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The neurobiology of prefrontal transcranial direct current stimulation (tDCS) in promoting brain plasticity: a systematic review and meta-analyses of human and rodent studies

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Abstract

The neurobiological mechanisms underlying prefrontal transcranial direct current stimulation (tDCS) remain elusive. Randomized, sham-controlled trials in humans and rodents applying *in vivo* prefrontal tDCS were included to explore whether prefrontal tDCS modulates resting-state and event-related functional connectivity, neural oscillation and synaptic plasticity. Fifty studies were included in the systematic review and 32 in the meta-analyses. Neuroimaging meta-analysis indicated anodal prefrontal tDCS significantly enhanced bilateral median cingulate activity [familywise error (FWE)-corrected $p < .005$]; meta-regression revealed a positive relationship between changes in median cingulate activity after tDCS and current density (FWE-corrected $p < .005$) as well as electric current strength (FWE-corrected $p < .05$). Meta-analyses of electroencephalography and magnetoencephalography data revealed nonsignificant changes (ps >.1) in both resting-state and event-related oscillatory power across all frequency bands. Applying anodal tDCS over the rodent hippocampus/prefrontal cortex enhanced long-term potentiation and brain brain-derived neurotrophic factor expression in the stimulated brain regions (ps <.005). Evidence supporting prefrontal tDCS administration is preliminary; more methodologically consistent studies evaluating its effects on cognitive function that include brain activity measurements are needed.

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1. Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation paradigm whereby a constant, weak direct current (1-2 mA) is applied through the brain. Electrodes are placed over the scalp and connected to a battery to stimulate the targeted brain regions directly underneath the stimulating electrode and the associated networks (E. S. Higgins & George, 2019). tDCS has been hypothesized to bring about behavioral effects through modulating the resting membrane potential of the targeted neuronal population and hence altering states of cortical excitability (Stagg, Antal, & Nitsche, 2018). For instance, subthreshold effects on a single neuron produced by tDCS (i.e., change in resting membrane potential of around 0.2 mV; Jackson et al., 2016) has been found to be collectively amplified at a neuronal network level and resulted in alterations in action potential generation (Anastassiou, Montgomery, Barahona, Buzsáki, & Koch, 2010; Rahman, Lafon, Parra, & Bikson, 2017). Changes in cortical excitability after tDCS has been found in a number of studies (e.g. M. A. Nitsche & Paulus, 2000; Lauro et al., 2014; Bai et al., 2017; Chrysikou, Wing, & van Dam, 2019), which collectively show that anodal tDCS enhances cortical excitability in humans, while cathodal tDCS reduces it. One of the applications of tDCS is cognitive enhancement (Flöel, 2014), defined in a general sense as the "improvement in performance related to cognitive tasks" (Dubljević, Venero, & Knafo, 2015, p.1) in both healthy individuals and clinical populations. Accumulating evidence has shown that tDCS applied by placing stimulating electrodes over different parts in prefrontal brain regions (Jana Wörsching et al., 2016) can positively affect cognitive function in both healthy people and patients with various diseases (Stagg et al., 2018). Although there is emerging evidence showing that prefrontal tDCS can also enhance motor functions (e.g. Benninger et al., 2010; Broeder et al., 2019), the focus of this review is on the neural mechanisms of tDCS on cognition.

1.1 Interindividual variability and the effect of tDCS on enhancing cognition

Meta-analyses have revealed that anodal stimulation over the dorsolateral prefrontal cortex can reduce the reaction times of healthy adult participants engaged in various executive function tasks (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Hill, Fitzgerald, & Hoy, 2016). In elderly subjects, Not only can tDCS enhance basic cognitive and language functioning as reflected in a meta-analysis (Summers, Kang, & Cauraugh, 2016), it also reverses age-related cognitive decline by improving working memory performance to a level comparable to that of younger subjects (Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013). In line with studies that recruited healthy individuals, memory performance in people with neurocognitive disorders has also been shown to be enhanced after receiving tDCS (Meinzer et al., 2015). Although the above results highlight tDCS as a promising modality for enhancing cognition, negative results have also been reported in other empirical studies and meta-analyses including both healthy and diseased populations (Horvath, Forte, & Carter, 2015; Tremblay et al., 2014). Previous researchers have attributed the inconsistent effects of tDCS in cognitive mediation to interindividual variabilities (Polania, Nitsche, & Ruff, 2018). Specifically, from a neurophysiological perspective, previous research has documented that between-subject variations in functional connectivity predict treatment effectiveness in terms of verbal fluency (Rosso et al., 2014), while resting-state neural oscillations predict cognitive improvements in patients with depression receiving tDCS (Al-Kaysi, Al-Ani, Loo, Breakspear, & Boonstra, 2016). These reports collectively imply that between-subject differences in baseline neural oscillatory patterns and connectivity strength may be associated with the differential interplay between tDCS and the variable neurophysiological parameters across individuals.

1.2 Putative neurobiological mechanisms of tDCS

In addition to improving our understanding of which form of interindividual variability is relevant to tDCS cognitive enhancement effects, understanding how tDCS modulates these variables is also a fundamental question that must be answered to facilitate personalized tDCS treatment in day-to-day clinical settings (Polania et al., 2018). Cognitive functioning has been historically established to involve integration and manipulation of information (Bassett et al., 2010; Felleman & Van Essen, 1991; Piccinini & Scarantino, 2011; Reitman, 1965), which is supported by the interaction of the macroscopic (i.e., neuronal networks) and microscopic (i.e., molecular, cellular) mechanisms of the nervous system (Álvarez-Salvado, Pallarés, Moreno, & Canals, 2014; Park et al., 2013). Previous research has documented how tDCS modulates these neurobiological biomarkers, which are briefly introduced below.

1.2.1 Network effects of tDCS – neural oscillation and functional connectivity

Previous neurophysiological studies have shown that neural oscillation measured by electroencephalogram (EEG) or magnetoencephalogram (MEG) is a fundamental mechanism enabling coordinated brain activities (Buzsáki & Draguhn, 2004; Fries, 2009). Specifically, the amplitude of neural oscillations, which is commonly aberrant among people with neurological disorders (Schnitzler & Gross, 2005), is causally linked to cognition and learning (Thut, Miniussi, & Gross, 2012; Wang, 2010). Changes in the amplitude of the oscillatory activity induced by tDCS may imply possible clinical applications of this technique among people with these disorders. Indeed, some previous studies have shown that anodal tDCS over the primary motor cortex increased the amplitude of oscillations in the alpha and beta frequency bands during motor imagery and execution tasks (Mondini, Mangia, & Cappello, 2018; Wei, He, Zhou, & Wang, 2013), while cathodal stimulation decreased the amplitude (Baxter, Edelman, Nesbitt, & He, 2016). However, other studies have reported

nonsignificant changes (Di Bernardi Luft, Zioga, Thompson, Banissy, & Bhattacharya, 2018; Gordon et al., 2018). In addition, previous evidence has shown that tDCS can modulate functional connectivity (Amadi, Ilie, Johansen-Berg, & Stagg, 2014), in which functional connectivity is defined as the statistical dependencies reflecting the degree of the nondirectional synchrony between two brain regions (Friston, 2011). This evidence suggests the potential effects of tDCS on cognitive improvements in people with neurological disorders with abnormal functional connectivity networks, such as patients with attention-deficit/hyperactivity disorder (Sotnikova et al., 2017). While some studies have shown that tDCS modulates resting-state functional connectivity measured by functional magnetic resonance imaging (fMRI; Bachtiar, Near, Johansen-Berg, and Stagg, 2015) or EEG (De Ridder & Vanneste, 2017), other studies have revealed that event-related functional connectivity as measured by neurophysiological/neuroimaging techniques including fMRI (Rodrigues de Almeida, Pope, & Hansen, 2020), EEG (Jones, Johnson, & Berryhill, 2020) and MEG (Ikeda, Takahashi, Hiraishi, Saito, & Kikuchi, 2019) can as well be modulated by tDCS. However, nonsignificant changes in functional connectivity have also been revealed in subjects who undergo tDCS (Cosmo et al., 2015; Donaldson, Kirkovski, Yang, Bekkali, & Enticott, 2019; Jones, Peterson, Blacker, & Berryhill, 2017).

1.2.2 Cellular and molecular effects of tDCS – synaptic plasticity

Long-lasting synaptic plasticity has long been believed to be the neurophysiological basis of learning and memory (Hebb, 1949; Malinow & Malenka, 2002; Martin et al., 1997). In view of the behavioral effects of tDCS on cognitive enhancement, researchers have hypothesized that tDCS can modulate long-term potentiation (LTP), the most-studied model of long-lasting synaptic plasticity (Collingridge & Bliss, 1987). Indeed, previous *in vitro* studies have shown that direct current stimulation can modulate LTP when coupled with low-frequency synaptic activation as evidenced by changes in field excitatory postsynaptic

potential (fEPSP) in both cortical (Fritsch et al., 2010) and hippocampal (Kronberg, Rahman, Sharma, Bikson, & Parra, 2019; Rahman et al., 2017; Ranieri et al., 2012) brain slices. *In vivo* tDCS studies in animals, which are of enhanced translational value (Jackson et al., 2016; Stagg & Nitsche, 2011), have been conducted in recent years. While some of these studies have shown consistent positive results as reported in *in vitro* studies, showing that anodal tDCS over the hippocampus can enhance LTP formation (Rohan, Carhuatanta, McInturf, Miklasevich, & Jankord, 2015), some have reported inconsistent results; for example, modulation of LTP formation was found to be nonsignificant with *in vivo* cathodal tDCS stimulation applied over the hippocampus (Rohan et al., 2020), which was inconsistent with the *in vitro* study results reported by Ranieri et al. (2012) with direct current applied to hippocampal brain slices of the same polarity. At the molecular level, tDCS has been shown to modulate brain-derived neurotrophic factor (BDNF), which plays an important role in LTP formation (Lu, Cheng, Lim, Khoshnevisrad, & Poo, 2010; Minichiello, 2009). Previous results from *in vitro* studies have reported that anodal tDCS modulates both gene and protein expression levels of BDNF (Fritsch et al., 2010); some *in vivo* studies have also shown that tDCS interferes with BDNF and its related signaling pathways (Podda et al., 2016), although some researchers have reported the opposite results (Marques Filho et al., 2016).

