Transcranial Direct Current Stimulation (tDCS) as an intervention to improve empathic abilities and reduce violent behavior in forensic offenders: Study protocol for a randomized controlled trial.

CURRENT STATUS: ACCEPTED

Carmen Silva Sergiou
Erasmus University Rotterdam

ORCiD: https://orcid.org/0000-0002-8107-5615

Adam J Woods
University of Florida

Ingmar H.A. Franken
Erasmus University Rotterdam

Josanne D.M. van Dongen
j.d.m.vandongen@essb.eur.nlCorresponding Author

DOI:
10.21203/rs.2.11815/v2

SUBJECT AREAS
Internal Medicine Integrative & Complementary Medicine

KEYWORDS
Transcranial Direct Current Stimulation (tDCS), Empathy, Violent behavior, Substance use, Forensic offenders, Recidivism, Effectiveness, Ventromedial Prefrontal Cortex (vmPFC).
Abstract

Background

Recent studies show that changes in one of the brain areas related to empathic abilities (i.e. the Ventromedial Prefrontal Cortex (vmPFC)) plays an important role in violent behavior in abusers of alcohol and cocaine. According to the models of James Blair, empathy is a potential inhibitor of violent behavior. Individuals with less empathic abilities may be less susceptible and motivated to inhibit violent behavior, which causes a higher risk of violence. Recent neuroscientific research shows that modulating (stimulation or inhibition) certain brain areas could be a promising new intervention for substance abuse and to reduce violent behavior, such as the neurostimulation technique Transcranial Direct Current Stimulation (tDCS). This study aims to investigate tDCS as an intervention to increase empathic abilities and reduce violent behavior in forensic substance use offenders.

Methods/design A total sample of 50 male forensic substance abuse patients (25 active + 25 sham stimulation) will be tested in a double-blind placebo-controlled study, from which half of the patients will receive an active stimulation + treatment as usual (TAU) and the other half will receive a sham stimulation (placebo) + TAU. The patients in the active condition will receive multichannel tDCS stimulation targeting bilateral vmPFC two times a day for 20 minutes for five consecutive days. Before and after the stimulation period, the patients will complete self-report measurements, perform the Point Subtraction Aggression Paradigm (PSAP) and a passive viewing empathy task. Resting state electroencephalography (rsEEG) will be measured before and after the treatment period. A follow-up will be conducted after six months. Primary outcome is to investigate multichannel tDCS as a new intervention to increase empathic abilities and wit that reduce violent behavior in offenders with substance abuse problems. In addition, it will be studied whether electrophysiological responses in the brain are affected by the tDCS intervention. Lastly the effects of tDCS on reducing craving will be investigated.

Discussion

This study is one of the first studies using multichannel tDCS targeting the vmPFC in a forensic
sample. This study will explore the opportunities to introduce a new intervention to improve empathic abilities and reduce violence in forensic substance use offenders. Specifically, this study may give insight in how to implement the tDCS intervention in the setting of daily clinical practice for this complex, multiple problem target group and with that contribute to reduction of recidivism.

Trial registration

Dutch Trial Register, identifier: NTR7701. Registered on 12 January 2019; prospectively registered before the recruitment phase. Recruitment started on the 1st of February 2019 and approximitaly will be finished in the winter of 2019. https://www.trialregister.nl/trial/7459. Protocol version 1. 22th of May 2019.

Background

Repeatedly using substances has been found to lead to neuro-adaptations in the ventral striatum and ventral tegment mental areas and with that decreased dopamine secretion [1]. Decreased dopamine secretion leads to a higher craving for substances and increased saliency for addictive cues [2-4]. Impaired functioning of the Dorsolateral Prefrontal Cortex (DLPFC) in patients with substance abuse disorders, are underlying to a diminished cognitive and inhibitory control and increase the tendency to relapse and maintain in addictive behaviors [5-13]. Recent studies show that changes in the brain areas related to less empathic ability (ea. the Ventromedial Prefrontal Cortex (vmPFC)) in abusers of alcohol and cocaine plays an important role in violent behavior [14], [15]. Preller and colleagues found in their study [15] that cocaine users show deficits in emotional empathy and that substance abuse patients are less emotionally responsive to the emotions of other individuals and their mental state.

Empathy is crucial for social enhancement, social interactions and relationships, for our emotional and social life [16]. A deficit in empathic ability could lead to antisocial and deviant behavior and with that a higher risk of aggression [15]. Aggression is stated here as behavior that is mostly defined by any behavior that is intended to harm someone who is motivated to avoid being harmed [17]. As said before, antisocial behavior, especially aggression, is associated with dysfunctions in the prefrontal
cortex [18-24]. In addition, research has highlighted the importance of executive functions; the ‘higher’ cognitive functions that are controlled by the prefrontal cortex in control of aggression [25-28]. According to the models of James Blair [29], [30], [28] violent behavior is inhibited by empathy. Individuals with less empathic abilities may be less susceptible and motivated to inhibited violent behavior, which causes a higher risk of violence.

**The Role of the Prefrontal Cortex**

Several studies show evidence that impaired prefrontal cortex areas lead to the emergence of aggressive behavior. Most notably are the impairments in the vmPFC (e.g. emotion regulation, moral decision-making), and the DLPFC (e.g. disinhibition and impulsiveness), which is associated with aggression and violent behavior [25-28]. These dysfunctional prefrontal cortex areas are inducing psychopathic traits such as blunted emotions and a lack of empathy [31], impaired perspective taking with increased egocentrism and rigidity [32], [19], [33]. Research found that children with psychopathic traits showed abnormal activity in the ventromedial prefrontal cortex during a response reversal task in comparison to children without these traits (Finger et al., 2008). In addition, Raine and colleagues [34,35] demonstrated the relationship between violence and empathy and argued that abnormal brain structures of the vmPFC cause the most extreme form of empathic inability named ‘the psychopathic predatory violence’. This psychopathic predatory violence correlates with the lack of empathy, impaired moral judgment [34] and hyper metabolism [35], which is associated with increased aggressive impulses.

Figure 1 shows the hypothesized relationship between the impaired brain areas and the subsequent deficits in empathy and violent behavior.

Although, the DLPFC modulates cognitive control and response inhibition that are associated with aggression and violent behavior [25-28], in this study we focus on the vmPFC.

**Ventromedial Prefrontal Cortex (vmPFC)**

The vmPFC is particularly relevant for empathic abilities and antisocial behavior [36], [29], [37]. Studies using functional neuroimaging (i.e. fMRI) have shown that neural activity in the vmPFC
predicts empathic abilities and altruistic motivation [38], [39]. Another longitudinal study [19] demonstrated that lesions damaging the vmPFC, occurring in the first sixteen months of a human life, result in lifelong psychopathic antisocial traits and will also lead to impaired social and moral reasoning. In addition, damage to the vmPFC is associated with poor decision-making in antisocial behavior [40], [41].

