Archival Report

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Transcranial Direct Current Stimulation Targeting the Ventromedial Prefrontal Cortex Reduces Reactive Aggression and Modulates Electrophysiological Responses in a Forensic Population

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ABSTRACT

BACKGROUND: Studies have shown that impairments in the ventromedial prefrontal cortex play a crucial role in violent behavior in forensic patients who also abuse cocaine and alcohol. Moreover, interventions that aimed to reduce violence risk in those patients are found not to be optimal. A promising intervention might be to modulate the ventromedial prefrontal cortex by high-definition (HD) transcranial direct current stimulation (tDCS). The current study aimed to examine HD-tDCS as an intervention to increase empathic abilities and reduce violent behavior in forensic substance dependent offenders. In addition, using electroencephalography, we examined the effects on the P3 and the late positive potential of the event-related potentials in reaction to situations that depict victims of aggression.

METHODS: Fifty male forensic patients with a substance dependence were tested in a double-blind, placebo-controlled randomized study. The patients received HD-tDCS 2 times a day for 20 minutes for 5 consecutive days. Before and after the intervention, the patients completed self-reports and performed the Point Subtraction Aggression Paradigm, and electroencephalography was recorded while patients performed an empathy task.

RESULTS: Results showed a decrease in aggressive responses on the Point Subtraction Aggression Paradigm and in self-reported reactive aggression in the active tDCS group. Additionally, we found a general increase in late positive potential amplitude after active tDCS. No effects on trait empathy and the P3 were found.

CONCLUSIONS: Current findings are the first to find positive effects of HD-tDCS in reducing aggression and modulating electrophysiological responses in forensic patients, showing the potential of using tDCS as an intervention to reduce aggression in forensic mental health care.

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Substance abuse is a major concern in forensic patients and poses a major risk for violence in these individuals (1). Substance use offenders are found to have increased odds of violent behavior (2–9). Moreover, repeatedly using substances has been found to be associated with functional neuroadaptations in the prefrontal cortex (PFC) (2,3). Especially the ventromedial PFC (vmPFC) is found to be associated with substance use disorders in regulating reward processing and motivational salience (3,10–15). Recent studies (6,7) show that the vmPFC is also involved in antisocial behavior, especially aggression (16,17) and impulsivity, in abusers of alcohol and cocaine (18–24). The vmPFC is found to be crucial for regulating emotions (25–37) and has a specific role in theory of mind processes (31,32) that are vital in empathic processing as a result of cognitive adoption of the other's perspective (38).

In addition, neuroimaging studies showed that the structures that are relevant for empathy and the modulation of aggressive behavior, namely the vmPFC and medial frontal regions (7,39–49), are impaired in individuals with antisocial traits (50–54). One study (55) used the Point Subtraction Aggression Paradigm (PSAP) (56) and also indicated a link between brain activity in the vmPFC and aggressive behavior, proposing the vmPFC to be a neural substrate related to aggressive provocation (55). Other studies (57–62) demonstrated that the vmPFC is related to increasing costs and retaliation of the aggressor and greater punishment choices.

Following the proposed neurocognitive models of Blair (39,42,63), violence is inhibited by empathy, and therefore individuals with deficits in their empathic abilities are less susceptible to violence and are less motivated to inhibit aggression, which increases the risk of violent behavior (64).

Whereas the association between the PFC and aggression has been studied in different neuroimaging, behavioral, and clinical studies, to our knowledge, little is known about the

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causal role of the vmPFC in empathic abilities and violent behavior in forensic patients. Therefore, modulating the vmPFC to increase empathic abilities and reduce violent behavior in these patients could be of substantial importance for supporting a causal relation and for formulating new treatment interventions.

A promising tool to modulate empathic abilities and aggression is transcranial direct current stimulation (tDCS). In a review paper, Sergiou *et al.* (65) reviewed multiple studies that used tDCS to modulate aggression (66–68) or empathic abilities (41,69–71), and they concluded that the vmPFC would be the most promising target area for modulating these behaviors. tDCS is a neuromodulation technique that uses electrical currents to increase or decrease activity in the brain region of interest and has been proven effective in many disorders (72–74). tDCS uses a subthreshold modulation of the membrane potentials of neurons through altering cortical excitability (75,76) and can change synaptic neuronal plasticity (74). This change in neuronal plasticity is found to produce long-term potentiation–like learning in the modulated neurons (77–79). In this rapidly evolving field, studies have shown that the stimulation effect is based on the strength and duration of the current and on polarity-dependent changes (80–82) and that the results of modulation could be changed because of the nature of previous brain activity, as described by the Bienenstock-Cooper-Munroe rule (83) (84–88).

To date, the majority of the studies that investigate the modulation of the PFC have relied on conventional tDCS, upregulating one side of the brain and downregulating the contralateral region (89). An even more promising tDCS technique is high-definition tDCS (HD-tDCS), which uses multiple compact (i.e., <5 cm^2) circular electrodes to deliver the low current (90), and studies have shown that HD-tDCS can target brain structures with higher focality (91). In this way, deeper regions of the brain, such as the vmPFC, can be modulated in an optimal way (92–98). Therefore, in the present study we used a protocol using HD-tDCS targeting the vmPFC, with multiple sessions and with enhancing the brain state during modulation to maximize the effect (99–102).

