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The application of non-invasive brain stimulation techniques to reduce anger and violence proneness: Results of a systematic review and meta-analysis

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ABSTRACT

Since the 1990s, there has been a rise in the number of publications assessing the effects of applying non-invasive brain stimulation (NIBS) to treat patients with drug-resistant depression. This involves applying magnetic fields or electrical currents to the surface of the skull to influence the superficial neurons in the cerebral cortex. Due to the evidence regarding symptom reduction in these types of patients, such as irritability or hostility, there was a rise in the use of this technique to reduce negative mood, including anger state. This decrease in anger state could also help reduce other problems such as violence proneness. In this sense, the anger state of individuals who are prone to violence might be affected by interfering with the excitability of the prefrontal cortex (PFC), a key brain region responsible for behavioral regulation. Thus, we conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. After initially identifying 2426 sources, we eventually included a total of 69 publications for the systematic review, from which 45 were employed for the meta-analysis. Only a few of them highlighted a significant contribution of using NIBS techniques on different regions of the PFC to reduce anger state or violence when compared to participants receiving sham stimulation in normative and clinical samples. Furthermore, the comparison of effect sizes between groups that received real stimulation on several regions of the PFC and those that received sham stimulation did not reveal a significant difference in reducing anger state or violence. In addition, despite most of the conclusions being consistent, considerable heterogeneity existed across studies regarding certain PFC regions, which could be explained by the type of NIBS employed. Therefore, using superficial stimulation over the PFC as a general tool for reducing violence proneness should be approached with caution, except in specific cases.

1. Introduction

Due to the undesirable effects of violence in our society, many attempts have been made to adequately understand its underlying factors in order to prevent and/or reduce it (Marc, 2016; Sardinha et al., 2022). Given its multi-factorial etiology, the importance of combining the efforts of scientists using different perspectives to create an accurate model of violence proneness has been highlighted (Lee, 2015; Nussbaum, 2020). Recently, the rise of neuroimaging techniques has allowed professionals to study the role of specific cortical regions and brain structures that could lead individuals to act with violence in vivo, as well as to compare whether morphological and functional differences between groups with higher or lower proneness to violence exist (Lamsma et al., 2017; Nikolic et al., 2022). Theoretically, the better we understand the brain circuits underlying violence proneness, the better equipped scientists and clinicians will be to develop specific therapeutic strategies to reduce and/or prevent it (Marc, 2016; Sardinha et al., 2022).

The appearance and dissemination of psychopharmacology strategies (e.g., antidepressants, mood stabilizers, antipsychotics, and beta-blockers) offers a good opportunity to reduce proneness to violence by interfering in neurotransmitter and synaptic communication (e.g., serotoninergic, dopaminergic, noradrenergic, etc.) (Haden and Scarpa, 2007; Herttua et al., 2022; Romero-Martínez et al., 2019a,b; Weightman et al., 2020). However, despite the promising initial results in terms of controlling violence, there are several issues that require detailed analysis. Alternative treatments should be explored to overcome these limitations. For example, the main problem of pharmacological

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treatments is discontinuation (or dropout), given that many of these treatments are intended to be chronic or long-term (Rohden et al., 2017; Sharma et al., 2019). This discontinuation might be explained, at least in part, by the side effects that tend to appear during the initial stages. Some of these are extrapyramidal (e.g., dystonia, akathisia, parkinsonism symptoms, among others), while others include weight gain, somnolence, headaches, etc. (Kemmler et al., 2005; Niarchou et al., 2024). It should also be noted that some patients may show a certain degree of resistance to this kind of treatment (Adler et al., 2015; Blader et al., 2010; Cooper et al., 2011; Kimmel et al., 2020) and certain violent individuals might find it impossible to undergo these treatments due to potential interactions between these substances and the pharmacological drugs, especially those who consume substances such as alcohol, cocaine, or marijuana (Guerzoni et al., 2018; Radke et al., 2022). This highlights the importance of using alternative therapeutic strategies to effectively address and reduce violence, in order to maximize the effectiveness of current treatments.

Since the 1990s, there has been a rise in the number of publications assessing the effects of applying non-invasive brain stimulation (NIBS) to treat patients with drug-resistant depression (Bhattacharya et al., 2022). NIBS involves applying magnetic fields or electrical currents to the surface of the skull to interfere with the functioning of the superficial neurons in the cortex (Andrews & Fernández-Espejo, 2022). Applying changing magnetic current flows or pulses affects the depolarization of the neurons, which then disrupts the communication (transynaptically) with adjacent neurons, by transmitting signals across specific brain networks (Bhattacharya et al., 2022). Thus, it seems logical to conclude that mood, cognitive processes, and even the regulation of certain behaviors such as proneness to violence could be influenced by applying these currents to brain activity and specifically affecting cortical excitability (Zhang et al., 2022). Nonetheless, differences exist between techniques according to coil shape, stimulation site, stimulation pattern, polarity, or the applied current intensity (Bhattacharya et al., 2022). Therefore, it is completely necessary to understand the differences between the various types of NIBS techniques.

On the one hand, NIBS based on transcranial magnetic stimulation (TMS), refers to the application of an electric pulse to a device (or coil) placed on the head which induces a magnetic field through the scalp to the superficial neurons of the cortex, where the coil is located. This magnetic field then induces a current, which interferes with the neuronal excitability of the cortical neurons (Kropotov, 2016). Depending on the type of pulses applied, the TMS can be single or repetitive (sTMS or rTMS). Additionally, using high or low frequency (HF or LF-TMS) can change how effective these devices are at increasing or decreasing cortical excitability (Kropotov, 2016). There is another variant of rTMS known as theta-burst stimulation (TBS), which consists of applying a series of short magnetic pulses (bursts) at a high frequency (50 Hz) with time intervals of 200 ms between bursts (Chung et al., 2015). TBS can also be subdivided according to the application of continuous (cTBS) or intermittent bursts (iTBS) (Stoby et al., 2022).

The other type of NIBS implies the use of weak transcranial electric stimulation via electrodes placed on the head to modulate cortical excitability (Jamil & Nitsche, 2017). These techniques can be divided into transcranial alternating (tACS) or direct current stimulation (tDCS). When tDCS facilitates neural excitation through neuronal depolarization, it is known as anodal tDCS, whereas inhibition of neural activity through neuronal hyperpolarization is known as cathodal tDCS (Garnett et al., 2015).

Given that NIBS might affect the functioning of cortical regions, it would be particularly important to analyze the effects of key regions that sustain or regulate violence proneness. The prefrontal cortex (PFC) appears to play a critical role in behavior regulation, as suggested by an extensive scientific literature based on patients with brain injury in the PFC or studies comparing PFC functioning in violent individuals without brain damage and control groups (non-violent) in response to certain laboratory tasks or in resting conditions (Bannon et al., 2015; Nikolic et al., 2022). In this sense, the key finding is that when this brain region malfunctions in individuals affected by these dysfunctions (or PFC hypoactivity), it could lead to outbursts and violent reactions due to significant challenges in controlling or regulating negative emotional states (e.g., anger, negative mood, etc.) (Nikolic et al., 2022). This theoretical framework is mainly applied to reactive or emotionally-guided violence. Nonetheless, a homogeneous role of all regions of the PFC cannot be established as it seems that stimulation or inhibition of some regions, such as the medial prefrontal, ventrolateral (VLPFC), and dorsolateral (DLPFC) cortices, differently affect violence proneness and other constructs such as anger state, irritability or hostility, which tend to be directly related to this type of behavior and might also affect the threshold for violent reactions (Birkley & Eckhardt, 2015; Romero-Martínez et al., 2019a,b, 2022).

A systematic review and meta-analysis have been conducted to clarify the role of NIBS (i.e., TMS, tDCS, among others) in violence proneness, as well as other constructs closely related to violence such as anger state, irritability or hostility in different samples (e.g., non-clinical or normative and clinical). First, considering the existing data so far, we tried to summarize the main empirical studies measuring whether applying NIBS to the PFC might reduce violence or other related constructs in different samples (clinical and non-clinical or normative), focusing on studies which compared the real stimulation group with another control group receiving sham (or placebo) stimulation. Second, a meta-analysis was conducted to calculate the precise effect sizes of NIBS for reducing violence proneness, when possible. That is, we used studies that provided the mean and standard deviation (e.g., in the manuscript, as supplementary material or upon request to the authors) and employed the same or similar variables to calculate differences between groups (e.g., stimulation vs sham group). This will help guide future research in this field to determine if applying NIBS could be a potential and valid tool which could be used as an alternative to current treatments for reducing violence in specific groups. It may also help identify alternative targets (e.g., focusing of specific samples, other constructs related to violence, different brain regions, combinations with other types of treatment, among others) to address violence treatment or control.

