Non-invasive neuromodulation can reduce aggressive behaviors in humans: A critical perspective

Giuseppe Volpe MSc | **Serena Tagliente MSc** | **Annalisa Palmisano MSc** | **Ignazio Grattagliano PhD** | **Davide Rivolta PhD**

Abstract

Containing aggressive behavior is an ongoing challenge in modern society. Aggressiveness is a multi-level construct that can be driven by emotions (reactive aggression) or can be "cold-blooded" and goal-directed (proactive). Aggressive behavior could arise because of a misjudgment of others' intentions or can follow frontal brain lesions leading to a reduction of impulse control and emotion regulation. In the last few years, interventional and basic research studies adopting Non-Invasive Brain Stimulation (NIBS) have significantly risen. Those techniques have been used both in healthy people, to better understand the role of certain brain regions in psychological processes, and in aggressive subjects to improve their symptoms. From an overview of the literature, focusing on the paper that uses transcranial direct current stimulation (tDCS) to reduce aggressiveness, it emerges that tDCS can (i) enhance facial emotion expression recognition, (ii) improve impulses control, and (iii) affect approach/withdrawal motivation. The current work shows the strengths and weaknesses of tDCS intervention on aggressive individuals, suggesting that this instrument could be adopted on violent people, and paves the way for intervention in some applied settings such as prison.

KEYWORDS

aggression, aggressive behavior, neuromodulation, tDCS

Highlights

- tDCS is effective in mediating aggressive behaviors in humans.
- Recidivism is an important issue in the forensic system. tDCS, by reducing aggressiveness, can also reduce recidivism.
- Reducing levels of aggressiveness of prisoners can improve relationships and communication with police, prison workers, and other inmates.
- tDCS intervention on aggressiveness may represent an innovative non-pharmacological approach, tailored for specific populations resistant to other treatments.

1 | INTRODUCTION

Aggression can be defined as any behavior directed toward another person that is carried out to cause physical or psychological harm [1]. In addition, the *perpetrator* must believe that the behavior will harm the *target*, which, in turn, tries to avoid the behavior [2]. Among the wide range of definitions adopted, a common distinction concerns proactive (also named instrumental or premeditated

or "cold-blooded") and reactive (or impulsive or "hot-blooded") aggression. When aggressive behavior occurs because of provocation, and it is not goal-driven, it is classified as "reactive". These aggressive acts are rapid and unplanned reactions to external or internal stimuli, leading to aggressive outbursts. If aggression is unprovoked and goal-driven, it is classified as "proactive". Indeed, the core features of proactive aggression are goal-directedness and planning; in addition, the level of emotional arousal is relatively low or, in any case, secondary [3]. Aggressiveness represents a challenging social burden. As a matter of fact, modern societies would benefit from the development of therapeutic options to reduce aggressive behaviors (e.g., by reducing recidivism).

An interesting review associated violent, criminal, and aggressive behaviors with different brain structural and functional impairments [4]. The neural model of antisocial behavior proposed by Raine and Yang [4], underlines that common abnormalities characterize antisocial, violent, and psychopathic populations exhibiting violent and criminal behaviors, including (i) reduced glucose metabolism, (ii) diminished frontal blood flow, and (iii) reduced gray matter volume. Moreover, the impaired cortical and subcortical structures in which these impairments are observed, such as Orbitofrontal Cortex (OFC), Dorsolateral Prefrontal Cortex (DLPFC), amygdala, and angular gyrus, are involved both in moral reasoning and in aggressive behavior, suggesting that these two processes are strongly connected. These brain regions are crucial in comprising the *feeling* of what is moral (pointing out the important role of emotional processing), and in the process of regulatory control, which allows the downregulation of behavioral uncontrolled reactions. This model shows that both cognitive and emotive aspects are implicated in violent, antisocial, and aggressive behavior [4].

2 | AGGRESSION AND THE BRAIN

Among animals, aggressive behaviors are adaptive to feeding and reproduction; indeed, certain hormones (e.g., testosterone) predispose males to competition and aggressiveness to obtain reproductive success. The relation between testosterone and aggressiveness in humans is less overt than in animals [5]. For instance, adult volunteers treated with testosterone do not show an increase in aggressiveness [6]. Invasive brain electrical stimulation clarified the importance of subcortical structures in the genesis of aggressiveness; for example, electrical stimulation of the hypothalamus elicited aggressions both in male and in female rodents [7]. Furthermore, in non-human primates, electrical stimulation of the hypothalamus gave rise to aggressive behavior [8,9]. Given the role of inhibitory inputs from the frontal cortex to the hypothalamus and amygdala [10] in modulating aggressiveness, lesions of the OFC increase aggressive behaviors in male rats [11].

Since cortical and subcortical aggressiveness-routes have been mainly identified, current neuroscientific research is trying to develop methodologies and techniques that can modulate aggressive behaviors in both experimental settings and applied contexts (such as prisons) (Figure 1).

3 | NON-INVASIVE BRAIN STIMULATION (NIBS)

Neuroscientists can now benefit from a robust corpus of non-invasive neuroimaging techniques to study the human brain in vivo. Electroencephalography (EEG) and functional Magnetic Resonance Imaging (fMRI), among others, allow the recording of various forms of brain activity (i.e., electrical signals and blood flow), indicating correlations between brain activity and behavior. However, to establish *causal* links between brain and behavior, Non-Invasive Brain Stimulation (NIBS) techniques can be adopted [12].