To study the effect of tDCS on brain functioning, the temporal dynamics could be studied using electroencephalography (EEG) (103–105). The event-related potential (ERP) technique has mostly been used to investigate empathy by measuring brain responses to pictures. Studies have shown that both early and late ERP components are related to perceived pain in others (103,106,107) and in reaction to self-reported trait empathy (105, 108–110). Two ERPs that have been studied extensively are the P3 and late positive potential (LPP).

The P3 is an ERP that has a positive voltage in the latency of 300–650 ms (111). The P3 is typically associated with controlling sustained attention toward salient stimuli (111) and has been linked to empathy for pain (103,106,112–116). The LPP is a positively sustained ERP that occurs around 400–1000 ms, is located at the parietal locations and the central midline (117), and is associated with empathy and emotional cues. A study of Cuthbert *et al.* (112) demonstrated that the LPP indicates an increase in amplitude toward emotional stimuli, arousal, regulation, facial expressions, and affective experience regulation, and the study of Van Dongen *et al.* (105) found reduced P3 and LPP in individuals with decreased empathic abilities. Therefore, studying these positive potentials contributes to the understanding of emotional regulation (103,112,118,119) and serves as an indication that the temporal dynamics of empathic processing in the brain can be studied using late ERPs in the EEG.

The main aim of the current study was to examine whether modulating activity in the vmPFC using HD-tDCS would increase empathic abilities and reduce aggressive behavior in forensic patients with substance dependence. In addition, in this study we investigated the effects of the HD-tDCS intervention on electrophysiological responses (P3 and LPP) to situations that depict victims of aggression (i.e., empathy). Based on prior literature, it was expected that after active tDCS, compared with sham, empathic abilities would increase and aggression would decrease. Additionally, it was expected that the P3 and LPP amplitude after viewing pictures that depict victims of aggression would be increased after active tDCS compared with sham tDCS.

Knowledge gained from the current study will give insight in the casual relation among activity in the vmPFC, empathy, and aggression and can inform in the development of new neuromodulation (e.g., tDCS) protocols for treatment interventions in violent forensic populations.

METHODS AND MATERIALS

Participants

Fifty male participants (mean age = 37.40 years, SD = 9.19 years, range: 22–62 years) were recruited from two departments of the division for forensic addiction mental health care in Antes, Poortugaal, the Netherlands, between February and October 2019. Twenty-one participants were recruited at the Forensic Addiction Clinic and 29 from the Department of Forensic Care. The patients were randomly assigned to one of the conditions and participated in a double-blind, placebo-controlled study with two conditions. Twenty-five participants received treatment as usual (TAU) + active stimulation, and 25 participants received TAU + sham (placebo). For an overview of the demographic characteristics of the sample, see Table 1. Inclusion and exclusion criteria are presented in the Supplement.

The participant flow and recruitment according to CONSORT (Consolidated Standards of Reporting Trials) can be found in Figure S1.

Procedure and Design

The study consisted of a double-blind, placebo-controlled, randomized trial comparing a group that received active HD-tDCS intervention with a sham control group. Baseline assessments including self-report questionnaires, a resting-state EEG task, passive viewing task (105), rating empathy task (105), and the PSAP (56) were conducted during the preintervention. During the following week, the participants received two 20-minute sessions of HD-tDCS stimulation or sham intervention targeting the vmPFC for 5 consecutive days (see Figure S2 for a flowchart of the procedure). There were approximately 3–4 hours between the two sessions, depending on the patients' schedule and TAU. Outcome measurements were conducted 1 week later during the postintervention. Self-report questionnaires and tasks were conducted in a fixed order.

Table 1. Demographic Characteristics

	tDCS Group		Sham Group	
Characteristic	*n*	%	*n*	%
Caucasian	25	100	23	92
Non-Caucasian	0	–	2	8
Primary Education	9	36	8	32
High School	7	28	6	24
Secondary Education (VET)	9	36	11	44
DSM-5 Axis I	7	28	10	40
DSM-5 Axis II	8	32	10	40
Mono Substance Use	8	32	9	36
Poly Substance Use	17	68	16	64

Characteristics are displayed in percentage of participants per group, $N = 50$ ($n = 25$ for each condition). Participants were on average 36.4 years old (SD = 8.88) in the tDCS group and on average 38.4 years old in the sham group (SD = 9.56), and participant age did not differ by condition.

VET, Vocational Education and Training.

A study by Nissim *et al.* (82) using functional magnetic resonance imaging demonstrated that the optimal gains from using tDCS could be realized by increasing the activity of the brain area of interest (i.e., the brain state). Therefore, to optimize our intervention, we increased the activity of the vmPFC while triggering these brain states by showing the subjects two empathic movies [*Wonder* (120) and *I am Sam* (121)] and using the Reading the Mind in the Eyes task (122). Patients and investigators were blinded to the tDCS allocation. The principal investigator of the project, who was not involved in data collection and initial statistical analysis, preprogrammed the tDCS device in active condition or sham condition matched with a number.

The study was conducted in accordance with the ethical standard of the Declaration of Helsinki (123) and was approved by Medical and Ethical Review Board of the Erasmus Medical Centre Rotterdam, Rotterdam, the Netherlands. The trial protocol was registered at the Dutch Trial Register (NTR7701). See also Sergiou *et al.* (124) for the complete published study protocol.