Furthermore, a recent study [42] combining tDCS with fMRI demonstrated that anodal tDCS placed on the forehead led to increased vmPFC activity and decreased negative emotions. Taken together, these studies suggest a potential link between vmPFC functioning and anger regulation.

**Transcranial Direct Current Stimulation (tDCS)**

tDCS is a non-invasive neuromodulation technique that modulates the brain region of interest by increasing or decreasing neuronal excitability through constant, low direct current electrodes. tDCS has been proven to be an effective intervention to modify brain activity [43], [44], [45] and has been investigated in many different disorders [46-48].

In this current study, the effectiveness of tDCS as a new intervention to increase empathy and reduce violent behavior in substance abuse offenders will be investigated. Through modulating (stimulating and inhibiting) certain areas of the brain, tDCS causes a change in the function of the brain, due to an increase in susceptibility to generate and facilitate brain related electrical impulses. This susceptibility is achieved through repeated sessions of brain stimulation and is thought to produce Long Term Potentiation (LTP)-like ‘learning’ in stimulated neurons. Functional alterations in the brain due to the long abuse of substances are hypothesized to improve by the intervention with tDCS [49-61] and will reduce craving.

Several studies found that through anodal stimulation of the PFC with tDCS, emotional processes can be influenced. tDCS can modulate emotional pain [62,63] and enhance pain empathy [63]. Interestingly, studies [65-67] suggest that anodal tDCS of the PFC can enhance empathy and increase the feeling of morality. Although there seems to be a clear association between empathy and vmPFC
function, only a few studies have investigated modulation of the vmPFC. Abend and colleagues [68] show in their study combining tDCS and fMRI that stimulating with tDCS demonstrated increased emotion-related activation in the vmPFC. Two studies show that anodal stimulation of the (right) vmPFC increases empathic ability and morality [67, 68]. Furthermore, the study of Gilam and colleagues [69] used tDCS simultaneously with fMRI and demonstrates that activity of the vmPFC was increased during active compared to sham stimulation.

In addition to empathy, also antisocial behavior, including aggression, is associated with dysfunctions in the prefrontal cortex [18-24]. Research shows that studies targeting the PFC with anodal tDCS can reduce social exclusion and the aggressive behavior that emerges from this exclusion [70], can reduce unprovoked aggressive behavior [71] and reduce the intentions of aggressive behavior [72, 73]. Based on the earlier mentioned theory of Blair, linking impaired empathic abilities to violence, and the model demonstrated (Figure 1), it could be proposed that the vmPFC plays a crucial role in modulating both empathic abilities and thereby also in violent behavior. Previous mentioned study of Gilam and colleagues [69] also demonstrates the relationship between the vmPFC and violent behavior and showed a decrease in violent behavior in the first session after active tDCS.

In addition to aberrant functioning of specific brain areas, recent research [74, 75] also shows that functional connectivity of brain areas is also affected in individuals with less empathic abilities. Therefore, it is important for the evaluation of the effectiveness of a tDCS intervention, to determine how the resting-state connectivity of the patients, measured with resting state electroencephalography (rsEEG), changes from pre-to post-test to the intervention. Prior research demonstrates that tDCS can alter functional connectivity and that connectivity change is related to the treatment response (i.e. effectiveness) [76]. To optimize the intervention and increase current focality we use a newer development of the original. This technique, called high-definition tDCS (HD-tDCS or multichannel tDCS) uses gel-based electrodes similar to those used in EEG [77] and is more precise in targeting the brain area of interest.
Therefore, in this study we will investigate the idea that multichannel tDCS applied over the vmPFC will increase empathic abilities and subsequently reduce violence risk.

**Aims of the study**

The aim of this study is to investigate the effectiveness of tDCS in increasing empathy and reducing violent behavior in offenders with substance abuse problems.

The following research questions will be addressed in this study:

1. Does stimulation with multichannel tDCS targeting the vmPFC increase empathic abilities in forensic substance abuse patients during an empathy task from pre-to post intervention?
2. Does stimulation with multichannel tDCS targeting the vmPFC reduce aggressive responding and violence risk in forensic substance abuse patients from pre-to post intervention?
3. Does multichannel tDCS targeting the vmPFC reduce craving in forensic substance abuse patients?
4. Does multichannel tDCS targeting the vmPFC affect electrophysiological responding in the brain measured through EEG from pre-to post intervention?

Outcomes will contribute to the development of more effective diagnostics and treatment of substance use patients. Furthermore, these data will potentially contribute to improving treatment through increasing understanding of specific targets for treatment interventions. In addition, outcomes may provide better insight in the functioning of the vmPFC and the relationship between empathy and violence risk.

**Methods/design**

**Setting**

The study will be carried out in two forensic institutions. The sample will be recruited from the Forensiche Verslavings Kliniek (FVK), the forensic addiction clinic of Bouman, Antes. The institution is located in Rotterdam, The Netherlands. The sample size is based on other studies, we will operate
according to the ‘Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS)’ published in 2017 [78], and seen as achievable, due to the fact that the applicant is currently obtaining research at FVK Bouman Antes, which will make the inclusion of the patients more feasible.

**Procedure /Design**

In this double blind, placebo-controlled study, a total of 50 male participants between the age of 18-60 will be randomly assigned to either the active condition, or the sham condition. Eligible participants will be given written and oral information about the study and will be invited to participate. After informed consent they will participate at the forensic clinic where they are admitted and all the data collected will be anonymous linked to their participant number.

**Blinding and randomization**

Participants and investigators are blind to the tDCS condition allocation. An external researcher is the only one who knows which participant number corresponds with each condition. The principal investigator, neither the patients nor research assistants know which condition is being executed. The trial established procedures to maintain separation in knowledge between the head researcher and the principal investigator. Randomization is before T0, the random assignment will be carried out by the first author. A participant number that is corresponding with either the active condition or the sham condition determines the random allocation. In a situation where unblinding is permissible and to maintain the overall quality and legitimacy of the clinical trial, unblinding should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management and safety of the patient according to the SPIRIT statement [79]. Investigators are encouraged to discuss this with the Medical Ethical Review Committee of the Erasmus Medical Center (registration number: 2018.065 – NL65209.078.18.

As a standard for effectiveness of the reduction of violent behavior, the results of a violence risk assessment instrument the Historical and Clinical Future Risk-assessment tool (HKT-R) [80] will be assessed before the intervention starts. During the first session the self-reported measures will be assessed. In addition; EEG will be measured during a resting-state task and during a Passive-viewing
Empathy task [75]. Following the participants will perform a rating viewing Empathy task [75]. To measure behavioral indices of the level of aggression the patients will perform in the Point Subtraction Aggression Paradigm (PSAP) [81] will be used.