1.3 tDCS protocols and differential neurobiological effects

Our understanding of the neurobiological effects of tDCS effects has been complicated by the adoption of a great variety of stimulation protocols in different studies. In particular, montage placement, stimulating electrode polarity and stimulation intensity are some of the factors that are believed to substantially mediate the neurobiological effects of tDCS (Thair, Holloway, Newport, & Smith, 2017). In the context of prefrontal tDCS stimulation, montage placement targeting the dorsolateral prefrontal cortex (DLPFC) has

been commonly used based on the tDCS literature (Dedoncker et al., 2016; Imburgio & Orr, 2018), and other brain regions such as the inferior frontal gyrus (Mayseless & Shamay-Tsoory, 2015) and frontopolar cortex (Frase et al., 2016) have been targeted as well; a previous computational study has shown that different prefrontal tDCS montage placements result in differential electric field distribution over the brain (Laakso et al., 2016), which has been believed to be mediating the observed tDCS neurobiological effects (Chan & Han, 2020). The polarity of the electrode being placed over the targeted brain region also affects the observed neuromodulatory effects; a study conducted by (Wörsching et al., 2018) showed that anodal stimulation (versus cathodal stimulation) over the left DLPFC resulted in significantly different modulatory effects on resting-state functional connectivity of the left medial prefrontal cortex. Regarding stimulation intensity, previous reports have indicated that stronger stimulation intensities tended to yield more significant cortical excitability effects (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Nitsche & Paulus, 2000), however other studies have reported contrasting results (Ho et al., 2016; Jamil et al., 2017).

1.4 Aims and objectives of this review

In summary of the above literature review, discrepancies are found across studies regarding the effects of prefrontal tDCS on neural network changes as well as synaptic plasticity, which have contributed to the largely unknown neurobiological mechanisms of tDCS. Systematic summaries and meta-analyses can provide hints on how tDCS modulates the following putative neurobiological mechanisms: neural oscillation, functional connectivity and synaptic plasticity. This review aims to investigate how tDCS affects neural networks with a specific focus on examining whether prefrontal tDCS in humans can modulate 1) resting-state network functional connectivity, 2) functional connectivity during cognitive tasks, 3) the amplitude of resting-state neural oscillations, and 4) the amplitude of

neural oscillations during cognitive tasks. In addition, animal studies were analyzed to examine whether tDCS elicits its effect on neural plasticity by affecting LTP formation and BDNF expression levels. To understand how heterogeneous tDCS protocols play a role in mediating the observed neurobiological effects, covariate and subgroup analyses, as well as meta-regression analyses, were conducted.

2. Methods

2.1 Literature search

This systematic review was performed according to guidance from the Preferred Reporting Items for Systematic Reviews and Meta-analysis [PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009); see **Table S1** for the PRISMA checklist], and the protocols were registered in the International Prospective Register of Systematic Reviews system (PROSPERO; CRD42020168671, CRD42020183616). A preliminary search was conducted in January 2020 to confirm the choice of keywords and electronic databases among all authors. The main literature searches with the electronic databases Embase, ScienceDirect, PubMed and Scopus were conducted in March 2020. A title/abstract/keyword search was performed in all databases using the terms ("transcranial direct current stimulation" OR "tDCS") AND ("electroencephalography" OR "functional magnetic resonance imaging" OR magnetoencephalography") for identifying human studies and ("transcranial direct current stimulation" OR "tDCS") AND ("synaps*" OR "synaptic plasticity" OR "synaptogenesis") AND "animal" for animal studies. The search was repeated with the same keywords on May 4-5, 2020, to ensure that all of the recently published papers identifiable through the database search were covered. No limit was imposed on publication date. The reference lists of the relevant articles were manually searched to identify additional records (Cavaleiro, Martins,

Goncalves, & Castelo-Branco, 2020; Cirillo et al., 2017; Horvath, Forte, & Carter, 2015; Jackson et al., 2016).

2.2 Study inclusion for systematic review

The main aim of this review was to investigate the neurobiology of tDCS in cognitive function. Given the established role of the frontal cortex in cognition (Romine & Reynolds, 2005) and previous human studies using tDCS for cognitive remediation and focusing on stimulating prefrontal brain regions (see J. Wörsching et al., 2016 for a review), we only include studies involving placement of the anode/cathode over frontal regions (according to the EEG 10-10 system) as highlighted in **Figure 1**. In the context of animal studies, we only include studies applying *in vivo* tDCS with extracephalic electrodes over the hippocampus or the prefrontal cortex of rodents.

For human studies, we included papers reporting randomized parallel group/crossover trials with 1) active tDCS stimulation administered in the experimental group and sham tDCS stimulation administered in the control group and 2) electrophysiological or neuroimaging outcomes. Duplicate records were first removed. The title and abstracts of the articles were then screened, and non-English papers, studies without peer-reviewed empirical data (e.g., reviews, conference proceedings, book chapters and editorials), observational studies (e.g., case series, nonrandomized studies and studies without a sham tDCS control group), nonhuman studies and studies that did not apply tDCS as the sole brain stimulation technique were excluded. During full-text screening, a paper was included if 1) neural oscillation/functional connectivity measures recorded by EEG/fMRI/MEG were reported; 2) EEG/fMRI/MEG measurements were conducted at both baseline and after treatment/concurrently during active/sham tDCS administration; 3) the time × stimulation

(sham vs. active tDCS) interaction effect was investigated; and 4) post hoc between-group (i.e., active versus sham) comparisons reflected the reported tDCS effects.

For animal studies, *in vivo* rodent studies that conducted randomized, sham-controlled tDCS trials measuring changes in synaptic plasticity *ex vivo*/*in vivo* were included. To increase the translational value of the included data, we only included studies with a current density (in A/m^2) of the direct current applied that was lower than the tDCS safety limits in rodents (Liebetanz et al., 2009). During title and abstract screening, 1) duplicate records, 2) conference proceedings, 3) records that did not report empirical data (e.g., reviews, editorials, book chapters), and 4) studies that did not use rodents as the animal model to study tDCS effects were excluded. During full-text evaluation, studies 1) that did not employ a sham tDCS control group, 2) *in vitro* DCS studies and 3) studies that did not conduct *ex vivo*/*in vivo* measurements of synaptic plasticity were excluded.

The above screening processes were independently conducted by the first author and an experienced research assistant, and their decisions were recorded in separate Excel spreadsheets. When discrepancies occurred, the second author made the final decision regarding inclusion of the study.

2.3 Data extraction and recoding

Two researchers conducted the data extraction and recoding procedures separately for the included studies. Extracted data were input into Excel spreadsheets, and each researcher was blinded to the decisions of the other. When discrepancies occurred, the third author revisited the articles and made the final decision.

2.3.1 Data extraction

For human studies, the demographic data, study design, as well as experimental and outcome measurement details of the included papers were extracted and entered into an Excel

spreadsheet. Demographic data included the participants' mean age, health condition, and the number of participants in the active and sham stimulation group (N). Experimental details included the size of electrodes, placement of the anode and cathode, tDCS stimulation current intensity (mA), the duration of stimulation for each session (minutes), the concurrent task during stimulation, and the total number of stimulations applied. Outcome measures included the modality used to measure changes in the nervous system (i.e., fMRI/EEG/MEG) and the physiological state of participants during the neurophysiological/neuroimaging measurements; specifically, "resting-state" conditions refer to experimental conditions requiring participants' minimal task engagement (e.g., eye-closed rest, passive fixation) for a sustained period of time (usually around five minutes; e.g., Frase et al., 2016), while "event-related" conditions refer to experimental conditions in which participants actively perform a cognitive task that engages specific neural processes (e.g., n-back task to engage participants' working memory network). Other outcome measures included between-group contrast of measures indicating changes in neural oscillations and synchrony (i.e., amplitude, power, functional connectivity), which could be presented as 1) the group mean and standard deviation/error, 2) statistical values showing differences in the comparisons, or 3) for coordinate-based fMRI studies only, the MRI coordinates in the Montreal Neurological Institute (MNI)/Talairach space showing the brain regions with significant differences between actively stimulated versus sham-stimulated groups, the corresponding analytical method (whole-brain analysis/regions-of-interest analysis), and the threshold p-value for obtaining significant peaks. For EEG/MEG studies reporting changes in the oscillatory power during resting-state/cognitive tasks, we extracted results focusing on frontal brain regions to enhance the homogeneity of the dataset for further analyses.

For rodent studies, data regarding the animal models (i.e., rodent species; number, age of the rodents used), details of the study design and tDCS protocols used in the experiment

(i.e., active/reference electrode size and placement; current intensity, the duration and number of sessions given to the same animal) and all relevant information regarding the synaptic plasticity outcomes (i.e., the method of analysis, the time point of LTP/BDNF measurement, and the results of between-group comparisons in terms of statistical values or the group mean and standard deviation/error) of the included papers were extracted.

2.3.2 Data recoding

In view of the possible differential effects of participants' age (Leach, McCurdy, Trumbo, Matzen, & Leshikar, 2019) and health status (O'Neil-Pirozzi, Doruk, Thomson, & Fregni, 2017), stimulation intensity, polarity of the stimulating electrode and montage placement on the observed tDCS efficacy (Thair et al., 2017), covariate and subgroup analyses involving these variables were planned to control the effects of heterogeneity on the meta-analytic results. In addition, outcomes from rodent studies were categorized for subgroup analyses. The following paragraphs illustrated how these variables were recoded.

2.3.2.1 Participants' age. The participants' mean age was recoded into three age groups, namely the "child" group (i.e. mean age of participants = 17:11 or below), the "adult" group (i.e. mean age of participants = 18:0 – 64:11) and "elderly" group (i.e. mean age of participants ≥ 65:0).

2.3.2.2 Participants' health status. As previous studies have shown that the neural architecture in people with various kinds of neurological/neuropsychiatric disorders, such as schizophrenia (Kambeitz et al., 2016) and substance abuse (Hampton, Hanik, & Olson, 2019), are different from healthy individuals, studies were categorized into a group involving healthy individuals (including subclinical population) and another group involving clinical populations (i.e. study participants received one or more diagnosis of neurological/neuropsychiatric disorders when they were recruited for tDCS treatment).

2.3.2.3 Current density. The current density at the stimulating electrode (A/m^2), which is a widely adopted parameter representing the current applied to the participants (Jackson et al., 2016), was calculated by dividing the current intensity (mA) by the electrode's surface area (cm^2).

2.3.2.4 Montage placement. Based on a previous review (J. Wörsching et al., 2016), anodal stimulation over the left DLPFC (i.e., anode placement over F3 according to the 10-20 system) was categorized as one of the standard electrode montages for prefrontal tDCS; studies that did not adopt left DLPFC anodal stimulation were categorized as using "other", rather than "standard", montage placements.

2.3.2.5 Polarity of the stimulating electrode. For human studies, this variable contains three categories (i.e. anodal, cathodal and bilateral), which was generated by recoding information on anode and cathode placement of a study. Although polarity effects (anodal versus cathodal) of tDCS have been an important area of study in tDCS research (Jacobson, Koslowsky, & Lavidor, 2012), classifying different prefrontal tDCS montages into cathodal or anodal stimulation can be complex. Nasseri, Nitsche, and Ekhtiari (2015) suggested a framework categorizing tDCS electrode montages into four categories: unilateral, bilateral, midline and dual-channel, which is the first systematic framework for montage categorization that aids the organization and analysis of results in reviews. Taking one step further, we would like to extend the classification with the use of conventional nomenclatures, i.e., "anodal" and "cathodal". To achieve this, a dichotomous classification key (**Figure 2**) was built for data recoding in this paper. The key consisted of six guiding questions constructed largely based on the nomenclature suggested by Nasseri et al. (2015) and incorporating the classification of a recently developed montage, HD-tDCS configuration (Edwards et al., 2013; Kuo et al., 2013). In addition, for event-related fMRI/EEG/MEG data, concurrent tasks during tDCS were recoded under neurocognitive domains such as attention

and memory. For rodent studies, the categorization of "polarity of the stimulating electrode" was based on the polarity of extracephalic electrode.

