)

Bifrontal stimulation was not considered cathodic, therefore it was included. Single measure (Accuracy).

18. Vanderhasselt et al., 2016 (RT and ACC)

Vanderhasselt et al., 2016_1 (Response Time) and Vanderhasselt et al., 2016_2 (Accuracy).

19. Vanderhasselt et al., 2013 (RT and ACC)

Vanderhasselt et al., 2013_1 (RT of internal shift) and Vanderhasselt et al., 2013_2 (Internal shift task error rates).

NOTE: ES di Vanderhasselt et al., 2013_2 4 was reversed since the outcome corresponds to *"Error rates in all the IST conditions were calculated as the difference between the correct number and the stated number of faces seen in the preceding block (i.e., series of faces), always depending on the condition (emotion or non-emotion).* Error rates refer to the total number of errors over all blocks in that condition".