High-Definition tDCS Intervention

HD-tDCS was administered with the European Conformity–certified Neuroelectrics Starstim8 (Neuroelectrics Barcelona, SLU), operating according to the evidence-based guidelines of LeFaucheur *et al.* (125). Before commencement of the study, the HD-tDCS montage optimization was based on the current-flow modeling of the NIC software of the tDCS Starstim8 system [see the protocol (124) for detailed description]. In addition, the induced E-field of the HD-tDCS montage was computed in SimNibs (version 3.2) (126). Detailed description on biophysical modeling can be found in the Supplement.

The currents were transmitted through six circular Ag/AgCl PiStim high-definition electrodes (1 cm radius, π cm^2) that were applied with conductive gel (Figure 1). The resulting Norm-E field and Normal E-field distribution is created in Gmsh (version 4.7.1) (127) with an output range from 0 to 0.25 V/m. The HD-tDCS device was programed for stimulation with 2 mA tDCS during 20 minutes for modulating the vmPFC of the participants in the active condition. The sham condition followed the same procedure, with a 30-second ramping-up and down the tDCS currents at the beginning and end of the protocol, based on earlier research indicating this method being effective for blinding (128). The anodal electrode was placed on the Fpz location, and the five return or cathodal electrodes were placed on AF3, AF4, F3, Fz, and F4 (see Figure 1 for the electrical field model and the Supplement for detailed description of the biophysical modeling).

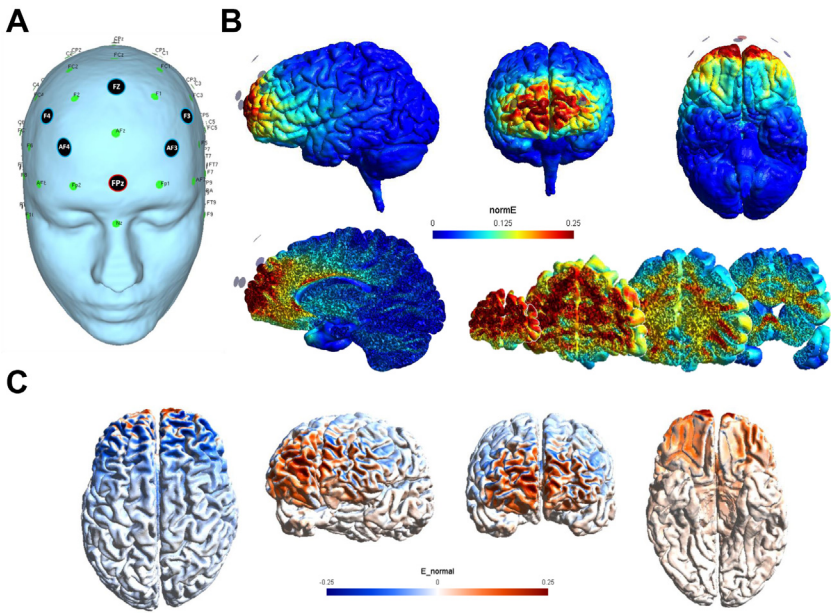

Figure 1. **(A)** Placement of the electrodes at 32 standard 10–20 electroencephalography system on the scalp with anodal high-definition transcranial direct current stimulation (HD-tDCS) with 6 × 1-cm radius (π cm^2) electrodes over the Fpz (2 mA) and cathodal tDCS over AF3, AF4, F3, F4, and Fz (−0.4 mA each). **(B)** Different views and slices of the map of electrical field induced by HD-tDCS montage as expressed in normE (V/m). This measure allows us to see the intensity of the stimulation independently by the polarity. **(C)** Views of the map of the electrical field expressed in normalE (E_normal) (V/m) showing the polarity (anodal/cathodal) of the stimulation.

Electrophysiological Measurement Empathy

To assess EEG measuring empathy, the patients had to perform a passive viewing empathy task (105). This task was designed to measure empathic abilities through EEG. This task consists of 95 pictures displaying scenes for 6000 ms with an aggressive interaction (40), a neutral interaction (40), or a neutral object (i.e., fillers; 15). The aggressive pictures consisted of either a sexual, verbal, or physical interaction. Participants were instructed to view all the pictures passively; in this way, the automatic neural responding in the brain could be determined in the most optimal way (105).

State Empathy

To assess state empathy, the patients had to perform a rating empathy task (105). Following the passive viewing empathy task, the 95 pictures were presented another time to the patients. In this task, they were instructed to rate the pictures by answering four questions regarding arousal, emotional valence, and empathy for victim and perpetrator.

Aggression Task

To assess aggression, we used the PSAP (56). The PSAP is one of the best-validated paradigms to measure aggression in a lab environment (129).

A detailed description of the tasks used in this study included in the Supplement.

Self-report Questionnaires

For a complete overview of the self-report questionnaires used in the overall study, see Sergiou *et al.* (124). The questionnaires used in the analysis of this paper mentioned below and described in more detail in the Supplement.

Reactive and Proactive Aggression Questionnaire. In order to index aggression over a week-long period, we used the Dutch translation of the Reactive and Proactive Aggression Questionnaire (RPQ) (130,131).

Interpersonal Reactivity Index. In order to assess trait empathy, we used the Dutch translation of the Interpersonal Reactivity Index (132,133); this is a commonly used self-report instrument designed to assess empathic tendencies.