2. Methods

2.1. Search strategy

This study was conducted in accordance with the guidelines established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Hutton et al., 2015), and was also registered in OSF (Registration DOI: https://doi.org/10.17605/OSF.IO/29ZJY). Furthermore, the AMSTAR 2 Checklist recommendations (Shea et al., 2017) were followed to guarantee the quality of this meta-analysis. Accordingly, the need to conduct the literature research in at least 2 databases was established, resulting in searching through four multidisciplinary digital databases: Cochrane Library: Cochrane Reviews, Scopus, Web of Knowledge, and PubMed. In fact, the selection of these databases followed the recommendations outlined by Bramer et al. (2017), highlighting databases that guarantee an efficient coverage of relevant scientific literature. Some of these databases provide filters to reduce the number of entries based on the inclusion and exclusion criteria for our study. Filters were applied to remove “books”, “PhD”, “comment”, “note”, “editorial”, “erratum”, “book”, “book series”, “letter to the editor”, “conferences papers”, “conference proceeding”, “case reports”, “animal studies”, “systematic reviews”, “literature review”, “meta-analysis”, other languages different from “English and/or Spanish”, among others.

The search for published studies was conducted during May 2024 (from the 1st to the 14th).

The terms employed, as well as their combinations, are presented in Supplementary Table 1.

2.2. Inclusion and exclusion criteria

We established the inclusion criteria based on the recommendations by McKenzie et al. (2022) for conducting systematic reviews and meta-analysis. Accordingly, inclusion criteria for the systematic review were: (a) research applying NIBS to the PFC; (b) measuring the impact of NIBS on violence or aggression, anger, hostility and/or irritability (e.g., comparing before and after applying these techniques). In this sense, studies which did not specifically analyze anger subscales without explicitly differentiating them from general scales (e.g., mood general assessment without considering anger subscale) were also excluded. (c) empirical studies published following a peer-reviewed process in academic journals; case studies, letters to the editors, comments, erratum, and conference proceedings were excluded. Additionally, empirical studies that did not provide enough information regarding procedure, instruments and stimulated PFC regions, which would question the quality and replicability of this study, were also removed; (d) based on human participants; (e) sham-controlled; (f) studies written in English or Spanish.

To be included in the meta-analysis the studies needed to meet all the above-mentioned criteria, and additionally provide direct data (e.g., published, as supplementary material or provided upon request) to calculate the effect sizes. Nonetheless, studies which provided direct data, but did not clarify typos or errors (e.g., negative values for standard deviation; interpretation of data, etc.), were not included in the meta-analysis. A minimum of two empirical studies which are sufficiently homogeneous (e.g., instrument employed, anger or aggression construct measured, prefrontal region stimulated, among others) is recommended (Ryan, 2016). That is, it was necessary to have a minimum of 2 empirical studies which provided direct data (e.g., mean, and standard deviation published, as supplementary material or provided by authors after a request) (PRISMA flow diagram; Fig. 1).

2.3. Quality assessment

As previously recommended by Higgins (2011), the National Institutes of Health (NIH) (2021) and Romero-Martínez et al. (2023) regarding the assessment of the potential risk of bias when interpreting data in randomized and non-randomized cross-sectional studies, we established a set of quality criteria to assess the studies included in our review. In fact, we included thirteen statements that would be answered with a dichotomous answer (Yes/No) indicating whether each criterion was met or not. In this sense, empirical studies that only neglected four or less statements were classified as having "low risk of bias". Empirical studies which neglected five to eight statements were qualified as having "moderate risk of bias", and, finally, those neglecting nine or more criteria were classified as having "high risk of bias" (See Supplementary Table 2). See below the list of statements for assessing risk of bias.

2.3.1. Objectives and hypotheses

1) Objectives and hypothesis clearly defined based on previous scientific literature by citing references and specifying the main outcomes (e.g., PFC region stimulated and effects on anger state).

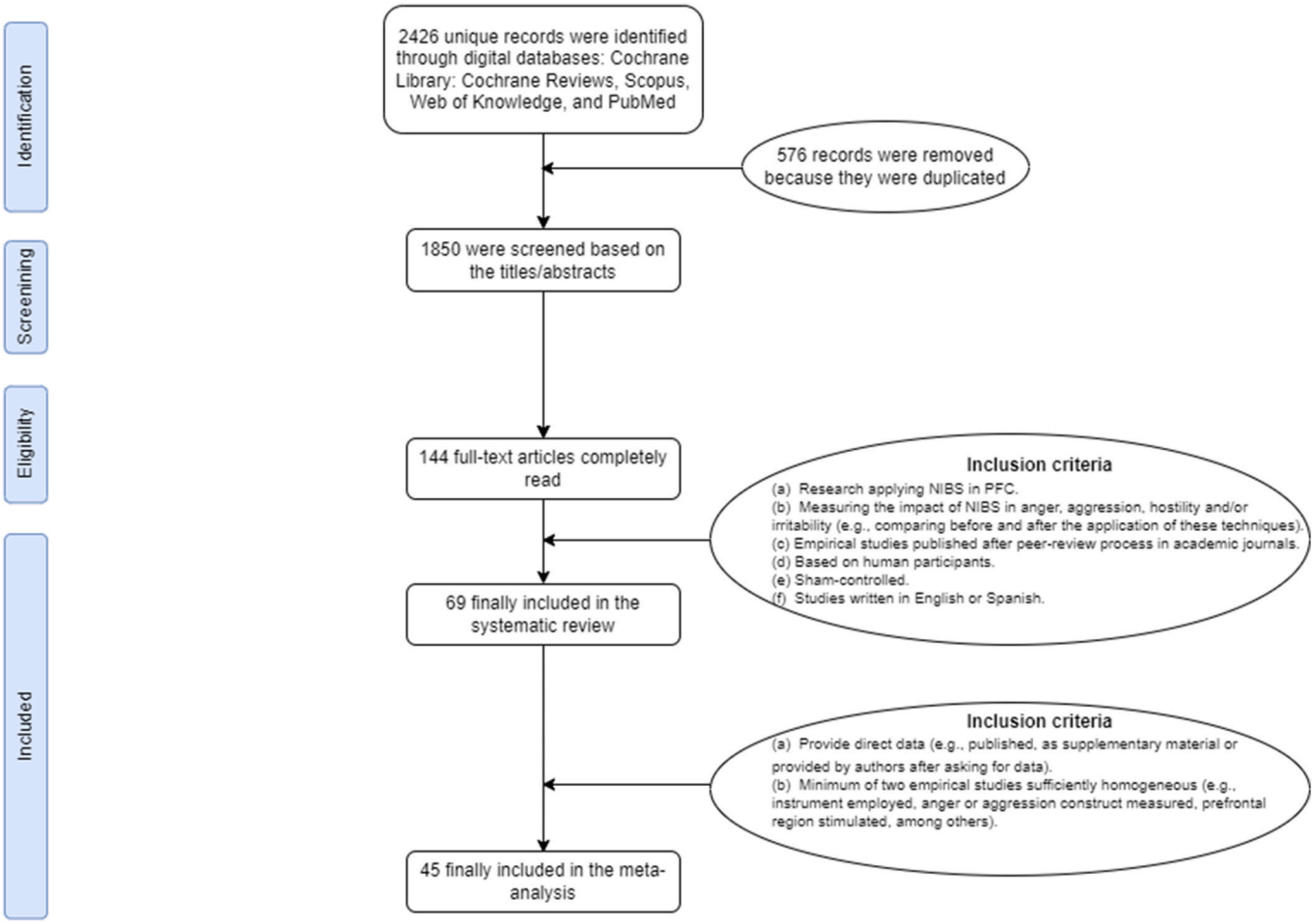

Fig. 1. PRISMA flow chart of literature search with inclusion criteria.

2.3.2. Sample

2a) Calculated the sample size needed for conducting their study (reporting bias).
2b) Sample size equal to or higher than 50 participants per group (reporting bias).
2c) Inclusion criteria specified and clearly stated for each group or sample included in the study (reporting bias).
2d) Offered enough information about experimental mortality or missing data (attrition bias).

2.3.3. Procedure

3a) Clearly defined the procedure (e.g., time frame, experimental phases, instruments employed, etc.).
3b) Randomization and counterbalance of each condition (e.g., stimulation vs sham) (Selection bias).
3c) Blinded participants (performance and detection bias).
3d) Blinded researchers (performance and detection bias).
3e) Pre-registration of the research project.

3. Results

4a) Clearly reported an absence of differences between groups in potential confounding variables (e.g., number of participants per group, sociodemographic differences such as age, educational level, among others) (reporting bias).
4b) Covariated potential confounding variables (reporting bias).
4c) Provided mean values and standard deviations of relevant variables of the study (e.g., published or as supplementary material) (reporting bias; transparency of the process).

3.1. Data extraction and analysis

Of the study's three authors, two of them conducted the article selection, with an interrater agreement above 88 %. The appearance of discrepancies in several studies (e.g., meeting the inclusion criteria or not) between both raters was discussed between them and by asking the third author of the study.

3.2. Data analysis

The new version of RefWorks was used for reference management (ProQuest, 2016).