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that involves the use of electrodes (i.e., an "anode" and a "cathode") placed on the scalp to deliver a weak direct current that modulate cortical excitability [13]. Standard parameters establish that the current should be lower than 2.5 mA

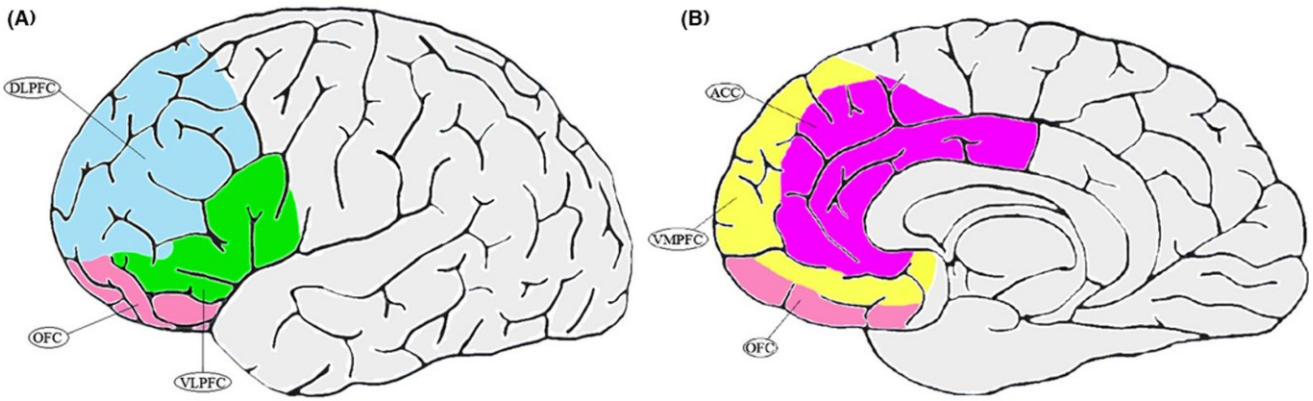

FIGURE 1 Schematic diagram of cortical aggressiveness-routes. (A) DLPFC, Dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; VLPFC, Ventrolateral prefrontal cortex. (B) ACC, Anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex; OFC, orbitofrontal cortex [Color figure can be viewed at wileyonlinelibrary.com]

(usually 1–2 mA), with a duration of less than 20–60 min per session [14]. tDCS does not induce directly action potentials, but rather modulates cortical excitability via subthreshold depolarization or hyperpolarization of resting membrane potentials, with "anodal" stimulation inducing excitatory effects and "cathodal" stimulation exerting inhibitory effects [14,15]. It has been observed that longer and stronger stimulations produce longer and stronger after-effects [13,16,17].

4 | AGGRESSIVE BEHAVIORS AND TDCS IN HEALTHY PEOPLE

tDCS can be applied to modulate human emotional processing such as emotion regulation [18], cognitive reappraisal [19], and facial emotion recognition [20,21]. Emotions play a crucial role in aggression (e.g., negative emotions, such as fear or anger, are related to reactive, "hot-blooded" aggression). It seems that anger is usually associated with aggression [22]. As a matter of fact, deficits in anger regulation [23], as well as poor anger facial expression recognition, are related to higher aggression and violence levels [24]. Given that tDCS can modulate human emotional processing [18–21], this technique could be useful in the attempt to modulate the above-reported phenomena, thus reducing aggressiveness.

4.1 | Anger, frontal activity, aggressiveness and tDCS

Left and right frontal cortical regions are asymmetrically associated with approach and avoidance motivational and emotional tendencies. Anger is often linked to the approach motivation [25,26] and drives people toward the stimulus. fMRI studies suggest that greater left than right frontal cortical activation is associated with approach motivational tendencies [27,28]; in fact, "feeling angry" increases left frontal cortical activity [29]. Instead, when anger is associated with low personal relevance or withdrawal-oriented motivation, it does not elicit cortical activity patterns usually associated with approach motivation [29].

In line with findings on the relationship between anger and frontal activity in healthy people, Hortensius et al. [30] reported that anger associated with greater left frontal cortical excitability can lead to aggression. In their study, tDCS was combined with a social psychological provocation scenario. Participants received adverse comments from other participants after 15 min of anodal-tDCS (a-tDCS) (2 mA × 15 min) over the left or right frontal cortex. Later, they were allowed to aggress the supposed insulting participant. Results showed that individuals who received a-tDCS on the left Prefrontal Cortex (lPFC) behaved more aggressively when they scored higher on insult-related anger. No relation between anger and aggression was observed in the Sham and on the right Prefrontal Cortex (rPFC) conditions. These results highlight a correlation between anger, approach motivation, and aggression, in line with the motivational direction model of frontal asymmetry [26]. Moreover, this study clarifies the relation between left frontal cortical activity, approach motivational tendencies, and anger in aggressive behavior: approach-oriented angerleads to reactive aggression.

Since the rPFC is related to avoidance or withdrawal motivation [31,32], increased excitability in this area should inhibit aggressive behavior. Based on this, Dambacher et al. [33] tried to investigate if tDCS could help to reduce aggressive behaviors. Authors distinguished aggressive behavior caused by provocation (reactive) from goal-driven and instrumental aggression, classified as "proactive" [34]. To measure proactive and reactive aggression in healthy participants, Dambacher et al. [33] adopted a self-report, Reactive and Proactive Aggression Questionnaire (RPQ; [35]), and a behavioral task, the Taylor Aggression Paradigm (TAP; [36]). The TAP consists of a competitive reaction-time game against a contrived participant. Participants were able to release a noise blast, choosing intensity and duration, at the beginning of the task (proactive aggression) and in response to the opponent's noise blast (reactive aggression). Results showed that, as compared to Sham, right Dorsolateral Prefrontal Cortex (rDLPFC) a-tDCS (2 mA × task duration) reduces proactive aggression in man; this result holds potential helpful applications, for instance, in treating patients with psychopathic traits.