The Alcohol Use Disorders Identification Test. In order to assess alcohol use, we used the Dutch translation of the Alcohol Use Disorders Identification Test (134,135). The ten-item Alcohol Use Disorders Identification Test includes questions to assess alcohol, intake, alcohol dependence, and alcohol-related problems.

The Drug Use Disorders Identification Test. In order to assess drug use, we used the Dutch translation of the Drug Use Disorders Identification Test (136,137). The Drug Use Disorders Identification Test is an eleven-item screening instrument to assess nonalcohol drug use patterns and various drug-related problems.

EEG Recording

EEG was recorded using a mobile version of the Brain Products Active-Two System amplifier (Brain Products GmbH). Thirty-two electrodes were placed on the scalp of each participant following the international 10–20 EEG-system. Two other additional electrodes were placed vertically above and beneath the left eye (electro-oculogram); the electrodes for the left and right mastoid placement were incorporated in the EEG cap. The EEG and electro-oculogram signals were digitized with a sampling rate of 500 Hz and 24-bit analog-to-digital conversion with offline filtering.

EEG Data Preprocessing

Data were preprocessed offline using Brain Vision Analyzer (Brain Products GmbH). Segmentation was done per condition (neutral vs. aggression) for both P3 and LPP at pretest and posttest, in an interval of 1200 ms (−200 to 1000 ms) [see Van Dongen *et al.* (105)] relative to stimulus presentation. Next, the data were filtered using a bandpass filter ranging from 0.01 to 30 Hz (phase shift-free Butterworth filters; 24 dB/octave slope), the signal was corrected for ocular artifacts using the Gratton and Coles algorithm (138), trials with remaining artifacts (i.e., segments with an EEG signal exceeding an amplitude of 100 μV) were excluded from further analysis (105), and data were baseline-corrected (200 ms preresponse or prestimulus period served as baseline). Nine participants had to be removed from the analyses owing to excessive amounts of artifacts in the data (i.e., $<$15 artifact-free segments). Bad channels with too many artifacts were corrected with topographical interpolation. This resulted in a set of EEG data of 41 participants, 21 in the sham condition and 20 in the active tDCS condition.

Because the highest amplitude of P3 and LPP typically is seen at Pz (139,140), inspection of the grand average ERPs demonstrated a maximal amplitude for aggressive pictures around 400 ms after stimulus onset (P3) and followed by the slow wave activity of the LPP, which returned to baseline after 6000 ms. For analyzing the ERPs, the P3 amplitude was defined as the mean amplitude of the Pz between 350 and 450 ms after stimulus onset (105,106). The LPP was analyzed at the mean amplitude of the Pz between 500 and 1000 ms after stimulus onset (105,141). The average signal per condition was then used for determining the characteristics of the ERP.

Statistical Analyses

Self-report and the electrophysiological outcomes were analyzed using SPSS 25 (IBM Corp.). To test the differences between the active and the sham group from pre- to posttest on the state empathy following the aggression versus the neutral condition, four 2 (time; pre vs. post) $\times$ 2 (group; active tDCS vs. sham) analyses of variance were conducted for the scoring on arousal, emotional valence, victim, and perpetrator. Similarly, to test the differences between the active and the sham group from pre- to posttest on state aggression (PSAP), a repeated measures analysis of variance was performed. Aggression was indicated by the proportion of aggressive responses, that is, the number 2 (aggressive response option) presses divided by the total amount of presses (i.e., [no. option 2]/[no. of total button presses]).

To investigate the electrophysiological outcomes of the P3 and LPP, two 2 (time; pre vs. post) × 2 (emotion; aggressive vs. neutral) × 2 (group; active tDCS vs. sham) repeated measures analyses of variance were conducted. For all statistical tests, the level of significance was set at $p < .05$.

RESULTS

The result from the HD-tDCS simulation (Figure 1B) demonstrates that the vmPFC was reached with intensity sufficient to induce effect of the stimulation (0.11–0.2 V/m) (see the Supplement for details).

See Table S1 for a report on adverse effects. Descriptive statistics for all the measures used in this study, including all the self-report questionnaires, can be found in Table 2. Results showed no significant difference between medication use and the two conditions (tDCS and sham), χ^2_3 (N = 50) = 3.1, p = .378 (Table S2).

State Empathy Outcomes

Concerning state empathy, there were no significant main effects for arousal, emotional valence, empathy for victim, or empathy for perpetrator between the tDCS group and the sham group from pre- to posttest. Furthermore, we did not find any significant interaction effects.

Aggression Outcomes

Regarding the PSAP task, there were no significant main effects for time or group.

Table 2. Descriptive Statistics for Self-report Questionnaires, Rating Task, PSAP, P3, and LPP Amplitudes