2.3.2.6 Outcome measures for rodent studies. Regarding the measurement time point, we calculated the time between a particular LTP/BDNF measurement and the time when the final *in vivo* tDCS stimulation was administered; taking LTP measurement as an example, the measurement time point was "24 hour" if an *ex vivo* LTP measurement was taken 24 hours after the last administration of tDCS (e.g., Podda et al., 2016), LTP measurements taken < 60 minutes were recoded as "immediate", and those taken ≥ 60 minutes were recoded as "delayed".

2.4 Meta-analytic methods and narrative syntheses of data

For human neurophysiological, neuroimaging and rodent studies that fulfilled additional inclusion criteria, separate meta-analyses were conducted. For studies that did not fulfill these additional criteria, narrative syntheses were used to summarize the results of these studies, supplementing the meta-analytic results.

2.4.1 Additional inclusion criteria for meta-analyses

The heterogeneity of outcome measures was subjectively evaluated as recommended by Rao et al. (2017) to determine the suitability of inclusion of a study/experiment in a meta-analysis. Specifically, the experimental paradigm used to elicit brain activities and the data analysis methods contribute to the determination of whether a pool of studies is homogenous. Theoretically, at least two studies/experiments using similar experimental paradigms (e.g. resting-state measurements or measuring brain activity during similar working memory tasks) with the same data analysis methods (e.g. coherence as functional connectivity measures in neurophysiological studies) are required to formulate a meta-analysis (Higgins, Thomas, et al., 2019); meta-analyses were only performed when there were two or more

studies/experiments adopting a homogeneous experimental paradigm and data analysis method. To enhance the homogeneity of studies for meta-analyses, additional inclusion criteria were applied specifically to human and rodent studies. For human neuroimaging studies, we included only fMRI papers that provided coordinates from whole-brain analysis; studies reporting peaks obtained from region-of-interest (ROI) analyses with a statistically significant threshold that was more liberal than the threshold selected for the rest of the brain were excluded from meta-analysis to avoid overestimations of the results (Radua & Mataix-Cols, 2009). For human neurophysiological studies, we conducted separate meta-analyses for EEG and MEG to enhance homogeneity for each of our comparisons as suggested in the study by Fox et al. (2016), which suggested that possible heterogeneity might exist between EEG and MEG studies. For rodent studies, papers that did not report changes in either LTP or BDNF before and after *in vivo* tDCS were excluded from the meta-analysis.

2.4.2 Coordinate-based meta-analysis for human neuroimaging studies

To address the question of whether prefrontal tDCS modulates the resting-state network, coordinate-based fMRI studies were included for meta-analysis using signed differential mapping with permutation of subject images (SDM-PSI) software (Albajes-Eizagirre, Solanes, Fullana, et al., 2019; Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019). This software is an extension of ES-SDM (J Radua et al., 2012) that imputes effect-size images for included studies for meta-analysis using random effects models that also allow the inclusion of covariates in the analysis. In particular, we adopted SDM-PSI rather than ES-SDM as it showed greater sensitivity than ES-SDM when only peak-coordinates are available, which is usually the case for published tDCS papers (e.g., Ficek et al., 2018); additionally, SDM-PSI is considered a conservative approach by adopting a less biased stimulation of the population effect size, threshold-free cluster enhancement (TFCE) statistics (i.e., a familywise error correction method), which reduces the detection of false effects by

controlling the familywise error rates below 5% (Albajes-Eizagirre, Solanes, Vieta, et al., 2019). After preprocessing of data with anisotropy = 1, the isotropic full width at half maximum (FWHM) was set at 20 mm, and with a voxel size of 2 mm on a gray matter mask, the main meta-analysis was conducted by pooling the data of "active tDCS – sham tDCS" contrast. Variables including mean age of participants in the treatment group, health status, polarity of the stimulating electrode and montage placement were included in the covariate analysis. To investigate how current density influences the changes in fMRI activation patterns, simple linear regressions weighted by the square root of the sample size were performed across studies (Radua & Mataix-Cols, 2009); the output of this analysis was brain regions showing statistically significant changes per unit increase in current density. To test whether the activity of brain regions showing significant changes after tDCS associates with the strength of the electric field induced in these brain regions by different montage setups, a post hoc meta-regression analysis was performed; for each montage arrangement included in the meta-analysis, the localized electric field strength (V/m) over the brain regions within the significant clusters that survived TFCE-corrected threshold was simulated with the computational model proposed by Ruffini, Fox, Ripolles, Miranda, and Pascual-Leone (2014); the values obtain from the simulations were then regressed with the activity of brain regions within the significant clusters. As suggested by Albajes-Eizagirre, Solanes, Fullana, et al. (2019), we produced two sets of results of significance levels thresholded at p =.005 (uncorrected) and p = .05 (TFCE-corrected). To facilitate interpretation of the results in terms of the resting-state network, significant clusters identified in the main and subgroup analyses were classified into resting-state networks according to Yeo et al. (2011) and Schaefer et al. (2018). Heterogeneity of studies included in the meta-analyses was measured with the I-squared (I^2) statistic (Borenstein, Hedges, Higgins, & Rothstein, 2011), and the level of heterogeneity was classified based on J. P. Higgins, Thompson, Deeks, and Altman (2003),

with I^2 values of 25%, 50% and 75% being considered indicative of low, medium and high heterogeneity, respectively.

2.4.3 Meta-analyses for human neurophysiological and rodent studies

Using comprehensive meta-analysis (CMA; Biostat, Englewood, NJ), we conducted separate meta-analyses to address whether prefrontal tDCS modulates the amplitude of 1) resting-state and 2) event-related neural oscillations and whether *in vivo* tDCS modulates 3a) immediate and 3b) delayed LTP and 4) BDNF levels. These analyses were performed using a random effects model. For prefrontal tDCS studies conducted in humans, studies with experiments reporting resting-state or event-related neural oscillatory changes in different frequency bands (i.e., delta 1-4 Hz; theta 4-7 Hz; alpha 8-12 Hz; beta 15-30 Hz; gamma 30-80 Hz; Wang, 2010) measured by EEG/MEG were included in two separate meta-analyses (one for resting-state data and another for event-related data). For animal studies, papers with obtainable numerical data representing immediate (i.e., measured within 60 minutes after the last session of tDCS applied) and delayed (i.e., measured beyond 60 minutes after the last session of tDCS applied) changes were included in a meta-analysis; studies with experiments reporting changes in brain BDNF were included in a separate meta-analysis. Although performing covariate analyses is not feasible using CMA, we planned to delineate the mediating effects of age (in terms of age group), health status, polarity of the stimulating electrode and montage placement by conducting separate subgroup analyses. To investigate how current density influences the change in resting/event-related oscillatory power, LTP formation and BDNF expression, meta-regression analyses were separately conducted when the results from the main analyses were significant. A combination of test statistics (e.g., F-values, t-values) was used for effect size calculation and generation of the forest plot. If test statistics were unable to be obtained after contacting the corresponding authors but the results were described in the text, nonsignificant and significant results were assumed to have p-

values of 0.5 and 0.05 [1-tailed; Fox et al. (2016)] respectively. The forest plot was generated with the effect size Hedges g with 95% confidence intervals. Heterogeneity of the studies included in the meta-analyses was measured with the I^2 statistic, with I^2 at 25%, 50% and 75% being considered indicative of low, medium and high heterogeneity, respectively. To adjust for multiple comparisons for the five frequency bands in EEG and MEG measurements for human studies, the significance level for these comparisons was adjusted to p = .01 with Bonferroni adjustments.

2.5 Risk of bias evaluation

The risk of bias in individual human studies was assessed by Cochrane Collaboration's tool (Higgins et al., 2011), while animal studies were evaluated by SYRCLE's risk of bias tool (Hooijmans et al., 2014). Studies included in meta-analyses of more than ten experiments were further assessed for the risk of reporting bias with tests for funnel plot asymmetry. This test examines whether a difference between an estimated effect size and the study effect size is greater than would be expected to occur by chance (Higgins, Savović, Page, Elbers, & Sterne, 2019). Funnel plots were generated for visual inspection of potential publication bias. In the presence of publication bias, the plot is expected to be symmetrical at the top, while an increasing number of data points are missing from the middle to the bottom of the plot (Borenstein et al., 2011). Egger's tests (Egger, Smith, Schneider, & Minder, 1997) were then performed for the peak coordinates of brain regions showing differences between active and sham tDCS. Significant Egger's tests indicate "small-study effects", i.e., smaller studies might sometimes yield larger effects than studies with larger sample sizes (Sterne et al., 2011), which might be due to one of the possible reasons for publication bias (Schwarzer, Carpenter, & Rücker, 2015). As suggested by Higgins, Savović, et al. (2019), we restricted our evaluation of publication bias with tests for funnel plot asymmetry and Egger's test to meta-analyses with fewer than ten experiments as

the power of these analyses is too low to detect real asymmetry and therefore a real publication bias.

3. Results

3.1 Study selection

Electronic database searches and manual searches of the reference lists from previously published reviews yielded a total of 1946 human and 155 animal studies. After applying the inclusion and exclusion criteria, a total of 42 human RCTs and eight rodent studies were included in the systematic review. A total of 38 studies, including ten coordinate-based fMRI studies, 16 EEG studies, six MEG studies and six animal studies, were included in the meta-analyses. **Figure 3** illustrates the details of the article screening procedures.

3.2 Risk of bias within studies

Figure 4 shows the risk of bias assessments for EEG (**Figure 4a**), fMRI (**Figure 4b**), MEG (**Figure 4c**) and rodent (**Figure 4d**) studies. Overall, studies showed unclear bias across several assessment items. For human studies, most did not specify their measures to minimize selection bias with random sequence generation and allocation concealment. Although all included studies incorporated participant blinding using a sham-tDCS control group, most of the studies did not report how experimenter and assessor blinding was implemented to reduce performance and detection bias. Additionally, most of the studies did not report attrition of participants, although most of the studies reported data according to the planned data analysis methods to minimize reporting bias. For crossover studies, most of the studies adopted an adequate washout period of more than seven days, while a minority of studies employed minimal washout periods of one to two days with doubtful carryover effects. For animal studies, all of the studies showed a low risk of bias in random housing (item D4), detection

blinding (item D7) and selective outcome reporting (item D9). Five of eight studies reported nonsignificant results in baseline comparisons between active and sham tDCS groups (item D2). Three of eight studies illustrated the process to ensure allocation concealment (item D3), and all of the studies exhibited unclear bias in random sequence generation (item D1), performance blinding (item D5), random outcome assessment (item D6) and complete data reporting (item D8).