The right Ventrolateral Prefrontal Cortex (rVLPFC) is involved in inhibitory control for both motor and emotional responses [37,38]. Thus, neuromodulation of this area could reduce aggression [39]. After a-tDCS (2 mA × task duration), both reactive and proactive aggression decreased, without any gender difference [39]. These results extend Hortensius' findings [30] and demonstrate that both reactive and proactive aggression can be attenuated. This study also highlights the potentiality of targeting the Ventrolateral Prefrontal Cortex (VLPFC). On the basis of previous fMRI findings [40], Gilam et al. [41] aimed to enhance anger regulation using a-tDCS on ventromedial Prefrontal Cortex (vmPFC) during fMRI scanning. Authors elicited anger using the anger-infused Ultimate games (aiUG; [40]). In this task, a proposer decides how to split a sum of money between himself and a responder, and in case of acceptance, they both earn money. To further induce anger, unfair monetary offers were matched with written provocations. Self-reported anger and the reactive aggressive behavior were evaluated via a Likert scale and the TAP, respectively. Active stimulation (1.5 mA × task duration) targeting the vmPFC led to increased activity during the unfair offers processing and mitigated self-reported anger following the aiUG. The authors reported a reduction in reactive aggressive behavior following active stimulation.

4.2 | Interpersonal aggression and tDCS

Social pain represents the emotional suffering that arises from the perception of being excluded (i.e., from desired relationships, or from being devalued by partners or groups [42]). This can eventually lead to aggression [43,44]. tDCS intervention can reduce social pain [45], and the resulting aggressive behavior by modulating

rVLPFC excitability with anodal stimulation (1.5 mA × 20 min) [46]. Exclusionary experiences motivate adolescents to engage with violent videogames, which, in turn, could make these adolescents more inclined to aggression [47]. A recent study [48] indicated that a-tDCS (1.5 mA × 20 min) over rVLPFC could diminish proactive (but not reactive) aggressive behavior that occurs from playing violent videogames. Overall, VLPFC is a critical area for self-control and emotion regulation processes [49,50]; In particular, rVLPFC is related to impulses control [49,51], which could include control over reactive aggressive behavior. Gallucci et al. [52] investigated whether tDCS (2 mA × 20 min) on VLPFC can modulate frustration-induced aggression. Three tasks were adopted to assess reactive and proactive aggression: (i) the Competitive Reaction-Time Task (CRTT; [53]), which required participants and their partner to press a button as fast as possible on each trial; here the winner on each trial was allowed to induce noise blasts in the loser's headphones; (ii) the Sequences Chosen Task, which consisted in choosing six numerical sequences for a partner to solve between easy and "difficult" (impossible) sequences; in the third task (iii) eleven Tangram puzzles [54] selected by the participants for their partners to solve between easy, medium and difficult conditions. The authors found a null effect of a-tDCS on rVLPFC, disconfirming findings obtained by Riva et al. [46,48]. Consistently with the motivational direction model of frontal asymmetry, a-tDCS over the left Ventrolateral Prefrontal Cortex (lVLPFC) increased reactive aggression. Qualitative differences between aggression causes (e.g., social exclusion, violent video games, or frustration) and tDCS set-up might explain these inconsistencies.

4.3 | Intention to commit aggression, antisocial behaviors and tDCS

The neural model of antisocial behavior proposed by Raine and Yang [4], demonstrates that criminal and violent individuals present structural and functional abnormalities, and that brain areas associated with moral reasoning and antisocial behavior overlap significantly. Thus, the rule-breaking, immoral behavior of antisocial and psychopathic individuals may in part be due to impairments in brain regions subserving moral cognition and emotion [4]. On the basis of this model, it is possible to study reactive and proactive aggressiveness as intentions to commit aggressive acts and the perception of moral wrongfulness of their acts [55,56]. Compared to the Sham condition, participants who saw vignettes representing physical and sexual aggression showed a reduced intention to commit those acts after receiving a-tDCS (2 mA × 20 min) on DLPFC. Moreover, they judged those acts as more deplorable [55]. Anodal stimulation on Prefrontal Cortex (PFC) did not affect aggressive behavior [55,56] assessed through the Voodoo Doll Task [57], which requires participants to insert many pins in a doll on a computer screen [57]. Moreover, after High Definition-transcranial Direct Current Stimulation (HD-tDCS) (2 mA × 20 min) on PFC, Ling et al. [56] discovered a null effect of stimulation on the intention to commit antisocial behaviors. Some methodological aspects could explain the differences between the mentioned studies. While Choy et al. [55] analyzed results the day after stimulation (i.e., long-lasting after-effect), Ling et al. [56] assessed outcomes immediately after tDCS. Furthermore, rather than using conventional tDCS, Ling et al. [56] used HD-tDCS, with higher spatial resolution than tDCS, and they stimulated a broader area compared to the DLPFC considered by Choy et al. [55]. In addition, both studies were conducted on healthy students that likely have well-functioning prefrontal cortices and do not exhibit high levels of aggressive and antisocial behavior. However, given the complexity of aggressive and antisocial behaviors, future studies will consider functional connections between PFC and other brain areas.