To calculate the effect sizes and address the first aim of this study, we employed Review Manager 5.4 software from the Cochrane Collaboration (Review Manager, 2020). Accordingly, this study employed random-effects modeling and included the calculation of the total effect (Z value) for standardized mean differences (SMD) across studies with 95 % confidence intervals (95 % CI). The inverse-variance weighting was applied. According to this method, the weight assigned to each of the included studies was based on the inverse of the variance of the effect estimate (Higgins et al., 2008). Moreover, heterogeneity across studies was calculated by including Tau^2, Chi^2, and I^2.

4. Results

4.1. Selection of studies

Applying the algorithm by combining the terms selected for this study and applying, when possible, the above-described filters yielded a total of 2426 sources across the four databases. Afterwards, the analysis of duplicates in RefWorks was applied resulting in the removal of 576 references. The remaining 1850 articles were screened based on their title or abstract. Following this review, a total of 144 full-text articles were completely read resulting in a total of 69 to finally be included in the systematic review. Nonetheless, after an additional screening, only 45 were finally included in the meta-analysis (see the flowchart described in Fig. 1).

4.2. Systematic review

4.2.1. Dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC)

The great majority of the articles included in this review measured the impact of NIBS on anger (e.g., mainly assessed with self-reports) and only a few addressed its effects on aggression (e.g., measured with laboratory tasks). Specifically, 95 % of the included empirical research stimulated one hemisphere or the other separately (left or right), while a minority of them stimulated simultaneously and bilaterally. Lastly, all the studies in this section evaluated the effects of NIBS of the DLPFC, except for a single study that described the effects of bilateral stimulation of the DMPFC in patients with borderline disorder (Calderón-Moctezuma et al., 2020) (Table 1).

Most of the included studies applied NIBS in healthy young adults (non-clinical or normative group), representing approximately 75 % of the included research. The rest of the studies included patients with depression (Baeken et al., 2009; Duprat et al., 2016; Leyman et al., 2011; Schrijvers et al., 2012), borderline (Cailhol et al., 2014; Lisoni et al., 2009b, 2020), and schizophrenia disorders (Hansbauer et al., 2018), military veterans (McIntire et al., 2017; van't Wout-Frank et al., 2021), addicts (He et al., 2023), and violent offenders (Molero-Chamizo et al., 2019) (Table 1).

From the fifty-five included studies, only seven studies reported a significant effect of NIBS on anger (Cailhol et al., 2014; Molero-Chamizo et al., 2019; Rêgo et al., 2015; Schaller et al., 2011; Schutter et al., 2001) or aggression (Weidler et al., 2022; Choy et al., 2018). The rest of the studies failed to promote changes after applying these techniques compared to those receiving sham stimulation (Table 1).

Regarding the studies that found an initial significant effect of NIBS, only a small percentage of the total studies included (16 %) highlighted a significant contribution to reducing anger state or aggression proneness. Specifically, the application of anodal TDCs and rTMS in healthy participants to the left (Hortensius et al., 2012) and right DLPFC (Schutter et al., 2001) led them to experience an increase in anger state. In the rest of the studies, applying rTMS or iTBS to the right (Cailhol et al., 2014; van't Wout-Frank et al., 2021) and left DLPFC (Schaller et al., 2011) as well as bilateral simultaneous stimulation with anodal tDCS (Choy et al., 2018; Molero-Chamizo et al., 2019) entailed a decrease in anger state in military veterans, borderline patients, healthy participants, and violent inmates. Lastly, healthy participants experienced an increase of aggressive behavior after receiving sham stimulation with anodal tDCS to the left and right DLPFC (Rêgo et al., 2015; Weidler et al., 2022). Furthermore, two studies initially failed to present a significant "time x condition" effect but revealed a significant contribution of NIBS to anger proneness. Particularly, one of them considered anger trait levels, with participants who scored high in anger traits experiencing an increase of aggressive behavior after receiving anodal stimulation to the left DLPF (Hortensius et al., 2012). The other study did not present a "time (pre-post) x stimulation (real vs sham)" significant effect, but participants (military veterans) receiving iTBS to the right DLPFC, exhibited lower averaging scores (pre-stimulation + post-stimulation) in anger than those receiving sham stimulation (van't Wout-Frank et al., 2021) (Table 1).

4.2.2. Ventrolateral prefrontal cortex (VLPFC) and ventromedial prefrontal cortex (VMPFC)

Six studies measured the impact of NIBS to the VLPFC (Chen, 2018; Gallucci et al., 2020; Riva et al., 2015, 2017) or partly affecting this PFC region (Dambacher et al., 2015b; Smits et al., 2022). All the studies that included self-reports for measuring changes in anger state after applying

Table 1
Summary of characteristics of the studies assessing the effects of non-invasive brain stimulation techniques in the dorsolateral and dorsomedial prefrontal cortices, as well as prefrontal cortex, alphabetically ordered by first author's surname.

Authors	Sample	Age	Gender	Handedness	Type of technique	Assessment	Prefrontal cortex region	Interaction "time x stimulation condition"
Allaert et al. (2019)	Healthy (n = 48)	21.35 ± 2.21	33 % ♂	100 % right-handed	2.0 mA anodal tDCS; 20 min; two sessions in each condition for all subjects	VAS	DLPFC (left and right)	Ns
Baeken et al. (2006)	Healthy (n = 28)	24.68 ± 5.85	100 % ♀	100 % right-handed	10 Hz HF-rTMS session; 20 min; single session (stimulation or sham)	POMS and VAS	DLPFC (left)	Ns
Baeken et al. (2008)	Healthy (n = 27)	25.2 ± 5.0	100 % ♀	100 % right-handed	10 Hz HF-rTMS session; 20 min; two sessions; 1 week between sessions; all participants received stimulation and sham	POMS and VAS	DLPFC (left and right)	Ns
Baeken et al. (2009)	Depress. (n = 19)	44.3 ± 10.6	35 % ♂	100 % right-handed	10 Hz HF-rTMS session; 20 min; single session; all participants received both conditions	VAS	DLPFC (left)	Ns
Baeken et al. (2011a)	Healthy (n = 24)	22.29 ± 2.58	100 % ♀	100 % right-handed	10 Hz HF-rTMS session; 20 min; all participants received both conditions	POMS	DLPFC (right)	Ns
Baeken et al. (2011b)	Healthy (n = 20)	21.20 ± 1.44	100 % ♀	100 % right-handed	10 Hz HF-rTMS session; 20 min; single session; single session; all participants received both conditions	POMS	DLPFC (left)	Ns
Baeken et al. (2012)	Healthy (n = 36)	From 18 to 30	100 % ♀	100 % right-handed	10 Hz HF-rTMS session; 20 min; single session participants received stimulation or sham condition	POMS	DLPFC (left and right)	Ns
Baeken et al. (2014)	Healthy (n = 30)	21.53 ± 2.85	100 % ♀	100 % right-handed	20 Hz HF-rTMS session; 20 min; 2 sessions receiving stimulation and sham	VAS	DLPFC (left)	Ns
Baeken et al. (2017)	Healthy (n = 40)	22.55 ± 2.33	100 % ♀	100 % right-handed	1.5 mA anodal tDCS; 20 min; single session; all participants receiving stimulation and sham	VAS	DLPFC (left)	Ns
Baeken et al. (2018)	Healthy (n = 28)	22.13 ± 2.16	100 % ♀	100 % right-handed	1.5 mA anodal tDCS; 20 min; two sessions; all participants receiving stimulation and sham	VAS	DLPFC (left)	Ns
Cailhol et al., 2014	BPD (n = 10)	From 20 to 45	–	–	10 Hz HF-rTMS session; 5 days; 20 min per session; all participants received stimulation and sham	BPDSI	DLPFC (right)	Lower anger scores in stimulation
Dambacher et al. (2015a)	Healthy (n = 32)	22.14 ± 2.00	41 % ♂	–	2.0 mA anodal tDCS; 12,5 min; single session assigned participants to stimulation or sham	TAP RPQ	DLPFC (right)	Ns Ns
De Putter et al. (2015)	Healthy (n = 66)	23.09 ± 5.03	20 % ♂	–	2.0 mA anodal tDCS; 25 min; single session assigned participants to stimulation or sham	POMS	DLPFC (left)	Ns
de Raedt et al. (2017)	Healthy (n = 32)	22.6 ± 2.3	100 % ♀	100 % right-handed	1.5 mA anodal tDCS; 20 min; 2 sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Dedoncker et al. (2019)	Healthy (n = 41)	22.9 ± 2.61	100 % ♀	100 % right-handed	1.5 mA anodal tDCS; 20 min; 2 sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
De Wandel et al. (2020)	Healthy (n = 33)	23.38 ± 3.06	100 % ♀	100 % right-handed	50 Hz burst iTBS; 1620 pulses; two sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
De Witte et al. (2020)	Healthy (n = 38)	23.53 ± 3.00	100 % ♀	100 % right-handed	50 Hz burst iTBS; 1620 pulses; two sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Duprat et al. (2016)	Depress. (n = 47)	42 ± 12	30 % ♂	100 % right-handed	50 Hz burst iTBS; 5 sessions/day; 1620 pulses per session); all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Hansbauer et al. (2018)	SZ (n = 146)	35 years	75 % ♂	82 % right-handed	10 Hz rTMS; 5 sessions/week; 20 min aprox.; 5 sessions/week for 3 weeks; participants received stimulation or sham	PANSS	DLPFC (left)	Ns
Hortensius et al. (2012)	Healthy (n = 80)	–	50 % ♂	100 % right-handed	2.0 mA anodal tDCS; 15 min; single session; participants received stimulation or sham	Anger self-reported	DLPFC (left and right)	When angry, left stimulation increased aggression, but not in right or sham conditions