After this, a series of ten tDCS sessions (two per day for five consecutive days) will follow. After every tDCS session the participants will fill in a questionnaire that assesses side effects. On Monday, after the last modulation on Friday, the patients will receive a post-intervention in which the rsEEG and the tasks (empathy task and PSAP task) again will be conducted. As a follow up, risk assessment scores of the participant will be obtained after six months to see whether risk reduction is maintained together with one last EEG session with the PSAP task.

**Overview procedure**

1). Inclusion of patients after informed consent.

2). Collecting information from patients regarding diagnosis, substance abuse, demographic information and HKT-R.

3). Pre-intervention in which the patients will receive a resting-state EEG (rsEEG) and perform the aggression task (PSAP) and the empathy task (victims of aggression). In addition, the patients will fill in the self-report questionnaires.

4). Intervention multichannel tDCS+TAU or Sham+TAU: twenty minutes of anodal stimulation of the vmPFC and cathodal stimulation of the left supraorbital area with multichannel tDCS, two times daily for a period of 5 consecutive days.

5). Post-intervention where the patients receive a rsEEG and will perform the aggression task (PSAP) and the empathy task (victims of aggression), and fill out the self-report questionnaires again.

6). Outcome variables: The results on the aggression task and empathy task as well as the score on the HKT-R and the self-report questionnaires will be lower with respect to the results on the pre-test. Furthermore, it will be investigated whether the functional connectivity (EEG) has changed at the post-test in contrast to the pre-test and if this differs within the two conditions (tDCS vs. Sham).

7). A follow-up after six months where the patients will perform the aggression task and the empathy
task one more time and the HKT-R will be administered. See Figure 2 and 3 for a detailed overview over the procedure of the trial.

Multiple studies [82-85] have concluded that activating the brain state of the area of interest during stimulation, increases the effect of the modulation and contribute to optimize the intervention. An interesting study of Nissim and colleagues [86] demonstrated with fMRI that the optimal gains from using tDCS can be realized by simultaneously using behavior and modulation for stimulating neural networks. Therefore, to optimize our intervention and increase the activity of the vmPFC and the empathic abilities the participants will be occupied with tasks and movies that trigger these brain states. On the first day, the participants will complete the Multifacetted Empathy Task (MET) [87] and the Reading the Mind in the Eyes test (rMET) [88], to actively enhance their perspective taking and emotion recognition. When finished, they will watch the movie ‘Wonder’ (2017), for the first part of the stimulation week. For the remaining sessions they will watch the movie ‘I am Sam’ (2001). The two movies are enhancing the empathic abilities and perspective taking, and therefore will contribute to the optimization of brain state.

**Sample**

A total sample of 50 male forensic substance abuse patients (25 active + 25 sham stimulation) will be tested in a double-blind placebo-controlled study, from which half of the patients will receive an active stimulation+ treatment as usual (TAU) and the other half will receive a sham stimulation (placebo) + TAU.

**Inclusion**

In order to be eligible to participate in this study, a subject must meet all of the following criteria: male, age 18-60, good understanding of the Dutch language, diagnosed with an alcohol and/or cocaine SUD according to the DSM-5. The patients have to be abstinent and have an index offense in violence category listed in the HKT-R. These criteria have been selected due to the fact that male subjects will show more aggression on the PSAP task and show more violent behavior in general than females.

**Exclusion**
Subjects meeting any of the following criteria will be excluded from participation in this study: major neurological conditions (e.g. traumatic brain injury), or major mental disorders (i.e. major depression, psychotic symptoms). Also patients taking antipsychotic or other severe medication cannot participate in the study.

**Recruitment**

The recruitment will be active within the forensic institutions. Patients will be actively approached by the PhD student, or can sign up through a form at the department in which they receive their treatment. Research assistants will assist with the assessments. The entire research team will be trained extensively before they have an active role in the research.

After a screening for exclusion criteria, the patients will receive more detailed information about the study and can decide to participate definitive. An informed consent will be signed prior to the actual test day.

**Conditions**

**Experimental**

The patients participating in the active, experimental condition start on Friday with completing the before mentioned self-report questionnaires. Also, EEG will be measured during a resting-state task (rsEEG) and during the passive viewing empathy task. After disconnecting the EEG device, participants will perform the empathy rating task and the PSAP. On Monday, the participants will start with the tDCS intervention; they will receive two times 20-minute tDCS stimulation each day. There will be a time interval of 3-4 hours between the sessions, depending on the schedule of the patients. This will last for five consecutive days. One anodal electrode is placed on the position of Fpz and the other five cathodal electrodes are placed on AF3, Fz, AF4, F3, F4, according to the international 10-10 EEG system. The electrodes used are the Pistim EEG & tDCS hybrid electrodes with a 12 mm diameter.

**Sham**

The patients participating in the sham condition will follow exactly the same routine as the participants in the active condition except they will receive 2 mA during 30 seconds instead of the 20
minute stimulation. This has proven to be effective for blinding as participants habituate to the sensation of stimulation within seconds of current initiation [89].

**tDCS**

For the intervention we will operate according to the ‘Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS)’ [78]. Multichannel tDCS will be administered with a CE-certified neurostimulator (StarStim-8, NeuroElectrics) following the protocol [79] the device is preprogrammed for stimulation with 2mA during 20 minutes (experimental condition), or with 2 mA during 30 seconds (sham condition). We program the device for each participant, ensuring that the participant and investigator are blinded for experimental condition. The experimental treatment is a 20 minutes tDCS session, two times a day for five consecutive days (ten sessions per participant). Multichannel tDCS stimulation will be applied over the vmPFC. Sham condition is the same as the experimental condition with the exception that there will only be a ramp up of the electrical stimulation to mimic the sensation of the stimulation.

*Primary Objective*

The primary objective is to investigate tDCS as a new intervention to increase empathy and reduce violent behavior in offenders with substance abuse problems. This will be measured with the results of the empathy and aggression task from pre-to posttest. In addition, it will be studied whether electrophysiological responses in the brain are affected by tDCS intervention, this will be demonstrated through comparing the EEG from pre-to posttest. A mixed design will be carried out to test whether ERP amplitudes pre-post intervention differs between the active- and sham group.

*Secondary Objective(s)*

The secondary objective is to reduce craving in offenders with substance abuse problems. This will be assessed using the four self-report measurements about alcohol- and drug craving, and to compare the results from pre-to posttest. Other study parameters are the results from the self-report questionnaires. These will be compared with the other variables mentioned before and also compared from pre-to posttest.