5 | AGGRESSIVENESS, IMPULSIVITY, CLINICAL CONDITIONS, AND TDCS

Aggression can arise from medical or psychiatric conditions. In fact, Borderline Personality Disorder (BDP) is a pervasive pattern of instability in interpersonal relationships, identity, affects, and marked impulsivity, which can lead to self-injurious behaviors, suicidality, substance abuse, and other high-risk behaviors such as aggression [58,59]. Impulsivity has a cognitive facet, that is the inability to delay satisfaction due to the ineptitude in comparing sudden consequences with long-term future events [60]. In fact, bi-frontal tDCS (1.6 mA × 20 min), anodal-left Dorsolateral Prefrontal Cortex (a-lDLPFC), and cathodal-right Dorsolateral Prefrontal Cortex (c-rDLPFC) administrated during a delay-discounting task, led healthy people to choose disadvantageous, albeit immediate, rewards instead of larger delayed options [61]. On the contrary, a-tDCS over the rDLPFC coupled with cathodal-left Dorsolateral Prefrontal Cortex (c-lDLPFC) (1 mA × 15 min) made participants choose the safest option faster as compared to Sham [62] during a *Risk task* [63] (i.e., a task to measure decision-making under risk). Looking at the behavioral component of impulsivity, a relationship between behavioral impulsivity and aggression emerges between impulsivity and aggression in both BPD and healthy subjects [64]. For this reason, Lisoni et al. [65], adopted bilateral tDCS by placing anode on the right DLPFC and cathode on the left DLPFC (2 mA × 20 min × 5 days × 3 weeks) on a BPD patients' sample. Compared to the baseline, the stimulation improved some core dimensions of BDP, by reducing impulsive manifestation and reactive aggression, as emerged from the Barratt Impulsivity Scale-11 (BIS-11; [66]), the Buss-Perry Aggression Questionnaire (BAQ; [67]), and the Iowa Gambling Test (IGT; [68]).

Molavi et al. [69] focused on BPD executive functions deficits. They aimed to investigate the effect of bilateral DLPFC stimulation (2 mA × 20 min × 10 days) on executive dysfunctions, emotional dysregulation, and emotional processing, assessed by the *Executive Skills Questionnaire for Adults* (ESQ; [70]), the *Emotion Regulation Questionnaire* (ERQ; [71]), and the *Emotional Processing Scale* (EPS; [72]), respectively. Some studies have also linked the lDLPFC activity with cognitive control functions [73,74]. Hence, in contrast with Lisoni et al. [65], Molavi et al. [69] adopted bilateral tDCS with the anode on lDLPFC and cathode on rDLPFC. Results showed that repeated bilateral tDCS stimulation on DLPFC improved executive functioning and cognitive control in BPD

patients. Moreover, subjects in the active stimulation group showed a significant improvement in their cognitive reappraisal strategy, but not in terms of experienced negative emotions. Despite [65,69] focusing on BPD patients, these studies [64,68] investigated different aspects. Lisoni et al. [65] explored the core dimensions of BDP (e.g., impulsivity), reporting results in the reduction of impulsivity and aggressiveness dimensions, whereas the study from Molavi et al. [69] focused on emotional and cognitive deficits, by demonstrating that tDCS interventions can facilitate cognitive reappraisal strategy.

The pivotal role of DLPFC has been confirmed by TMS studies. Transcranial Magnetic Stimulation (TMS) is a NIBS technique that induce neurophysiological modifications in the human brain via magnetic pulses [75]. Typically, single-pulse TMS is used to modify cognitive skills "online" (i.e., "virtual lesion approach"), whereas repetitive TMS (rTMS) is used to induce plastic changes in brain activity that can outlast the stimulation period [76].

Multiple sessions of rTMS targeting DLPFC reduce anger, affective instability, planning, and impulsiveness [77,78]. As in BPD patients, aggressiveness is strongly expressed in patients with Substance Use Disorder (SUD) [79,80]. Within this category, Alcohol Use Disorder (AUD) seems to be strongly related to aggressiveness due to decreased activity in the prefrontal cortex, as shown by Denson et al. [81]. Moreover, alcohol consumption has a stronger association with aggressive behaviors than any other psychotropic substance [82–84]. Several studies documented a relation between alcohol consumption and aggressive crimes, such as homicides, assaults, and rapes [84–87]. tDCS modulated aggressive behavior in a male sample of Alcohol-Dependent (AD) patients [88]. After a-tDCS stimulation (1.5 mA × 20 min) over rDLPFC, AD patients showed less reactive aggressive behavior as measured with the Modified Taylor Aggression Paradigm [89], while no variations emerged in tobacco users (TU) [88].

Smits et al. [90] found a null effect of tDCS on aggressiveness. Authors recruited a military sample with PTSD or impulsive aggression and performed a-tDCS stimulation over the right Inferior Frontal Gyrus (IFG) coupled with inhibitory control training. Aggressiveness and impulsiveness were measured through the State-Trait Anger Expression Inventory (STAXI-2; [91]); the PTSD Checklist for DSM-5 (PCL-5; [92]); a *go/no go task*; and an Implicit Association Task (IAT; [93]). After 5 sessions of stimulations (1.25 mA × 20 min) no improvements were detected neither in aggression nor in impulsivity as compared to Sham. Further studies are needed since both positive and negative results arise from the tDCS literature on aggressiveness.

6 | AGGRESSIVENESS, OFFENDERS, AND TDCS

According to previous literature, a-tDCS over the PFC can reduce the propensity to aggress in healthy populations. A challenging goal could be to extend tDCS' beneficial effect on individuals who exhibit aggressiveness, such as criminal offenders, to reduce recidivism. Molero-Chamizo et al. [94] used the BAQ [67] to explore the effects of bilateral a-tDCS (1.5 mA × 15 min × 3 days) over the PFC on aggressiveness in two groups of inmates (murders n = 15 vs. non-murders n = 26). All participants completed the BAQ before the first tDCS stimulation and immediately after the last stimulation, while the non-inmates control group completed the BAQ at the baseline only. Comparing inmates and non-prisoners at the baseline, there were differences in two out of four dimensions of BAQ (Physical Aggression and Hostility). Murders and non-murders received active stimulation or sham. After bilateral a-tDCS on left–right DLPFC, both inmates groups reported reduced Physical Aggression, Anger, and Verbal Aggression. Moreover, in murder inmates only, a significant reduction emerged in all BAQ dimensions in comparison to the Sham murder inmates group. The authors concluded that stimulation was associated with a more general effect in the murders group because of the involvement of all the aggressiveness dimensions.