	tDCS Group			Sham Group		
Variable	Mean	SD	Range	Mean	SD	Range
Time 1 (Pretest)						
DIFF_Arousal	2.52	2.14	−0.40 to 7.28	3.99	2.49	0.08 to 7.47
DIFF_Emotion	−1.15	2.34	−4.15 to 4.63	−2.18	2.35	−6.95 to 3.3
DIFF_Victim	1.76	1.89	−3.07 to 5.05	2.11	2.60	−3.42 to 6.65
DIFF_Perpetrator	−1.22	1.99	−3.75 to 4.00	−2.33	2.05	6.80 to 1.60
PSAP	0.12	0.09	0.0 to 0.47	0.09	0.10	0.00 to 0.37
RPQ Total	21.08	8.14	6 to 43	17.68	8.61	6 to 39
RPQ Reactive	12.48	4.01	3 to 22	11.40	4.37	4 to 22
RPQ Proactive	8.60	4.69	2 to 21	6.28	4.82	0 to 17
IRI Total	55.00	14.73	26 to 84	56.60	14.60	33 to 88
SRP-SF Total	78.56	14.28	54 to 98	72.88	20.54	43 to 133
AUDIT	12.35	12.61	0 to 37	11.41	12.76	0 to 40
DUDIT	22.44	12.51	0 to 40	18.74	13.63	0 to 40
P3 Amplitude NEU	2.41	5.23	−7.91 to 11.59	2.93	4.25	−4.87 to 11.89
P3 Amplitude AGG	3.34	4.38	−5.56 to 14.14	3.21	4.97	−8.74 to 12.82
LPP Amplitude NEU	1.29	6.86	−18.21 to 15.19	1.76	4.85	−9.92 to 11.52
LPP Amplitude AGG	2.42	5.48	−13.43 to 10.23	3.27	5.85	−10.13 to 13.13
Time 2 (Posttest)						
DIFF_Arousal	2.78	2.44	−1.05 to 7.55	3.29	2.61	−0.23 to 7.60
DIFF_Emotion	−1.38	2.33	−5.72 to 3.45	−1.73	2.17	−7.25 to 1.90
DIFF_Victim	1.45	2.24	−4.00 to 3.78	1.27	2.86	−3.75 to 7.60
DIFF_Perpetrator	−1.74	3.77	3.95 to 3.77	−1.67	2.34	−7.60 to 2.60
PSAP	0.07	0.07	0.0 to 0.33	0.15	0.19	0 to 66
RPQ Total	18.58	9.66	8 to 45	16.36	8.53	2 to 36
RPQ Reactive	11.20	4.71	3 to 22	10.32	4.25	2 to 20
RPQ Proactive	7.37	5.54	0 to 23	6.04	4.75	0 to 16
IRI Total	56.30	10.45	39 to 75	56.45	12.66	37 to 80
SRP-SF Total	74.96	18.09	37 to 113	65.32	15.85	28 to 99
AUDIT	13.76	13.03	0 to 37	8.36	9.18	0 to 33
DUDIT	19.95	11.59	0 to 38	14.47	12.20	0 to 38
P3 Amplitude NEU	3.13	2.99	−1.87 to 8.65	0.51	3.96	−8.14 to 8.89
P3 Amplitude AGG	4.18	3.85	−1.87 to 13.59	1.79	6.12	−12.57 to 14.73
LPP Amplitude NEU	2.15	5.87	−19.45 to 10.44	−0.11	3.79	−12.88 to 5.68
LPP Amplitude AGG	5.20	3.65	−0.89 to 13.09	2.82	6.04	−17.48 to 12.18

AGG, aggression condition; AUDIT, Alcohol Use Disorder Identification Test; DIFF, difference score; DUDIT, Drug Use Disorder Identification Test; IRI, Interpersonal Reactivity Index; LPP, late positive potential; NEU, neutral condition; PSAP, Point Subtraction Aggression Paradigm; RPQ, Reactive Proactive Aggression Questionnaire; SRP-SF, Self-Report Psychopathy Short Form.

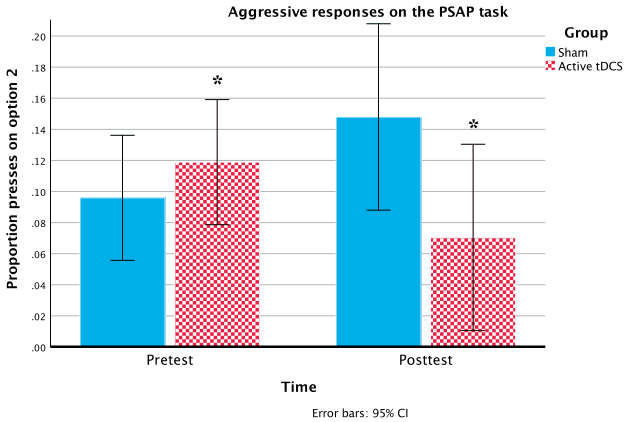

Figure 2. Proportion of aggressive responses on the Point Subtraction Aggression Paradigm (PSAP) for the sham group and active transcranial direct current stimulation (tDCS) group from pre- to posttest. *Significant effect at $p \leq .05$.

We did find a significant time × group interaction effect (Figure 2), with $F_{1,48} = 5.87$, $p < .019$, $\eta_p^2 = 0.11$. Post hoc tests revealed that the effect is significant ($p = .027$) for the tDCS group and not significant for the sham group ($p = .192$). These results imply that the decrease in aggression from pre- to posttest was significantly stronger in the tDCS group than in the control group, with a moderate to large effect (142).

Self-report Questionnaires

Regarding the RPQ, we found a significant effect of time on the RPQ total score $F_{1,47} = 9.51$, $p = .003$, $\eta_p^2 = 0.25$) and RPQ reactive aggression subscale ($F_{1,48} = 10.68$, $p = .002$, $\eta_p^2 = 0.19$) over the two groups. There were no main effects of group. These results indicate a significant reduction in self-reported reactive aggression after the intervention as compared with the pretest across both groups. There were no significant findings for the Self-Report Psychopathy Short Form, Interpersonal Reactivity Index, Alcohol Use Disorders Identification Test, or Drug Use Disorders Identification Test.

