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

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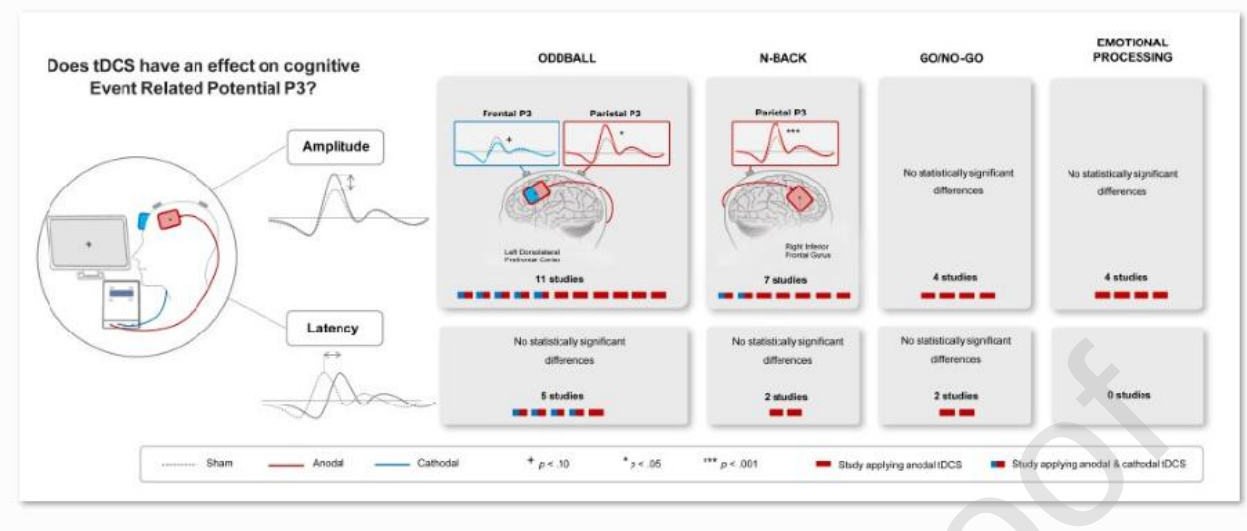
Graphical abstract



Highlights

- Meta-analysis about the tDCS effect on P3 elicited by cognitive tasks.
- Anodal frontal tDCS significantly increases parietal P3 amplitude during oddball and n-back tasks.
- No tDCS effect was detected on P3 latency, however, few studies analyzed this marker.
- P3 brain potential may be useful to assess the effects of tDCS during attention and memory processes.

Abstract

Transcranial direct current stimulation (tDCS) has been widely used to modulate cognition and behavior. However, only a few studies have been probing the brain mechanism underlying the effects of tDCS on cognitive processing, especially throughout electrophysiological markers, such as the P3. This meta-analysis assessed the effects of tDCS in P3 amplitude and latency during an oddball, n-back, and Go/No-Go tasks, as well as during emotional processing. A total of 36 studies were identified, but only 23 were included in the

quantitative analysis. The results show that the parietal P3 amplitude increased during oddball and n-back tasks, mostly after anodal stimulation over the left dorsolateral prefrontal cortex ($p = 0.018$, SMD = 0.4) and right inferior frontal gyrus ($p < 0.001$, SMD = 0.669) respectively. These findings suggest the potential usefulness of the parietal P3 ERP as a marker of tDCS-induced effects during task performance. Nonetheless, this study had a low number of studies and the presence of considerable risk of bias, highlighting issues to be addressed in the future.

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

1. Introduction

Transcranial direct current stimulation (tDCS) is one of the most studied techniques in non-invasive neuromodulation. With a very good safety profile and low cost, tDCS has been used to modulate cognition in both experimental and clinical settings (Coffman et al., 2014; Fregni et al., 2020). tDCS relies on the application of a weak direct current through two electrodes with different polarities – the anode and the cathode. The cortical excitability modulation depends on the polarity. The concept is that anodal stimulation leads to a subthreshold neuronal depolarization augmenting the likelihood of spontaneous neuronal firing, whilst the cathode has the opposite hyperpolarization effect

(Stagg and Nitsche, 2011). Additionally, tDCS induced after-effects occur through neuroplastic changes at molecular level, e.g. in the N-methyl-D-aspartate (NMDA) receptors and brain-derived neurotrophic factor (BDNF), namely by inducing long-term potentiation (LTP) and long-term depression (LTD) (Chan et al., 2021; Monte-Silva et al., 2013). The neuroplastic modulation is not only dependent on tDCS polarity, but it is also contingent on other stimulation parameters (e.g., current density, stimulation duration). Recent studies showed that the dose-response relationship follows a non-linear inverted U-shaped function (Batsikadze et al., 2013; Goldsworthy and Hordacre, 2017). Moreover, resting neuronal state seems also to be relevant for understanding the neurophysiological impact of tDCS. For instance, recent studies showed that tDCS effects are dependent on the timing of stimulation, task difficulty, or ongoing neuronal activity (Fertonani and Miniussi, 2017).

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

The P3 (or P300) is one of the most studied event-related potentials (ERP) (Sutton et al., 1965). This positive component peaks with a latency around 300 – 400 ms after the stimulus onset in any sensory modality, and is thought to underlie attention and working memory processes (Kok, 2001; Polich, 2007). Deviations in P3 amplitude and latency are

associated with cognitive deficits in several neuropsychiatric disorders, such as alcohol use disorder (Hamidovic and Wang, 2019), attention-deficit/hyperactivity disorder (ADHD; Kaiser et al., 2020), bipolar disorder (Wada et al., 2019), post-traumatic stress disorder (PTSD; Johnson et al., 2013), and psychopathy and antisocial behavior (Pasion et al., 2018).

Often referred in the literature as a single component, P3 can be divided in two additional subcomponents: P3a and P3b. P3a signals an attentional and orientation processes (P3a) occurring after the exposure of an unpredictable stimulus (e.g., a distracter or a novel stimulus in a three-stimulus oddball paradigm) and it is elicited in the frontocentral brain region (Friedman et al., 2001). This subcomponent might be a neuronal representation of attentional allocation and orientation to something unexpected (Simons et al., 2001; Spencer et al., 2001). The amplitude and latency of P3a are modulated by the stimulus salience with more relevant stimuli eliciting a larger and faster P3a (Kok, 2001). The amplitude of this component is also modulated by habituation as novelty and/or salience of the stimulus decreases in repeated presentations, especially with short interstimulus intervals (Rushby and Barry, 2009). On the other hand, P3b is elicited in parieto-temporal region approximately 60-80 ms after the P3a during a standard oddball paradigm, specifically after an infrequent stimulus (i.e., target) that is intermingled in a series of frequent stimuli (i.e., non-target). Participants are instructed to respond to a target stimulus (e.g., press a button or count the number of targets), whilst they need to ignore the non-target stimulus. (Polich, 2007). Low uncertainty in stimulus prediction is necessary to elicit the P3b component and this component occurs when the target does not match the representation maintained on the WM, suggesting a role in

processing task-relevant information and subsequent memory storage (Polich, 2007). P3b is thought to be a neural signature of goal-directed target identification in complex cognitive processes such as goal-directed learning and decision making (Rac-Lubashevsky and Kessler, 2019).

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

Additionally, P3 is also elicited during tasks requiring the inhibition of a forthcoming response, such as the Go/No-Go (GNG) task and the Stop Signal Reaction Time task (SSRT). Both paradigms require distinct frontal-basal-ganglia circuits due to different functional demands in the inhibitory processing via proactive (e.g., GNG task) and reactive inhibition (e.g., SSRT; Aron, 2011). In GNG tasks, P3 is elicited during the "no-go" and "go" trials. The "no-go" P3 amplitude has been highlighted as an important marker of inhibitory control and is often elicited in frontocentral regions during

successful inhibition trials (Huster et al., 2013). Thus, this component has been associated with P3a due to its topographic similarities, whilst the "go" P3 is observed in parietal regions after a stimulus requiring a motor action (Ruchsow et al., 2008). On the other hand, during the SSRT, the P3 component is elicited during "stop" trials that demand an inhibition of an action that was already initiated. Moreover, changes in P3 amplitude have also been shown to reflect inhibitory processes. For instance, P3 amplitude has been shown to increase under high inhibitory load conditions, such as the one required by faster response times or decreased probability of stop-signal (Huster et al., 2013). Additionally, a recent meta-analysis also demonstrated the importance of P3 latency for inhibitory processes, showing a strong correlation between early P3 latency (and not the amplitude) with successful inhibition in stop trials (Huster et al., 2020).

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

Overall, P3 has been used frequently as an index of attention and working memory underlying several cognitive processes and can be used to assess the impact on cognitive

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

2. Methods

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

2.1. Literature Search and Study Selection

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

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

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

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

In the case of multiple publications related to one cohort, we included the most updated report. We did not exclude studies because of language or publication date. Moreover, before the

screening phase, the reviewers screened titles and abstracts from one random sample of 100 search results to ensure an inter-rater agreement of at least 90%. The Cohen's kappa was estimated as a measure of the inter-rater reliability assessment (McHugh, 2012). The mean inter-rater agreement and kappa estimators were 94% and 90% respectively (see Table B in Supplementary Materials for more details).

2.2. Data extraction

The relevant information was extracted from the second-stage included studies, namely, first author, year of publication, mean, and standard deviation of P3 amplitude and latency post or during tDCS, number of subjects analyzed (i.e., excluding outliers or subjects with noisy EEG data), EEG electrode(s), brain region of stimulation (i.e., anode and cathode location), tDCS parameters (i.e., intensity, density, and duration), number of sessions (e.g., single or multi-session), population (e.g., healthy subjects or with clinical diagnostic), computerized cognitive task that elicited P3, target probability and stimulus modality in the computerized task, (e.g., auditory, visual), and study design (e.g., crossover, parallel). In studies lacking the required statistical information to estimate effect size in the text or tables, however with the information available on the graphs, the Web Plot Digitizer was used to extract those data (Rohatgi, 2017). In case of the inexistence of the required statistical information in any format, an email was sent to the corresponding author requesting the intended information. Furthermore, considering that P3 is a component more prominent in frontal and parietal regions (Polich, 2007), the amplitude and the latency of P3 were extracted from the Fz and Pz electrodes when available. Otherwise, the regions of interest (ROI) analyzed in the studies are considered to extract the data, namely P3 on parietal and frontal areas (Table I in Supplementary Materials). Therefore, the meta-analysis of P3 was performed independently for frontal and parietal areas since they represent the main

regions of interest with distinct functional significances. Additionally, the GNG subsection is also divided by type of trial (i.e., No-Go and Go trials).