(*continued on next page*)

Table 1 (*continued*)

Authors	Sample	Age	Gender	Handedness	Type of technique	Assessment	Prefrontal cortex region	Interaction "time x stimulation condition"
He et al. (2023)	Addicts (n = 88)	32 years average	100 % ♂	–	2.0 mA anodal tDCS; 20 min five consecutive days; twice per day; participants assigned to stimulation (anodal or cathodal) or sham	TAP	DLPFC (left)	Ns
Hu et al. (2022)	Healthy (n = 81)	21.4 ± 1.9	39 % ♂	–	1.5 mA anodal tDCS; 20 min; single session assigned participants to stimulation or sham	Anger self-reported	DLPFC (right)	Ns
Kelley et al. (2013)	Healthy (n = 90)	–	33 % ♂	100 % right-handed	2 mA anodal tDCS; 15 min; single session assigned participants to stimulation or sham	Anger self-reported	DLPFC (left and right)	Ns
Leyman et al. (2009)	Healthy (n = 33)	24 ± 2.33	100 % ♀	100 % right-handed	10 Hz HF-rTMS; 1560 pulses per session; two sessions; participants received stimulation and sham	POMS	DLPFC (left and right)	Ns
Leyman et al. (2011)	Depress. (n = 12)	44.3 ± 7.55	29 % ♂	100 % right-handed	10 Hz HF-rTMS; 1560 pulses per session; 10 sessions (5 days per week); all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Lisoni et al. (2020)	BPD (n = 30)	38 ± 10.9 42.6 ± 13.6	40 % ♂	90 % right-handed	2 mA anodal-tDCS; 20 min; 5 working days per week for 3 weeks; participants received stimulation or sham	BPAQ	DLPFC (right)	Reduction in anger in active stimulation
McIntire et al. (2017)	Military (n = 50)	27 ± 5	72 % ♂	–	2 mA anodal tDCS; 30 min; 36 consecutive hours experiment; all participants received stimulation and sham	POMS and VAS	DLPFC (left)	Ns
Motohashi et al. (2013)	Healthy (n = 11)	22 ± 2.2	100 % ♂	91 % right-handed	1 mA anodal tDCS; 20 min; 8 sessions + 3 wash-out; all participants received stimulation and sham	POMS	DLPFC (left)	Ns
Moulier et al. (2016)	Healthy (n = 20)	From 18 to 65	60 % ♂	100 % right-handed	10 Hz rTMS; 2000 pulses/ session; 10 daily sessions for 2 weeks; participants received stimulation or sham	VAS	DLPFC (left)	Ns
Perach-Barzilay et al. (2013)	Healthy (n = 16)	28 ± 4.678	70 % ♂	100 % right-handed	50 Hz cTBS; 900 pulses at 5 Hz; 20 min; two sessions; all participants received stimulation and sham	SOC	DLPFC (left and right)	Ns
Plazier et al. (2012)	Healthy (n = 17)	21.47 ± .91	100 % ♂	–	1.5 mA anodal tDCS; 20 min; three sessions; all participants received stimulation and sham	POMS	DLPFC (left and right)	Ns
Plewnia et al. (2015)	Healthy (n = 28)	27.9 ± 9.3	100 % ♂	100 % right-handed	1 mA anodal tDCS; 20 min; single session; participants received stimulation or sham	PANAS	DLPFC (left)	Ns
Pulopulos et al. (2019)	Healthy (n = 38)	23.60 ± 2.87	100 % ♀	100 % right-handed	50 Hz (5 Hz burst frequency) iTBS; 1620 pulses; two sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Pulopulos et al. (2022)	Healthy (n = 25)	21.80 ± 2.10	100 % ♀	–	20 Hz HF-rTMS; 9.33 min; three sessions; all participants received stimulation and sham	VAS	DLPFC (left and right)	Ns
Rêgo et al., 2015	Healthy (n = 24)	23 ± 2.57	50 % ♂	–	2 mA anodal tDCS; 15 min; single session; participants received stimulation or sham	VAS	DLPFC (left and right)	High hostility after sham
Remue et al. (2016)	Healthy (n = 38)	22 years average	100 % ♀	100 % right-handed	20 Hz HF-rTMS; 10 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (left and right)	Ns
Sánchez et al., 2016	Healthy (n = 30)	23.27 ± 4.15	33 % ♂	100 % right-handed	2 mA anodal tDCS; 20 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (right)	Ns
Sánchez et al., 2018	Healthy (n = 54)	23 years average	41 % ♂	100 % right-handed	2 mA anodal tDCS; 20 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Schaller et al. (2011)	Healthy (n = 38)	24 ± 2.77	100 % ♂	100 % right-handed	25 Hz HF-rTMS; 6750 pulses per session; 9 sessions for 9 consecutive days; participants received stimulation or sham	BDI	DLPFC (left)	Anger reduction in stimulation condition
Schrijvers et al. (2012)	Depress. (n = 21)	44.7 ± 10.3	38 % ♂	100 % right-handed	10 Hz HF-rTMS; 20 min; 10 sessions for 15 days; all participants received stimulation and sham	VAS	DLPFC (left)	Ns

(*continued on next page*)

Table 1 (*continued*)

Authors	Sample	Age	Gender	Handedness	Type of technique	Assessment	Prefrontal cortex region	Interaction "time x stimulation condition"
Schutter et al. (2001)	Healthy (n = 12)	28.4 ± 8.9	67 % ♂	100 % right-handed	1 Hz rTMS; 20 min; two sessions; all participants received stimulation and sham	STAXI-2	DLPFC (right)	Elevations of anger in stimulation condition
Vanderhasselt et al., 2006	Healthy (n = 20)	23 ± 2.3	100 % ♀	100 % right-handed	10 Hz HF-rTMS; 20 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (right)	Ns
Vanderhasselt et al. (2006b)	Healthy (n = 28)	23 ± 4.4	100 % ♀	100 % right-handed	10 Hz HF-rTMS; 20 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Vanderhasselt et al. (2007)	Healthy (n = 20)	24 ± 2.6	100 % ♀	100 % right-handed	10 Hz HF-rTMS; 20 min; 20 min; all participants received stimulation and sham	VAS	DLPFC (right)	Ns
Vanderhasselt et al., 2009a	Depres. (n = 13)	45.6 ± 5.9	40 % ♂	100 % right-handed	10 Hz rTMS; 20 min; 10 sessions for 2 weeks; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Vanderhasselt et al. (2009b)	Depress. (n = 14)	42 ± 11.20	38 % ♂	100 % right-handed	10 Hz rTMS; 20 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Vanderhasselt et al. (2010)	Healthy (n = 19)	27.7 ± 2.67	100 % ♀	100 % right-handed	10 Hz HF-rTMS; 20 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (left)	Ns
Vanderhasselt et al. (2011)	Healthy (n = 28)	22.29 ± 2.58	100 % ♀	100 % right-handed	10 Hz HF-rTMS; 20 min; two sessions; all participants received stimulation and sham	POMS	DLPFC (right)	Ns
Vanderhasselt et al. (2017)	Healthy (n = 35)	23.40 ± 4.43	35 % ♂	100 % right-handed	2 mA anodal tDCS; 20 min; two sessions; all participants received stimulation and sham	VAS	DLPFC (right)	Ns
van't Wout-Frank et al., 2021	Veterans (n = 50)	From 18 to 70	84 % ♂	–	iTBS; 1800 pulses/session; 10 sessions; once per week; participants received stimulation or sham	DAR	DLPFC (right)	Lower anger across sessions in stimulation
Weidler et al. (2022)	Healthy (n = 51)	From 18 to 60	100 % ♂	–	1.5 mA anodal tDCS; 20 min; single session; participants received stimulation or sham	TAP	DLPFC (right)	Increased aggression in sham condition
Weidler et al. (2024)	Healthy (n = 89)	25.73 ± 4.79	100 % ♂	100 % right-handed	1.5 mA anodal tDCS; 20 min; single session; participants received stimulation or sham	TAP	DLPFC (right)	Ns
Calderón-Moctezuma et al. (2020)	BPD (n = 14)	26.03 ± 7.08	–	–	5 HF-rTMS; 15 sessions; 30 trains; once a day for 5 days per week; participants received stimulation or sham	CGI-BPD	DMPFC (bilateral)	Ns
Choy et al. (2018)	Healthy (n = 81)	20.21 ± 3.31	44 % ♂	–	2 mA anodal tDCS; 20 min; single session; participants received stimulation or sham	TAP Voodoo doll task	DLPFC (bilateral)	Low aggression in stimulation condition Ns
Molero-Chamizo et al. (2019)	Inmates (n = 41)	36.2 ± 12.3	100 % ♂	–	1.5 mA anodal tDCS; 15 min; three session; participants received stimulation or sham	BPAQ	DLPFC (bilateral)	Reduction in anger in active stimulation