P3 and LPP

See Figure 3 for an overview of the grand average of P3 and LPP in the active tDCS and sham group from pre- to posttest.

Analyses of the P3 amplitude showed no significant main effect for time, group, or emotion. The results indicated a significant interaction effect between time and group ($F_{1,39} = 4.52$, $p = .040$, $\eta_p^2 = 0.10$) but not for emotion. Follow-up t tests revealed that the sham group showed a significant ($t_{20} = 3.07$, $p < .01$) decrease in P3 amplitude from pretest (mean = 3.07, SD = 3.82) to posttest (mean = 1.47, SD = 4.76). Graphs are displayed in Figure 4.

Analyses of the LPP amplitude resulted in a significant main effect for emotion ($F_{1,39} = 5.62$, $p = .023$, $\eta_p^2 = 0.13$), meaning that aggression pictures led to higher LPP amplitudes compared with the neutral pictures in both groups. There were no main effects for time or group. In addition, we found a significant interaction effect between time and group ($F_{1,39} = 5.66$, $p = .022$, $\eta_p^2 = 0.009$). Follow-up t tests revealed that the tDCS group showed a significant ($t_{19} = -2.29$, $p = .03$) increase

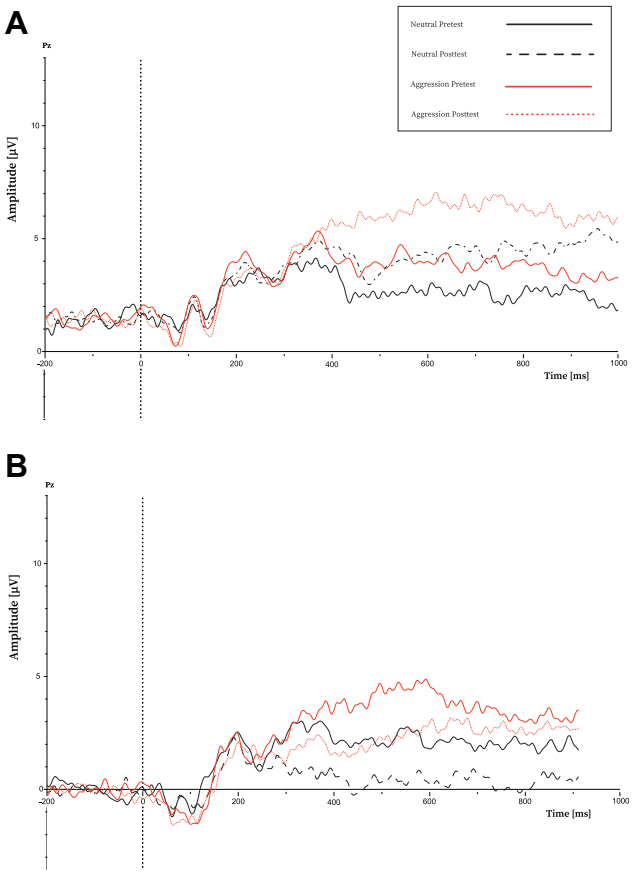

Figure 3. **(A)** Event-related potentials grand mean recorded at Pz during the passive empathy task for the active high-definition–transcranial direct current stimulation condition. **(B)** Event-related potentials grand mean recorded at Pz during the passive empathy task for sham condition.

in LPP amplitude compared with the sham group, from pre- to posttest, independent of emotion, meaning an overall increase in amplitude after the intervention for the tDCS group. Graphs are displayed in Figure 5.

To check whether the increase in LPP amplitude from pre- to posttest for both aggression and neutral pictures was also present in the filler pictures, an additional analysis was performed (see the Supplement). Results showed no significant effects on time, group, or emotion.

DISCUSSION

The aim of this study was twofold. First, we examined HD-tDCS as an intervention to increase empathic abilities and reduce violent behavior in forensic patients with a substance dependence. Second, we examined the HD-tDCS effects on the electrophysiological responses (P3 and LPP) to situations depicting victims of aggression. Because the intervention was the tDCS treatment in addition to TAU, all the found effects are a product of the interaction between the intervention (or placebo) and the TAU.

Results showed no effects of tDCS on state empathy. Although this is not what we had expected, it can be explained by the fact that the vmPFC may not be directly related to