**Instruments**
**Passive-viewing Empathy task [74]**

To measure empathic abilities and how it changes between pre- and post-intervention, patients will participate in a passive-viewing empathy task. This measurement is based on previous research [74]. The pictures used in the passive-viewing task are selected based on ratings conducted through an anonymous online study (i.e. Amazon’s Mechanical Turk). 188 individuals participated in this study and each individual rated 45 pairs of pictures. These were aggression pictures and matched neutral pictures, both were rated on levels of arousal, aggressiveness and valence. The study resulted in 40 pairs of pictures selected for the empathy tasks. The pictures display scenes with either two males, or one male and one female aged between 20 and 25 years old. The males have a white complexion and the female has a black skin tone. For the aggression pictures, the majority of cases (99%), had a male perpetrator and either a male or a female as the victim. The scenes involved physical, sexual, and verbal aggression. To control for stimulus-related confounding factors, all neutral pictures are carefully matched to the aggressive pictures. The neutral photographs were identical to the aggression-related photographs (pair-wise; i.e. the same persons, same location, same colors, same light), only without the aggressive action. Three types of pictures will be used in the experiment: (1) 40 pictures displaying an interaction between two individuals that is of a violent tone; (2) 40 pictures displaying an interaction between two individuals that is neutral and (3) fifteen pictures displaying neutral objects like a bridge or a lamp (fillers). The fillers will not be used for further analyses. 95 pictures in total will be presented, for 6 seconds with intervals of 1.8 seconds between the pictures, randomly. Participants are instructed to look at each picture passively, because then the automatic neural responding in the brain can be determined [74].

**Rating Empathy task [74]**

Following the Passive Viewing Empathy task, the pictures displaying the neutral and aggressive situations will be presented a second time. Participants are now instructed to rate the pictures by answering four questions. The first question is ‘Does this picture give you arousal?’ assessed to score arousal on a 9-point Likert scale (1 = no arousal to 9 = very high arousal). The following question was to assess the valence of the picture ‘Does this give you a negative or a positive feeling?’ on a 9-point
Likert scale (1 = negative emotions, 5 = no emotions, 9 = positive emotions). The last two questions assess the measure of state empathy. Lastly, there are two questions concerning empathy (i.e. measure of state empathy). One question assessed to what extent the participant could empathize with the perpetrator and the other question assessed to what extent the participants could empathize with the victim in the aggressive situations. Both questions will be scored on a 9-point Likert scale (1 = no empathy to 9 = high empathy). The total empathy task (passive viewing and rating) on average lasts 40 minutes [73].

The Point Subtraction Aggression Paradigm (PSAP) [81]

Although multiple paradigms are used to measure aggression on an experimental manner in the labs, the PSAP-task is known to be one of the best-validated instruments [90]. During the PSAP-task participants are playing a game against a (fictive) opponent. The goal of the game is to earn more points than your opponent. Participants are offered 3 choices: 1). Participants can earn points by pressing a 100 times on the ‘1’ button on the keyboard. 2). Stealing points from your opponent by pressing ten times on the ‘2’ button or 3). Guarding your own points as an escape so the opponent cannot steal from you by pressing ten times on the ‘3’ button. When a participant picks option number 2 (aggressive response), the points that they steal will not add up at their own score, but only will subtracted from the score of the opponent. If the (fictive) opponent is stealing points from the participants it will be shown in red letters on the screen, in this way the participant will be ‘provoked’. If this provoking leads to the participant pressing the ‘2’ (stealing) button more frequently, this can be seen as reactive aggression. When the participant is not provoked by this event, the aggression can be seen as proactive aggression. In this study the e-prime version of the PSAP consists of three sessions of each twelve minutes. The outcome of the PSAP, the aggressive response, is the amount of ‘2’ responses of the participant. When the ‘2’ response is a result of the provocation (the fictive opponent stealing points), then this indicates a reactive aggression response. If the ‘2’ response is not a reaction on the provocation, than the reaction will be seen as proactive aggression response. Research [90] concludes that the PSAP has more ecological validity then for example the Taylor Aggression Paradigm (TAP) [91]. This is due to the following advantages: First, the PSAP task offers
the participant an option to actively withdraw (pressing the ‘3’ key), something that is not included in other paradigm tasks. Secondly, in the PSAP task the aggressive response (pressing the ‘2’ button is not receiving points) and therefore more ecological valid then other tasks that do not have this option. An aggressive reaction is a cost-benefit consideration, so choosing an option to steal points that will not add up to your own score of winning could be considered as a costly option.

**Self-report questionnaires**

**Self-Report Psychopathy Scale Short-Form (SRP-SF)** [92]

In order to assess psychopathic traits we use the Dutch short version of the SRP-SF. The SRP-SF consists of a subset of 29 of the 64 original items and is a self-report questionnaire in which participants are asked to rate statements with a 5-point Likert scale. The questionnaire consists of four subscales: Interpersonal manipulation (manipulation and deception), Callous affect (lack of empathy or regret), Instable lifestyle (impulsivity and sensation seeking behavior) and Criminal behavior (delinquency and criminal behavior).

**Reactive and Proactive Aggression Questionnaire (RPQ)** [93]

In order to assess aggression we use the Dutch version of the RPQ. The RPQ is a 23-item self-report questionnaire in which the participant has to give a rating on how often this behavior has occurred in the past on a 3-point scale (“never”, “sometimes” or “often”). Next to an overall total aggression score, the test provides two separate measures to proactive aggression (deliberate and planned aggression) and reactive aggression (agression as a reaction on an unplanned circumstance).

**Interpersonal Reactivity Index (IRI)** [94]

In order to assess empathy we use the Dutch version of the IRI, this is a commonly used self-report instrument designed to assess empathic tendencies. The IRI consists of four separate subscales: Perspective Taking (PT), Fantasy (FS), Empathic Concern (EC), and Personal Distress (PD).

**Toronto Alexithymia Scale (TAS-20)** [95]
In order to assess alexithymia we use the Dutch version of the TAS-20. The TAS-20 is a self-report scale comprised of 20 items. Each item is rated on a five point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The TAS20 is a reliable and valid measure of emotion processing in adults that includes a total score and three subscales: Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF), and Externally-Oriented Thinking (EOT).

**Risky, Impulsive, and Self-Destructive Behavior Questionnaire (RISQ) [96]**

In order to assess risky and impulsive behavior we use the Dutch version of the RISQ. The RISQ is a 38-item self-report questionnaire-based measure, assessing eight domain-specific factors (measuring drug use, aggression, self-harm, gambling, risky sexual behavior, impulsive eating, heavy alcohol use, and reckless behavior).