2.3. Statistical analysis

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

2.3.1. Pooled effect estimates and subgroup analysis

A random-effect model was performed due to the expected high level of heterogeneity, assuming that the true effect size among the studies might not be identical (Borenstein et al., 2010). The effect size was calculated by subtracting sham P3 values from the active tDCS condition measured during/after tDCS. The standard mean difference (SMD) between both tDCS conditions, namely the effect size of the intervention relatively to its variability, was calculated following the unbiased method of Hedges' *g* (Hedges, 1981). Thus, the pooled effect estimates were analyzed independently for anodal and cathodal tDCS due to its potential antagonistic effects (Cochrane, 2019). The subgroup analysis were performed accordingly to the tDCS polarity and brain region of stimulation (e.g., left dorsolateral prefrontal cortex - lDLPFC, right Inferior Frontal Gyrus - rIFG). These analyses were performed only when there were the effect estimates from at least two studies. Furthermore, the I^2 index was performed to assess heterogeneity (Higgins and Thompson, 2002).

2.3.2. Influential analysis

The influential analysis was performed using the leave-one-out method. This technique allows the recalculation of the estimates of the meta-analysis by removing one study per recalculation in a total of N-1 times (Viechtbauer and Cheung, 2010). This sensitivity analysis tests the

robustness of the detected effects by observing the influence of each comparison in the significant findings.

2.3.3. Moderator analysis

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

2.3.4. Publication bias

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

2.4. Risk of Bias

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

2.5. Evidence certainty assessment

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

3. Results

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

reported the data from the electrode site Cz. Furthermore, six studies did not report sufficient information to estimate the effect size and the corresponding author did not reply to the request via e-mail. We excluded five studies evaluating P3 on other cognitive tasks, such as flanker task, recognition task, naming task, and a decision-making paradigm (Figure 1). The results of the study characteristics, pooled effect estimates, and subgroup analysis are divided into four main analyses, namely in GNG, n-back, oddball, and emotional processing. Finally, we presented the moderator and influential analysis, the publication bias, risk of bias, and evidence certainty assessment.

<INSERT HERE FIGURE 1>

3.1. Oddball

3.1.1. Study Characteristics

Thirteen studies met the eligibility criteria. However, two studies were excluded because, in one, no relevant data was available directly from the article, and another study only analyzed the P3 in the Cz electrode. Therefore, 11 studies (with 22 comparisons) with a total of 236 participants were analyzed (see Table H in Supplementary Materials). Seven (out of 11) studies (with 16 comparisons) analyzed the P3 amplitude in the frontal region and nine studies (with 16 comparisons) in the parietal area. In the frontal P3 assessment, the anodal stimulation was performed in seven studies (with 10 comparisons and the cathodal in five studies, with eight comparisons). Considering the studies that analyzed parietal P3 amplitude, all the studies (nine studies with 11 comparisons) studied the effect of anodal stimulation, whilst four of them (with five comparisons) also tested the effects of cathodal tDCS. In line with other tasks, the P3 latency was less frequently analyzed, specifically four studies (with five comparisons) tested

anodal and cathodal tDCS in frontal P3, while two studies (with four comparisons) explored the anodal effect and one study (with two comparisons) on parietal P3 (see Table E in Supplementary Materials).

Taking into account the brain region of tDCS, most of the studies targeted to the lDLPFC (six studies with 16 comparisons), others the cerebellum (two studies with six comparisons), rIFG (one study and one comparison), supraorbital area (one study and two comparisons) and motor cortex (one study and one comparison) (see Table F in Supplementary Materials). Most of the studies performed tDCS before the assessment of P3 (nine studies), whilst only one did it during tDCS and another one assessed the after effects of tDCS on the P3 component. Additionally, the oddball tasks were mostly designed using auditory stimuli (nine out of 11 studies) and only two studies used visual cues (i.e., one employed letters and numbers and another one used human faces). Finally, six studies (with 10 comparisons) explored P3 in healthy subjects and five studies (with eight comparisons) in a clinical population (i.e., three in people with schizophrenia, one in people with multiple sclerosis and Alzheimer's disease).

3.1.2. Pooled effect estimates and subgroup analysis

The pooled effect estimated from the seven studies (with 10 comparisons) that analyzed anodal tDCS on the frontal P3 amplitude did not present significant heterogeneity (p = 0.685, I^2 = 2.429). Moreover, this set of studies did not show a significant effect on frontal P3 amplitude (p = 0.576, SMD = -0.062, 95% CI [-0.28 0.16]). Further subgroup analysis did not show significant heterogeneity in the studies applying anodal stimulation on cerebellum (p = 0.928, I^2 = 0), neither on the lDLPFC (p = 0.385, I^2 = 22.448). Nonetheless, both subgroup analysis revealed a non-significant effect of stimulation on the frontal P3 amplitude, namely when using

anodal tDCS over the cerebellum (p = 0.668, SMD = -0.104, 95% CI [-0.58 0.37]) or over the lDLPFC (p = 0.839, SMD = -0.029, 95% CI [-0.31 0.25]). Additionally, five studies (with six comparisons) that analyzed the effect of cathodal tDCS in frontal P3 amplitude did not reveal significant heterogeneity (p = 0.18, I^2 = 22.141) and showed that cathodal tDCS significantly decreased frontal P3 amplitude (p = 0.017, SMD = -0.404, 95% CI [-0.73 -0.07]) (Figure 2). The subsequent subgroups analysis regarding brain region stimulation did not show significant result in heterogeneity test for cathodal tDCS over the cerebellum (p = 0.109, I^2 = 54.612) or over the lDLPFC (p = 0.215, I^2 = 38.57). Cathodal stimulation over the cerebellum did not show a significant effect on frontal P3 amplitude (p = 0.383, SMD = -0.325, 95% CI [-1.05 0.41]), whilst a non-significant trend was showed when the cathodal tDCS was delivered over the lDLPFC (p = 0.076, SMD = -0.42, 95% CI [-0.88 0.04]).

<INSERT HERE FIGURE 2>

For frontal P3 latency, the four studies (with five comparisons), in which anodal stimulation was applied, were significantly heterogeneous (p < 0.001, I^2 = 92.818). However no significant effects of anodal tDCS in frontal P3 latency were found (p = 0.47, SMD = 0.493, 95% CI [-0.84 1.83]). Furthermore, the heterogeneity test in the subgroup analysis revealed a non-significant heterogeneity in anodal cerebellar tDCS (p = 0.79, I^2 = 0), but a significant heterogeneity in the studies applying anodal stimulation over the lDLPFC (p < 0.001, I^2 = 97.817). The subgroup analysis probing the effects of anodal tDCS in the frontal P3 latency was non-significant, regardless of the stimulation site (p = 0.937, SMD = 0.019, 95% CI [-0.46 0.5] for cerebellum) and (p = 0.518, SMD = 1.221, 95% CI [-0.31 4.92] for the lDLPFC). Concerning the same for studies, but for the cathodal stimulation comparisons (five comparisons), a significant heterogeneity was revealed (p < 0.001, I^2 = 91.403. However, there were no significant effects of

cathodal tDCS on the frontal P3 latency (p = 0.172, SMD = 0.843, 95% CI [-0.37 2.05]). Subgroup analysis suggested significant heterogeneity in cathodal cerebellar ($p < 0.001$, I^2 = 93.107)) and in the lDLPFC tDCS(p = 0.006, I^2 = 86.523). In line with the pooled effect estimate analysis, both subgroups showed no significant effect on the frontal P3 latency, namely with cerebellar (p = 0.283, SMD = 1.17, 95% CI [-0.97 3.31]) or the lDLPFC tDCS (p = 0.465, SMD = 0.492, 95% CI [-0.88 1.81]).

For probing the effects of anodal tDCS in the parietal P3 amplitude, nine studies (with 11 comparisons) were retrieved. There was a non-significant trend regarding heterogeneity (p = 0.058, I^2 = 42.218) and there was no significant anodal tDCS effect (p = 0.596, SMD = 0.081, 95% CI [-0.22 0.38]). Moreover, subgroup analysis did not present significant heterogeneity in studies with anodal tDCS over the cerebellum (p = 0.68, I^2 = 0) or the lDLPFC (p = 0.338, I^2 = 11.264). No significant effect of anodal cerebellar tDCS on parietal P3 amplitude was shown (p = 0.984, SMD = 0.005, 95% CI [-0.47 0.48]), however there was a significant effect of anodal stimulation over the lDLFPC (p = 0.018, SMD = 0.4, 95% CI [0.07 0.73]). The anodal tDCS over the lDLPFC increased the frontal P3 amplitude in comparison with the sham condition (Figure 3). The subgroup analysis of anodal tDCS over supraorbital, rIFG or M1 are not reported because they were comprised by only one study. For cathodal tDCS, the four studies (with five comparisons) did not show significant heterogeneity (p = 0.857, I^2 = 0) and there was no significant effect of cathodal tDCS in the parietal P3 amplitude (p = 0.837, SMD = -0.036, 95% CI [-0.38 0.31]). The subgroup analysis with the cathodal cerebellar tDCS comparisons neither reveal heterogeneity (p = 0.578, I^2 = 0), nor significant effect of cathodal tDCS (p = 0.78, SMD = -0.068, 95% CI [-0.55 0.41]). The subgroup analysis of cathodal tDCS over the supraorbital region, or the lDLPFC is not reported because there is only one study targeting those regions.

<INSERT HERE FIGURE 3>

Finally, the pooled effect estimate and subgroup analysis was not performed in the parietal P3 latency during oddball due to the lack of data.

3.2. N-back tasks

3.2.1. Study Characteristics

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

Every study explored the effect of tDCS on frontal areas, namely over the lDLPFC (five studies out of seven with 15 comparisons assessed frontal P3; and two studies with six comparisons in total, assessed parietal P3) and rIFG (two studies out of seven with three comparisons assessed frontal P3 and five comparisons in parietal P3) (see Table F in Supplementary Materials). All the studies performed tDCS before assessing the P3 component. Moreover, the study population was different between the included studies, comprising healthy

adults (five studies with 15 comparisons), healthy elderly (one study with two comparisons), patients with Alzheimer disease (one study with two comparisons) and children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD; one study with two comparisons). Finally, the P3 was assessed in 0-back and 1-back (three studies with five comparisons), 2-back (five studies with eight comparisons), and 3-back (four studies with seven comparisons).