3.3 Can prefrontal tDCS modulate resting-state network functional connectivity?

3.3.1 Study characteristics

Eighteen studies with 21 experiments investigated the effects of prefrontal tDCS in modulating resting-state network functional connectivity, including 16 fMRI studies (with 19 experiments) and two EEG studies (**Table 1**). Among the included fMRI studies, ten studies reported whole-brain data (Holla et al., 2020; Keeser, Meindl, et al., 2011; Marangolo et al., 2016; Mondino et al., 2019; Mondino, Poulet, Suaud-Chagny, & Brunelin, 2016; Palm et al., 2016; Park et al., 2013; Sandrini et al., 2020; Shahbabaie et al., 2018; Sotnikova, Soff, Tagliazucchi, Becker, & Siniatchkin, 2017), which were further included in the coordinate-based meta-analysis. For the remaining 6 fMRI studies (with 9 experiments), only the results of ROI analyses were reported (Abellaneda-Perez et al., 2019; Cosmo et al., 2015; J. Dedoncker et al., 2019; Ficek et al., 2018; Kajimura, Kochiyama, Nakai, Abe, & Nomura, 2016; Thibaut, Piarulli, Martens, Chatelle, & Laureys, 2019; Worsching et al., 2018; Yang et al., 2017) and were included only in the narrative synthesis. For EEG papers, heterogeneous analytic methods for functional connectivity were adopted [i.e. the whole-brain weighted node degree in Cosmo et al. (2015) and the beta phase-lagged index in Thibaut et al. (2019)]; these two papers were also included in the narrative synthesis.

3.3.2 Meta-analytic results

As revealed in **Table 2** and **Figure 5**, meta-analysis with SDM-PSI showed that activation of the ventral attention network (VAN) and the frontoparietal network (FN) were significantly increased after prefrontal tDCS (compared to sham tDCS) with mean age and health status of participants, polarity of the stimulating electrode and montage placement as covariates (uncorrected p <.005; **Figure 5a**). Specifically, for the VAN, the significant peak was observed in the bilateral median cingulate gyrus, with the cluster extending to the bilateral anterior cingulate gyrus, bilateral supplementary motor area and left superior frontal gyrus; for the FN, significant peaks were noted in the right inferior parietal gyri, with the cluster extending to right angular and supramarginal gyrus. Notably, the VAN cluster survived familywise error correction (784 voxels; SDM-Z = 4.10; TFCE-corrected p<.005; **Figure 5b**). Post hoc meta-regression between the averaged electric field strength in the VAN cluster induced by different montage placements (**Table S2**) and the resting VAN activation revealed a significant positive relationship between electric field strength and changes in resting-state VAN activation after tDCS (SDM-Z = 2.00; TFCE-corrected p = .013). As planned, we did not perform post hoc meta-regression for the right inferior parietal gyri cluster as it did not survive TFCE-corrected threshold of p = .05 in the main analysis. The I^2 statistic of the right median cingulate peak was 14.1%, indicating low heterogeneity.

3.3.3 Narrative synthesis of the remaining studies

Narrative synthesis of ROI-based fMRI studies (n=6, 9 experiments) and EEG functional connectivity studies (n=2) yielded inconsistent results. For instance, within-default mode network (DMN) functional connectivity was found to be increased in one study (Abellaneda-Perez et al., 2019), reduced in another study (Ficek et al., 2018) and nonsignificant in the study by Kajimura et al. (2016); two studies reported a reduction in functional connectivity between the VAN and the DMN with F4 and F7 as the brain regions stimulated by the anode, respectively (Ficek et al., 2018; Wörsching et al., 2018), but when

F3 was stimulated with the anode, nonsignificant changes in resting-state functional connectivity were found between the VAN and the DMN (Wörsching et al., 2018; experiments 2 and 3). Two studies reported changes in resting-state functional connectivity between the VAN and other resting-state networks; Yang et al. (2017) reported a significant increase in resting-state functional connectivity between the VAN and the visual network, while J. Dedoncker et al. (2019) reported a significant reduction in resting-state functional connectivity between the VAN and the somatomotor network (SMN). For EEG studies, different parameters were used to indicate changes in functional connectivity, while Thibaut et al. (2019) showed a significant increase in the frontal beta phase-lagged index with a bilateral prefrontal montage among people with disorders of consciousness, and Cosmo et al. (2015) reported nonsignificant changes in the whole-brain weighted node degree after prefrontal tDCS was applied in patients with ADHD.

3.4 Can prefrontal tDCS modulate functional connectivity during cognitive tasks?

3.4.1 Study characteristics. Five studies with seven experiments investigated the effects of prefrontal tDCS in modulating functional connectivity during cognitive tasks, including 3 fMRI studies (with 4 experiments) and two MEG studies (with 3 experiments; **Table 3**). All of these papers were included in the narrative synthesis as they failed to meet our additional inclusion criteria for meta-analysis. For instance, all fMRI studies reported results of ROI analyses and adopted markedly different experimental paradigms to measure performance across a variety of cognitive domains, including attention (Sandrini et al., 2020), working memory; (Rodrigues de Almeida, Pope, & Hansen, 2020) and language performance (Nissim et al., 2019), whereas the MEG experiments adopted different analytic methods i.e. ROI-based theta coherence in Wiesman et al. (2018) and theta-gamma cross frequency phase-amplitude coupling (PAC) in Ikeda et al. (2019).

3.4.2 Narrative synthesis of studies

An fMRI study (Nissim et al., 2019) showed increased functional connectivity between the VAN and FN nodes when participants perform working memory tasks, while a MEG study (Ikeda et al., 2019) reported a significant reduction in theta-gamma cross frequency PAC within the frontal regions. During an attentional control task, tDCS was found to enhance functional connectivity between the VAN and the caudate (Sandrini et al., 2020), while functional connectivity within the FN and DMN was found to be enhanced during a language task regardless of anodal tDCS over the inferior frontal gyrus, with enhanced connectivity also between FN and DMN when cathodal tDCS was applied (Rodrigues de Almeida, P. A. Pope, & P. C. Hansen, 2020).

3.5 Can prefrontal tDCS modulate the amplitude of resting-state neural oscillations?

3.5.1 Study characteristics

Ten studies with 12 experiments investigated the effects of prefrontal tDCS in modulating the amplitude of resting-state neural oscillations across different frequency bands over the frontal brain regions during resting-state conditions (Frase et al., 2016; Frase et al., 2019; Holgado et al., 2019; L. Jacobson, Ezra, Berger, & Lavidor, 2012; Keeser, Padberg, et al., 2011; Liu et al., 2016; Saadi, Saadat, Kamali, Yahyavi, & Nami, 2019; To, Eroh, Hart, & Vanneste, 2018; Ulam et al., 2015; Wirth et al., 2011), all of which were EEG studies involving adult sample (**Table 4**). All of these papers were included in the meta-analysis.

3.5.2 Meta-analytic results

Meta-analysis of these studies showed that prefrontal tDCS did not significantly modulate the amplitude of resting-state neural oscillations across all frequency bands (ps > .277; **Figure 6**). The results remained nonsignificant when subgroup analyses of participants' health status (**Figure S1**), polarity of stimulation (**Figure S2**) and montage

placement (**Figure S3**) were conducted. The I^2 of the main analysis was 3.75%, indicating low heterogeneity.

3.6 Can prefrontal tDCS modulate the amplitude of neural oscillations during cognitive tasks?

3.6.1 Study characteristics

Thirteen studies with 20 experiments investigated the effects of prefrontal tDCS in modulating the amplitude of oscillatory power during cognitive tasks, including seven EEG studies (with 11 experiments) and six MEG studies (with nine experiments; **Table 5**). All included EEG (Adelhöfer, Gohil, Passow, Beste, & Li, 2019; Boudewyn, Roberts, Mizrak, Ranganath, & Carter, 2019; Choe, Coffman, Bergstedt, Ziegler, & Phillips, 2016; A. T. Hill, Rogasch, Fitzgerald, & Hoy, 2018; Holgado et al., 2019; O'Neil-Pirozzi et al., 2017; Powell, Boonstra, Martin, Loo, & Breakspear, 2014) and MEG studies (Heinrichs-Graham, McDermott, Mills, Coolidge, & Wilson, 2017; Ikeda et al., 2019; Koshy et al., 2020; McDermott et al., 2019; Wiesman et al., 2018; Wilson, McDermott, Mills, Coolidge, & Heinrichs-Graham, 2018) reported group comparisons of amplitude differences in theta, alpha and gamma frequency bands. These studies involved healthy adults except two EEG studies that recruited participants with clinical diagnoses including traumatic brain injury (O'Neil-Pirozzi et al., 2017) and mood disorders (Powell et al., 2014). One EEG (Powell et al., 2014) and one MEG (Ikeda et al., 2019) study employed bilateral prefrontal stimulation; these studies were included in the corresponding main analysis, but were excluded from the subgroup analyses of polarity of stimulation.

3.6.2 EEG meta-analytic results

Meta-analysis of the included EEG studies (**Figure 7**) showed trends that prefrontal tDCS enhanced the event-related neural oscillations across theta (p = .029; **Figure 7a**) and

gamma (p = .034; **Figure 7c**) frequency bands in the frontal brain regions; these enhancements did not survive Bonferroni corrections. The modulation of frontal alpha event-related oscillatory power remained nonsignificant (p = .559; **Figure 7b**). When corrected for multiple comparisons (p = .01), results remained nonsignificant across all frequency bands for subgroup analyses of participants' health status (**Figure S4**), polarity of stimulation (**Figure S5**) and montage placement (**Figure S6**). The I^2 statistic of the main analysis was 36.6%, indicating low to moderate heterogeneity.

3.6.3 MEG meta-analytic results

Meta-analysis of MEG studies (**Figure 8**) showed that prefrontal tDCS did not significantly modulate event-related oscillatory power over the frontal cortex at theta (p = .339), alpha (p = .338) and gamma (p = .125) frequency bands. The results remained nonsignificant when subgroup analyses of stimulation electrode polarity (**Figure S7**) was conducted. The I^2 statistic of the main analysis was 44.4%, indicating moderate heterogeneity.

3.7 Can *in vivo* tDCS modulate neural plasticity?

3.7.1 Study characteristics

Eight studies with ten experiments investigated the effects of *in vivo* hippocampal/prefrontal tDCS in modulating synaptic plasticity in rodent models (**Table 6**). Four studies with seven experiments reported LTP measurements (Podda et al., 2016; Rohan et al., 2015; Rohan et al., 2020; Yu, Wu, Chien, & Hsu, 2019), and all of these experiments (five anodal, two cathodal stimulation) showed immediate LTP formation changes, while four experiments (all employing anodal stimulation) showed LTP changes more than 60 minutes after the last administration of tDCS; all of these experiments employed healthy adult mouse models (thus, subgroup analyses of healthy status and age were not applicable here). Four

studies (all employing anodal stimulation) reported between-group brain BDNF measurements within the stimulated brain regions (i.e., the hippocampus/prefrontal cortex) after tDCS, with two studies stimulating healthy adult rodent models over the hippocampus (Podda et al., 2016; Yu et al., 2019) and the remaining two stimulating disease adult models over the prefrontal cortex (Leffa et al., 2016; Wu et al., 2017). Two studies did not report either LTP or brain BDNF changes [Stafford, Brownlow, Qualley, and Jankord., 2018; Jung et al., 2019) and were included only in the narrative synthesis.