In the study conducted by Hofhansel et al. [95], criminal offenders and control participants completed an *emotion regulation task* in fMRI before and after receiving a single session of a-tDCS over the rDLPFC (20 min × 1.5 mA). Results showed a decrease in rDLPFC activity after a-tDCS in the offenders' group only. However, a-tDCS on rDLPFC did not improve the ability to regulate negative emotions either in non-criminal controls or in violent offenders. These findings should be taken into account when developing tDCS intervention on criminal offenders, as their brains could respond differently to the modulation of prefrontal brain activity as compared to healthy participants [4].

Another brain region that could be involved in typical criminal mind functioning is the vmPFC. As a matter of fact, Sergiou et al. [96] investigated if anodal HD-tDCS on vmPFC (2 mA × 20 min × twice a day × 5 days) could increase empathic abilities and reduce violent behavior in forensic substance abuse patients. The authors also investigated how tDCS impacts on *Event-Related Potentials* associated with the empathic process (i.e., ERPs: P3 and LPP) [97–99], while participants were watching aggression scenes. The authors hypothesized an increase of P3 and LPP in response to pain scenes after HD anodal-tDCS (HD-a-tDCS). Concerning aggressiveness that could arise from their medical conditions, their results showed that multiple sessions of active stimulation reduced reactive aggression in the RPQ [35] and during the Point Subtraction Aggression Paradigm (PSAP; [100]), a computer task in which participants attempt to gain points while virtual opponents try to steal themes. Contrary to expectations, P3 showed an amplitude decrease. Furthermore, they found a notable increase in LPP amplitude in the a-tDCS group for both images representing victims of aggressions and neutral scenes. The authors interpreted this finding as an effect of vmPFC implication in social interaction. In fact, its modulation could determine an increase in LPP also following the exposure to neutral social situations.

7 | AGGRESSIVE BEHAVIORS AND ANGER

During their lives, humans collect experiences and information in cognitive schemes. With reference to clinical depression, Beck [101] described the scheme as a cognitive-response category related to

TABLE 1 Descriptive characteristics for tDCS studies on aggressive behavior

tDCS and aggressiveness				
Study	**Sample**	**Study design**	**Brain structure**	**Set-up**
Healthy people				
Hortensius et al. (2012)	80 psychology students (40 M)	Between subjects: anodal right vs. anodal left vs. sham	PFC	Anode_lPFC (F3) and cathode_rPFC (F4); anode_rPFC (F4) and cathode_lPFC (F3)
Dambacher et al. (2015)	43 healthy university students (20 M); age 22.14 ± 2	Between subjects: anodal vs. sham	rDLPFC	Anode_rDLPFC (F4) and cathode_left eyebrow
Riva et al. (2015)	80 healthy university students (17 M); age 23.06 ± 4.36	Between subjects: 2 (social inclusion vs. exclusion) × 2 (anodal vs. sham)	rVLPFC	Anode_rVLPFC (F6) and cathode_contralateral supraorbital area
Riva et al. (2017)	79 healthy subjects (42 M); age 21.73 ± 2.38	Mixed factorial design: 2 (non-violent vs. violent) between subjects × 2 (sham vs. anodal) between subjects × 2 (unprovoked vs. provoked) within subjects	rVLPFC	Anode_rVLPFC (F6) and cathode_contralateral supraorbital area
Chen (2018)	32 healthy subjects (16 M); age 20.25 ± 1.34	Between subjects: anodal vs. sham	rVLPFC	Anode_rVLPFC (F6) and cathode_occipital cortex (Oz)
Choy et al. (2018)	81 healthy subjects (36 M); age 20.21 ± 3.31	Between subjects: anodal vs. sham	DLPFC	Anode_rDLPFC (F4), anode_lDLPFC (F3); cathode_posterior base of the neck
Gilam et al. (2018)	25 healthy subjects (10 M); age 26.16 ± 3.63	Within subjects: anodal vs. sham	vmPFC	Anode_vmPFC (Fpz) and cathode_right shoulder
Gallucci et al. (2020)	90 healthy subjects (45 M); age 22.27 ± 2.46	Between subjects: anodal right vs. anodal left vs. sham	VLPFC	Anode_rVLPFC (F6), anode_lVLPFC (F5); cathode_contralateral supraorbital area
Ling et al. (2020)	94 university students (44 M); age 19.98 ± 1.65	Between subjects: anodal vs. sham	PFC	Anode_central (AFz) and cathode_PFC (Fp1, Fp2, F1, F2)
Clinical conditions				
Lisoni et al. (2020)	30 patients BDP or comorbidity (12 M); age 40.3 ± 12.8	Between subjects: active stimulation vs. sham	DLPFC	Anode_rDLPFC (F4) and cathode_lDLPFC (F3)
Molavi et al. (2020)	32 BPD patients according to the DMS-5-based clinical interview (15 M); age 30.63 ± 5.39	Between subjects: 2 (pre vs. post) × 2 (anodal vs. sham)	DLPFC	Anode_ lDLPFC (F3) and cathode_rDLPFC (F4)