3.2.2. Pooled effect estimates and subgroup analysis

The pooled effect estimates of the six studies (and 15 comparisons) with anodal tDCS that incorporated frontal P3 amplitude in their analysis revealed a significant heterogeneity ($p < 0.001$, $I^2 = 70.497$). Considering all the studies, there were no differences between anodal and sham tDCS in frontal P3 amplitude ($p = 0.959$, SMD = 0.008, 95% CI [-0.31 0.33]). The studies with anodal tDCS over the lDLPFC presented a significant heterogeneity ($p = 0.03$, $I^2 = 47.561$). Furthermore, there were no significant effects of anodal tDCS over the lDLPFC in frontal P3 amplitude ($p = 0.169$, SMD = 0.202, 95% CI [-0.09 0.49]). The subgroup analysis of anodal tDCS over rIFG is not reported because only one study analyzed the frontal P3 amplitude. Additionally, both studies that explored the effects of cathodal tDCS over the frontal P3 amplitude did not present significant heterogeneity ($p = 0.368$, $I^2 = 2.664$), but no significant effects were detected ($p = 0.888$, SMD = -0.032, 95% CI [-0.48 0.41]). Finally, regarding the frontal P3 latency, the two studies (with seven comparisons) did not reveal significant heterogeneity ($p = 0.936$, $I^2 = 0$) and no significant effects of anodal tDCS on frontal P3 latency were found ($p = 0.201$, SMD = -0.173, 95% CI [-0.44 0.09]).

Regarding the P3 evaluated in the parietal region, the four studies (with 8 comparisons) with anodal tDCS analysis did not reveal a significant heterogeneity ($p = 0.49$, $I^2 = 64.786$) and there

was a significant effect of tDCS on parietal P3 amplitude (p = 0.001, SMD = 0.477, 95% CI [0.2 0.76]). In fact, there is an increase in the P3 amplitude during the performance of the n-back tasks after anodal tDCS (Figure 4). Subgroup analysis performed in the studies that applied anodal tDCS over rIFG did not reveal a significant heterogeneity level (p = 0.572, I^2 = 0) and showed even a significant larger positive mean estimated effect size (p < 0.001, SMD = 0.669, 95% CI [0.31 1.03]). Additionally, subgroup analysis on studies with anodal stimulation over the lDLPFC did not present significant heterogeneity (p = 0.672, I^2 = 47.561), but also did not reveal a significant effect estimate (p = 0.398, SMD = 0.19, 95% CI [-0.25 0.63]). Concerning both studies assessing cathodal tDCS effect, neither significant results in terms of heterogeneity between comparisons was found (p = 0.891, I^2 = 2.664), nor a significant effect on parietal P3 amplitude (p = 0.939, SMD = -0.017, 95% CI [-0.46 0.42]). Finally, only one study assessed the parietal P3 latency in n-back tasks, which did not allow the analysis to be performed.

<INSERT HERE FIGURE 4>

3.3. Go/No-Go task

3.3.1. Study Characteristics

Six studies were eligible according to the aforementioned criteria, nonetheless, in two of them it was not possible to extract the required information and the corresponding author did not reply to our requests. Therefore, four studies (with seven comparisons) comprising 120 participants were analyzed (see Table H in Supplementary Materials). All the studies used anodal tDCS. Every study analyzed the No-Go P3 amplitude, while only two (out of five) analyzed the No-Go latency. Nonetheless, two of them evaluated the No-Go P3 in the frontal region, whilst the other two in the parietal. Regarding the Go-P3, data was extracted from parietal electrodes,

and amplitude was assessed in two studies, and latency in one of them. Most of the studies applied tDCS over frontal areas (three out of four), whilst only one applied tDCS over the motor cortex. Considering the studies of frontal tDCS, the targeted regions were the rIFG, and the right and left DLPFC (see Table F in Supplementary Materials). All the studies applied tDCS before the EEG recording. Moreover, every study included a sample of healthy adults, but one study included an additional sample of binge drinkers (BDs) and another a sample of elderly subjects. Finally, two studies used emotional-charged stimuli in the GNG, namely alcohol-related and food-related pictures.

3.3.2. Pooled effect estimates and subgroup analysis

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

3.4. Emotional processing

3.4.1. Study Characteristics

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

3.4.2. Pooled effect estimates and subgroup analysis

The two studies (with three comparisons) which assessed the frontal P3 amplitude after emotional stimuli in their analysis presented significant heterogeneity ($p < .001$, $I^2 = 92.713$). Additionally, no significant effect of tDCS on frontal P3 amplitude was revealed ($p = 0.506$, SMD = 0.425, 95% CI [-0.83 1.68]). Regarding the parietal P3 amplitude, the three studies (with eight comparisons) revealed significant heterogeneity ($p < .001$, $I^2 = 90.163$), without a significant tDCS effect ($p = 0.706$, SMD = -0.134, 95% CI [-0.83 0.56]). Subgroup analysis with

the two studies (with six comparisons) that applied anodal tDCS over the lDLPFC revealed a significant heterogeneity ($p < 0.001$, $I^2 = 90.163$), without a significant effect ($p = 0.706$, SMD = -0.134, 95% CI [-0.83 0.56]). Additionally, excluding the comparison with online anodal tDCS over the lDLPFC with EEG recording, the subgroup analysis still maintained a significant heterogeneity ($p = 0.029$, $I^2 = 54.85$) and without a significant effect in parietal P3 amplitude ($p = 0.249$, SMD = 0.214, 95% CI [-0.15 0.58]). No data about P3 latency was not included in the analysis since this data was not reported in the included studies.

3.5. Moderator and Influential Analysis

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

The leave-one-out method revealed similar results when compared to the pooled effect estimates and subgroup analysis in general. The anodal tDCS effect detected on the pooled effect

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

3.6. Publication Bias

The publication bias analysis was only performed in anodal comparisons on frontal P3 amplitude during n-back and on frontal and parietal P3 amplitude during oddball paradigms (i.e., same requirement of moderator analysis about the minimum comparisons). Thus, comparisons on P3 latency, GNG, emotional processing, and other comparisons from n-back and oddball were not analyzed regarding publication bias (Sterne et al., 2011). In oddball paradigms, frontal P3 amplitude studies do not suggest publication bias in the funnel plot (see Figure A1 in Supplementary Materials) and in Egger's test (p = 0.158, z = 1.413). Moreover, parietal P3 studies also show some deviations in the funnel plots (see Figure A2 in Supplementary Materials), namely two studies out of the CI boundaries, one on each side, which was verified in the Egger's test (p = 0.004, z = -1.839). Nonetheless, this result is strongly influenced by one study applying tDCS over M1 and that measured P3 in an oddball speller (Izzidien et al., 2016). At last, the studies with anodal tDCS in n-back tasks that evaluated frontal P3 amplitude suggest a lack of publication bias due to its symmetry in funnel plot, although four studies are out of the CI boundaries (see Figure A3 in Supplementary Materials) and the non-significant effect in Egger's test (p = 0.32, z = 0.995).

3.7. Risk of Bias and Certainty of Evidence

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

The certainty of the included evidence was judged from very low to moderate. Most of the assessed outcomes were graded as very low certainty, only one oddball outcome (frontal P3 amplitude during cathodal stimulation) and one n-back outcome (parietal P3 amplitude during anodal stimulation) were graded as low and moderate certainty, respectively. We started the

evaluation from high certainty since we included only randomized and counterbalanced experiments. We downgraded according to the risk of bias of the studies (more than 75% of the studies had an unclear risk of bias on critical domain such as allocation concealment and participant blinding) and due to imprecision (wide confidence interval and small sample sizes), additionally we downgraded two outcomes due to publication bias (see Table G in Supplementary Materials).

4. Discussion

The current study aimed to study the usefulness of the P3 component as a potential neural signature for probing the neuromodulatory effects of tDCS. P3 is an ERP observed in different neurocognitive processes, such as attentional allocation, WM, response inhibition, and emotional processing. This meta-analysis focused on the assessment of P3 elicitation during three tasks, namely GNG, n-back, and oddball, as well as an additional analysis during emotional processing. Overall, the data suggests that tDCS over frontal region significantly increases parietal P3 amplitude during oddball and n-back tasks. No effects were found for GNG and emotional processing.

4.1. Oddball

During oddball paradigms, parietal P3 amplitude was significantly increased after tDCS, but only when anodal tDCS was applied over the lDLPFC (SMD = 0.4). Moreover, a significant decrease in terms of amplitude was detected in frontal P3 after cathodal tDCS (SMD = -0.4), although it was strongly influenced by the results of one study (Rassovsky et al., 2018). Additionally, long duration tDCS was associated with larger effects on parietal P3, even though the intervals from the analyzed studies only ranged from 15 to 27.29 minutes. Moreover, both significant effects were observed in a set of studies comprising healthy and clinical populations,

namely schizophrenia and multiple sclerosis (see Table H in Supplementary Materials). The differential effect of anodal and cathodal tDCS on P3 might be explained by distinct modulations in cortical excitability as suggested by the initial studies testing the physiological effects of tDCS in motor cortex (Stagg and Nitsche, 2011). The depolarization of the neuronal membrane might counteract a regular decrease in P3 amplitude observed in oddball tasks (Fiene et al., 2018), whilst the hyperpolarization might enhance the decrease in P3 amplitude. Nonetheless, the effect on parietal P3 should be interpreted accordingly to its functional significance in the frontoparietal network and the neurobiology behind both subcomponents.

The P3a component in frontal regions during the oddball task has been associated with the attentional allocation and orienting toward salient stimuli (Friedman et al., 2001). Moreover, studies approaching the EEG band powers associated with the P3 showed a predominant theta activity over the frontal cortex (Bernat et al., 2007; Demiralp et al., 2001). In fact, the midfrontal theta oscillation has been associated to attentional and orienting processes (Cavanagh et al., 2012). Additionally, a recent model suggested that the frontal midline theta is associated with the synchronization of other task-relevant brain regions (e.g., parietal areas), which is commonly observed in attention tasks that require conflict detection and memory operations (Cohen, 2014). tDCS has been shown to improve attentional capacity, as illustrated in phasic attention and conflict resolution (Coffman et al., 2012; Miler et al., 2018). However, the effects of tDCS on oscillatory activity synchronization during attention is still unclear. For instance, a study testing the application of anodal tDCS over the medial PFC showed a resting state increase in the power of theta over the frontal midline region, although these changes were not observed during a sustained attention task (Miller et al., 2015). On the other hand, a study by Spooner and colleagues (2020) tested the effects of bilateral HD-tDCS over the DLPFC and showed that

anodal stimulation over the lDLPFC increased theta connectivity between frontal and visual cortices in the contralateral hemisphere. Anodal stimulation over the rDLPFC did not change theta connectivity, although performance in a visual attention task improved in both tDCS conditions (Spooner et al., 2020). Hence, the effect detected of cathodal tDCS over the lDLPFC in P3 might be related to the modulation of frontal mid-line theta. However, there is lack of consistent regarding the mechanisms of action of cathodal stimulation on this oscillatory activity.