3.7.2 Meta-analytic results for LTP formation

When anodal tDCS was applied to rodent models over hippocampal/prefrontal regions (**Figure 9**), a significant increase in immediate LTP (within 60 minutes) was found compared with sham-stimulated rats [g=4.755; p< .001; 95% CI (2.93,6.58); **Figure 9a**]; the results remained nonsignificant [g=-1.94; p = .152; 95% CI (-4.59,0.152)] for cathodal stimulation. Regarding delayed LTP (> 60 minutes after the last administration of tDCS stimulation), a significant increase was found with anodal tDCS application [g=3.16; p <. 005; 95% CI (1.07,5.26); **Figure 9b**]. The I^2 statistic of all six experiments included in this part of the analysis was 93.0%, indicating high heterogeneity.

3.7.3 Meta-analytic results for BDNF modulation

Meta-analysis indicated a significant increase in brain BDNF levels [g=1.69; p<.005; 95% CI (0.525,2.845)]. Subgroup analyses of healthy and diseased rodents show significant increases in both subgroups (**Figure 9c**). The I^2 statistic of all ten studies included in this part of the analysis was 47.8%, indicating moderate heterogeneity.

3.7.4 Narrative synthesis of the remaining studies

Although Stafford et al. (2018) and (Jung et al., 2019) did not report changes in LTP formation and brain BDNF, these studies reported significant changes in other indicators of

synaptic plasticity after active tDCS compared to sham-stimulated rodents. For instance, Stafford et al. (2018) reported an increase in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor translocation to synapses in the hippocampus, and S. H. Jung et al. (2019) reported an increase in BDNF synaptoneurosomes in the hippocampus in mice that received anodal stimulation over hippocampus.

3.8 How does current density mediate tDCS neurobiological effects?

Meta-regression of the resting-state fMRI studies revealed a significant positive relationship between activation of the bilateral median cingulate [MNI coordinates (x,y,z): (4,12,36); number of voxels: 910) and current density (SDM-Z = 2.802; TFCE-corrected $p<.005$). For rodent studies, meta-regression analyses showed a trend of a positive relationship between current density induced by anodal stimulation with delayed LTP formation ($Z = 1.73$, $p = .083$), but not for immediate LTP formation ($Z = .5$; $p = .619$) and BDNF levels ($Z = .23$; $p = .815$). The meta-regression results from the rodent studies should be treated with caution given the very limited number of studies/experiments involved in the analyses.

3.9 Risk of reporting bias across studies

Figure 10 shows the funnel plots with effect sizes of each study included in the meta-analyses plotted against 1/SE (precision). Notably, tests for funnel plots of asymmetry and Egger's test were performed only in human fMRI, EEG and MEG studies as fewer than 10 experiments were included in the meta-analyses of rodent data. For fMRI studies, visual inspection of the funnel plot of the TFCE-corrected significant cluster (right median cingulate; **Figure 10a**) showed no prominent asymmetry, indicating no obvious publication bias; Egger's test was nonsignificant ($t=.23$, $df = 8$, $p = .95$), indicating that no obvious small-study effect was present among the fMRI studies included in the meta-analysis. For resting-

state EEG studies, although visual inspection of the funnel plot (**Figure 10b**) revealed a nonsignificant publication bias, Egger's test was significant ($t = 2.28$, $df = 50$, $p < .05$), indicating small-study effects. For event-related EEG studies, visual inspections of the funnel plot (**Figure 10c**) and Egger's test for all experiments revealed no obvious publication bias and a small-study effect ($t = 0.372$, $df = 19$, $p > .05$). For event-related MEG studies, a forest plot (**Figure 10d**) revealed no obvious publication bias with a statistically nonsignificant Egger's test ($t = 0.28$, $df = 14$, $p = .78$).

4. Discussion

This paper aimed to investigate the neurobiological mechanisms of prefrontal tDCS in modulating neural plasticity at both network and neuronal levels. While 42 human RCTs and eight rodent studies were included in this systematic review, 32 human studies and six rodent studies were included in the meta-analysis. The main results of our review can be summarized as follows: 1) tDCS with the anode placed over the lateral prefrontal regions enhanced the frontal midline VAN activity at rest; 2) prefrontal tDCS yielded nonsignificant modulations in both resting-state and event-related oscillatory power in all frequency bands evident from both EEG and MEG studies; 3) anodal tDCS over brain regions associated with learning and memory in rodents enhanced LTP formation, as well as BDNF levels, in the stimulated brain regions (i.e., the hippocampus/prefrontal cortex); 4) meta-regressions of resting-state fMRI studies revealed positive relationships between changes in activation of the bilateral median cingulate cortex after tDCS and current density over the stimulating electrode, as well as the localized electric field strength in the frontal midline brain regions. In the following paragraphs, we discuss the implications and translational value of these results.

4.1 Effects of tDCS on the functional connectivity of the ventral attention network

Consistent with previous tDCS studies stimulating the primary motor cortex (Amadi et al., 2014; Bachtiar, Near, Johansen-Berg, & Stagg, 2015), prefrontal tDCS was found to be effective in modulating the functional connectivity of the brain compared with sham stimulation. Specifically, from the meta-analysis of ten coordinate-based fMRI studies providing whole-brain analysis data, we found that tDCS with anode placement over the lateral prefrontal cortex significantly enhanced the activity of the median cingulate cortex, a brain region within the VAN, with participants' mean age and health status, polarity of the stimulating electrode and montage placement variations as covariates. Previous studies have shown that the VAN is involved in filtering irrelevant information to protect goal-driven behavior (Vossel, Geng, & Fink, 2014). An increase in the VAN at rest may imply an enhanced ability to attend to upcoming tasks, resulting in improved task performance, especially for demanding cognitive tasks (e.g., working memory tasks with a high cognitive load), which has been shown to be improved after tDCS (Brunoni & Vanderhasselt, 2014). Indeed, median cingulate cortex activation has been shown to be positively correlated with cognitive control ability (Zhang, Geng, & Lee, 2017).

Interestingly, the frontal midline brain region within the VAN (i.e., the median cingulate) showed consistent activation despite the variability in montage placement. Two possible explanations may account for this phenomenon. First, we hypothesized that the frontal midline enhancement may be elicited by the higher concentration of electric current in that region, given a previous simulation study showing that the electrical field generated by the F3 anodal montage induced the highest electric current density over the frontal midline regions regardless of the placement of the cathode over Fp2 or F4 (Laakso et al., 2016); we testified this hypothesis by conducting a post hoc meta-regression, which indeed revealed that there was a statistically significant positive relationship between current density and changes

in median cingulate cluster activation after tDCS. Second, the dorsolateral prefrontal cortex, which was targeted by most of the included studies, belongs to the VAN (Yeo et al., 2011); given that brain regions within the same resting-state network are highly correlated with each other, stimulation of the DLPFC also enhances the activation of other nodes within the same resting-state network, i.e., the bilateral median cingulate.

Qualitative analysis of ROI-based fMRI results revealed that functional connectivity between the VAN and other resting-state networks i.e., the DMN, VN, and SMN, were also modulated by tDCS. Previous studies have suggested that the coordination between resting-state networks might be associated with the development and progression of chronic neurological disorders (Broyd et al., 2009; Greicius, 2008), showing that tDCS modulation of between-network functional connectivity might be an important finding for supporting tDCS as a treatment for patients with neurological disorders. However, our observation remained preliminary, and further empirical studies are required to support our claim.

4.2 Effects of tDCS on the amplitude of oscillatory power

Previous empirical studies have reported that tDCS can modulate the amplitude of oscillatory power (Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011), which has been regarded as one of the possible neural mechanisms underlying tDCS behavioral effects (Lapenta, Minati, Fregni, & Boggio, 2013). Interestingly, our meta-analyses showed contrasting results; both EEG and MEG studies showed nonsignificant differences between active and sham tDCS in terms of amplitude changes across all frequency bands during resting and event-related conditions. The converging nonsignificant results in the EEG and MEG meta-analyses might imply that tDCS does not have an effect on both resting-state and event-related oscillatory power. Other reasons for obtaining nonsignificant results might include 1) the substantial variation in montage placement between studies, 2) possible

underestimation of effects sizes for some studies when we took the most conservative estimates for effect sizes (i.e., p = .5 for nonsignificant results and p = .05 for significant results) as exact t/F-values were not obtainable or 3) the power of the EEG meta-analysis was not sufficient for detecting significant effects with a limited number of studies.

4.3 Effects of tDCS on synaptic plasticity

To increase the likelihood of the success of tDCS in enhancing learning and memory outcomes, understanding its mechanism of action on synaptic plasticity is important. Given that long-lasting synaptic plasticity has long been recognized as the neurophysiological basis of learning and memory (Hebb, 1949; Malinow & Malenka, 2002; Martin et al., 1997) and altered synaptic plasticity has been associated with various neurological disorders (Marsden, 2013; Rossini, Ferilli, Rossini, & Ferreri, 2013), understanding how tDCS is associated with synaptic plasticity may provide important insights for the development of tDCS-based cognitive interventions (Stagg & Nitsche, 2011). Some previous human studies, although limited, have provided indirect evidence that tDCS effects are associated with changes in long-term synaptic plasticity. For instance, M. Nitsche et al. (2003) and Monte-Silva et al. (2013) have shown that with the administration of dextromethorphan, an N-methyl-D-aspartate (NMDA) receptor antagonist, the enhanced TMS-induced motor-evoked potentials after applying anodal tDCS became nonsignificant compared to sham-tDCS controls. Notably, these human studies focused on stimulation over the primary motor cortex; for prefrontal tDCS, such evidence remains to be found in future studies. Applying *in vivo* tDCS beyond the motor cortex to brain regions associated with learning and memory in animal models might be helpful to strengthen our understanding of the neural mechanism of tDCS in cognitive enhancement in addition to the evidence from human studies (Podda et al., 2016; Wu et al., 2017). The included rodent studies in our review provided some evidence that both

immediate and delayed LTP, as well as brain BDNF, can be enhanced by anodal tDCS over the hippocampus/frontal cortex, which is consistent with previous *in vitro* results with direct current stimulation to the brain slices of the motor cortex (Fritsch et al., 2010) as well as the hippocampus (Kronberg et al., 2019; Rahman et al., 2017; Ranieri et al., 2012). For cathodal tDCS applied over the hippocampal region, our preliminary results showed nonsignificant modulation of LTP formation, which might be due to the possible mechanism that tDCS modulates long-term depression (LTD) but not LTP as shown in previous *in vitro* studies (Sun et al., 2016), although some other *in vitro* studies revealed that cathodal direct current stimulation reduced LTP formation in hippocampal CA1, which was associated with reduced BDNF expression levels (Ranieri et al., 2012). Our observation should be considered very preliminary due to the limited number of available empirical studies; the synaptic mechanisms of *in vivo* cathodal tDCS over hippocampal/frontal regions of rodents warrants further investigation.