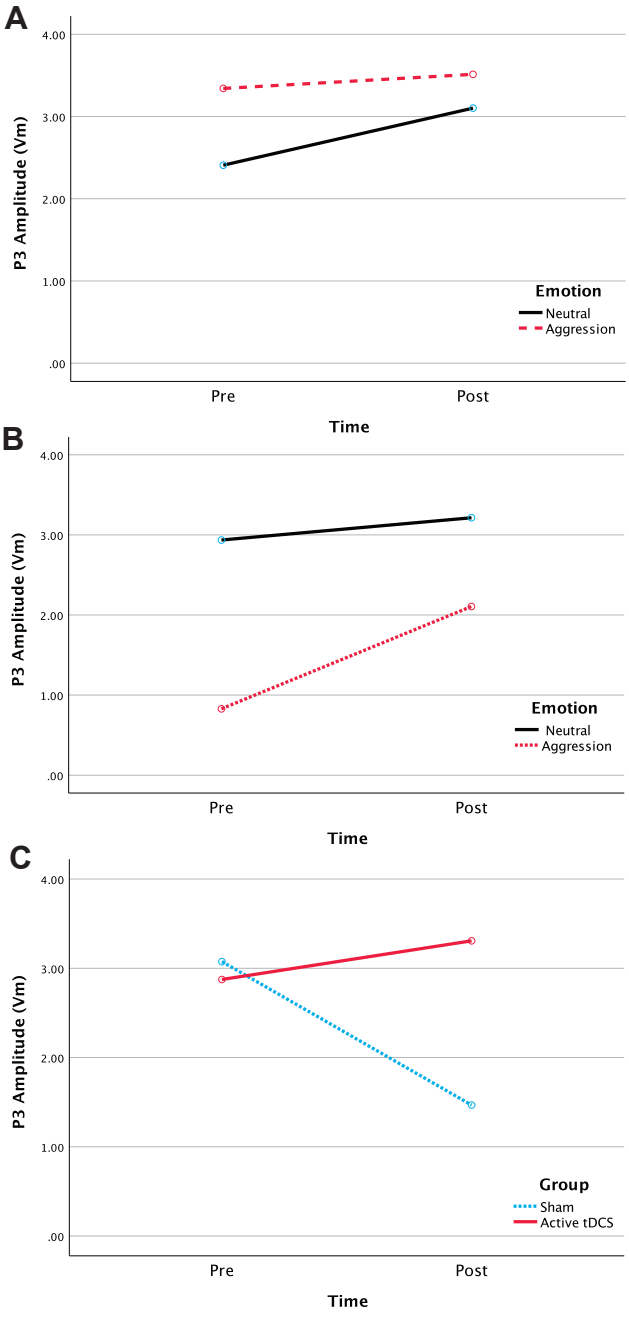

Figure 4. **(A)** Intervention effects on the P3 amplitude (μV) for the active transcranial direct current stimulation (tDCS) group on emotion from pre- to posttest. **(B)** Intervention effects on the P3 for the sham group on emotion from pre- to posttest. **(C)** Intervention effects on the P3 post hoc between the active tDCS group and the sham group from pre- to posttest.

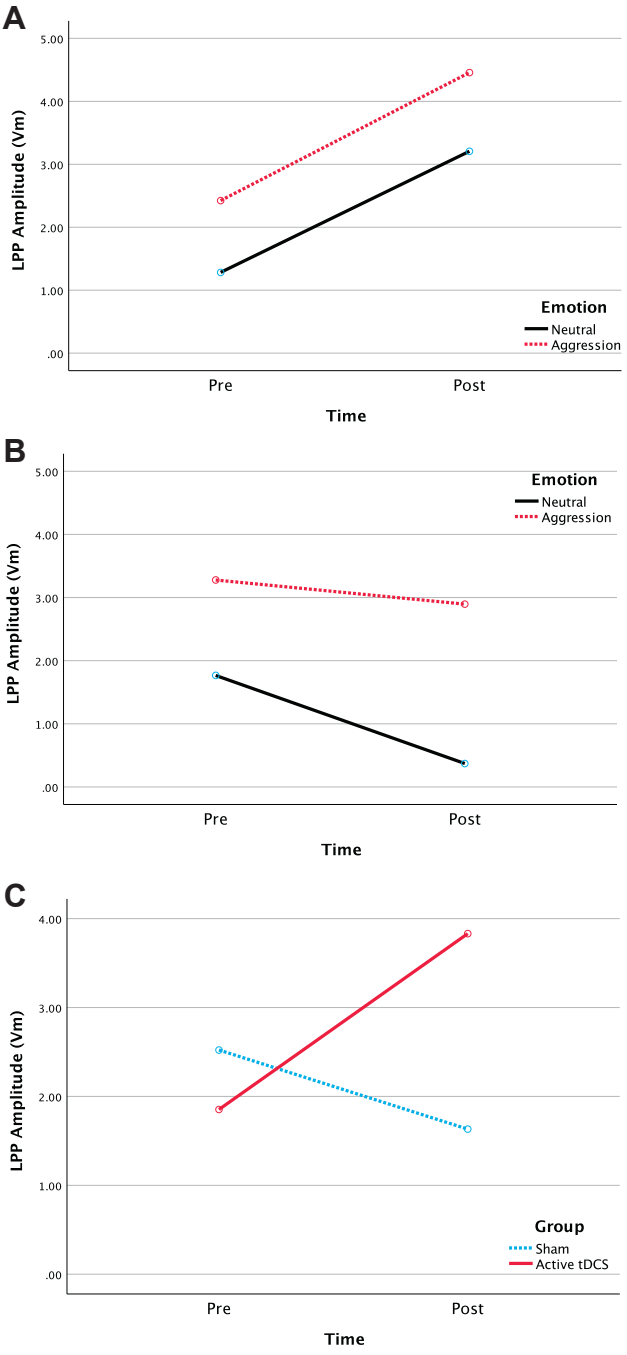

Figure 5. **(A)** Intervention effects on the late positive potential (LPP) amplitude (μV) for the active transcranial direct current stimulation (tDCS) group on emotion from pre- to posttest. **(B)** Intervention effects on the LPP for the sham group on emotion from pre- to posttest. **(C)** Intervention effects on the LPP post hoc between the active tDCS group and the sham group from pre- to posttest.

empathic abilities. As shown in the model of Blair (63), decreased activity in the vmPFC is linked to impaired social and affective decision making, and the vmPFC is found to be involved in perspective-taking and regulating emotions (103–105), which are vital for empathic processing (31) but not related to empathy directly.