Note. BDI: Beck Depression Inventory; BDP: borderline personality disorder; BPAQ: Buss–Perry Aggression Questionnaire; BPDSI: Borderline Personality Disorder Severity Index; CGI-BPD: Clinical Global Impression for Borderline Personality Disorder; cTBS: continuous theta-bursts stimulation; DAR: Dimensions of Anger Reactions scale; DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex; HF-rTMS: High frequency repetitive transcranial magnetic stimulation; Hz: hertz; iTBS: intermittent theta-bursts stimulation; mA: milliamps; ns: non-significant; PANSS: Positive and Negative Syndrome Scale; POMS: Profile of Mood States; RPQ: Reactive Proactive Questionnaire; rTMS: repetitive transcranial magnetic stimulation; STAXI-2: State-Trait Anger Expression Inventory 2; SOC: Social Orientation Paradigm; SZ: schizophrenia; TAP: Taylor Aggression Paradigm; tDCS: transcranial direct current stimulation; VAS: Visual Analogue Scales.

NIBS failed to report significant changes after the treatment (Chen, 2018; Riva et al., 2015; Smits et al., 2022). Nonetheless, those which measured aggressive behavior with laboratory tasks offered mixed results. Two studies failed to report significant changes (Riva et al., 2015; Dambacher et al., 2015b) and the other three concluded that NIBS promoted significant changes in aggressive behavior (Chen, 2018; Gallucci et al., 2020; Riva et al., 2017). Accordingly, it seemed that the anodal stimulation of the right VLPFC reduced aggression in laboratory tasks (Chen, 2018; Riva et al., 2017), but the stimulation of the left VLPFC increased the aggression of healthy young adults (Gallucci et al., 2020) (Table 2).

Regarding the stimulation of the VMPFC, only three studies were finally included, although none of them clarify the specific region of the stimulation (e.g., left, right or bilaterally). Choy et al. (2023) applied anodal stimulation in healthy participants and failed to modify aggressive behavior, whereas Sergiou et al. (2022) repeated the same procedure in a forensic sample and observed a decrease in aggressive behavior (measured with a laboratory task) compared to those who received the sham stimulation, but they also failed to report changes in anger state in this sample. Lastly, another study revealed that active stimulation of the VMPFC reduced aggressive behavior and anger state, specifically, when measured after participants had been frustrated with a laboratory task (Gilam et al., 2018) (Table 2).

4.2.3. PFC (without specifying region)

Lastly, we also considered a group of articles measuring the impact of these techniques on the PFC without specifying the specific region (George et al., 2014; Grisaru et al., 2001; Koenigs et al., 2009; Ling et al., 2020; Szuba et al., 2001). Most of these studies failed to establish the existence of a significant impact of these treatments in healthy young

Table 2
Summary of characteristics of the studies assessing the effects of non-invasive brain stimulation techniques in the ventrolateral and ventromedial prefrontal cortices, as well as prefrontal cortex, alphabetically ordered by first author's surname.

Authors	Sample	Age	Gender	Handedness	NIBS	Assessment	Prefrontal cortex	Interaction "time x stimulation condition"
Chen (2018)	Healthy (n = 16)	20.25 ± 1.34	50 % ♂	–	2.0 mA anodal tDCS 750 s; single session per participant (stimulation or sham)	TAP	VLPFC (right)	Less reactive and proactive aggression after active
Dambacher et al. (2015b)	Healthy (n = 69)	21.89 ± 3.26	39 % ♂	–	1.5 mA anodal tDCS; 21.75 min single session per participant (stimulation or sham)	TAP	VLPFC (left and right)	Ns
Gallucci et al., 2020	Healthy (n = 90)	22.27 ± 2.46	50 % ♂	–	1.5 mA anodal tDCS; 20 min; single session per participant (stimulation or sham)	Frustration task	VLPFC (left and right)	Stimulation of the left VLPFC entailed high aggression
Riva et al. (2015)	Healthy (n = 80)	23.06 ± 4.36	21 % ♂	–	1.5 mA anodal tDCS; 20 min single session per participant	Hot-sauce paradigm	VLPFC (right)	Ns
Riva et al. (2017)	Healthy (n = 79)	21.73 ± 2.38	52 % ♂	–	1.5 mA anodal tDCS; 20 min; single session per participant (stimulation or sham)	TAP	VLPFC (right)	Low aggression in stimulation condition
Smits et al. (2022)	Military (n = 96)	From 18 to 60	93 % ♂	–	1.25 mA anodal tDCS; 20 min per session (stimulation or sham); 5 sessions with 1–5 days per session; +3 months and 1 year following	STAXI-2	VLPFC (right)	Ns
Choy et al. (2023)	Healthy (n = 88)	23.82 ± 5.60	48 % ♂	–	2.0 mA anodal tDCS; 20 min; single session per participant (stimulation or sham)	PSAP	VMPFC (non-specified)	Ns
Gilam et al. (2018)	Healthy (n = 25)	26.16 ± 3.63	40 % ♂	–	1.5 mA anodal tDCS; 22 min; two sessions receiving stimulation and sham	TAP Anger state	VMPFC (non-specified)	Stimulation during the first session entailed less aggressive behavior than those in sham condition Less anger was reported following the aiUG for active compared to sham
Sergiou et al. (2022)	Forensic (n = 50)	37.40 ± 9.19	100 % ♂	–	2.0 mA HD-tDCS; 20 min during 5 consecutive days (stimulation or sham)	RPQ PSAP	VMPFC (non-specified)	Ns Only group receiving stimulation experienced a decreased in their aggressive behavior in comparison with sham group
George et al. (2014)	Suicidal (n = 41)	42.5 ± 15.7	85 % ♂	–	10Hz rTMS; 30 min; 3 daily session for 3 consecutive days; participants received stimulation or sham	VAS	PFC (left)	Sham group reported higher reductions in irritability than real stimulation
Grisaru et al. (2001)	Healthy (n = 18)	40.5 ± 11.6	39 % ♂	100 % right-handed	1Hz rTMS; 500 ms; four sessions in each condition for all subjects	VAS	PFC (bilateral)	Ns
Koenigs et al. (2009)	Healthy (n = 21)	25.6 ± 5.8	57 % ♂	–	2.5 mA anodal tDCS; 35 min three sessions in each condition for all subjects	POMS	PFC (bilateral)	Ns
Ling et al. (2020)	Healthy (n = 92)	19.98 ± 1.65	48 % ♂	–	2.5 mA HF-rTDCS; 20 min; single session (stimulation or sham)	Voodoo Doll Task Intentions to commit violent criminal behavior	Mid-cingulate cortex Rostral mesial superior frontal gyrus Superior and middle frontal gyri (bilateral)	Ns Ns
Szuba et al. (2001)	Depression (n = 14)	39.7 ± 12.1	43 % ♂	–	10 Hz rTMS; 10 min; 5 days per week for 2 weeks (stimulation and sham during the same day)	POMS	PFC (left)	Reduction of anger during stimulation

Note. HD-tDCT: high-definition-transcranial direct current stimulation; Hz: hertz; ns: non-significant; PFC: prefrontal cortex; POMS: Profile of Mood States; PSAP: Point Subtraction Aggression Paradigm; RPQ: Reactive Proactive Questionnaire; rTMS: repetitive transcranial magnetic stimulation; STAXI-2: State-Trait Anger Expression Inventory 2; TAP: Taylor Aggression Paradigm; tDCS: transcranial direct current stimulation; VAS: Visual Analogue Scales; VLPFC: ventrolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex.

adults. In this sense, they failed to promote changes in anger state or aggressive behavior compared to participants receiving sham stimulation (Grisaru et al., 2001; Koenigs et al., 2009; Ling et al., 2020). Conversely, the only study applying rTMS to modify the anger state of depressive patients revealed a significant decrease in the active condition compared to the session receiving sham stimulation (Szuba et al., 2001). Finally, another study revealed a decrease in irritability in the sham condition for individuals who have attempted suicide. That is, the opposite result to the one initially hypothesized (Table 2).