4.4 Treatment implications – considerations in targeted populations and tDCS protocol parameters

Given the results discussed above, it is reasonable to hypothesize that prescribing prefrontal tDCS to patients with abnormalities in functional connectivity and synaptic plasticity may potentially yield promising outcomes. For instance, clinical populations that are known to have network and synaptic dysfunctions, such as people with schizophrenia (Frantseva et al., 2008; Jindal et al., 2010; Uhlhaas & Singer, 2010) or autism spectrum disorders [ASD; Han and Chan (2017); Jung et al. (2013); Ricci et al. (2013)], might benefit from receiving prefrontal tDCS. Specifically, a meta-analysis of resting-state functional connectivity in patients with schizophrenia showed that these patients have core problems in the VAN as evidenced by hypoconnectivity within the VAN as well as between the VAN, FN

and DMN (Dong, Wang, Chang, Luo, & Yao, 2018); these patients have also been shown to have dysregulated NMDA receptor (NMDAR)-mediated synaptic plasticity (Stephan, Friston, & Frith, 2009). For ASD individuals, apart from impairments in synaptic plasticity (Bourgeron, 2009), hypoconnectivity within the VAN was also found in ASD adults (Bourgeron, 2009; Farrant & Uddin, 2016). Combining this evidence together with the results from this review, we hypothesize that resting-state functional connectivity within the VAN may be enhanced with anodal tDCS applied over the lateral prefrontal cortex in patients with schizophrenia as well as adults with ASD; in animal models for these diseases, enhancements in LTP formation and brain BDNF will be expected with anodal tDCS applied over rodent frontal cortex/hippocampus.

In the meta-regression analysis of resting-state fMRI data, we show that there is a statistically positive linear correlation between tDCS current density (A/m^2) and activation of the frontal midline VAN. Consistent with previous empirical studies showing that a stronger stimulation intensity (mA) is associated with a more significant cortical excitability effect in the primary motor cortex (Batsikadze et al., 2013; Nitsche & Paulus, 2000), we provided meta-analytic evidence to support that enhancing current density over the tDCS stimulating electrode in the prefrontal cortex, which is contributed by a higher stimulation intensity coupled with a smaller size of stimulating electrode, might result in greater gain in neurobiological modulations and subsequent cognitive enhancing effect. From the clinical point of view, clinicians with experience in applying prefrontal tDCS may consider using a smaller (e.g. $25cm^2$) stimulating electrode instead of those with a size of $35cm^2$ or larger in their daily practice, given the stimulation intensity is kept at 1mA to 2mA so as to maintain the current density below the threshold for tissue damage, that is $20A/m^2$ for anodal stimulation (Jackson et al., 2017) and $142.9A/m^2$ for cathodal stimulation (Liebetanz et al., 2009).

Although tDCS applied over the primary motor cortex has been shown to be polarity-specific (i.e., Nitsche et al., 2003), this pattern is not observable with prefrontal tDCS. However, small number of cathodal tDCS studies may have limited the power for observing a significant reduction in network, neuronal and molecular parameters, which may also be due to the interplay of electrical current and neuronal orientation (Rahman et al., 2013; Rawji et al., 2018) and cortical gyri-sulci morphology (Datta, 2012). Given the higher interindividual variability in terms of sulcal depth and positions in the prefrontal cortex between subjects (J. Hill et al., 2010), the polarity specificity may be more complex among non-M1 stimulations, while the optimal electrode positions are yet to be determined.

In addition to the consideration of tDCS current density and montage placement, other tDCS protocol parameters to be considered could include the number of stimulation sessions, the combination of specific cognitive tasks with concurrent stimulation and the complexity of the tasks. A previous study showed that repeated tDCS sessions resulted in a cumulative increase in cortical excitability (Ho et al., 2016). Regarding the coupling of stimulation with cognitive tasks, as tDCS with conventional stimulation intensity has subthreshold effects on resting membrane potential, combining ongoing task-specific cognitive training at appropriate complexity can help recruit the targeted brain network, such that the amplification of neural activity by tDCS can be achieved, thus resulting in meaningful modifications (e.g., LTP formation, functional connectivity; (Jackson et al., 2016). Indeed, Li et al. (2019) showed that cathodal stimulation over the right inferior frontal gyrus coupled with a sustained attention task resulted in augmented functional connectivity within the DMN network that was correlated with enhanced task performance, which implies the importance of tasks in promoting neural plasticity by tDCS. To achieve the aim of cognitive enhancement, the physiological state of the participants (e.g., quality of sleep before stimulation) is also an essential factor to be considered, given it has been documented that

sleep deprivation inhibits LTP formation (Kim, Mahmoud, & Grover, 2005) and prevents the formation of new memories in humans (Yoo, Hu, Gujar, Jolesz, & Walker, 2007).

4.5 Implications for future research

ROI-based fMRI studies provide preliminary evidence that prefrontal tDCS modulates inter-network resting-state functional connectivity, especially between the VAN and other resting-state networks. However, the results remain inconclusive: the differential choice of ROI across studies might impact the direction of the results and complicate interpretation of the results. We encourage future tDCS studies to include whole-brain analysis results [also suggested in Heinrichs-Graham et al. (2017)] such that reviews and meta-analyses comparing the effects of prefrontal tDCS on internetwork functional connectivity across studies will be possible.

Studying tDCS effects on neurophysiological/molecular changes across the entire functional network in animal models, in addition to investigating the local effects of stimulated brain regions, would help researchers and clinicians gain a more comprehensive picture regarding the mechanisms of tDCS action on neural network modulation. Emerging data have shown that *in vivo* prefrontal tDCS is effective in modulating neural oscillations and functional connectivity in macaques based on local field potential measurements (Krause et al., 2017), while *in vitro* studies support the *in vivo* findings that functional neural networks can be modulated with enhanced power and frequency of gamma oscillations after passing direct current through rat brain slides (Reato, Bikson, & Parra, 2015; Reato, Rahman, Bikson, & Parra, 2010).

In view of the critical role of BDNF in promoting synaptic plasticity, as shown in rodent studies, the effects of tDCS with human BDNF as a biomarker can be evaluated to examine the treatment outcomes of tDCS with synaptic plasticity modulation. Although brain

BDNF is difficult to measure in humans, peripheral serum and plasma BDNF levels may be a feasible alternative measure given that the plasma BDNF level is correlated with the brain BDNF level (Klein et al., 2011), and that these measurements are largely reproducible (Polacchini et al., 2015). Future studies with precise experimental designs and adequate power to detect statistically significant changes (Naegelin et al., 2018) are important for further revealing the molecular mechanism of tDCS in humans.

5. Limitations

To investigate the currently available evidence on the neurobiology of prefrontal tDCS, through extensive electronic database screening and manual searching, we attempted to include a comprehensive set of human and rodent randomized controlled trials employing common methods to detect changes in the neural network (for humans) and synapses (for rodents). We specifically compare and contrast studies to investigate the changes induced by tDCS in functional connectivity and oscillatory power during both resting-state and cognitive task performance for human studies and synaptic plasticity changes indicated by LTP formation and brain BDNF level changes in rodent studies. Although we limited the diversity of the included studies with a set of inclusion/exclusion criteria, these studies remained heterogeneous due to the 1) recruitment of participants with different health statuses, 2) application of different tDCS protocols, 3) data collection using different measurement methods and during different physiological states of participants, and 4) results analyzed with different analytic methods. We attempted to address these issues by using covariate/subgroup analysis to control the effects of heterogeneity among 1) participants, 2) tDCS protocols, 3) separate meta-analyses for resting-state and event-related data recorded by different measurement techniques (i.e., fMRI, EEG, MEG), and 4) excluding studies/experiments from meta-analyses if the analytic methods adopted were vastly different from those in most

studies [e.g., Cosmo et al. (2015) and Thibaut et al. (2019) reported EEG resting-state functional connectivity results analyzed with two different methods]. Indeed, we have minimized the heterogeneity of each meta-analysis involving human studies to a low-to-moderate level (ranging from 3.75% to 44.4%) according to the classification suggested by J. P. Higgins et al. (2003). However, carrying out separate analyses would substantially limit the power of studies. Thus, our results must be considered a preliminary overview regarding the neurobiology of prefrontal tDCS, and empirical studies investigating the functional connectivity effects of tDCS using different neurophysiological/neuroimaging techniques are highly encouraged.

To present our ideas in a more practical manner that might potentially facilitate future development of tDCS research, we attempted to classify the montage placements adopted by different studies using a dichotomous key established based on the concepts suggested by Nasseri et al. (2015). As our review focused on the effects of prefrontal tDCS, our classification key specifically focused on the polarity of the frontal electrodes in relation to other extracephalic electrodes and recoded the polarity of the montage for a particular study/experiment based on the polarity of the frontal electrode. The use of this classification is considered exploratory; we suggest further reviews and meta-analyses to continuously explore the usefulness of this dichotomous key in classifying studies into anodal/cathodal/bilateral stimulation to further validate this model, which might be potentially useful for standardizing the nomenclature for montage placement and facilitate relevant research.

Regarding data availability, although we attempted to obtain the most accurate data from the original studies for the calculation of the effect sizes, some studies did not provide exact p-values, t-values or F-values for the calculation, and assumptions were made based on recommendations from previous studies (i.e., Fox et al., 2016). In view of the importance of

whole-brain analysis in studying the effects of tDCS on functional connectivity (Heinrichs-Graham et al., 2017), and the recommendation that ROI analyses might not be suitable for incorporation into coordinate-based meta-analysis for fMRI studies (Müller et al., 2018), we encourage future studies to analyze and report whole-brain neurophysiological/neuroimaging data to facilitate future large-scale systematic reviews and meta-analyses with enhanced precision.

6. Conclusion

Prefrontal transcranial direct current stimulation (tDCS) has been shown to improve cognitive performance in both healthy people and those with neurological disorders. However, the underlying neurobiological mechanisms remain elusive, with discrepancies found across current studies. We performed a systematic review with meta-analyses of both human and rodent studies to explore whether prefrontal tDCS modulates resting-state and event-related functional connectivity, the resting-state and event-related amplitudes of neural oscillatory power and synaptic plasticity as indicated by changes in LTP formation and BDNF expression levels in the brain.