**Behavioral Impulsivity Scale (BIS-11) [97]**

In order to assess the personality and behavioral construct of impulsivity we use the Dutch version of the BIS-11. The BIS-11 is a questionnaire which consists of one of the three second-order facets of impulsivity. The 30-item self-report questionnaire consists of six subscales: attention, (i.e. focusing on current tasks), cognitive instability, (i.e. intruding thoughts), motor impulsiveness, (i.e. acting quickly), perseverance (stable lifestyle), cognitive complexity, (i.e. enjoys mental challenges) and self-control, (i.e. plans and thinks deliberatively).

**Alcohol Use Disorders Identification Test (AUDIT) [98]**

In order to assess alcohol use we use the Dutch version of the AUDIT. The 10-item AUDIT includes questions to assess alcohol intake (questions 1–3), alcohol dependence (questions 4–6) and alcohol-related problems (questions 7–10). Questions 1–8 are scored from 0 to 4, questions 9 and 10 are scored 0, 2 or 4, resulting in a maximum AUDIT score of 40.

**Drug Use Disorder Identification Test (DUDIT) [99]**

In order to assess drug use we use the Dutch version of the DUDIT. The DUDIT is an 11-item screening instrument to assess non-alcohol drug use patterns and various drug-related problems. The items range from on a 5-point Likert scale for the first nine items, the last two items are scored on a 3-point scale. The higher scores suggest more severe drug problems.
**Obsessive Compulsive Drug Use Scale (OC-DUS-version Cocaine) [100]**

In order to assess drug craving we use the Dutch version of the OC-DUS. The OC-DUS version Cocaine is a 13-item self-report questionnaire that assesses the inability to control or resist cocaine-related thoughts and behaviors, frequency and impact of thoughts and impulses related to cocaine use, and the degree of interference.

**Obsessive Compulsive Drinking Scale (OCDS) [101]**

In order to assess alcohol craving we use the Dutch version of the OCDS. The 22-item Dutch version of the OCDS was developed to reflect obsession and compulsivity related to craving and drinking behavior. The OCDS has been shown to be specific for the obsessive and compulsive characteristics of drinking-related thought, urges to drink, and the ability to resist those thoughts and urges in alcohol-abusing and alcohol-dependent population.

**Outcomes**

**Primary Outcomes**

The primary outcomes are *empathic abilities, aggressive behavior* and the *electrophysiological responding* in the brain.

*Empathic abilities* will be measured using the Passive Viewing Empathy Task [74], followed by the Rating Empathy Task [74]. The Passive Viewing Empathy task examines the electrophysiological outcomes of empathic processing while observing aggressive situations. The results will be measured in the amplitude of specific event-related potential’s (ERPs). The early ERP component resembles the P300, which is a positive voltage in the latency of 300-650 milliseconds (ms) and the late ERP component reflects the LPP, a sustained positive potential identified around 400-1000 ms. Specifically P3 and LPP, appear to be a measure of empathic processing, and therefore make EEG an adequate tool to indicate any change in empathic abilities, reflected as a change in the amplitude of the ERPs [75]. In the Rating Empathy Task [74] the pictures displaying the neutral and aggressive situations will be presented a second time. Participants are now instructed to rate the pictures by answering four questions that will result in an outcome in emotional valence, empathy for the perpetrator, empathy for the victim and arousal. The outcome of the self-reported assessment of empathy is used
to measure state empathy.

Aggressive behavior will be assessed using the PSAP-task. The PSAP-task is known to be one of the best-validated instruments in provoking aggression in the lab [90]. In this task the participants will be ‘provoked’ by a (fictive) opponent that will steal points from them. If the (fictive) opponent is stealing points from the participants it will be shown in red letters on the screen. If this provoking leads to the participant pressing the ‘2’ (stealing) button more frequently, this can be seen as reactive aggression. The results of the PSAP task will be the amount of pressing the ‘2’ button in proportion to the total amount of pressing the buttons.

As a standard for effectiveness of the reduction of violent behavior next to the PSAP, the results of a violence risk assessment instrument (HKT-R) [80] will be assessed before the intervention starts. The HKT-R is one of the mandatory risk-assessment tools in forensic institutions. The clinical, historical and future indicators of violent behavior and the risk of recidivism will be used as outcome for the reduction of violent behavior.

Functional brain changes will be measured using resting state EEG (rsEEG), with a resting state task to measure the baseline of the brain activity of the participant in resting state condition and the passive viewing empathy task to measure the electrophysiological changes in brain function during empathic induction caused by the intervention. The expectation is that patients who receive tDCS intervention will show higher event-related potential (ERP) towards the pictures of the victims after the intervention and compared patients who have received the sham-condition.

After six months, as a standard for effectiveness of the reduction of violent behavior, the results of the aggression task (PSAP) and the risk-assessment tool (HKT-R) will be compared to the results previous to the intervention. The HKT-R risk level will be obtained to see whether there is a longitudinal effect of tDCS on aggression and risk reduction. In addition to check whether the effect of the tDCS intervention is long lasting, the participants will perform the self-report questionnaires, empathy task and the aggression task once more.

Secondary Outcomes
Beside the primary outcomes, the current study distinguishes multiple secondary outcomes. These will be measured using self-report questionnaires. All the secondary outcomes will be assessed during T0 and again at T6.

*Psychopathic traits* will be assessed using the *Self-Report Psychopathy Scale Short-Form (SRP-SF)* [92]. The participants have to rate 29 statements and the SRP-SF consists of four subscales: Interpersonal manipulation (manipulation and deception), Callous affect (lack of empathy or regret), Instable lifestyle (impulsivity and sensation seeking behavior) and Criminal behavior (delinquency and criminal behavior).

*Reactive and Proactive Aggression* will be measured using the Reactive and Proactive Aggression Questionnaire (RPQ) [93]. The RPQ is a 23-item self-report questionnaire in which the participant has to give a rating on how often this behavior has occurred in the past on a 3-point scale (“never”, “sometimes” or “often”). Next to an overall total aggression score, the test provides two separate measures to proactive aggression (deliberate and planned aggression) and reactive aggression (aggression as a reaction on an unplanned circumstance).

*Empathic tendencies* will be measured using the Interpersonal Reactivity Index (IRI) [94]. The IRI consists of four separate subscales: Perspective Taking (PT), Fantasy (FS), Empathic Concern (EC), and Personal Distress (PD).

*Alexithymia* will be measured using the Toronto Alexithymia Scale (TAS-20) [95]. Alexithymia is a personality construct identified by the inability to describe one’s emotions or the emotions of others. The TAS-20 includes a total score and three subscales: Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF), and Externally-Oriented Thinking (EOT).

*Risky and impulsive behavior* will be assessed using the Risky, Impulsive, and Self-Destructive Behavior Questionnaire (RISQ) [96]. The RISQ is a 38-item self-report questionnaire-based measure, assessing eight domain-specific factors (measuring drug use, aggression, self-harm, gambling, risky sexual behavior, impulsive eating, heavy alcohol use, and reckless behavior).