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

P3b in parietal (and temporal) areas has been associated to stimulus categorization and context updating during WM (Polich, 2007). The parietal P3 elicited in oddball paradigms has been associated with the delta band over centroparietal regions and linked to categorization of task-relevant stimuli (Bernat et al., 2007; Cooper et al., 2016). Moreover, the interregional communication of relevant information in the frontoparietal network is crucial during the oddball paradigm, namely with enhanced functional connectivity in theta and delta-band between frontal and parietal areas after a target stimulus requiring categorization and updating of the context (Güntekin and Başar, 2010; Harper et al., 2017). Additionally, a recent model suggested that the frontal midline theta is associated with the synchronization of other task-relevant brain regions (e.g., parietal areas), which is commonly observed in attention tasks requiring conflict detection and memory operations (Cohen, 2014). Interestingly, the current meta-analysis demonstrated that tDCS over the lDLPFC had an impact on parietal P3 amplitude suggesting an interregional effect of tDCS during the oddball paradigm. These findings are in line with previous studies that observed the modulatory effects of tDCS on midfrontal theta power and its connectivity with others task-relevant brain regions (Miller et al., 2015; Spooner et al., 2020). Hence, these findings are in line with the P3 generation model suggested by Polich (2007), the attention and memory processes are controlled by functional connectivity within the frontoparietal network.

In line with this model, P3b arises from phasic response of the noradrenergic activity of the locus coeruleus-norepinephrine (LC-NE) pathway (Nieuwenhuis et al., 2005), and the resulting release of norepinephrine after target stimulus presentation (although this response is also observed after non-target stimuli in a weaker form). Likewise, P3 co-occurs along with several psychophysiological reactions related with LC-NE activity, such as pupil dilation and heart rate increase (Nieuwenhuis et al., 2011). However, few studies have explored the

neuromodulatory effects of tDCS in the LC-NE system. For instance, one study showed an effect of tDCS over the motor cortex in the pupil diameter (i.e., an indirect marker of LC-NE activity) and theta activity on frontal areas during an inhibitory control task (Adelhöfer et al., 2019). Thus, the effect observed in parietal P3 amplitude after anodal stimulation on frontal areas might be related with the LC-NE, given that the noradrenergic fibers initially innervate frontal regions followed by posterior cortical areas (Morrison et al., 1982). Likewise, the modulation of distal LC neurons through PFC stimulation was already observed in animal studies (Aston-Jones et al., 1991). Therefore, the parietal P3 amplitude increase after frontal tDCS might be associated with the LC-NE, nonetheless, the evidence is still very scarce in humans.

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

4.2. N-back tasks

tDCS modulated differently the P3 amplitude during n-back task in parietal regions, however no effects were found on frontal regions. P3 amplitude increased after active tDCS over frontal areas in comparison with sham (SMD = 0.33), especially when tDCS was applied over the rIFG

(SMD = 0.67). The significant effect estimate of frontal tDCS was observed in healthy and clinical populations, specifically Alzheimer's disease and ADHD (see Table H in Supplementary Materials). This is consistent with what has been found after programs of cognitive training with WM exercises (O'Brien et al., 2013; Tusch et al., 2016). Hence, an enhanced parietal P3 amplitude might be related to better WM processing, as some studies suggest this correlation (e.g., Cespón et al., 2017). This finding is in line with Polich (2007) about the role of P3b in the updating WM, given that behavioral performance increase in n-back were associated with the parietal P3 and not in frontal P3 that is more related to attentional processes.

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

Therefore, studies aiming at the enhancement of WM processing using NIBS techniques targeted the frontoparietal network, given its role in the access, maintenance and manipulation of information. A recent study found a coupling between the phase of frontal midline theta rhythm and gamma oscillatory amplitude on the parietal region during a visuospatial WM task (Berger et al., 2019). In fact, changes on phase-amplitude coupling between frontal theta and parietal gamma activity were observed after four sessions of WM cognitive training coupled with tDCS over frontal and parietal regions associated with WM improvements (Jones et al., 2020). Another study, in which intermittent Theta Burst Stimulation (iTBS) was delivered to the lDLPFC, resulted in an improvement in WM skills coupled with stronger connectivity of frontoparietal theta and an enhancement of parietal gamma activity (Hoy et al., 2016). A similar effect was found in a study testing tDCS over the lDLPFC in patients with schizophrenia, who shown behavioral gains and an increased synchronization of gamma activity during the task (Hoy et al., 2015). Thus, gamma oscillations assume an important role in WM processes, which intriguingly is co-occurring with the P3 component, in parietal regions after task-relevant stimuli, although both markers might index different mental events (Pitts et al., 2014).

More recently, Riddle and colleagues (2020) explored theta and alpha oscillations using repetitive Transcranial Magnetic Stimulation (rTMS) in the frontal and parietal regions respectively to improve WM processing through an optimal engagement and disengagement of neuronal resources. Results have shown that both entrainments enhanced WM abilities, specifically frontal theta entrainment improved the prioritization of information, whilst parietal alpha assisted the inhibition of irrelevant information (Riddle et al., 2020). These studies propose an inter-dependency between both cortical areas for successful access and maintenance of task-relevant information that can be modulated by NIBS. In line with these findings, the

current meta-analysis shows a modulation within the frontoparietal network through an increase in parietal P3 amplitude after the application of tDCS over frontal areas. In fact, a comparable effect was already found using neuroimaging techniques in the frontoparietal network after tDCS over the lDLPFC (Keeser et al., 2011). Moreover, enhanced parietal P3 amplitude might be related with gamma synchronization in parietal areas, given that both are enhanced by NIBS and related to successful WM processing (Berger et al., 2019; Hoy et al., 2016).

4.3. Go/No-Go task

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

The P3 elicited during no-go trials is thought to be generated in fronto-medial areas and it is highly associated with delta band processes (Huster et al., 2013). The frontal delta activity has been associated with the motivational salience of stimuli, which suggests its importance in the attentional processes required towards a no-go trial (Knyazev, 2012). Likewise, these electrophysiological markers were also observed during the oddball paradigm, namely the enhancement in the delta band, suggesting similar mental operations related to information processing between both cognitive tasks (Bernat et al., 2007; Demiralp et al., 2001). In fact, delta

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

These findings should be cautiously interpreted accordingly to recent models of inhibitory control. Specifically, inhibition is a broad concept that can be divided into several subtypes, such as the proactive and reactive processes. The proactive inhibition aims the inhibition a forthcoming response (i.e., GNG task), whilst reactive inhibition is dependent on an external cue (i.e., SSRT task; Aron, 2011). The rIFG assumes an important role in both processes, although proactive inhibition is related to an indirect pathway that connects the rIFG with the striatum, whilst reactive inhibition has been associated with a hyperdirect pathway from rIFG to subthalamic nucleus (Jahfari et al., 2011). Therefore, anodal tDCS over the rIFG might modulate differently both subtypes of response inhibition. In fact, a recent meta-analysis showed

that tDCS enhanced inhibitory control only in the SSRT task (and a marginally significant in GNG) and the effect estimate was larger in the anodal stimulation over rIFG in comparison with other cortical areas (Schroeder et al., 2020). Nevertheless, the effect of anodal tDCS over the rIFG in P3 during GNG were analyzed in only one study out of the four.

4.4. Emotional Processing

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

In line with the previous findings from GNG tasks, this analysis was comprised of a reduced number of studies that share important differences among them. First, the study population was different in the four studies, namely Binge drinkers, people suffering from alcohol use disorder, with crack/cocaine addiction, and healthy controls. This might be a potential confounder in the

present meta-analysis, given that the pooled effects were observed on distinct effects of craving and consumption pattern (den Uyl et al., 2018; Den Uyl et al., 2015). Second, two studies analyzed the P3 component in a cue-reactivity task, whilst the other two in a GNG with emotional stimulus. Although the analysis included only the P3 evaluated after the affective stimulus, in the cue-reactivity task participants were only instructed to observe the picture and in the GNG they were required to press a button (or not) depending on the type of trial. Therefore, the cognitive operations required during the GNG task might difficult the interpretation of P3 as a marker of cue-reactivity, especially because task dependent effects of tDCS have been shown. Overall, the tDCS effect on cue-reactivity P3 still needs further clarification due to the heterogeneous and small set of studies analyzed. The P3 related to emotional processing might be dependent on specificities of the population (e.g., BDs vs alcoholics) and also on the experimental task (e.g., observation vs press a button).

4.5. Future Directions

The effects of tDCS on the brain during cognitive processing are still unclear (Chan et al., 2021). The current study showed how tDCS can modulate the cognitive P3 in distinct contexts, but the underlying neurophysiological mechanisms are still unclear. For a better understanding, it is important to test how tDCS can influence the connectivity within frontoparietal network during cognitive processing. In particular, the frontal theta activity is a common marker observed in several cognitive processes that rely on the PFC and has been associated with the synchronization of other task-related regions (Cohen, 2014). Although recent studies have approached the tDCS effect on frontal theta within the frontoparietal network in resting-state (Jones et al., 2020), the dynamics during cognitive functioning are not fully understood yet. Furthermore, the neurotransmitters dynamics are also an important component to understand the

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

4.6. Limitations

The low number of studies in some subsections did not allow all the intended analysis, such as the publication bias and the meta-regression analysis. For instance, the meta-regression was only performed in parietal and frontal P3 amplitude after anodal stimulation during oddball

and the parietal P3 amplitude after anodal tDCS in the n-back task (see Table E in Supplementary Materials). Also, the set of studies included share high variability among them (e.g., tDCS intensity, duration), which can difficult the evaluation of the impact of different parameters of tDCS in P3.

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

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

5. Conclusion

This meta-analysis suggests the usefulness of P3 component to study the neurophysiological effects of tDCS during cognition. Specifically, the current study has shown that tDCS over frontal areas had an impact in P3 amplitude assessed in parietal regions during oddball and n-back tasks (Figure 5). Nonetheless, these effects must be cautiously interpreted due to the low number of studies in this analysis, the low-to-moderate certainty of evidence, and the heterogeneity among them (e.g., study population). Additionally, no tDCS effect was detected in P3 evaluated in the GNG task, after emotionally charged stimulus, or in latency. Even so, the low number of analyzed comparisons and the small sample sizes included in these subsections might undermine the statistical power (Button et al., 2013).

Our findings suggest the broad spatial resolution of tDCS impact, given that the changes were not observed in the brain region of stimulation, but in the task-related brain network. In particular, the connectivity within the frontoparietal network might assume an important role in the neurophysiological effects of frontal anodal tDCS during oddball and n-back tasks, mostly via theta band (Gulbinaite et al., 2014). The frontal midline theta has an important role in several cognitive tasks and it has been associated with the synchronization of other task-relevant brain regions (Cohen, 2014), which can be a mediator of the frontal tDCS impact in other areas (i.e., parietal region). In line with this hypothesis, recent evidence demonstrated that NIBS techniques are able to modulate not only the cognitive functioning but also its electrophysiological markers in a spatially distributed manner (Hoy et al., 2015; Jones et al., 2020). Therefore, those neuromodulatory effects observed in the oscillatory synchronization might co-occur in parallel with the modulation of P3, namely the increase of parietal P3 amplitude after the application of anodal tDCS over frontal areas.