4.2.4. Meta-analysis

4.2.4.1. DLPFC (left, right and bilateral). The comparison of effects on anger (mood, state) after applying electrical stimulation to the left

DLPFC (n = 491) or sham stimulation (n = 501) revealed an absence of group differences. Heterogeneity assessment revealed that conclusions across studies were relatively homogeneous (Table 3 and Supplementary Figs. 1 and 2). Conclusions were similar after removing the study by Perach-Barzilay et al. (2013), who applied a completely different task to the rest of the studies. In this sense, the values were the following (24 studies: SMD = .08 [-.05, .21]; Test for overall effect: Z = 1.23, p = .22; Heterogeneity: Tau^2 = .00; Chi^2 = 17.04, p = .81; I^2 = 0 %). Furthermore, conclusions were the same when based only on healthy participants. That is, those who received the real stimulation (n = 387) did not differ from those in the sham group (n = 392) regarding the effects on anger state (21 studies: SMD = .06, 95 % CI [-.11, .23]; test for overall effect: Z = .74, p = .48; Heterogeneity: Tau^2 = .05; Chi^2 = 28.42, p = .10; I^2 = 30 %). In terms of the selection of participants with a mental illness, those in stimulation (n = 126) did not differ from those in the sham group (n = 131) (5 studies: SMD = −.09, 95 % CI [-.37, .20]; test for overall effect: Z = .61, p = .54; Heterogeneity: Tau^2 = .02; Chi^2 = 4.86, p = .30; I^2 = 18 %).

The analysis of the effects of applying electrical stimulation to the right DLPFC (n = 359) compared to the sham stimulation (n = 358) revealed an absence of significant effects regarding anger modifications. Nonetheless, these studies presented a significant heterogeneity, given that I^2 was higher than 40 % (Table 4 and Supplementary Figs. 3 and 4). To clarify the heterogeneity across studies, we differentiate those applying TMS (9 studies: SMD = .14 [-.12, .39]; Test for overall effect: Z = 1.07, p = .29; Heterogeneity: Tau^2 = .03; Chi^2 = 10.06, p = .26; I^2 = 20 %) from those employing anodal tDCS (7 studies: SMD = .02 [-.32, .35]; Test for overall effect: Z = .11, p = .92); Heterogeneity: Tau^2 = .12; Chi^2 = 15.28, p = .02; I^2 = 61 %). Thus, the high degree of heterogeneity across conditions might only be applicable to the studies employing anodal tDCS, but not in the case of rTMS. Lastly, paying attention only to normative populations, the conclusions were as described above. In other words, there was an absence of group differences (n = 312, per group), with a considerable heterogeneity across studies (14 studies: SMD = −.11 [-.44, .21]; Test for overall effect: Z = .69, p = .49; Heterogeneity: Tau^2 = .29; Chi^2 = 52.35, p = .00001; I^2 = 75 %). Focusing only on clinical samples, those who received stimulation (n = 45) did not differ from those in the sham condition (n = 44), but studies differed in their conclusions (3 studies: SMD = −.28 [−1.26, .69]; Test for overall effect: Z = .57, p = .57; Heterogeneity: Tau^2 = .51; Chi^2 = 7.68, p = .02; I^2 = 74 %). Removing the only study that employed anodal tDCS (Lisoni et al., 2020) removed the significant heterogeneity across studies (2 studies: SMD = −.74 [−1.74, .26]; Test for overall effect: Z = 1.45, p = .15; Heterogeneity: Tau^2 = .27; Chi^2 = 1.70, p = .19; I^2 = 41 %).

Regarding the impact of applying bilateral NIBS on anger, there were no significant differences between participants who received bilateral electrical stimulation on the DLPFC (n = 59) and those who received the sham stimulation (n = 62) (Table 5). This heterogeneity disappeared

Table 3
Comparison of groups receiving real stimulation vs those receiving sham stimulation in left dorsolateral prefrontal cortex on anger state or aggressive behavior.

Study	Tecnique	Anger/aggression assessment	Stimulation			Sham			Weight	Std. Mean difference
			Mean	SD	Sample size	Mean	SD	Sample size		IV, Random, 95 % CI
Allaert et al. (2019)	anodal tDCS	VAS	5.67	8.8	24	7.33	7.39	24	4.9 %	−.20 [-.77, .37]
Baeken et al. (2006)	HF-rTMS	VAS	.52	.83	14	.33	.36	14	2.8 %	.29 [-.46, 1.03]
Baeken et al. (2008)	HF-rTMS	VAS	.46	1.15	19	.23	.31	19	3.9 %	.27 [-.37, .91]
Baeken et al. (2009)	HF-rTMS	VAS	.30	1.25	19	.30	.38	19	3.9 %	.00 [-.64, .64]
Baeken et al. (2011b)	HF-rTMS	POMS	.18	.39	10	.47	1.31	10	2.0 %	−.29 [-1.17, .59]
Baeken et al. (2012)	HF-rTMS	POMS	1.2	3.0	18	.85	1.5	18	3.7 %	.14 [-.51, .80]
Baeken et al. (2014)	HF-rTMS	VAS	1.08	1.15	14	.73	.81	14	2.8 %	.34 [-.41, 1.09]
Baeken et al. (2017)	anodal tDCS	VAS	.40	.82	21	.32	.66	19	4.1 %	.10 [-.52, .73]
Baeken et al. (2018)	anodal tDCS	VAS	.29	.66	13	.29	.66	15	2.9 %	.00 [-.74, .74]
De Putter et al. (2015)	anodal tDCS	POMS	1.05	1.99	21	.36	.79	22	4.3 %	.45 [-.15, 1.06]
De Wandel et al. (2020)	iTBS	VAS	.59	1.16	17	.38	.41	17	3.5 %	.24 [-.44, .91]
Duprat et al. (2016)	iTBS	VAS	2.4	2.48	22	3.36	2.94	25	4.7 %	−.35 [-.92, .23]
Hansbauer et al. (2018)	rTMS	PANSS	1.12	.32	60	1.29	.78	62	12.4 %	−.28 [-.64, .08]
Kelley et al. (2013)	anodal tDCS	Self-reported anger	2.53	1.11	29	2.22	1.22	33	6.3 %	.26 [-.24, .76]
Leyman et al. (2009)	HF-rTMS	POMS	.45	.55	13	.28	.30	13	2.6 %	.37 [-.40, 1.15]
Leyman et al. (2011)	HF-rTMS	VAS	.87	1.19	12	.53	.58	12	2.4 %	.35 [-.46, 1.16]
Motohashi et al. (2013)	anodal tDCS	POMS	1.4	2.6	6	2.2	2.6	6	1.2 %	−.28 [-1.42, .86]
Moulier et al. (2016)	rTMS	VAS	2.24	1.58	10	3.0	1.03	10	2.0 %	−.55 [-1.44, .35]
Perach-Barzilay et al. (2013)	cTBS	SOC	4.668	1.583	16	3.133	1.324	16	2.8 %	1.03 [.28, 1.77]
Plewnia et al. (2015)	anodal tDCS	PANAS	1.86	1.57	14	2.0	2.57	14	2.9 %	−.06 [-.80, .68]
Pulopulos et al., 2019	iTBS	VAS	.62	1.16	35	.36	.40	35	7.1 %	.30 [-.17, .77]
Pulopulos et al. (2022)	HF-rTMS	VAS	6.96	13.82	25	3.63	5.72	25	5.1 %	.31 [-.25, .87]
Remue et al. (2016)	HF-rTMS	VAS	.54	.82	19	.36	.56	19	3.9 %	.25 [-.39, .89]
Sánchez et al., 2018	anodal tDCS	VAS	4.22	4.63	27	4.0	5.08	27	5.5 %	.04 [-.49, .58]
Vanderhasselt et al., 2009a	rTMS	VAS	.86	1.24	13	.43	.42	13	2.6 %	.45 [-.33, 1.23]
Total (95 % CI)					491			501	100.0 %	.11 [-.02, .23]
Heterogeneity: Tau^2 = .00; Chi^2 = 23.08, p = .51; I^2 = 0 %; Test for overall effect: Z = 1.67, p = .10										

Note. CI: Confidence interval; cTBS: continuous theta-bursts stimulation; HF-rTMS: High frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-bursts stimulation; IV: inverse-variance; PANAS: Positive and Negative Affect Schedule; POMS: Profile of Mood States; rTMS: repetitive transcranial magnetic stimulation; Std: standard deviation; SOC: Social Orientation Paradigm; tDCS: transcranial direct current stimulation; VAS: Visual Analogue Scales.

Table 4
Comparison of groups receiving real stimulation vs those receiving sham stimulation in right dorsolateral prefrontal cortex on anger state or aggressive behavior.