*Impulsivity*, specifically the personality and behavioral construct of it will be measured using the Behavioral Impulsivity Scale (BIS-11) [97]. The 30-item self-report questionnaire consists of six
subscales: attention, (i.e. focusing on current tasks), cognitive instability,(i.e. intruding thoughts),
motor impulsiveness, (i.e. acting quickly), perseverance (stable lifestyle), cognitive complexity, (i.e.
enjoys mental challenges) and self-control, (i.e. plans and thinks deliberatively).

**Substance use**

_Alcohol use_ will be assessed using the _Alcohol Use Disorders Identification Test (AUDIT)_[98]. The 10-item AUDIT includes questions to assess alcohol intake (questions 1–3), alcohol dependence
(questions 4–6) and alcohol-related problems (questions 7–10).

_Drug use_ will be measured using the _Drug Use Disorder Identification Test (DUDIT)_[99]
The DUDIT is an 11-item screening instrument to assess non-alcohol drug use patterns and various
drug-related problems.

_Drug craving_ will be assessed using the _Obsessive Compulsive Drug Use Scale (OC-DUS-version Cocaine)_[100]. The OC-DUS version Cocaine is a 13-item self-report questionnaire that assesses the inability to control or resist cocaine-related thoughts and behaviors, frequency and impact of thoughts and impulses related to cocaine use, and the degree of interference.

_Alcohol craving_ will be assessed using the _Obsessive Compulsive Drinking Scale (OCDS)_[101]
The 22-item OCDS has been shown to be specific for the obsessive and compulsive characteristics of
drinking-related thought, urges to drink, and the ability to resist those thoughts and urges in alcohol-
abusing and alcohol-dependent population.

**Statistical analysis**

Different General Linear Models (GLM) in SPSS will be carried out to analyze the main parameters. For instance, analyzing the empathy and aggression outcome (empathy ratings and b responses on PSAP task), the outcome variables will be handled as the dependent variables. In addition, the group variable (active vs. sham) will be used as the independent between-group variables, whereas the pre-post time will be included as a within subject independent variable. A mixed design will be carried out in which the pre-post intervention of the experimental group will be compared with the pre-post intervention aggression outcomes of the sham-group of patients. The mixed design will be carried out for the PSAP outcomes, empathy ratings, self-report questionnaires and violence risk with the HKT-R
Power analysis

The sample size is based on the primary outcome and other studies from the previous mentioned guidelines [78] and seen as achievable. The sample size is based on research [102] that reported large effect sizes (i.e. partial eta squared 0.25 and 0.21) for the active vs. sham condition using 15 participants per condition for three conditions. Because we have two experimental conditions, but also include covariates, a sample size of 50 subjects (25 per condition) is considered to have enough power to detect an effect, when power is set to 80% and alpha of 5%, two sided.

Discussion

This study protocol describes the design of an intervention with multichannel tDCS targeting bilateral vmPFC next to TAU, in comparison with sham condition and TAU. This study will explore the opportunities to introduce a new intervention to improve empathy, reduce violence and reduce craving in substance use offenders.

The present study has several strengths. First, to our knowledge only a few studies focus on increasing empathic abilities [62-68] or modulate externalizing behavior [69-72], but none of the studies focus on the implication of tDCS in a forensic sample. These individuals are in need of effective care, and by modulating the brain activity this can be a first step towards a new treatment program.

Secondly, tDCS may also influence substance abuse [49-61] and, in turn, influence the relationship between substance abuse and violent behavior. This could lead to a decrease in recidivism in forensic institutions.

Thirdly, we will use a wide range of instruments and will gather information through multiple sources. We will obtain rsEEG, questionnaires about psychopathic traits (SRP-SF) [92], aggression (RPQ) [93], empathy (IRI) [94], alexithymia (TAS-20) [95], risky and impulsive behavior (RISQ) [96] and impulsivity (BISS11) [97]. For measuring substance abuse the study includes questionnaires that focus on alcohol use (AUDIT) [98], alcohol craving (OCDS) [99], drug use (DUDIT)[100], and drug...
craving (OC-DUS-version Cocaine)[101]. In addition we have the results on the PSAP and empathy task.

Moreover, we will also include the participants who drop out during intervention in our five-day intervention program. This will give insight into the consequences of the formal procedures preceding intervention and may eventually enable us to describe profiles of the intervention with tDCS in treatment success and failure.

Finally, this study will contribute to development of a cheaper and less invasive treatment for substance abuse. As mentioned before, problems that substance abuse patients cause are an enormous burden to the community (financial and safety). Previous research has found that substance abuse, especially alcohol and cocaine, are related to (violent) criminal behavior. Money invested in treatment may lead to a large reduction in the costs associated with substance abuse. Nevertheless, current interventions seem insufficient in treatment of substance abuse in forensic mental health care and are not sufficient enough to reduce violence risk, 66% of the patients reoffend.

Despite the strengths of this current study, several limitations may threaten the quality of our study. The greatest challenge will be to have an adequate response rate at baseline and at the end of the five-day treatment. Our target group will be conducted in a forensic institution and is participation is voluntary, so the participants can decide to quit at any time. The population has an extensive history of treatment and criminal justice, so they might have negative experiences with treatment or research studies. Moreover, the participants already have filled in numerous questionnaires in their time spend in institutions, that they may have become tired or suspicious about the purpose of the proposed study.

To keep the nonresponse rate as low as possible, the researches conducting this study are trained to motivate and encourage the participants to complete the program. The interaction will be transparent, attentive and flexible and the researchers will be prepared to give clear information about the purpose, goal and aim of the current study at any time. Furthermore, a treatment that uses neurostimulation and EEG might seem scary and new to the participants as compared to TAU, so
extra explanation might be needed to insure the participants that it is safe. So, to recruit as many participants as we aim to in this study it will require a high degree of motivation.

Finally, an active control group (i.e., sham modulation + TAU) might lead to smaller effect sizes of active tDCS than when the tDCS treatment would be compared to no treatment or a wait-list group. However, considering the seriousness of the problems of the forensic substance use offenders it would not be ethical to let them wait for an intervention and it remains important to get a sense of the effects of placebo versus the effects of active stimulation.

In conclusion, with the present study design we are able to explore what the added effectiveness is of tDCS + TAU in comparison to sham + TAU, which could provide valuable information for institutions, researchers, psychologists and the professionals in the field of criminal justice. In addition, this study may help to reduce craving in forensic substance use offenders and with that reduce not only violent behavior but also recidivism. The study will contribute to knowledge about increasing empathic abilities and the functioning of the vmPFC.

Specifically, this study may give insight into implementing tDCS on the vmPFC in the TAU and the setting of daily clinical practice for this complex, multiple problem target group.