<INSERT HERE FIGURE 5>

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Conflict of interest

All authors declare no conflict of interest.

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6. References

Adelhöfer, N., Mückschel, M., Teufert, B., Ziemssen, T., Beste, C., 2019. Anodal tDCS affects

neuromodulatory effects of the norepinephrine system on superior frontal theta activity during response inhibition. Brain Struct. Funct. 224, 1291–1300. https://doi.org/10.1007/s00429-019-01839-3

Aron, A.R., 2011. From reactive to proactive and selective control: Developing a richer model for stopping inappropriate responses. Biol. Psychiatry 69, e55–e68. https://doi.org/10.1016/j.biopsych.2010.07.024

Aston-Jones, G., Chiang, C., Alexinsky, T., 1991. Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance, in: Progress in Brain Research. Elsevier, pp. 501–520. https://doi.org/10.1016/S0079-6123(08)63830-3

Balshem, H., Helfand, M., Schünemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., Vist, G.E., Falck-Ytter, Y., Meerpohl, J., Norris, S., Guyatt, G.H., 2011. GRADE guidelines: 3. Rating the quality of evidence. J. Clin. Epidemiol. 64, 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.-F., Nitsche, M.A., 2013. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J. Physiol. 591, 1987–2000. https://doi.org/10.1113/jphysiol.2012.249730

Berger, B., Griesmayr, B., Minarik, T., Biel, A.L., Pinal, D., Sterr, A., Sauseng, P., 2019. Dynamic regulation of interregional cortical communication by slow brain oscillations during working memory. Nat. Commun. 10, 1–11. https://doi.org/10.1038/s41467-019-12057-0

Bernat, E.M., Malone, S.M., Williams, W.J., Patrick, C.J., Iacono, W.G., 2007. Decomposing delta, theta, and alpha time-frequency ERP activity from a visual oddball task using PCA.

Int. J. Psychophysiol. 64, 62–74. https://doi.org/10.1016/j.ijpsycho.2006.07.015

Boggio, P.S., Zaghi, S., Fregni, F., 2009. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 47, 212–217. https://doi.org/10.1016/j.neuropsychologia.2008.07.022

Borenstein, M., Hedges, L. V., Higgins, J.P.T., Rothstein, H.R., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Methods 1, 97–111. https://doi.org/10.1002/jrsm.12

Brunoni, A.R., Vanderhasselt, M.A., 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. Brain Cogn. 86, 1–9. https://doi.org/10.1016/j.bandc.2014.01.008

Button, K.S., Ioannidis, J.P.A., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S.J., Munafò, M.R., 2013. Power failure: Why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14, 365–376. https://doi.org/10.1038/nrn3475

Carvalho, S., Leite, J., Galdo-Álvarez, S., Gonçalves, Ó.F., 2011. Psychophysiological Correlates of Sexually and Non-Sexually Motivated Attention to Film Clips in a Workload Task. PLoS One 6, e29530. https://doi.org/10.1371/journal.pone.0029530

Carvalho, S., Sampaio, A., Mendes, A.J., Lema, A., Vieira, D., Gonçalves, Ó.F., Leite, J., 2019. Polarity Specific Effects of Cross-Hemispheric tDCS Coupled With Approach-Avoidance Training on Chocolate Craving. Front. Pharmacol. 9, 1500. https://doi.org/10.3389/fphar.2018.01500

Cavanagh, J.F., Zambrano-Vazquez, L., Allen, J.J.B., 2012. Theta lingua franca: A common mid-frontal substrate for action monitoring processes. Psychophysiology 49, 220–238. https://doi.org/10.1111/j.1469-8986.2011.01293.x

Cespón, J., Rodella, C., Rossini, P.M., Miniussi, C., Pellicciari, M.C., 2017. Anodal transcranial direct current stimulation promotes frontal compensatory mechanisms in healthy elderly subjects. Front. Aging Neurosci. 9, 420. https://doi.org/10.3389/fnagi.2017.00420

Chan, M.M.Y., Yau, S.S.Y., Han, Y.M.Y., 2021. The neurobiology of prefrontal transcranial direct current stimulation (tDCS) in promoting brain plasticity: A systematic review and meta-analyses of human and rodent studies. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2021.02.035

Cochrane, 2019. Cochrane Handbook for Systematic Reviews of Interventions, Cochrane Handbook for Systematic Reviews of Interventions. Wiley. https://doi.org/10.1002/9781119536604

Coffman, B.A., Clark, V.P., Parasuraman, R., 2014. Battery powered thought: Enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. Neuroimage. https://doi.org/10.1016/j.neuroimage.2013.07.083

Coffman, B.A., Trumbo, M.C., Clark, V.P., 2012. Enhancement of object detection with transcranial direct current stimulation is associated with increased attention. BMC Neurosci. 13, 1–8. https://doi.org/10.1186/1471-2202-13-108

Cohen, M.X., 2014. A neural microcircuit for cognitive conflict detection and signaling. Trends Neurosci. https://doi.org/10.1016/j.tins.2014.06.004

Cooper, P.S., Darriba, Á., Karayanidis, F., Barceló, F., 2016. Contextually sensitive power changes across multiple frequency bands underpin cognitive control. Neuroimage 132, 499–511. https://doi.org/10.1016/j.neuroimage.2016.03.010

Demiralp, T., Ademoglu, A., Istefanopulos, Y., Başar-Eroglu, C., Başar, E., 2001. Wavelet analysis of oddball P300. Int. J. Psychophysiol. 39, 221–227.

https://doi.org/10.1016/S0167-8760(00)00143-4

den Uyl, T.E., Gladwin, T.E., Lindenmeyer, J., Wiers, R.W., 2018. A Clinical Trial with Combined Transcranial Direct Current Stimulation and Attentional Bias Modification in Alcohol-Dependent Patients. Alcohol. Clin. Exp. Res. 42, 1961–1969. https://doi.org/10.1111/acer.13841

Den Uyl, T.E., Gladwin, T.E., Wiers, R.W., 2015. Transcranial direct current stimulation, implicit alcohol associations and craving. Biol. Psychol. 105, 37–42. https://doi.org/10.1016/j.biopsycho.2014.12.004

Dubreuil-Vall, L., Chau, P., Ruffini, G., Widge, A.S., Camprodon, J.A., 2019. tDCS to the left DLPFC modulates cognitive and physiological correlates of executive function in a state-dependent manner. Brain Stimul. 12, 1456–1463. https://doi.org/10.1016/j.brs.2019.06.006

Dunning, J.P., Parvaz, M.A., Hajcak, G., Maloney, T., Alia-Klein, N., Woicik, P.A., Telang, F., Wang, G.-J., Volkow, N.D., Goldstein, R.Z., 2011. Motivated attention to cocaine and emotional cues in abstinent and current cocaine users - an ERP study. Eur. J. Neurosci. 33, 1716–1723. https://doi.org/10.1111/j.1460-9568.2011.07663.x

Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. Br. Med. J. 315, 629–634. https://doi.org/10.1136/bmj.315.7109.629

Fertonani, A., Miniussi, C., 2017. Transcranial electrical stimulation: What we know and do not know about mechanisms. Neuroscientist 23, 109–123. https://doi.org/10.1177/1073858416631966

Fiene, M., Rufener, K.S., Kuehne, M., Matzke, M., Heinze, H.J., Zaehle, T., 2018. Electrophysiological and behavioral effects of frontal transcranial direct current stimulation on cognitive fatigue in multiple sclerosis. J. Neurol. 265, 607–617.

https://doi.org/10.1007/s00415-018-8754-6

Fonteneau, C., Redoute, J., Haesebaert, F., Le Bars, D., Costes, N., Suaud-Chagny, M.-F., Brunelin, J., 2018. Frontal Transcranial Direct Current Stimulation Induces Dopamine Release in the Ventral Striatum in Human. Cereb. Cortex 28, 2636–2646. https://doi.org/10.1093/cercor/bhy093

Fregni, F., El-Hagrassy, M.M., Pacheco-Barrios, K., Carvalho, S., Leite, J., Simis, M., Brunelin, J., Nakamura-Palacios, E.M., Marangolo, P., Venkatasubramanian, G., San-Juan, D., Caumo, W., Bikson, M., Brunoni, A.R., 2020. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. Int. J. Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyaa051

Friedman, D., Cycowicz, Y.M., Gaeta, H., 2001. The novelty P3: An event-related brain potential (ERP) sign of the brain's evaluation of novelty. Neurosci. Biobehav. Rev. https://doi.org/10.1016/S0149-7634(01)00019-7

Fukai, M., Bunai, T., Hirosawa, T., Kikuchi, M., Ito, S., Minabe, Y., Ouchi, Y., 2019. Endogenous dopamine release under transcranial direct-current stimulation governs enhanced attention: a study with positron emission tomography. Transl. Psychiatry 9, 1–10. https://doi.org/10.1038/s41398-019-0443-4

Goldsworthy, M.R., Hordacre, B., 2017. Dose dependency of transcranial direct current stimulation: implications for neuroplasticity induction in health and disease. J. Physiol. 595, 3265–3266. https://doi.org/10.1113/JP274089

Gulbinaite, R., van Rijn, H., Cohen, M.X., 2014. Fronto-parietal network oscillations reveal relationship between working memory capacity and cognitive control. Front. Hum.

Neurosci. 8, 761. https://doi.org/10.3389/fnhum.2014.00761

Güntekin, B., Başar, E., 2016. Review of evoked and event-related delta responses in the human brain. Int. J. Psychophysiol. https://doi.org/10.1016/j.ijpsycho.2015.02.001

Güntekin, B., Başar, E., 2010. A new interpretation of P300 responses upon analysis of coherences. Cogn. Neurodyn. 4, 107–118. https://doi.org/10.1007/s11571-010-9106-0

Hajcak, G., MacNamara, A., Olvet, D.M., 2010. Event-Related Potentials, Emotion, and Emotion Regulation: An Integrative Review. Dev. Neuropsychol. 35, 129–155. https://doi.org/10.1080/87565640903526504

Hamidovic, A., Wang, Y., 2019. The P300 in alcohol use disorder: A meta-analysis and meta-regression. Prog. Neuro-Psychopharmacology Biol. Psychiatry 95, 109716. https://doi.org/10.1016/j.pnpbp.2019.109716

Harper, J., Malone, S.M., Iacono, W.G., 2017. Theta- and delta-band EEG network dynamics during a novelty oddball task. Psychophysiology 54, 1590–1605. https://doi.org/10.1111/psyp.12906

Hedges, L. V., 1981. Distribution Theory for Glass's Estimator of Effect size and Related Estimators. J. Educ. Stat. 6, 107–128. https://doi.org/10.3102/10769986006002107

Herrmann, M.J., Weijers, H.G., Wiesbeck, G.A., Böning, J., Fallgatter, A.J., 2001. Alcohol cue-reactivity in heavy and light social drinkers as revealed by event-related potentials. Alcohol Alcohol. 36, 588–593. https://doi.org/10.1093/alcalc/36.6.588

Higgins, J.P.T., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks, L., Sterne, J.A.C., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343. https://doi.org/10.1136/bmj.d5928

Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med.