Relevant randomized, sham-controlled trials in humans and rodents applying *in vivo* prefrontal tDCS were included. Signed differential mapping with permutation of subject images (SDM-PSI) was used to meta-analyze functional magnetic resonance imaging data, while CMA was used to analyze human/rodent neurophysiological results. Narrative syntheses of studies excluded from meta-analyses were performed to supplement the meta-analytic results. Fifty studies were included in the systematic review, with 32 studies included in the meta-analyses. SDM-PSI analysis with the tDCS montage, stimulating electrode polarity, participants' mean age and health status as covariates indicated that anodal tDCS over the lateral prefrontal cortex significantly enhanced the activity of the bilateral median

cingulate cortex, a brain region within the VAN; the neural activity enhancement in this region positively correlated with current density of the stimulating electrode and the electric field strength induced by different montage setup in this region. Meta-analyses of EEG and MEG data revealed nonsignificant changes in the amplitude of resting-state/event-related frontal oscillatory power across all frequency bands. Rodent studies applying anodal tDCS over the hippocampus/prefrontal cortex showed enhanced LTP formation and brain BDNF expression levels over the stimulated brain region.

Although diversity of the included studies was limited by a set of inclusion/exclusion criteria, these studies remained heterogeneous, and these issues were addressed in this review by using covariate/subgroup analyses to control the effects of heterogeneity among participants and tDCS protocols and conducted separate meta-analyses for resting-state and event-related data recorded by different measurement techniques (i.e., fMRI, EEG, MEG). In conclusion, this review reported some key findings regarding prefrontal tDCS, including 1) some evidence showed positive effects of anodal tDCS over the lateral prefrontal cortex in enhancing the frontal midline VAN, which was correlated with the stimulating electrode current density as well as the electric current strength over the median cingulate cortex; 2) some evidence demonstrated that anodal tDCS can modulate synaptic plasticity as indicated by LTP formation and brain BDNF expression levels localized to the stimulated brain regions. While these results enhance understanding of the neurobiology of prefrontal tDCS, further investigation is warranted with regard to the 1) differential effects of prefrontal tDCS applied in various clinical populations, 2) the effects of different prefrontal montage placements in modulating the neurobiology and the association with the resultant behavioral changes, and 3) the effects of tDCS on synaptic plasticity in humans as indicated by serum/plasma BDNF levels.

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Figure captions

Figure 1: The definition of 'prefrontal' stimulation in this study. Empirical studies involving placement of the tDCS anode/cathode over frontal regions according to the EEG 10-10 system (highlighted in yellow) were included in this review.

Figure 2: A dichotomous classification key for recoding included human and rodent studies into 'anodal', 'cathodal', 'unilateral', 'bilateral' and 'dual channel' stimulation. Note that this classification key applies only to the tDCS prefrontal stimulation studies included in our study.

Figure 3: Flowchart of the article screening process.

Figure 4: Risk of bias summaries: review authors' judgements about each risk of bias item for each included study. Figures a), b), c) and d) are summary charts for human EEG, human fMRI, human MEG and rodent studies, respectively.

Figure 5: Effects of prefrontal tDCS on the resting-state network with montage placement and the health status of participants as covariates. Clusters highlighted in red indicate statistically significant increases in resting-state activity after participants received active-tDCS compared to those who received sham-tDCS. Figures a) and b) correspond to the result threshold at an uncorrected $p < .005$ and a TFCE-corrected $p = .01$, respectively.

Figure 6: Effects of prefrontal tDCS on resting-state oscillatory power amplitude. Nonsignificant changes were noted across a) delta ($p = .771$), b) theta ($p = .428$), c) alpha ($p = .277$), d) beta ($p = .514$) and e) gamma ($p = .722$) frequency bands.

Figure 7: Effects of prefrontal tDCS on EEG event-related oscillatory power amplitude. With corrections for multiple comparison ($p = .01$), nonsignificant changes were noted across a) theta ($p = 0.029$), b) alpha ($p = .559$) and c) gamma ($p = .034$) frequency bands. Results in c) should be interpreted with caution as the results were derived from fewer than five studies.

Figure 8: Effects of prefrontal tDCS on MEG event-related oscillatory power amplitude. Nonsignificant changes were noted across a) theta ($p = .338$), b) alpha ($p = .339$) and c) gamma ($p = .125$) frequency bands. Results in b) and c) should be interpreted with caution as the results were derived from fewer than five studies.

Figure 9: Effects of *in vivo* tDCS over hippocampal/prefrontal regions on LTP and BDNF concentration. Figures a), b) and c) corresponds to the results of immediate LTP, delayed LTP and brain BDNF concentration, respectively. These results should be interpreted with caution as they are driven by less than five studies.

Figure 10: Funnel plots for examination of the risk of publication bias across studies. Effect sizes (Hedges's g) representing each study (x-axis) are plotted against precision (1/SE; y-axis) with a random effects model.

Table 1

Effects of prefrontal tDCS on resting-state functional connectivity (18 studies, 21 experiments)

Reference (year)	Participants' details			tDCS protocol						Outcome measures	
	Population	N	Mean Age (years)	Anode	Cathode	Polarity of the stimulating electrode	No. of sessions	Duration	Current density (A/m^2)	Modality	Changes in outcomes
Studies included in the meta-analysis											
Keeser (2011b)	Healthy	13 13	27.4	F3	Fp2	Anodal	1	20	0.571	fMRI (WB)	DMN ↑ VAN ↑ FN ↑
Park (2013)	Healthy	25 14	n.r.	F3	Fp2	Anodal	1	20	0.4	fMRI (WB)	VAN ↑ VN ↑ DMN ↑
Mondino (2019)	Healthy	15 15	28.7	F3	F4	Bilateral	1	30	0.286	fMRI (WB)	FN ↑
Marangolo (2016)	Stroke-induced aphasia	9 9	58.2	F5	F6	Bilateral	15	20	0.571	fMRI (WB)	SMN ↑ VAN ↑ DMN ↑
Sotnikova (2017)	ADHD	13 13	14.3	F3	Cz	Anodal	1	20	0.769	fMRI (WB)	DMN ↑ VAN ↑ FN ↑
Shahbabaie (2018)	SA (drug)	15 15	31.3	F4	F3	Bilateral	1	20	0.571	fMRI (WB)	DMN ↑ VAN ↑ DAN ↑ FN ↑ VN ↑
Holla (2020)	SA (alcohol)	12 12	39.0	F4	F3	Bilateral	5	20	0.571	fMRI (WB)	DMN ↑ VAN ↑ FN ↑
Palm (2016)	Sz	11 12	36.1	F3	Fp2	Anodal	10	20	0.571	fMRI (WB)	DMN ↑
Mondino (2016)	Sz	10 10	37.0	Between F3 and FP1	Between T3 and P3	Anodal	10	20	0.571	fMRI (WB)	DMN ↑ VAN ↑ DAN ↑ FN ↑
Sandrini (2020)	Healthy	15 15	26.5	F8	Fp1	Anodal	1	15	0.6	fMRI (WB)	VAN ↑ DAN ↑
Studies included in the narrative synthesis only											
Worsching (2018) Expt 1	Healthy	28 28	26.0	F4	F3	Bilateral	1	20	0.571	fMRI (ROI – ROI)	VAN - DMN ↓
Worsching (2018) Expt 2	Healthy	28 28	26.0	F3	Fp2	Anodal	1	20	0.571	fMRI (ROI – ROI)	AN – DMN n.s.
Worsching (2018) Expt 3	Healthy	28 28	26.0	F3	F4	Bilateral	1	20	0.571	fMRI (ROI – ROI)	AN – DMN n.s.
Abellaneda-Perez (2019)	Healthy	15 15	25.2	F3	FP2	Anodal	1	20	0.571	fMRI (ROI – ROI)	DMN ↑
Kajimura (2016) Expt 1	Healthy	15 17	20.6	P4	AF7	Cathodal	1	20	0.429	fMRI (ROI – ROI)	DMN n.s.
Kajimura (2016) Expt 2	Healthy	15 17	20.6	AF7	P4	Anodal	1	20	0.429	fMRI (ROI – ROI)	DMN n.s.
Yang (2017)	Chronic smokers	32 32	26.7	F3	F4	Bilateral	1	30	0.286	fMRI (ROI – ROI)	VAN - VN ↑
Ficek (2018)	Primary progressive aphasia	12 12	65.2	F7	R cheek	Anodal	15	20	0.8	fMRI (ROI – ROI)	VAN - DMN ↓
Dedoncker (2019)	Subclinical (high perceived criticism)	23 41	22.9	F3	FP2	Anodal	1	20	0.6	fMRI (ROI – ROI)	VAN – SMN ↓
Cosmo (2015)	ADHD	30 30	32.2	F3	F4	Bilateral	1	20	0.286	EEG	WND n.s.
Thibaut (2019)	DoC	14 14	47.0	F3, F4	C3, C4	Anodal	1	20	N/A (reason: size of electrode not stated)	EEG	Beta PLI ↓

Note:
N = number of participants; WB = whole-brain analysis; ROI = regions of interest; DMN = default mode network; VAN = ventral attention network; FN = frontoparietal network; SMN = somatomotor network; DAN = dorsal attention network; VN = visual network; WND = weighted node degree; PLI = phase-lagged index; ADHD = attention-deficit/hyperactivity disorder; SA = substance abuse; Sz = schizophrenia; DoC = disorders of consciousness; n.r. = not reported; n.s. = nonsignificant; N/A = not applicable

Table 2

Effects of tDCS on the functional connectivity of resting-state networks

Brain regions with peak activation						Cluster breakdown	Resting-state network
Anatomical region	**L/R**	**Total number of voxels**	**MNI coordinates**	**SDM-Z**	**P (uncorr.)**	**Anatomical regions (Brodmann area)**	
tDCS>sham							
Median cingulate	L/R	1228	6,20,38	4.097	< .0005	L/R median cingulate (BA32, BA24) L/R anterior cingulate (BA24) L/R supplementary motor area (BA32, BA8) L superior frontal gyrus (BA32)	VAN
Inferior parietal gyri	R	541	52,-54,38	3.974	< .005	R inferior parietal gyri (BA40) R angular gyrus (BA39) R supramarginal gyrus (BA40)	FN
tDCS<sham							
n.s.							