**Trial status**

The current study started February 2019. The data collection will run until the 50 participants all completed the five-day program. After six-months a follow up will be conducted to test whether the effects of the intervention are still present. Until then, the intervention effects are unknown.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| ACC          | Anterior Cingulate Cortex |
| AIC          | Anterior Insular Cortex |
| AUDIT        | Alcohol Use Disorder Identification Test |
| BIS11        | Behavioral Impulsivity Scale |
| CCMO         | Central Committee on Research Involving Human Subjects; in Dutch: Central Commissie Mensgebonden Onderzoek |
| DSM-5        | Diagnostic and Statistical Manual of mental disorders |
| Abbreviation | Definition |
|--------------|------------|
| DUDIT        | Drug Use Disorder Identification Test |
| EEG          | Electroencephalography |
| EU           | European Union Eudra |
| CT           | European drug regulatory affairs Clinical Trials |
| GCP          | Good Clinical Practice |
| HKT-R        | Dutch Risk Assessment Tool |
| IB           | Investigator’s Brochure |
| IC           | Informed Consent |
| IMP          | Investigational Medicinal Product |
| IMPD         | Investigational Medicinal Product Dossier |
| IRI          | Interpersonal Reactivity Index |
| LTP          | Long Term Potentiation |
| METC         | Medical Research Ethics Committee (MREC); in Dutch: Medische Ethische Toetsings Commissie (METC) |
| OCDS         | Obsessive Compulsive Drinking Scale |
| OCDUS        | Obsessive Compulsive Drug Use Scale |
| RISQ         | Risky, Impulsive, and Self-Destructive Behavior Questionnaire |
| RPQ          | Reactive and Proactive Aggression Questionnaire |
| (S)AE        | (Serious) Adverse Event |
| SPC          | Summary of Product Characteristics |

in Dutch: Officiële Productinformatie Sponsor): The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsiding party.

| Abbreviation | Definition |
|--------------|------------|
| SRP-SF       | Self-Report Psychopathy Scale Short Form |
Declarations

Ethics approval and consent to participate

This study is being conducted in accordance with the ethical guidelines of the Declaration of Helsinki and has been approved by the Medical Ethical Review Committee of the Erasmus Medical Center (registration number: 2018.065 – NL65209.078.18. Informed consent will be obtained from all participants prior to the baseline measurement.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research project is funded by de Kwaliteit Forensische Zorg (KFZ). KFZ is an organization which allows professionals to cooperate to optimize and increase the quality of forensic care.

In addition Stichting Volksbond Rotterdam and Stichting Koningsheide gave funding for this study. Stichting Volksbond Rotterdam (SVR) initiates and finances innovative research of socially relevant cases of substance abuse and the background of behavior and genetically expression of the addiction. Stichting Koningsheide supports original and promising projects aimed towards forensic psychiatry.

The financers are not involved in the design of the study nor the drafting of the manuscript.

Furthermore, the financers are not and will not be involved in the subsequent process of data collection, analysis and interpretation.
Authors’ contributions

CS and JD are the principal investigators. JD obtained funding for the study. CS designed the trial in collaboration with JD. JD and AW designed the stimulation model for the tDCS.

CS coordinates the recruitment of the participants and the data collection during the study. CS drafted the manuscript with important contributions from JD, IF and AW.

All authors participated in the revision of the manuscript and approved the final version.

Acknowledgements

We would like to thank the Forensic Addiction Clinic Antes (FVA; Forensische Verslavings Afdeling) in Poortugaal, Zuid-Holland and the other participating institutions for their cooperation with this study.

References

[1] Volkow, N.D., Fowler, J.S., Wang, G.J., Bailer, R., Telang, F. (2009). Imaging dopamine’s role in drugs abuse and addiction. Neuropharmacology 56, 3-8.

[2] Everitt, B.J., & Robbins, T.W. (2005). Neural systems of reinforcement for drug addiction: from action to habits to compulsion. Nature Neuroscience 8, 1481-1489.

[3] Hyman, S.E. (2005). Addiction: a disease of learning and memory. The American Journal of Psychiatry 162, 1414-1422.

[4] Perry, J. & Carrol, M. (2008). The role of impulsive behavior in drugs abuse. Psychopharmacology 200, 1-26.

[5] Volkow, N.D., Fowler, J.S., Wang, G.J., Hitzemann, R., Logan, J., Schyler, D.J. et al. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse. 1993 Jun; 14(2): 169-77.

[6] Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S, Sedler, M. et al. (2001). Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. American Journal of Psychiatry 2001 Dec;158(12): 2015-12.

[7] Capriles, N., Rodaros, D., Sorge, R.E. & Stewart, J. (2003). A role for the prefrontal cortex in stress- and cocaine-induced reinstatement of cocaine seeking in rats. Psychopharmacology 168, 66-74.
[8] Paulus, M.P., Tapert, S.F. & Schukit, M.A. (2005). Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. Archives of General Psychiatry 62, 761-768.

[9] Kosten, T.R.S.B.E., Tucker, K.A., Oliveto, A., Prince, C., Sinha, R., et al. (2006). Cueinduced brain activity changes and relapse in cocaine-dependent patients. Neuropsychopharmacology: Official publication of the American College of Neuropsychopharmacology 31, 644-650.

[10] Garavan, H.H.R. (2007). The role of cognitive control in cocaine dependence. Neuropsychological Review 17, 337-345.

[11] Volkow, N.D., Fowler, J.S., Wang, G.J., Swanson, J.M. & Telang, F. (2007). Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol. 2007 Nov;64(11):1575-9.

[12] Janes, A.C.P.D.A., Richardt, S., deB, F.B., Chuzi, S. & Pachas, G. (2010). Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. Biological Psychiatry 67, 722-729.

[13] Van Holst, R.J. & Schilt, T. (2011). Drug-related decrease in neuropsychological functions of abstinent drug users. Current Drug Abuse Reviews 4, 42-56.

[14] Gizewski, E. R., Müller, B. W., Scherbaum, N., Lieb, B., Forsting, M., Wiltfang, J., Leygraf, N., & Schiffer, B. (2012). The impact of alcohol dependence on social brain function. Addiction Biology, 18, 109-120.

[15] Preller, K. H., Hulka, L. M., Vonmoos, M., Jenni, D., Baumgartner, M. R., Seifritz, E., Dziobek, I., & Quednow, B. (2014). Impaired emotional empathy and related social network deficits in cocaine users. Addiction Biology, 19(3), 452-466

[16] Bernhardt, B.C. & Singer, T. (2012). The neural basis of empathy. Annu Rev Neurosc. 2012; 35: 1-23.

[17] Baron, Robert A., and Deborah R. Richardson. 1994. Human aggression. 2d ed. New York: Plenum

[18] Raine, A., (1993). The Psychopathology of Crime. San Diego, Academic Press.