21, 1539–1558. https://doi.org/10.1002/sim.1186

Horvath, J.C., Forte, J.D., Carter, O., 2015. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2014.11.021

Hoy, K.E., Bailey, N., Michael, M., Fitzgibbon, B., Rogasch, N.C., Saeki, T., Fitzgerald, P.B., 2016. Enhancement of Working Memory and Task-Related Oscillatory Activity Following Intermittent Theta Burst Stimulation in Healthy Controls. Cereb. Cortex 26, 4563–4573. https://doi.org/10.1093/cercor/bhv193

Hoy, K.E., Bailey, N.W., Arnold, S.L., Fitzgerald, P.B., 2015. The effect of transcranial Direct Current Stimulation on gamma activity and working memory in schizophrenia. Psychiatry Res. 228, 191–196. https://doi.org/10.1016/j.psychres.2015.04.032

Huster, R.J., Enriquez-Geppert, S., Lavallee, C.F., Falkenstein, M., Herrmann, C.S., 2013. Electroencephalography of response inhibition tasks: Functional networks and cognitive contributions. Int. J. Psychophysiol. 87, 217–233. https://doi.org/10.1016/j.ijpsycho.2012.08.001

Huster, R.J., Messel, M.S., Thunberg, C., Raud, L., 2020. The P300 as marker of inhibitory control – Fact or fiction? Cortex 132, 334–348. https://doi.org/10.1016/j.cortex.2020.05.021

Izzidien, A., Ramaraju, S., Roula, M.A., Mccarthy, P.W., 2016. Effect of Anodal-tDCS on Event-Related Potentials: A Controlled Study. Biomed Res. Int. 2016. https://doi.org/10.1155/2016/1584947

Jahfari, S., Waldorp, L., van den Wildenberg, W.P.M., Scholte, H.S., Ridderinkhof, K.R., Forstmann, B.U., 2011. Effective connectivity reveals important roles for both the

hyperdirect (fronto-subthalamic) and the indirect (fronto-striatal-pallidal) fronto-basal ganglia pathways during response inhibition. J. Neurosci. 31, 6891–6899. https://doi.org/10.1523/JNEUROSCI.5253-10.2011

Johnson, J.D., Allana, T.N., Medlin, M.D., Harris, E.W., Karl, A., 2013. Meta-analytic review of P3 components in posttraumatic stress disorder and their clinical utility. Clin. EEG Neurosci. https://doi.org/10.1177/1550059412469742

Jones, Kevin T., Johnson, E.L., Berryhill, M.E., 2020. Frontoparietal theta-gamma interactions track working memory enhancement with training and tDCS. Neuroimage 211, 116615. https://doi.org/10.1016/j.neuroimage.2020.116615

Kaiser, A., Aggensteiner, P.M., Baumeister, S., Holz, N.E., Banaschewski, T., Brandeis, D., 2020. Earlier versus later cognitive event-related potentials (ERPs) in attention-deficit/hyperactivity disorder (ADHD): A meta-analysis. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2020.01.019

Keeser, D., Padberg, F., Reisinger, E., Pogarell, O., Kirsch, V., Palm, U., Karch, S., Möller, H.J., Nitsche, M.A., Mulert, C., 2011. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study. Neuroimage 55, 644–657. https://doi.org/10.1016/j.neuroimage.2010.12.004

Kellermeyer, L., Harnke, B., Knight, S., 2018. Covidence and Rayyan. J. Med. Libr. Assoc. 106, 580. https://doi.org/10.5195/jmla.2018.513

Kelly, R.M., Strick, P.L., 2003. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J. Neurosci. 23, 8432–8444. https://doi.org/10.1523/jneurosci.23-23-08432.2003

Kim, M., Kwak, Y. Bin, Lee, T.Y., Kwon, J.S., 2018. Modulation of electrophysiology by transcranial direct current stimulation in psychiatric disorders: A systematic review. Psychiatry Investig. https://doi.org/10.30773/pi.2018.01.10

Knyazev, G.G., 2012. EEG delta oscillations as a correlate of basic homeostatic and motivational processes. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2011.10.002

Kok, A., 2001. On the utility of P3 amplitude as a measure of processing capacity. Psychophysiology 38, S0048577201990559. https://doi.org/10.1017/S0048577201990559

Lapenta, O.M., Sierve, K. Di, de Macedo, E.C., Fregni, F., Boggio, P.S., 2014. Transcranial direct current stimulation modulates ERP-indexed inhibitory control and reduces food consumption. Appetite 83, 42–48. https://doi.org/10.1016/j.appet.2014.08.005

Leite, J., Morales-Quezada, L., Carvalho, S., Thibaut, A., Doruk, D., Chen, C.-F., Schachter, S.C., Rotenberg, A., Fregni, F., 2017. Surface EEG-Transcranial Direct Current Stimulation (tDCS) Closed-Loop System. Int. J. Neural Syst. 27, 1750026. https://doi.org/https://doi.org/10.1142/S0129065717500265

Li, L.M., Violante, I.R., Leech, R., Ross, E., Hampshire, A., Opitz, A., Rothwell, J.C., Carmichael, D.W., Sharp, D.J., 2019. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum. Brain Mapp. 40, 904–915. https://doi.org/10.1002/hbm.24420

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

McGuinness, L.A., Higgins, J.P.T., 2021. Risk- of- bias VISualization (robvis): An R package and Shiny web app for visualizing risk- of- bias assessments. Res. Synth. Methods 12, 55–61. https://doi.org/10.1002/jrsm.1411

McHugh, M.L., 2012. Interrater reliability: the kappa statistic. Biochem. Medica 22, 276–282. https://doi.org/10.11613/BM.2012.031

Miler, J.A., Meron, D., Baldwin, D.S., Garner, M., 2018. The Effect of Prefrontal Transcranial Direct Current Stimulation on Attention Network Function in Healthy Volunteers. Neuromodulation 21, 355–361. https://doi.org/10.1111/ner.12629

Miller, J., Berger, B., Sauseng, P., 2015. Anodal transcranial direct current stimulation (tDCS) increases frontal-midline theta activity in the human EEG: A preliminary investigation of non-invasive stimulation. Neurosci. Lett. 588, 114–119. https://doi.org/10.1016/j.neulet.2015.01.014

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 6, e1000097. https://doi.org/10.1371/journal.pmed.1000097

Monte-Silva, K., Kuo, M.F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., Nitsche, M.A., 2013. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul. 6, 424–432. https://doi.org/10.1016/j.brs.2012.04.011

Morrison, J.H., Foote, S.L., O'Connor, D., Bloom, F.E., 1982. Laminar, tangential and regional organization of the noradrenergic innervation of monkey cortex: Dopamine-β-hydroxylase immunohistochemistry. Brain Res. Bull. 9, 309–319. https://doi.org/10.1016/0361-9230(82)90144-7

Nakamura-Palacios, E.M., de Almeida Benevides, M.C., da Penha Zago-Gomes, M., de Oliveira, R.W.D., de Vasconcellos, V.F., de Castro, L.N.P., da Silva, M.C., Ramos, P.A., Fregni, F., 2012. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. Int. J. Neuropsychopharmacol. 15, 601–616. https://doi.org/10.1017/S1461145711001040

Neubauer, A.C., Fink, A., 2009. Intelligence and neural efficiency. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2009.04.001

Nieuwenhuis, S., Aston-Jones, G., Cohen, J.D., 2005. Decision making, the P3, and the locus coeruleus-norepinephrine system. Psychol. Bull. https://doi.org/10.1037/0033-2909.131.4.510

Nieuwenhuis, S., De Geus, E.J., Aston-Jones, G., 2011a. The anatomical and functional relationship between the P3 and autonomic components of the orienting response. Psychophysiology 48, 162–175. https://doi.org/10.1111/j.1469-8986.2010.01057.x

Nussbaumer, D., Grabner, R.H., Stern, E., 2015. Neural efficiency in working memory tasks: The impact of task demand. Intelligence 50, 196–208. https://doi.org/10.1016/j.intell.2015.04.004

O'Brien, J.L., Edwards, J.D., Maxfield, N.D., Peronto, C.L., Williams, V.A., Lister, J.J., 2013. Cognitive training and selective attention in the aging brain: An electrophysiological study. Clin. Neurophysiol. 124, 2198–2208. https://doi.org/10.1016/j.clinph.2013.05.012

Pasion, R., Fernandes, C., Pereira, M.R., Barbosa, F., 2018. Antisocial behaviour and psychopathy: Uncovering the externalizing link in the P3 modulation. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2017.03.012

Pitts, M.A., Padwal, J., Fennelly, D., Martínez, A., Hillyard, S.A., 2014. Gamma band activity

and the P3 reflect post-perceptual processes, not visual awareness. Neuroimage 101, 337–350. https://doi.org/10.1016/j.neuroimage.2014.07.024

Polich, J., 2007. Updating P300: An integrative theory of P3a and P3b. Clin. Neurophysiol. https://doi.org/10.1016/j.clinph.2007.04.019

Rac-Lubashevsky, R., Kessler, Y., 2019. Revisiting the relationship between the P3b and working memory updating. Biol. Psychol. 148, 107769. https://doi.org/10.1016/j.biopsycho.2019.107769

Rassovsky, Y., Dunn, W., Wynn, J.K., Wu, A.D., Iacoboni, M., Hellemann, G., Green, M.F., 2018. Single transcranial direct current stimulation in schizophrenia: Randomized, cross-over study of neurocognition, social cognition, ERPs, and side effects. PLoS One 13, e0197023. https://doi.org/10.1371/journal.pone.0197023

Riddle, J., Scimeca, J.M., Cellier, D., Dhanani, S., D'Esposito, M., 2020. Causal Evidence for a Role of Theta and Alpha Oscillations in the Control of Working Memory. Curr. Biol. 30, 1748-1754.e4. https://doi.org/10.1016/j.cub.2020.02.065

Rohatgi, A., 2017. WebPlot Digitizer.