Consistent with our hypothesis, we found a reduction in reactive aggression on the aggression task from pre-to post-test in the active tDCS group compared with the sham group. Additionally, we found the same effect for self-reported

reactive aggression and the total aggression score as measured with the RPQ. The reduction of reactive aggression is consistent with previous findings on the associating between the vmPFC and aggressive behavior (17–24). Previous research also indicated a link between the brain activity in the vmPFC and the aggressive behavior measured with the PSAP, proposing the vmPFC to be a neural substrate related to aggressive provocation (55,57–62). Consistent with these results is the proposed framework of Blair (64), which demonstrates that diminished activity in the vmPFC leads to frustration-based reactive aggression. Consequently, the present study provides insight into the functional role of the vmPFC in reactive aggression and how modulating activity in the vmPFC can reduce aggressive responses in the laboratory setting. Future research has to show the generalizability of these results to violent behavior outside the laboratory.

With respect to the electrophysiological measures (P3 and LPP), we expected that after a week of tDCS intervention, aggressive pictures would result in larger ERP amplitudes (more arousal, more empathy) compared with neutral pictures. This hypothesis was partly confirmed. Regarding the P3, only an interaction effect was found between time and group, showing that the P3 amplitude decreased from pre- to posttest in the sham group. One of the reasons could be that the inhibitory effect was caused by a learning effect. Studies (143–145) have shown that the P3 is very sensitive for learning effects in repeated measure design and that the amplitude becomes smaller when target probability increases (146–152).

Results for the LPP showed an increase in amplitude for the active tDCS group in both emotion conditions; although active tDCS did increase LPP amplitudes as expected, we did not expect that the LPP amplitude would also increase for neutral pictures. An explanation for this finding would be that modulating activity in the vmPFC resulted in a modulation effect in social interactions generally, regardless of the emotions displayed in the pictures. To test this hypothesis, we performed an additional analysis on the filler pictures (i.e., neutral objects) and indeed found no significant effects of tDCS on either the P3 or LPP after viewing filler pictures. Thus, even though the results did not differentiate between neutral or aggressive pictures as proposed, the current results are in line with previous research (82,98,141–144), indicating that the positive slow potentials indicate an increased emotional regulation and affective experience (see the Supplement for detailed description of the additional analysis).

Our model of current flow indicated that the HD-tDCS stimulation reached the vmPFC with intensity sufficient to induce an effect of the stimulation as also described in earlier studies (128,153,154). We do acknowledge that a factor of interindividual variability should also be taking in consideration. Future studies could implement specific algorithms or potential biophysical modeling to individualize montage and take into account the potentially influencing factors contributing to the direction of current flow (155–159).

This paper has several strengths. First, this study is the first to find a decrease in aggression in forensic patients using an EEG-tDCS design. Other studies (75,160,161) that have shown reduced aggression with tDCS did not include EEG in their protocol, although of significant importance for monitoring the activity of the brain region of interest. Second, we used a design that was double blinded and with multiple sessions of tDCS. It has been demonstrated in several studies (162–169) that modulation is most effective after multiple sessions because the induction of synaptic plasticity in the cortex requires a multiple-time stimulation to be effective and to mediate the durability of neocortical circuits (170). Third, in the current study the current flow montage sufficiently reached the vmPFC. We used HD-tDCS, which is found to have a better focality (170,171) than conventional tDCS and, as a result, reaches deeper regions of the brain (92–98). Fourth, compared with previous studies (96,97), we optimized the intervention by enhancing the brain state of interest during the tDCS sessions (82).

Albeit promising, our findings should be interpreted in the context of limitations that are important to consider in future studies investigating this matter. First, we found a significant decrease in the P3 amplitude for the sham condition. Future studies should try to correct for learning effects on the P3 by implementing slightly different pictures in the viewing task or have a longer period from pre- to posttest. Second, it might not just be the impairments of the PFC that influence aggression and antisocial behavior but also neural network disruptions associated with that behavior (172). Therefore, it would be relevant to investigate neural networks and functional connectivity in understanding aggressive behavior in future studies. Third, future studies should highlight the role of tDCS as a modulator, the effects of tDCS on synaptic activity as according to the Bienenstock-Cooper-Munroe rule (83–88), and using potential biophysical modeling to individualize montage. Finally, in this study, no long-term effects of the tDCS intervention were examined, nor were effects on violence in real life. Future studies should address these issues to further support the effectiveness of this tDCS intervention.

Conclusions

The development of successful evidence-based therapeutic interventions in forensic mental health is crucial for reducing violence risk. To our knowledge, this is the first study investigating HD-tDCS as an intervention to increase empathic abilities and reduce violent behavior in a forensic sample and that also examined the effects on electrophysiology. Our results showed that multiple sessions of HD-tDCS targeting the vmPFC resulted in reduced aggression. In addition, this modulation also resulted in increased LPP amplitudes after viewing aggressive pictures, indicating an increase in attention to, and emotional evaluation of, scenes depicting victims of aggression. Hence, our results significantly improved our understanding of the neural correlates of aggression posed by violent individuals, and although they must be interpreted with caution when implicating in a real-life setting, they support the effectiveness of tDCS as treatment intervention in forensic patients.

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