Study	Tecnique	Anger/aggression assessment	Stimulation			Sham			Weight	Std. Mean difference
			Mean	SD	Sample size	Mean	SD	Sample size		IV, Random, 95 % CI
Allaert et al. (2019)	anodal tDCS	VAS	4.08	6.7	24	7.75	12.13	24	6.5 %	−.37 [-.94, .20]
Baeken et al. (2008)	HF-rTMS	VAS	.42	.67	13	.34	.69	12	5.0 %	.11 [-.67, .90]
Baeken et al. (2011a)	HF-rTMS	POMS	.35	.76	12	.14	.47	12	4.9 %	.32 [-.49, 1.13]
Baeken et al. (2012)	HF-rTMS	POMS	2.1	3.64	13	1.15	2.78	13	5.1 %	.28 [-.49, 1.06]
Cailhol et al., 2014	anodal tDCS	BPDSI	.60	.52	5	2.1	1.14	4	1.9 %	−1.58 [-3.22, .06]
Dambacher et al. (2015a)	anodal tDCS	RPQ	3.84	1.16	23	4.0	1.33	22	6.4 %	−.13 [-.71, .46]
Hu et al. (2022)	anodal tDCS	Anger self-report	4.48	1.26	27	3.81	1.29	25	6.7 %	.52 [-.04, 1.07]
Kelley et al. (2013)	anodal tDCS	Anger self-report	2.71	.88	29	2.22	1.22	33	7.0 %	.45 [-.06, .96]
Leyman et al. (2009)	HF-rTMS	POMS	.41	.70	20	.25	.29	20	6.1 %	.29 [-.33, .92]
Lisoni et al. (2020)	HF-rTMS	BPAQ	86.73	12.85	15	77.4	18.13	15	5.3 %	.58 [-.15, 1.31]
Perach-Barzilay et al. (2013)	cTBS	SOC	1.56	.69	16	3.313	1.324	16	4.8 %	−1.62 [-2.43, −.80]
Pulopulos et al. (2022)	HF-rTMS	VAS	10.71	23.33	25	3.63	5.72	25	6.6 %	.41 [-.15, .97]
Remue et al. (2016)	HF-rTMS	VAS	.54	.82	19	.36	.56	19	6.0 %	.25 [-.39, .89]
Sánchez et al., 2016	anodal tDCS	VAS	1.33	2.13	30	2.23	2.51	30	7.0 %	−.38 [-.89, .13]
Vanderhasselt et al. (2011)	HF-rTMS	POMS	.57	2.11	28	.13	.46	28	6.9 %	.28 [-.24, .81]
Vanderhasselt et al. (2017)	anodal tDCS	VAS	1.32	2.12	35	2.23	2.51	35	7.3 %	−.39 [-.86, .09]
van't Wout-Frank et al. (2021)	iTBS	DAR	11.5	6.3	25	14.1	5.6	25	6.6 %	−.43 [-.99, .13]
Total (95 % CI)					359			358	100.0 %	−.01 [-.26, .24]
Heterogeneity: $Tau^2 = .16$; $Chi^2 = 42.17$, p = .0004; $I^2 = 62$ %; Test for overall effect: Z = .09, p = .93										

Note. BPAQ: Buss–Perry Aggression Questionnaire; BPDSI: Borderline Personality Disorder Severity Index; CI: confidence interval; cTBS: continuous theta-bursts stimulation; DAR: Dimensions of Anger Reactions scale; HF-rTMS: High frequency repetitive transcranial magnetic stimulation; iTBS: intermittent theta-bursts stimulation; IV: inverse-variance; POMS: Profile of Mood States; SOC: Social Orientation Paradigm; Std: standard deviation; tDCS: transcranial direct current stimulation; VAS: Visual Analogue Scales.

after removing data from the murderers of the Molero-Chamizo et al. (2019) research. Accordingly, results changed as follows: 2 studies: SMD = .16 [-.05, .38]; Test for overall effect: Z = 1.49, p = .14; Heterogeneity: $Tau^2 = .00$; $Chi^2 = .26$, p = .61; $I^2 = 0$ %.

4.2.4.2. VLPFC (left and right). The analysis of effects on aggressive behavior after applying electrical stimulation to the left VLPFC (n = 67) or sham stimulation (n = 65) revealed an absence of group differences, being this conclusion extremely heterogeneous as evidenced by the following analysis (Table 5).

Regarding the group differences for aggressive behavior in laboratory tasks after applying stimulation to the right VLPFC (n = 80) compared to sham stimulation (n = 76), the results revealed an absence of significant effects, being these conclusions homogeneous across studies as I^2 was higher than 40 %, but not significant (Table 5).

4.2.4.3. VMPFC (non-specified). With regards to the comparison of participants receiving bilateral stimulation to the VLPFC (n = 97) compared to those in the sham condition (n = 91), no significant group differences were found (3 studies: SMD = −.41, 95 % CI [−1.30, .48]; test for overall effect: Z = .90, p = .37). Heterogeneity assessment revealed that conclusions across studies were relatively homogeneous as I^2 was lower than 40 % (Heterogeneity: $Tau^2 = .28$; $Chi^2 = 3.15$, p = .21; $I^2 = 37$ %) (Table 5).

5. Discussion

Based on the empirical studies included in this systematic review and the meta-analysis, we found that only a few studies were able to report a significant impact of various NIBS techniques to different regions of the PFC on anger states or aggressive behaviors. In this sense, the effect size calculations between the groups that applied real stimulation to the DLPFC, DMPFC, VLPFC and VMPFC compared to those receiving sham stimulations did not exhibit significant differences regarding anger state or aggressive behavior. This conclusion is affected by the heterogeneity among studies regarding the right and bilateral stimulation of the DLPFC and left stimulation of the VLPFC.

As far as we know, this is one of the first attempts to summarize and calculate if there are any significant differences between the effects of real stimulation compared to sham stimulation over various PFC regions to induce changes in anger state and aggressive behavior. As stated in the results section, most of the included studies attempted to apply this type of technique to induce changes in mood, which, in turn, might affect proneness to aggressive behavior. This is based on the premise that the PFC plays an important role in behavioral regulation, especially aggressive behavior (Bannon et al., 2015; Nikolic et al., 2022). What is evident from the references gathered in this review is that among euthymic individuals or those without mental disorders, the stimulation of the left DLPFC did not alter their anger state.

One could argue that an intensive treatment (e.g., more consecutive sessions of stimulation during a sustained period) or focusing solely on individuals with mental disorders, could significantly impact the conclusions. However, taking into account only studies with intensive treatments or participants with mental disorders, the results were similar to those described above, that is, only a few of them reported a significant contribution of these NIBS techniques to changes in anger state (Baeken et al., 2009; Cailhol et al., 2014; Calderón-Moctezuma et al., 2021; Hansbauer et al., 2018; He et al., 2023; Lisoni et al., 2020; Schrijvers et al., 2009b, 2012; Szuba et al., 2001). Therefore, it might be useful to adopt an alternative perspective regarding changes in violence

Table 5
Comparison of groups receiving real stimulation vs those receiving sham stimulation in several prefrontal cortex regions on anger state or aggressive behavior.

Study	Tecnique	Anger/aggression assessment	Stimulation			Sham			Weight	Std. Mean difference
			Mean	SD	Sample size	Mean	SD	Sample size		IV, Random, 95 % CI
Dorsolateral prefrontal cortex (bilateral and simultaneous stimulation)										
Choy et al. (2018)	anodal tDCS	VAS	.34	.55	39	.18	.42	42	50.6 %	.16 [-.05, .37]
Molero-Chamizo et al. (2019)	HF-rTMS	VAS	21.92	5.51	13	20.53	6.8	13	25.6 %	1.39 [-3.37, 6.15]
Molero-Chamizo et al. (2019)	HF-rTMS	POMS	18.75	6.22	7	24.71	2.92	7	23.9 %	−5.96 [-11.05, −.87]
Total (95 % CI)					59			62	100 %	−.99 [-4.40, 2.43]
Heterogeneity: $Tau^2 = 6.00$; $Chi^2 = 5.80$, p = .05; $I^2 = 66$ %; Test for overall effect: Z = .57, p = .57										
Ventrolateral prefrontal cortex (left)										
Dambacher et al. (2015b)	anodal tDCS	TAP	2.9	1.62	22	3.36	1.42	20	50.1 %	−.30 [-.90, .31]
Gallucci et al., 2020	anodal tDCS	Frustration task	.24	.14	45	−.28	.14	45	49.9 %	3.68 [2.99, 4.37]
Total (95 % CI)					67			65	100 %	1.69 [-2.21, 5.59]
Heterogeneity: $Tau^2 = 7.80$; $Chi^2 = 71.98$, p < .00001; $I^2 = 99$ %; Test for overall effect: Z = .85, p = .40										
Ventrolateral prefrontal cortex (right)										
Choy et al., 2018	HF-rTMS	BPAQ	5.19	.92	16	5.96	1.17	16	21.9 %	−.71 [-1.43, .00]
Dambacher et al. (2015b)	cTBS	SOC	3.29	1.78	22	3.36	1.43	20	26.4 %	−.04 [-.65, .56]
Riva et al. (2017)	HF-rTMS	VAS	5.32	1.96	20	4.63	1.31	20	25.4 %	.41 [-.22, 1.03]
Smits et al. (2022)	anodal tDCS	VAS	2.37	.58	22	2.28	.64	20	26.3 %	.14 [-.46, .75]
Total (95 % CI)					80			76	100 %	−.03 [-.46, .41]
Heterogeneity: $Tau^2 = .09$; $Chi^2 = 5.64$, p = .13; $I^2 = 47$ %; Test for overall effect: Z = .12, p = .91										
Ventromedial prefrontal cortex (unspecified)										
Choy et al. (2023)	anodal tDCS	PSAP	41.62	42.65	47	46.6	41.77	41	.3 %	−4.98 [-22.65, 12.69]
Gilam et al. (2018)	anodal tDCS	Anger self-reported	1.58	2.19	25	2.84	2.71	25	26.8 %	−1.26 [-2.63, .11]
Sergiou et al. (2022)	HD-tDCS	PSAP	.07	.07	25	.15	.19	25	73.0 %	−.08 [-.16, −.00]
Total (95 % CI)					97			91	100 %	−.41 [-1.30, .48]
Heterogeneity: $Tau^2 = .28$; $Chi^2 = 3.15$, p = .21; $I^2 = 37$ %; Test for overall effect: Z = .90, p = .37										