Ruchsow, M., Groen, G., Kiefer, M., Hermle, L., Spitzer, M., Falkenstein, M., 2008. Impulsiveness and ERP components in a Go/Nogo task. J. Neural Transm. 115, 909–915. https://doi.org/10.1007/s00702-008-0042-7

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

Rushby, J.A., Barry, R.J., 2009. Single-trial event-related potentials to significant stimuli. Int. J.

Psychophysiol. 74, 120–131. https://doi.org/10.1016/j.ijpsycho.2009.08.003

Saliasi, E., Geerligs, L., Lorist, M.M., Maurits, N.M., 2013. The Relationship between P3 Amplitude and Working Memory Performance Differs in Young and Older Adults. PLoS One 8, e63701. https://doi.org/10.1371/journal.pone.0063701

Schroeder, P.A., Schwippel, T., Wolz, I., Svaldi, J., 2020. Meta-analysis of the effects of transcranial direct current stimulation on inhibitory control. Brain Stimul. https://doi.org/10.1016/j.brs.2020.05.006

Schünemann, H., Brozek, J., Guyatt, G., Oxman, A., 2013. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendation. Version 3.2. The GRADE Working Group.

Simons, R.F., Graham, F.K., Miles, M.A., Chen, X., 2001. On the relationship of P3a and the Novelty-P3. Biol. Psychol. 56, 207–218. https://doi.org/10.1016/S0301-0511(01)00078-3

Spencer, K.M., Dien, J., Donchin, E., 2001. Spatiotemporal analysis of the late ERP responses to deviant stimuli. Psychophysiology 38, 343–358. https://doi.org/10.1111/1469-8986.3820343

Spooner, R.K., Eastman, J.A., Rezich, M.T., Wilson, T.W., 2020. High- definition transcranial direct current stimulation dissociates fronto- visual theta lateralization during visual selective attention. J. Physiol. 598, 987–998. https://doi.org/10.1113/JP278788

Stagg, C.J., Nitsche, M.A., 2011. Physiological basis of transcranial direct current stimulation. Neuroscientist. https://doi.org/10.1177/1073858410386614

Sterne, J.A.C., Sutton, A.J., Ioannidis, J.P.A., Terrin, N., Jones, D.R., Lau, J., Carpenter, J., Rücker, G., Harbord, R.M., Schmid, C.H., Tetzlaff, J., Deeks, J.J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D.G., Moher, D., Higgins, J.P.T., 2011.

Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343. https://doi.org/10.1136/bmj.d4002

Sutton, S., Braren, M., Zubin, J., John, E.R., 1965. Evoked-potential correlates of stimulus uncertainty. Science (80-.). 150, 1187–1188. https://doi.org/10.1126/science.150.3700.1187

Thompson, S.G., Higgins, J.P.T., 2002. How should meta-regression analyses be undertaken and interpreted? Stat. Med. 21, 1559–1573. https://doi.org/10.1002/sim.1187

Tusch, E.S., Alperin, B.R., Ryan, E., Holcomb, P.J., Mohammed, A.H., Daffner, K.R., 2016. Changes in Neural Activity Underlying Working Memory after Computerized Cognitive Training in Older Adults. Front. Aging Neurosci. 8, 255. https://doi.org/10.3389/fnagi.2016.00255

van Dinteren, R., Arns, M., Jongsma, M.L.A., Kessels, R.P.C., 2014. P300 Development across the Lifespan: A Systematic Review and Meta-Analysis. PLoS One 9, e87347. https://doi.org/10.1371/journal.pone.0087347

Viechtbauer, W., 2010. Conducting Meta-Analyses in R with the metafor Package, JSS Journal of Statistical Software.

Viechtbauer, W., Cheung, M.W.-L., 2010. Outlier and influence diagnostics for meta-analysis. Res. Synth. Methods 1, 112–125. https://doi.org/10.1002/jrsm.11

Wada, M., Kurose, S., Miyazaki, T., Nakajima, S., Masuda, F., Mimura, Y., Nishida, H., Ogyu, K., Tsugawa, S., Mashima, Y., Plitman, E., Chakravarty, M.M., Mimura, M., Noda, Y., 2019. The P300 event-related potential in bipolar disorder: A systematic review and meta-analysis. J. Affect. Disord. https://doi.org/10.1016/j.jad.2019.06.010

Wörsching, J., Padberg, F., Helbich, K., Hasan, A., Koch, L., Goerigk, S., Stoecklein, S., Ertl-Wagner, B., Keeser, D., 2017. Test-retest reliability of prefrontal transcranial Direct Current

Stimulation (tDCS) effects on functional MRI connectivity in healthy subjects. Neuroimage 155, 187–201. https://doi.org/10.1016/j.neuroimage.2017.04.052

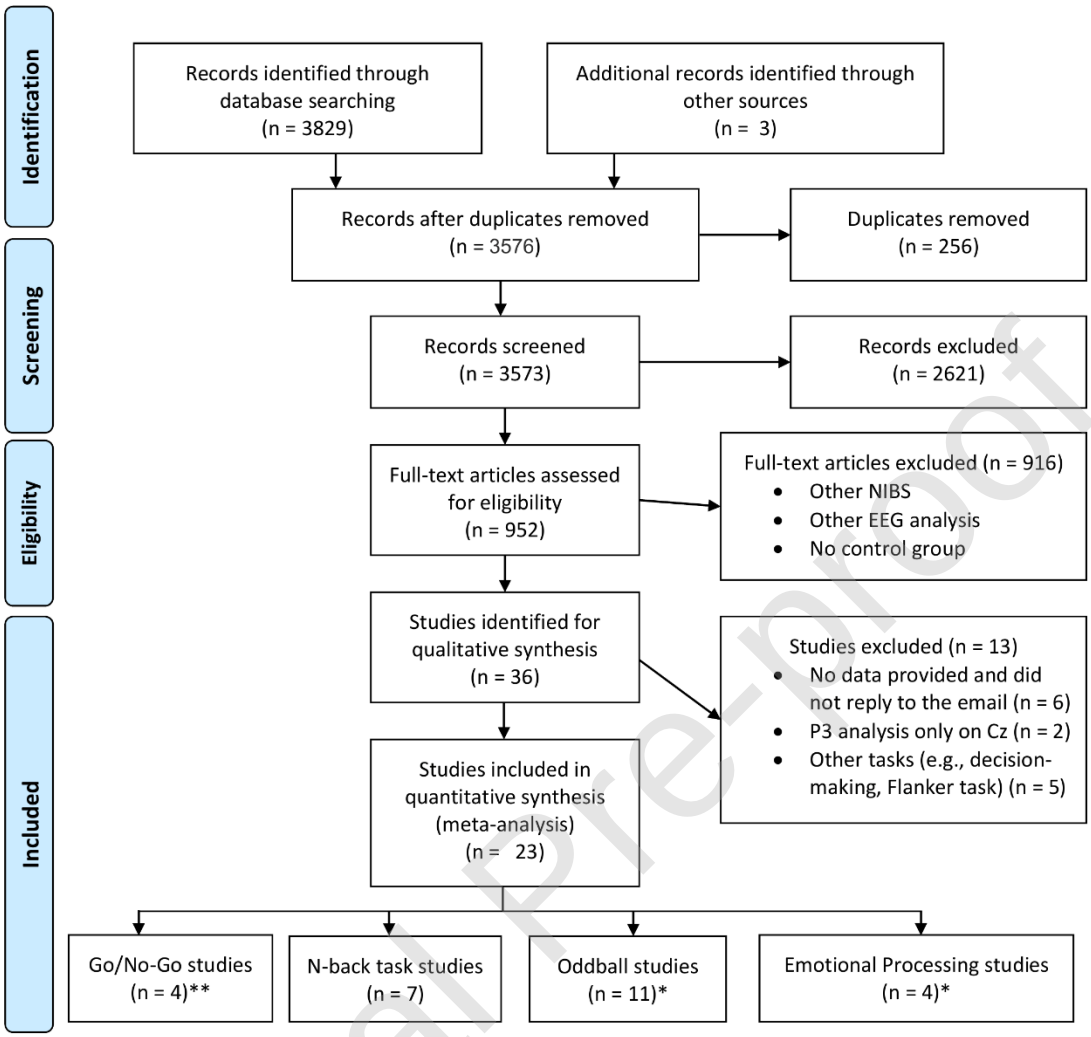

Figure 1. PRISMA flow diagram (*one study analyzed P3 on a GNG task and oddball paradigm; **two studies were included in GNG and emotional processing analysis because P3 was evaluated in an emotional GNG).

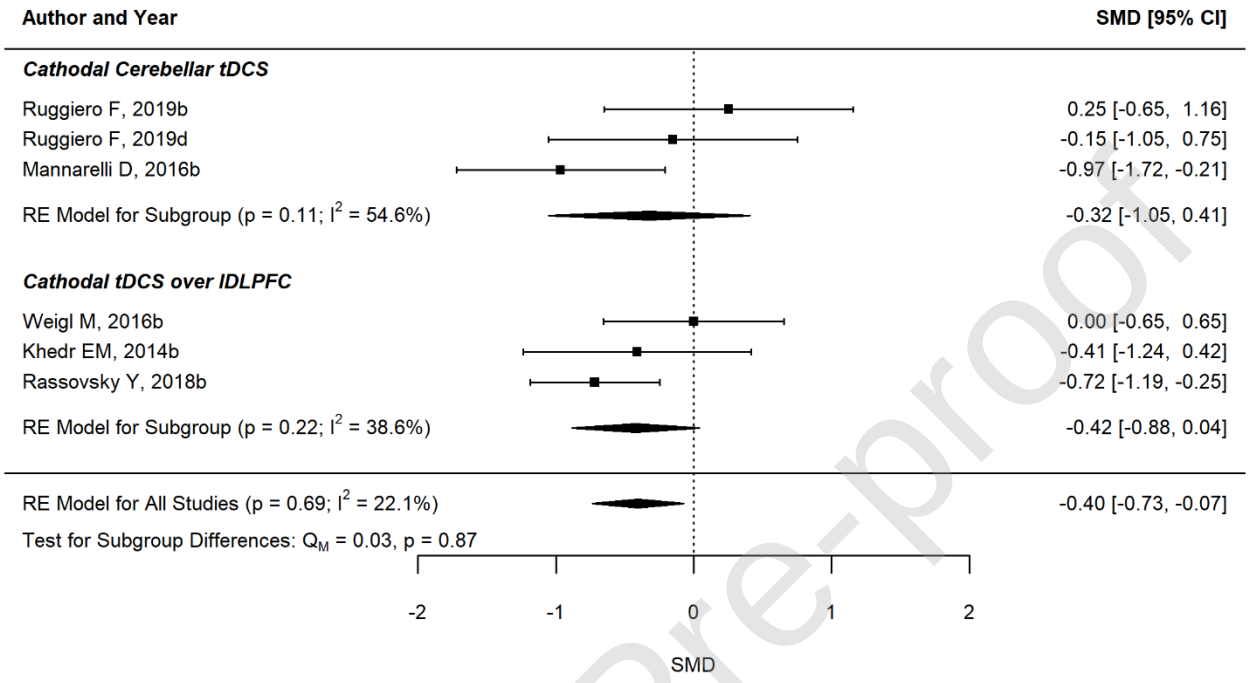

Figure 2. Forest plot with pooled effect estimate and subgroup analysis concerning the cathodal stimulation on frontal P3 amplitude during oddball.