Current × Time	Aggression measure	Results	Participant's characteristics
2 mA × 15 min	TAP	Angered subjects in a-tDCS on lPFC behave more aggressively. No relation between anger and aggression in a-tDCS on rPFC and sham	No psychiatric or neurological history; no contraindications for NIBS
2 mA × task duration	TAP; RPQ	a-tDCS on rDLPFC reduces proactive aggression in man	No history of neurological or psychiatric disorders
1.5 mA × 20 min	Hot Sauce Paradigm	a-tDCS applied over the rVLPFC decreases aggression following social exclusion	No prior or existing history of neurological disease, psychiatric disorder, epilepsy, head injury or any communication impairment
1.5 mA × 20 min	TAP	a-tDCS on rVLPFC reduces unprovoked aggression in violent-game players	N.A.
2 mA × task duration	TAP	a-tDCS on rVLPFC activity caused a reduction in both proactive and reactive aggression, in man and women	N.A.
2 mA × 20 min	Voodoo Doll	a-tDCS on DLPFC reduced intent to commit aggressive acts	No contraindications to brain stimulation; no unstable medical conditions or neurological, cardiovascular, or psychiatric illness; no participation in another NIBS study on the same day; no history of adverse reactions to tDCS.
1.5 mA × 22 min	TAP	a-tDCS on vmPFC reduced aggressive behavior following anger induction	No neurological or psychiatric disorders; no contraindications to MRI or tDCS
1.5 mA × 20 min	CRTT; Sequences Chosen Task; Tangram Task	a-tDCS on lVLPFC significantly increased aggression following frustration	No history of neurological or psychiatric disorders, and no contraindications to tDCS
2 mA × 20 min	Voodoo Doll	After a-tDCS on PFC there were no significant group differences in aggressive behavior or antisocial intentions	No neurological or psychiatric illness; no use of anticonvulsant, antipsychotic, sedative/hypnotic, or antidepressant medications; no participation in another NIBS study on the same day; no history of adverse reactions to tDCS; no pregnancy
2 mA × 20 min × 5 days × 3 weeks	BAQ	Bilateral tDCS with anodal stimulation on rDLPFC improve core dimensions of BPD (mainly impulsivity and aggression)	No: brain comorbidities, implantable medical devices, positive history for adverse events to benzodiazepines, recent brain surgery, intellectual disability, pregnancy, breastfeeding, discontinuation and variation of pharmacological medications (antidepressants, antipsychotics, mood stabilizers, benzodiazepines)
2 mA × 20 min × 10 days	Emotion Regulation Questionnaire; Emotional Processing Scale	Bilateral tDCS with anodal stimulation on lDLPFC improved cognitive reappraisal strategy, but no emotional expression or negative feelings	No previous history of neurological diseases, brain surgery, epilepsy, seizures, brain damage, head injury or metal brain implants; no psychiatric and substance use disorders; no intake of antipsychotic and anticonvulsant medications during and before the experiment for at least 8 weeks

tDCS and aggressiveness				
Study	**Sample**	**Study design**	**Brain structure**	**Set-up**
Weidler et al. (2020)	18 subjects diagnosed with alcohol dependence according to ICD-10 and 33 controls (51 M)	Between subjects: anodal vs. sham	rDLPFC	Anode_rDLPFC (F4) and cathode_contralateral supraorbital area
Smits et al. (2021)	96 military veterans and active-duty personnel of the Dutch Ministry of Defense fulfilling diagnostic criteria and receiving treatment for PTSD, an anxiety disorder or impulsive aggression problems. (89 M); age 18–60	Between subjects: 2 anodal vs. sham	rIFG	Anode_rIFG (T4-Fz and F8-Cz) and cathode_left orbital region
Offenders				
Molero-Chamizo et al. (2019)	41 imprisoned violent offenders (41 M); age 36.2 ± 12.3	Between subjects: 2 (murder vs. non murder) × 2 (anodal vs. sham)	DLPFC	Anode_lDLPFC (F3) and rDLPFC (F4); cathode_supraorbital ridges (Fp2 and Fp1)
Hofhansel et al. (2020)	23 male violent, criminal offenders and 26 male non-criminal controls. (49 M)	Between subjects: 2 (criminal offenders vs. non-criminal controls) × 2 (pre vs. post) × 2 (anodal vs. sham)	rDLPFC	Anode_rDLPFC (F4) and cathode_left supraorbital region
Sergiou et al. (2020)	50 participants from two forensic addiction clinics diagnosed with an alcohol and/or cocaine SUD (50 M); aged 18–60	Between subjects: 2 (pre vs. post) × 2 (anodal vs. sham)	vmPFC	Anode_vmPFC (Fpz) and cathode_PFC (AF3 and AF4), central (Fz), lDLPFC (F3), rDLPFC (F4)

Abbreviations: BAQ, Buss-Perry Aggression Questionnaire; CRTT, Competitive Reaction-Time Task; DLPFC, Dorsolateral Prefrontal Cortex; IFG, Inferior Frontal Gyrus TAP, Taylor Aggression Paradigm; l, left; PFC, Prefrontal Cortex; PSAP, Point Subtraction Aggression Paradigm; r, right; RPQ, Reactive and Proactive Aggression Questionnaire; VLPFC, Ventrolateral Prefrontal Cortex; vmPFC, ventromedial Prefrontal Cortex.

self-concepts and personal expectations. Due to people's propensity to seek information that does not disconfirm their vision of the world, beliefs and schemes tend to be reinforced and hardly modifiable [102]. One of the possible general schemes to interpret the social world is the *aggressive personality style* [103]. People adopting this style chronically interpret aggressive behaviors as intentionally hostile; this pattern operates in a self-fulfilling prophecy and in a self-reinforcing way, hence increasing its stability across the life span [104].