Note:
Analysis conducted with mean age, health status, polarity of stimulating electrode and montage placement as covariates
Significance threshold: uncorrected p<.005
n.s. = nonsignificant

Table 3

Effects of prefrontal tDCS on event-related functional connectivity (5 studies, 7 experiments)

Reference (year)	Participants' details			tDCS protocol						Outcome measures			
	Population	N	Mean Age (years)	Anode	Cathode	Polarity of the stimulating electrode	No. of sessions	Duration	Current density (A/m^2)	Modality	Name of the paradigm	Cognitive domain	Changes in outcomes
Studies included in the narrative synthesis only													
Sandrini (2020)	Healthy	15 15	26.0	F8	Fp1	Anodal	1	15	0.6	fMRI (ROI – ROI)	Sustained-attention to response	ATTN	VAN – caudate ↑
Nissim (2019)	Healthy	14 14	73.6	F4	F3	Bilateral	10	20	0.571	fMRI (ROI – ROI)	n-back	WM	FN ↑
Rodrigues (2020) Expt 1	Healthy	20 20	20.5	F5	Fp2	Anodal	1	20	0.8	fMRI (ROI – ROI)	Word naming	LANG	FN ↑ DMN ↑
Rodrigues (2020) Expt 2	Healthy	20 20	20.5	Fp2	F5	Cathodal	1	20	0.8	fMRI (ROI – ROI)		LANG	FN ↑ DMN ↑ FN – DMN ↑
Wiesman (2018) Expt 1	Healthy	19 21	24.1	Oz	Fp2	Cathodal	1	20	0.571	MEG	Visual discrimination	ATTN	Theta fronto-posterior ↓
Wiesman (2018) Expt 2	Healthy	17 21	24.1	Fp2	Oz	Anodal	1	20	0.571	MEG		ATTN	Theta L/R frontal ↑
Ikeda (2019)	Healthy	12 12	21.3	F3	F4	Bilateral	2	13	0.571	MEG	n-back	WM	Theta gamma cross frequency PAC ↓

Note:
N = number of participants; ROI = regions of interest; ATTN = attention; WM = working memory; LANG = language; DMN = default mode network; VAN = ventral attention network; FN = frontoparietal network

Table 4

Effects of prefrontal tDCS on the amplitude of resting-state oscillation (10 studies, 12 experiments)

Reference (year)	Participants' details			tDCS protocol						Outcome measures	
	Population	N	Mean Age (years)	Anode	Cathode	Polarity of the stimulating electrode	No. of sessions	Duration	Current density (A/m^2)	Modality	Changes in outcomes
Studies included in the meta-analysis											
Frase (2016)	Healthy	19 19	53.7	Fp1, Fp2	P3, P4	Anodal	1	12	0.286	EEG	Gamma ↑
Saadi (2019)	Healthy	8 8	23.8	F7	Arm	Anodal	8	20	2.22	EEG	Theta ↓ Alpha ↑ Beta ↑
To (2018) Expt 1	Healthy	15 15	23.5	F3	Fp1, Fp2, F7, F8	Anodal	1	20	3.18	EEG	Theta n.s. Beta ↑
To (2018) Expt 2	Healthy	15 15	23.5	Fp1, Fp2, F7, F8	F3	Cathodal	1	20	3.18	EEG	Theta ↑ Beta n.s.
Keeser (2011a)	Healthy	10 10	28.9	F3	FP2	Anodal	1	20	0.571	EEG	Delta ↑ Theta n.s. Alpha n.s.
Wirth (2011)	Healthy	20 20	23.5	F3	R shoulder	Anodal	1	7	0.429	EEG	Delta ↓ Theta n.s. Alpha n.s. Beta n.s. Gamma n.s.
Holgado (2019) Expt 1	Healthy	31 31	27.0	F3	Shoulder	Anodal	1	20	0.8	EEG	Theta n.s. Alpha n.s. Beta n.s.
Holgado (2019) Expt 2	Healthy	31 31	27.0	Shoulder	F3	Cathodal	1	20	0.8	EEG	Theta n.s. Alpha n.s. Beta n.s.
Jacobson (2012)	Healthy	11 11	26.3	F8	FP1	Anodal	1	15	0.8	EEG	Theta ↑ Alpha n.s. Beta n.s. Gamma n.s.
Frase (2019)	Insomnia	19 19	43.8	Fp1, Fp2	P3, P4	Anodal	1	12	0.286	EEG	Gamma n.s.
Liu (2016)	Epilepsy	21 12	43.3	F3	Fp2	Anodal	5	20	0.571	EEG	Delta n.s. Theta n.s. Alpha n.s.
Ulam (2015)	TBI	13 13	31.3	F3	Fp2	Anodal	1	20	0.357	EEG	Delta n.s. Theta n.s. Alpha ↑

Note:
N = number of participants; n.s. = nonsignificant; TBI = traumatic brain injury

Table 5

Effects of prefrontal tDCS on the amplitude of event-related oscillation (13 studies, 18 experiments)

Reference (year)	Participants' details			tDCS protocol						Outcome measures			
	Population	N	Mean Age (years)	Anode	Cathode	Polarity of the stimulating electrode	No. of sessions	Duration	Current density (A/m^2)	Modality	Name of the paradigm	Cognitive domain	Changes in outcomes
Studies included in the EEG meta-analysis													
Adelhofer (2019)	Healthy	20 20	22.0	1.8cm anterior to Cz	FPz	Anodal	1	15	0.8	EEG	Sustained-attention to response	ATTN	Theta n.s.
O'Neil-Pirozzi (2017) Expt 1	TBI	4 4	43.0	F3	Fp2	Anodal	1	20	0.571	EEG	Auditory oddball	ATTN	Theta n.s. Alpha n.s.
O'Neil-Pirozzi (2017) Expt 2	TBI	4 4	43.0	Fp2	F3	Cathodal	1	20	0.571	EEG		ATTN	Theta n.s. Alpha n.s.
Holgado (2019) Expt 1	Healthy	31 31	27.0	F3	Shoulder	Anodal	1	20	0.8	EEG	Flanker	ATTN	Theta n.s. Alpha n.s. Beta n.s.
Holgado (2019) Expt 2	Healthy	31 31	27.0	Shoulder	F3	Cathodal	1	20	0.8	EEG		ATTN	Theta n.s. Alpha n.s. Beta n.s.
Boudewyn (2019)	Healthy	20 20	21.0	F3	FP2	Anodal	1	20	0.571	EEG	Dot-pattern expectancy	WM	Gamma ↑
Hill (2018)	Healthy	16 16	32.8	F3	FP1, Fz, C3, F7, P7, Pz	Anodal	1	15	4.78	EEG	n-back	WM	Beta n.s. Gamma n.s.
Choe (2016)	Healthy	7 7	42.0	F6	Fp2, AF8, AF4	Anodal	1	60	3.18	EEG		WM	Theta ↑ Alpha n.s.
Powell (2014)	Mood disorders	14 14	40.4	F3	F8	Bilateral	1	20	N/A (reason: size of electrode not stated)	EEG	Delayed match-to-sample	WM	Theta ↓
Studies included in the MEG meta-analysis													
Wilson (2018)	Healthy	19 16	24.2	Oz	Fp2	Cathodal	1	20	0.571	MEG	Flicker	ATTN	Gamma ↑
Heinrichs-Graham (2017)	Healthy	19 16	24.2	Oz	Fp2	Cathodal	1	20	0.571	MEG	Flicker	ATTN	Alpha ↑
McDermott (2019) Expt 1	Healthy	16 16	24.1	Oz	Fp2	Cathodal	1	20	0.571	MEG	Flanker	ATTN	Theta ↓ Alpha ↑
McDermott (2019) Expt 2	Healthy	16 16	24.1	Fp2	Oz	Anodal	1	20	0.571	MEG		ATTN	Theta n.s. Alpha n.s.
Wiesman (2018) Expt 1	Healthy	19 21	24.1	Oz	Fp2	Cathodal	1	20	0.571	MEG	Visual discrimination	ATTN	Theta n.s. Alpha ↑ Gamma n.s.
Wiesman (2018) Expt 2	Healthy	17 21	24.1	Fp2	Oz	Anodal	1	20	0.571	MEG		ATTN	Theta n.s. Alpha n.s. Gamma ↓
Koshy (2020) Expt 1	Healthy	25 25	23.4	F3 (HD-tDCS)	Not stated	Anodal	1	20	N/A (reason: size of electrode not stated)	MEG	Visuospatial n-back	WM	Alpha ↑
Koshy (2020) Expt 2	Healthy	25 25	23.4	F4 (HD-tDCS)	Not stated	Anodal	1	20		MEG		WM	Alpha n.s.
Ikeda (2019)	Healthy	12 12	21.3	F3	F4	Bilateral	2	13	0.571	MEG	n-back	WM	Gamma ↑

Note:
N = number of participants; ATTN = attention; WM = working memory; n.s. = nonsignificant; TBI = traumatic brain injury; N/A = not applicable

Table 6

Effects of *in vivo* hippocampal/prefrontal tDCS on synaptic plasticity (8 studies, 10 experiments)

Reference (year)	Rodent characteristics				tDCS protocol						Outcome measures	
	Health condition modelled	Rodent species	Total N	Mean age (days)	Anode	Cathode	Polarity of stimulating electrode	Number of session	Duration	Current density (A/m^2)	Name of outcome(s)	Change in outcome
Studies included in meta-analyses												
Rohan (2015)	Healthy	Sprague Dawley rats	34	49	Bilateral hippocampus	Between shoulders	Anodal	1	30	10	LTP	↑ immediate and delayed (24h) LTP
Podda (2016) Expt 1	Healthy	C57bl/6 mice	N/A	30-45	Bilateral hippocampus	Ventral thorax	Anodal	1	20	56	LTP, BDNF	↑ immediate and delayed (24h; 168h) LTP ↑ hippocampal BDNF
Podda (2016) Expt 2	Healthy	C57bl/6 mice	N/A	30-45	Ventral thorax	Bilateral hippocampus	Cathodal	1	20	56	LTP	↓ immediate and delayed (24h) LTP
Yu (2019)	Healthy	Sprague Dawley rats	234	49-56	Bilateral hippocampus	Ventral thorax	Anodal	1	30	10	LTP, BDNF	↑ immediate and delayed (24h) LTP ↑ hippocampal BDNF
Rohan (2020)	Healthy	Sprague Dawley rats	40	49-56	Bilateral hippocampus	Ventral thorax	Anodal	1	30	12.5	LTP	↑ immediate LTP
Rohan (2020)	Healthy	Sprague Dawley rats	40	49-56	Bilateral hippocampus	Ventral thorax	Cathodal	1	30	12.5	LTP	n.s. immediate LTP
Leffa (2016)	ADHD	Spontaneous hypertensive rats; Wistar Kyoto rats (control)	48	60	Medial prefrontal cortex	Between neck and shoulder	Anodal	8	20	3.33	BDNF	↑ medial prefrontal cortex BDNF
Wu (2017)	Diabetes	Sprague Dawley rats	130	56	Medial prefrontal cortex	Ventral thorax	Anodal	8	30	64.5	BDNF	↑ medial prefrontal cortex BDNF
Studies included in systematic review only												
Stafford (2018)	Healthy	Sprague Dawley rats	16	n.r. (adult)	Left hippocampus	Not stated	Anodal	1	30	10	AMPA	↑ AMPA translocation to synapses in hippocampus
Jung (2019)	Healthy	Sprague Dawley rats	28	49-56	Bilateral hippocampus	Thorax	Anodal	1	30	39.7	BDNF synapto-neurosomes	↑ BDNF synapto-neurosomes

Note:
LTP = long term potentiation; BDNF = brain-derived neurotrophic factor; ADHD = attention-deficit/hyperactivity disorder; n.r. = not reported