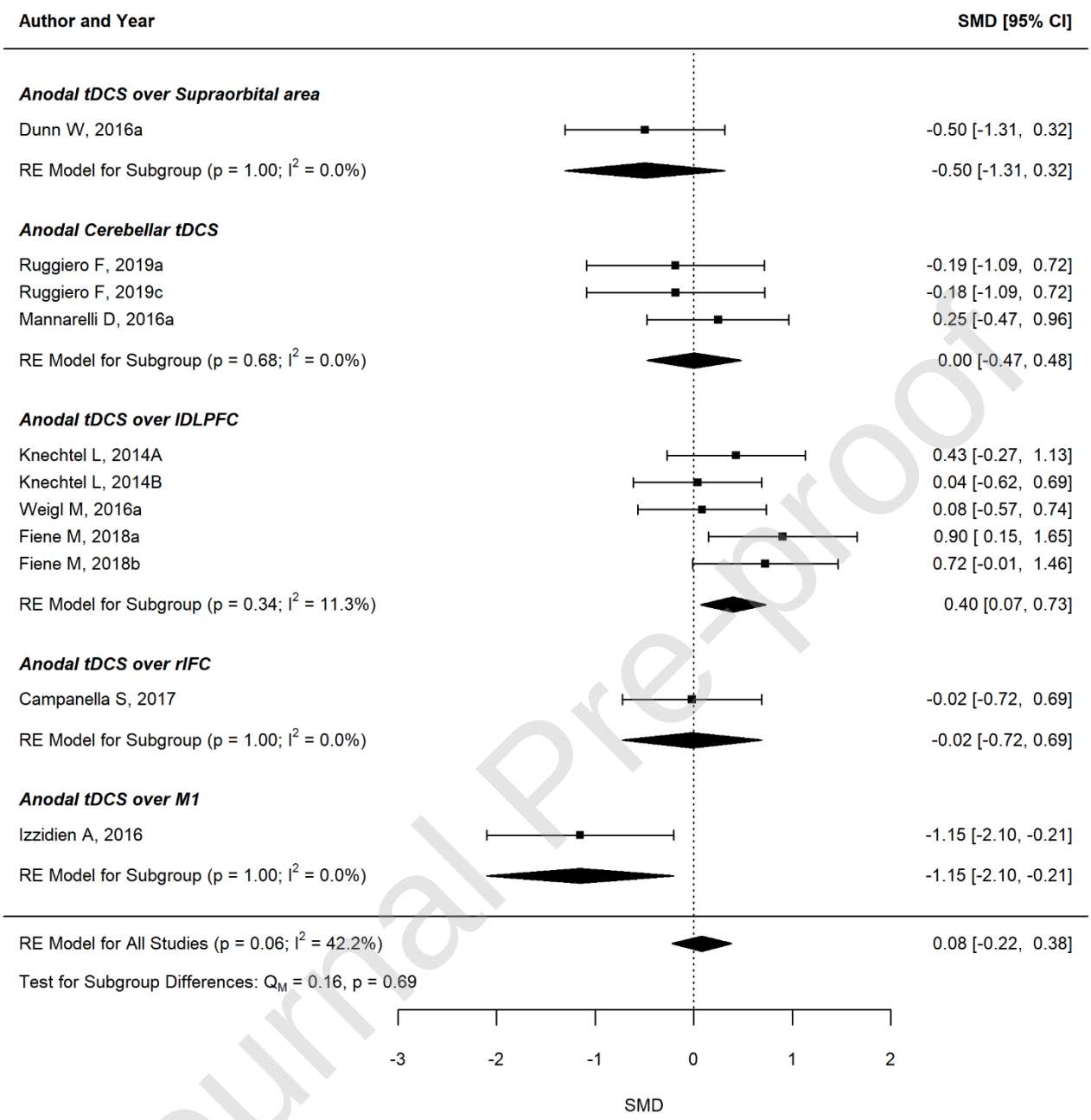

Figure 3. Forest plot with pooled effect estimate and subgroup analysis concerning the anodal stimulation on parietal P3 amplitude during oddball.

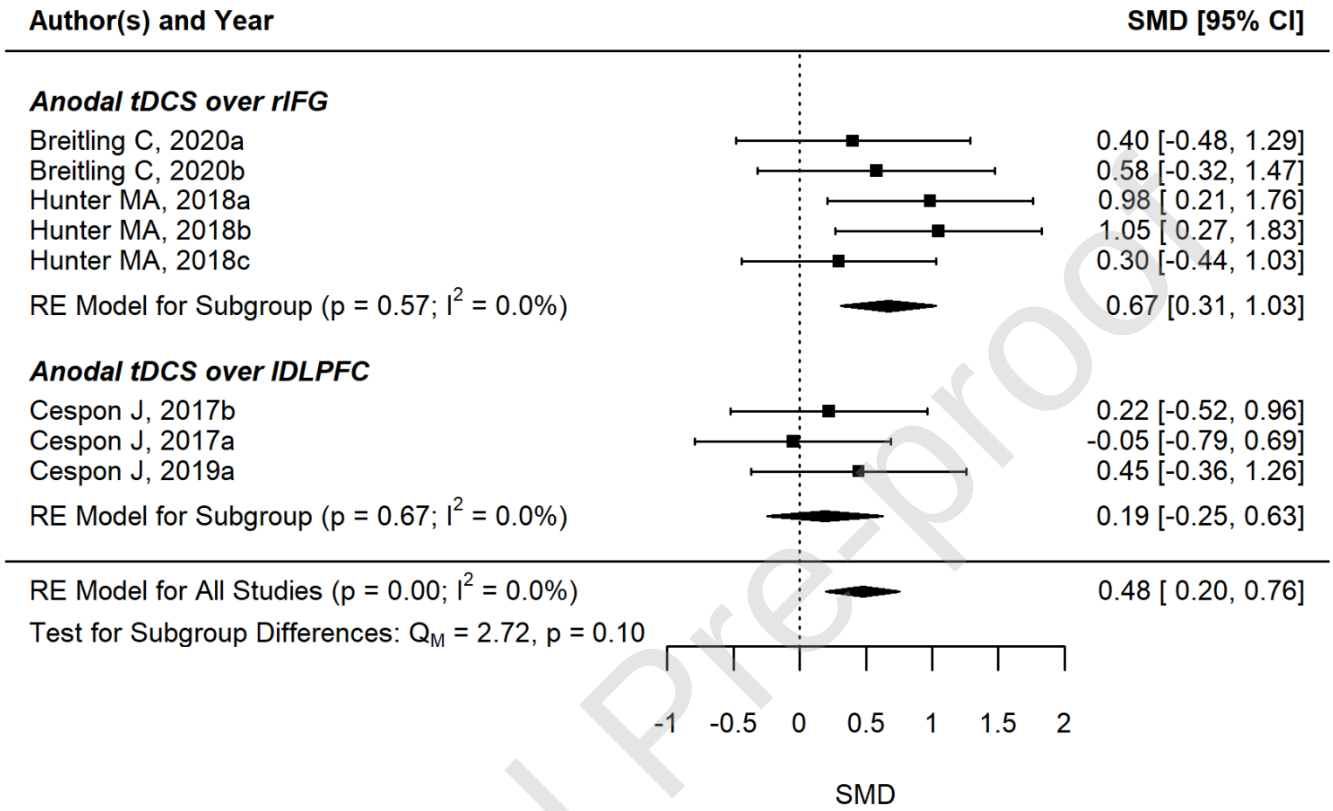

Figure 4. Forest plot with pooled effect estimate and subgroup analysis concerning the anodal stimulation on parietal P3 amplitude during n-back.

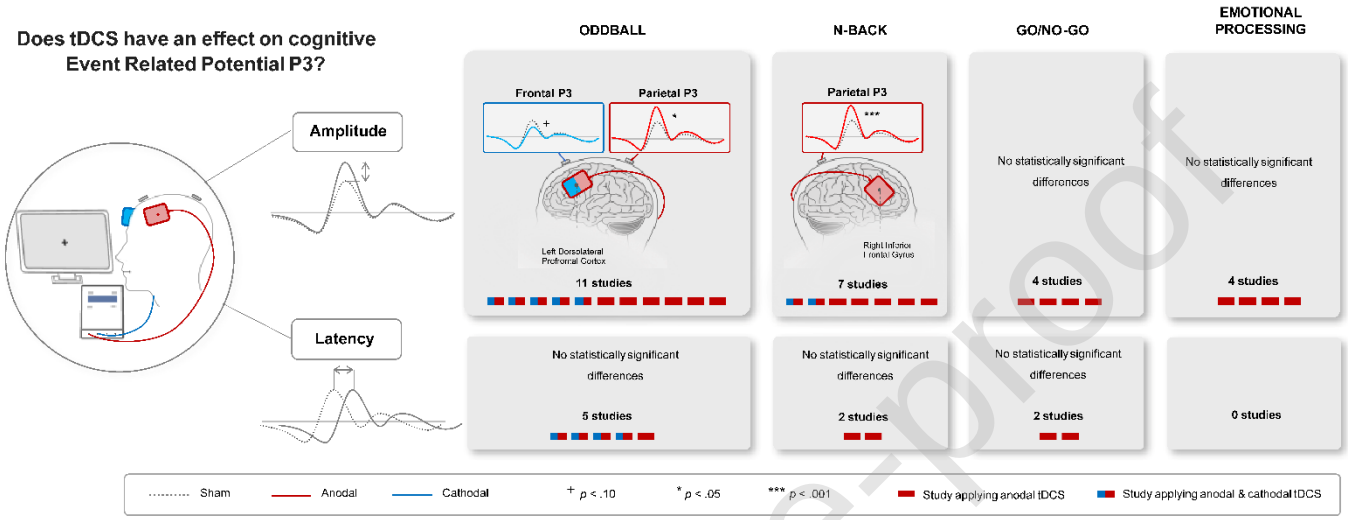

Figure 5. Overall effects observed on the meta-analysis of P3 amplitude and latency in each section.