7.1 | Angry facial expression in healthy people

Facial emotions play a crucial role in understanding the interlocutor's intentions. Aggressions could arise from a misidentification of an ambiguous face as angry [105]. People driven by hostile attribution bias could misjudge others' intentions and attack the interlocutor. Hall [24] showed that we perceive the world through our peculiar schemes and interpret environments coherently with them.

Current × Time	Aggression measure	Results	Participant's characteristics
1.5 mA × 20 min	Modified TAP	a-tDCS on rDLPFC can reduce impulsivity and enhance aggressive behaviors in Alcohol Dependent-patients	No history of seizures; no comorbidities if alcohol dependence was not the primary diagnosis. Comorbidities: depression (n = 6), PTSD (n = 2), social anxiety (n = 2), specific phobia (n = 1), dysthymia (n = 1), and panic disorder (n = 1). Medication affecting the central nervous system included atypical antidepressants (n = 3), benzodiazepines (n = 2), methadone (n = 2), antipsychotic medication (n = 1), selective serotonin reuptake inhibitors (n = 1), and anticonvulsants (n = 1). Nine patients did not take any medication
1.25 mA × 20 min × 1–5 days	STAXI-II	a-tDCS on rIFG did not influence symptoms of impulsivity and aggression	No primary diagnosis for: major depressive disorder (comorbid depression was not a reason for exclusion), substance addiction, severe neurological or psychotic disorder, serious head trauma or surgery, large metal or ferromagnetic parts in the head, implanted pacemaker or neurostimulator, pregnancy, skin damage on the scalp, and neurostimulation in the past month.
1.5 mA × 15 min × 3 days	BAQ	3 sessions of a-tDCS on PFC reduces self-perceived aggressiveness	No metal implants, diagnosis of epilepsy, psychosis or other neuropsychiatric disorders or being under central nervous system-active medication. Crimes committed non-murderer: robberies with violence (n = 7), fights for drug trafficking (n = 10) or gender violence (n = 9). Crimes of murderer: robberies with extreme violence (n = 3), fights for drug trafficking resulting in murder (n = 6), or gender murder (n = 5) (except one murder case categorized as "by offer or reward")
1.5 mA × 20 min	Emotion Regulation Task	Single session of a-tDCS on rDLPFC did not improve the self-reported ability to regulate negative emotions either in non-criminal controls or in criminal offenders.	Convictions of the criminal offenders included robbery (n = 11), assault (n = 8), sexual offenses (n = 2) and manslaughter (n = 2)
2 mA × 20 min × twice a day × 5 days	PSAP; RPQ	Multiple sessions of anodal HD-tDCS on vmPFC results in reduced aggression. In a-tDCS group increases in LPP amplitude for both images representing victims of aggressions and neutral interactions	No: major neurological conditions (e.g., traumatic brain injury), major mental disorders (e.g., psychotic disorders or major depression) or heavy medication such as antipsychotics.

In fact, the author found that people self-reporting high-aggressive attitudes tend to misperceive and misattribute anger even where it does not exist. Consistent with this, Taylor & Jose [106] showed that physically high-aggressive individuals make significantly more misattribution errors than participants with low levels of physical aggression. In agreement with Taylor & Jose's [106] hypothesis, among the general population, misattribution errors vary according to the level of physical aggression. Recognition of emotional facial expressions in healthy adults can be enhanced using tDCS. In fact, a-tDCS stimulation on the right Orbitofrontal Cortex (rOFC) (2 mA × 20 min) increases speed and efficiency in facial expressions recognition [20], whereas anodal stimulation (1 mA × 10 min) over the lDLPFC improves more affective positive identification than affective negative faces [20].

7.2 | Angry facial expression and offenders

To better understand the relationship between facial processing and aggressiveness, it could be useful to include prisoner samples, due to the prominent presence of violent or antisocial behaviors in this population. In fact, violent offenders seem to be less competent at recognizing negative emotions than non-violent offenders and non-offenders [107]. Moreover, violent offenders have been shown to interpret and perceive stimuli as threat signals when watching pictures in which fearful body language contrasts with a smiling face [108]. A possible explanation is that violent criminals tend to misjudge fearful body movements as aggressive ones. Violent offenders were also impaired in recognizing happy faces when simultaneously presented as part of aggressive body postures [108]. This way of interpreting reality is consistent with the hostile attribution bias, since violent people misjudge ambiguous facial expressions as angry and exhibit hostile behaviors. Wegrzyn et al. [109] presented morphed fear-anger faces to three different groups: violent crimes prisoners, inmates who committed child sexual abuse, and non-prisoners control participants. Only violent offenders exhibited the hostile attribution bias by rating ambiguous faces as more provocative than the child sexual abusers and controls. Given that the understanding of facial expressions is a decision-making process, the tendency to interpret ambiguous faces as angry could not simply arise from a bias. The decision-making process for angry faces is more efficient in violent people, since they are more accurate at identifying anger in ambiguous faces (e.g., fear-angry faces) [110]. Previous evidence suggests that the environment could play an important role in anger facial expression perception. In fact, aggressive individuals have stronger and more accessible hostile memory schemes, which are essentially latent memories of hostility-related events [1]. These schemes are made up by experiencing an aggressive environment and have a functional role for survival in a hostile context. Thus, we can speculate that individuals exhibiting aggressive behaviors perceive anger in faces more accurately and faster than others as a result of an evolutionary inheritance [110].