Note. BPAQ: Buss–Perry Aggression Questionnaire; cTBS: continuous theta-bursts stimulation; HD-tDCS: High-Definition transcranial Direct Current Stimulation; HF-rTMS: High frequency repetitive transcranial magnetic stimulation; IV: inverse-variance; POMS: Profile of Mood States; PSAP: Point Subtraction Aggression Paradigm; SOC: Social Orientation Paradigm; Std: standard deviation; TAP: Taylor Aggression Paradigm; tDCS: transcranial direct current stimulation; VAS: Visual Analogue Scales.

proneness by modifying anger state. In this regard, it could be important to pay attention to other variables that might be altering the threshold for the proneness to this kind of behavior. Some of these variables could include facial processing of hostile signals, analysis of contending intentions, interfering in planning abilities and making risky decisions, the appearance of pseudopsychopathy symptoms (e.g., emotional insensitivity), or apathy, among others.

The analysis of heterogeneity across studies emphasizes the need for caution regarding the conclusions due to the absence of effects of all these techniques compared to a sham group. In this sense, there was a considerable variability across studies regarding right and bilateral DLPFC stimulation and left VLPFC stimulation. For example, if we focus soley on anodal tDCS to the right DLPFC, heterogeneity was particularly high. This fact, along with significant heterogeneity in research on bilateral DLPFC and left VLPFC stimulation, highlights the importance of focusing on those key PFC regions for future research. In other words, it would be particularly important to increase the amount of research aiming to interfere in aggressive behavior. However, we would like to point out several factors. First, it seemed that including laboratory tasks instead of self-reports offered significant results as can be seen in Choy et al. (2018); Galluci et al. (2020) or Perach-Barzilay et al. (2013). Second, much of the research focused on the DLPFC and only a few studies measured the impact of NIBS on the DMPFC, VLPFC o VMPFC. Finally, most of the samples were healthy euthymic adults, with only a few studies including clinical or violent individuals. In this sense, Molero-Chamizo et al. (2019) based their conclusions on NIBS on inmates, who exhibited higher anger trait compared to non-inmates. Concretely, they concluded the existence of significant changes in a specific group of inmates (e.g., murders). Therefore, this emphasizes the importance of not only including healthy participants but also comparing them with other participants who have mood disorders or alterations. It should be noted that NIBS is increasingly used as an alternative way to treat refractory depressive patients (Bhattacharya et al., 2022), who might be particularly responsive to these techniques.

Although many of these studies did not aim to modify anger state, it is worth noting that studies conducted on damaged prefrontal regions published in the late 1900s and early 2000s concluded that local lesions in the middle prefrontal and orbitofrontal cortex (OFC) entailed higher scores in anger expression compared to focal lesions in other PFC regions. Additionally, these studies also indicated that temporal lobe lesions were directly responsible for the higher tendency to express anger (Brower and Price, 2001; Bufkin and Luttrell, 2005; Grafman et al., 1996). Furthermore, a review summarizing results of damaged PFC regions concluded that while DLPFC lesions were associated with a higher tendency toward physical expression of anger, OFC morphological alterations entailed a heightened risk for disinhibited-nonaggressive behavior (Giancola et al., 1995). This might explain why the majority of the studies assessing the interference in anger state failed to induce

changes. Additionally, the OFC was neglected in all the included studies because of its location for receiving NIBS stimulation. So, it would be particularly interesting to focus on these regions and, in turn, to analyze whether it affects violence proneness in violent individuals or other individuals affected by mood disorders.

Most of the scientific research included in this meta-analysis was cross-sectional research with relatively small sample sizes ($n \leq 50$ participants) mainly based on normative individuals, that is, not affected by mood disorders. This can be observed in detail in Table 1. As can be seen in Supplementary Table 1, many of these studies had robust designs (e.g., double blinded, randomization of participants, calculation of the sample size required, placebo controlled by including a sham stimulation condition, etc.) and the risk of bias in most of them was classified as moderate. A detailed analysis of the included studies revealed that most of the research was conducted by the same research teams and based on European participants. Unfortunately, the conclusions did not differ significantly from the studies included in the systematic review and those in the meta-analysis.

A significant number of studies were excluded because they did not provide descriptive data for each condition, which could have a notable impact on the conclusions (e.g., increasing heterogeneity across PFC regions). Furthermore, there is another limitation which might affect the type of instruments employed to measure the dependent variable analyzed in this review and the samples used to conduct these studies (healthy and young participants). For example, many of the studies did not provide psychometric properties, which might affect conclusions, or previous anger trait characteristics of the participants. Furthermore, many of them employed self-reports instead of crossing those results with other laboratory procedures or qualitative interviews which could provide additional insight into participants' anger traits. An additional limitation might be the absence of active control groups as a comparison group instead of sham controlled. This could be considered in future research. Another limitation was the absence of longitudinal studies which might affect the conclusions, as the electrical stimulation might change neuron communication after a sustained period of time, as can happen with different drugs like antidepressants. And obviously another limitation could be attributed to the type of instrument employed to stimulate the PFC, which might explain the heterogeneity of the results. In this sense, the local stimulation of PFC regions could be combined with other drugs, that might potentiate their effects. For example, a previous systematic review assessing the effects of a selective serotonin reuptake inhibitor such as sertraline noted that a minimum of two weeks is needed to start registering significant anger state changes (Romero-Martínez et al., 2019a,b).

Future empirical studies should overcome the limitations of the current research in this field. As described in the introduction, this treatment could be provided to violent individuals with drug misuse, those who have not responded well to current treatments, or as an alternative to drug treatment alongside psychotherapy. Additionally, it would be particularly important to increase the number of pathological or non-normative participants, presenting mood alterations or certain disorders that might lead to violence in some cases. It could also be important to systemize the TAP scales. That is, the exact moment analyzed in the TAP to avoid potential biases in the interpretation of the data given how the scores progress over time. It would also be interesting to incorporate other instruments assessing associated concepts to the construct of violence (e.g., anger expression-out or in, physical or verbal abuse, etc.). Finally, it might be reductionist to try to significantly impact violence by only targeting the PFC without stimulating other structures or regions. Therefore, it would also be particularly interesting to explore a simultaneous bilateral stimulation of different regions, rather than focusing on one hemisphere.

In summary, this systematic review and meta-analysis found that applying different types of NIBS to PFC regions did not promote significant changes in anger state or aggressive behavior when compared to groups of participants receiving sham stimulation (or placebo group). This conclusion was reinforced by only a reduced number of studies presenting a significant effect of time (before and after) x stimulation group (real vs sham stimulation) and non-significant effect sizes across studies. Conclusions on the left DLPFC, bilateral DMPFC, right VLPFC and VMPFC (hemisphere not specified) were relatively consistent across studies. However, some of the assessed regions exhibited an important heterogeneity in the research included, such as studies exploring right and bilateral stimulation of the DLPFC and left stimulation of the VLPFC. These facts reinforce the need to explore alternative ways to study the dependent variables considered in this study (e.g., anger state and aggressive behavior) with different instruments or constructs associated with violence in forensic samples or in participants with mood disorders, given that a great number of studies based their conclusions on normative or euthymic participants. Based on these conclusions, occasional NIBS application does not seem especially relevant for preventing violence proneness or interfering in it, at least, in euthymic individuals. Therefore, it may be important to explore other factors that are more closely linked to violence proneness by contemplating a wider number of cortical regions, as well as targeting other constructs associated with the construct of violence.

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CRediT authorship contribution statement

Ángel Romero-Martínez: Writing – review & editing, Writing – original draft. **Carolina Sarrate-Costa:** Writing – review & editing. **Luis Moya-Albiol:** Writing – review & editing.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.03.058.

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