8 | GENERAL DISCUSSION

During social interactions, a hostile world scheme could lead to a hostile and threatening attribution toward others' intentions. This pattern operates as a self-fulfilling prophecy and it is self-reinforcing, becoming stable across the lifespan [104]. Emotional facial expressions are salient cues we need to interpret in social interactions in order to act appropriately. A person driven by hostile attribution bias could misjudge others' intentions and react aggressively. Some studies demonstrated that violent inmates exhibit a hostile attribution bias [109]. In fact, they manifest a different perception of anger-related stimuli if compared to non-violent people [107,108]. Moreover, they exhibit higher accuracy at identifying anger in ambiguous faces [110]. This evidence suggests that aggressive behaviors could be the consequence of the interpretation of ambiguous facial expressions as hostiles. Hence, disambiguating equivocal faces could reduce reactive aggressiveness. Some studies already showed tDCS potentiality to improve the interpretation of facial expression [20,21], leading to decreased aggressive behaviors. In addition to facial emotion perception, inhibitory control abilities are necessary to control aggression too. As previously reported, BDP is characterized by marked impulsivity, which can lead to aggressive manifestations. Thus far, the literature on BPD interventions using NIBS is very sparse and focalized on PFC. Indeed, certain NIBS studies focused on DLPFC, showed that a higher number of TMS sessions can induce global improvement in BPD symptoms, particularly in impulsiveness, affective instability, and anger [77,78]. Despite the strict number of studies using tDCS, the available results are promising.

In fact, bilateral tDCS (anodal on the right and cathodal on the left hemisphere) targeting DLPFC improves core dimensions of BPD [65], and bilateral tDCS (anodal on the left lobe and cathodal on the left–right) over DLPFC facilitate executive functioning and cognitive control [69]. These variations in frontal activity could help to evaluate stimuli and situations as less threatening and reduce reactive aggressiveness. Similarly, alcohol-dependent patients showed an improvement in reactive aggressiveness after a-tDCS over rDLPFC [87].

Additionally, healthy people studies confirm the beneficial effect of tDCS over PFC. Hortensius et al. [30] targeted lPFC with a-tDCS, discovering that stimulation of the left hemisphere exacerbates aggressiveness. Consistently with Hortensius et al. [30], while a-tDCS on lDLPFC increased aggressiveness, the same protocol applied to rDLPFC reduced proactive aggression, although only in men [30,33]. Drawing attention to vmPFC, the increased excitability in this area reduces reactive aggression [41]; Furthermore, VLPFC stimulation diminishes both proactive and reactive aggression [39]. In particular, a-tDCS on rVLPFC decreases proactive aggression, pain following social exclusion, and its related reactive aggressive behaviors [46,48].

There are few attempts to extend the use of NIBS on violent prisoners. These studies highlight how tDCS can be a useful tool for integrating interventions aimed at this specific population. Indeed, tDCS seems to help reducing aggression in murders [94] as well as in increasing empathic abilities [96].

9 | LIMITS AND FUTURE PERSPECTIVES

The studies considered in this paper (Table 1) have some limitations. Deep knowledge of the participant's clinical condition is fundamental for understanding the interaction between pathology and the potential stimulation's effects. Given that only one [94] out of 3 studies provides clinical and psychopathological information about the forensic population under investigation, any assumption on the impact of tDCS on brain pathology might be very hazardous. Moreover, we can speculate that the clinical heterogeneity of the inmates' populations could impact the results and mediate the effects of the stimulation. Further research is needed in this field to control the effect of

confounding variables (e.g., substance abuse, psychiatric condition, medications, etc.).

Furthermore, many studies have enrolled male participants only, making it impossible to investigate potential gender effects [88,90,94,96]. Further methodological limitations concern the single tDCS sessions and absence of follow-up measures [30,33,39,41,46,48,52,88]; indeed, given that the literature focuses on the acute effects of the stimulation (i.e., immediately after the stimulation), no evidence is available for the long-term effects. In addition, limited sample sizes (approximately 30 participants) might represent an obstacle for results generalization [21,33,39,41]. Given that the authors did not demonstrate effects specificity in terms of brain region, it cannot be excluded that different target areas were responsible for the observed behavioral effects [46,48]. A final issue is related to ethical concerns about tDCS usage in the prison context. Since prisoners are vulnerable subjects experiencing a coercive environment, their autonomy to participate in studies could be undermined. However, the participation in research was based on informed consent, and their autonomy to self-determine was preserved. Moreover, participation did not benefit nor damage them.

An interesting perspective consists in the application of Virtual Reality (VR) in conjunction with brain stimulation for interventional purposes [111]. VR's advantage is in its potentiality to expose participants' to controlled, provocative virtual social situations, with a great level of ecological validity. VR could also represent a useful tool in perspective-taking interventions. In the study from Seinfeld et al. [112], violent male offenders were exposed to VR domestic violence scenes from a victim's perspective. After this intervention, offenders' sensitivity to recognize fear in female facial expressions improved significantly. Moreover, there was a reduction in offenders' bias toward misjudging happy facial expressions as fearful.

To sum up, analyzed studies highlight the important role of DLPFC in modulating aggression. Molero-Chamizo et al. [94] obtained interesting results in the application of tDCS interventions on aggressive prisoner populations, but further research is needed on other aggressive populations such as ASPD or Intermitting Explosive Disorder patients. Aggressive or violent people (e.g., criminals), may also benefit from gradual and controlled exposure to real provocative scenes. For this reason, we believe future interventions on violent offenders could combine multiple sessions of a-tDCS targeting rDLPFC and VR, in order to restrain aggressions through the exposure to realistic scenarios.

ORCID

Giuseppe Volpe https://orcid.org/0000-0002-1238-1774

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