[19] Anderson, S.W., Bechara, A., Damasio, H., Tranel, D. & Damasio, A.R. (1999b). Impairment of
social and moral behavior related to early damage in human prefrontal cortex. Nat. Neuroscience. 2, 1032-1037.

[20] Raine, A., Lencz, T., Bihrlle, S., LaCasse, L., and Colletti, P. (2000). Reduced prefrontal grey matter volume and reduced autonomic activity in antisocial personality disorder. Arch. Gen. Psychiatry 57, 119-127; discussion 128-119.

[21] Blair, R.J.R (2004). The roles of orbital frontal cortex in the modulation of antisocial behavior. Brain Cognition 55, 198-208.

[22] Krämer, U.M., Kopyciok, R.P.J., Richter, S. & Münde, T.F. (2009). Oscillatory brain activity related to control mechanisms during laboratory-induced reactive aggression. Frontiers in behavioral neuroscience, 3, 46.

[23] Calzada-Reyes, A., Alvarez-Amador, A., Galán-García, L. & Valdés-Sosa, M. (2013). EEG abnormalities in psychopath and non-psychopath violent offenders. Journal of Forensic and Legal Medicine 20. 19-26.

[24] Calzada-Reyes, A., Alvarez-Amador, A., Galán-García, L. & Valdés-Sosa, M. (2016). QEEG and LORETA in Teenagers With Conduct Disorder and Psychopathic Traits. Clinical EEG and Neuroscience I-II.

[25] Morgan, A.B., & Lillienfield, S.O. (2000). A meta-analytic review of the relation between antisocial behavior and neuropsychological measures of executive function. Clinical Psychology Review. 20, 113-136.

[26] Hoaken, P.N., Shaughnessy, V.K. & Pihl, R.O. (2003). Executive functioning and aggression: is it an issue of impulsivity? Aggressive Behavior 29, 15-30.

[27] Giancola, P.R. (2004). Executive functioning and alcohol-related aggression. Journal of Abnormal Psychology, 113, 541-555.

[28] Blair, K.S., Newman, C. Mitchell, D.G.V., Richell, R.A., Leonard, A. Morton, J. & Blair, R.J.R. (2006). Differentiating among prefrontal substrates in psychopathy: neurophysiological test findings. Neuropsychology 20, 153-165.

[29] Blair, R. J. R. (2001). Neurocognitive models of aggression, the antisocial personality disorders,
and psychopathy. Journal of Neurology, Neurosurgery & Psychiatry, 71(6), 727-731.

[30] Blair, R. J. R. (2005). Applying a cognitive neuroscience perspective to the disorder of psychopathy. Development and psychopathology, 17(03), 865-891.

[31] Damasio, H., Grabowski, T., Frank, R., Galaburda, A.M., & Damasio, A.R. (1994). The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science. 1994 May 20; 264(5162):1102-5.

[32] Price, B.H., Daffner, K.R., Stowe, R.M., & Mesulam, M. (1990). The Comportmental Learning Disabilities of Early Frontal Lobe Damage. Brain 113, no. 5: 1383-1393.

[33] Koenings, M., Young, L., Adolphs, R., Tranel, D., Cushman, F., Hauser, M., & Damasio, A. (2007). Damage to the prefrontal cortex increases utilitarian moral judgements. Nature 2007 Apr 19; 446(7138):908-11.

[34] Raine, A., Mellingen, K., Liu, J., Venables, P., & Mednick, S.A. (2003). Am J Psychiatry. 2003 Sep; 160(9):1627-35.

[35] Raine, A., Meloy, J.R., Bihrle, S., Stoddard, J., LaCasse, L., & Buchsbaum, M.S. (1998). Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behav Sci Law. 1998 Summer;16(3):319-32.

[36] Anderson, S.W., Barrash, J., Bechara, A., & Tranel, D. (2006). Impairments of emotion and real-world complex behavior following childhood-or adult-onset damage to ventromedial prefrontal cortex. J Int Neuropsychol Soc. 2006 Mar;12(2):224-35.

[37] Zheng, H., Huang, D., Chen, S., Wang, S., Guo, W., Luo, J., Ye, H., & Chen, Y. (2016). Modulating the Activity of Ventromedial Prefrontal Cortex by Anodal tDCS Enhances the Trustee’s Repayment through Altruism. Front Psychol. 2016; 7:1437.

[38] Mathur, V.A., Harada, T., Lipke, T., & Chiao, J.Y. (2010). Neural basis of extraordinary empathy and altruistic motivation. Neuroimage, 2010 Jul 15;51(4):1468-75.

[39] Waytz, A., Zaki, J., & Mitchell, J.P. (2012). Response of Dorsomedial Prefrontal Cortex Predicts Altruistic Behavior. The Journal of Neuroscience, May 30, 2012;32(22);7646-7650.

[40] Damasio, A.R., Tranel, D., & Damasio, H. (1990). Individuals with sociopathic behavior caused by
frontal damage fail to respond autonomic ally to social stimuli. Behav Brain Res. 1990 Dec 14; 41(2):81-94.

[41] Bechara, A., Damasio, H., Tranel, D., & Damasio, A.R. (1997). Science. 1997 Feb 28;275(5304):1293-5.

[42] Gilam, G., Abend, R., Gurevitch, G., Erdman, A., Baker, H., Ben-Zion, Z., & Hendler, T. (2018). Attentuating anger and aggression with neuromodulation of the vmPFC: A simultaneous tDCS-fMRI study. ScienceDirect.Cortex 109 (2018) 156-170.

[43] Barr, M.S., Fitzgerald, P.B., Farzan, F., George, T.P., Daskalakis, Z.J., 2008. Transcranial magnetic stimulation to understand the pathophysiology and treatment of substance use disorders. Current Drug Abuse Reviews 1, 328–339.

[44] George, M.S., Aston-Jones, G., 2010. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 35, 301–316.

[45] DaSilva, M.C., Conti, C.L., Klauss, J., Alves, L.G, do Nascimento Cavalcante, H.M.,Fregni, F., et al (2013). Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. Journal of Physiology. Paris, 107. 493-503.

[46] Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M.F., Saoud, M., Mechri, A. & Poulet, E. (2012) Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. American Journal of Psychiatry 169:719–724.

[47] Kalu, U.G., Sexton, C.E., Loo, C.K. & Ebmeier, K.P. (2012) Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychological Medication 42:1791–1800.

[48] Hermann, M.J., Horst, A.K., Löble, S., Möll, M.T., Katzorke, A. & Polak, T. (2017). Relevance of Dorsolateral and Fronto-temporal Cortex on the Phonemic Verbal Fluency – A fNIRS-Study. Neuroscience 367, 169-177.

[49] Jansen, J.M., Daams, J.G., Koeter, M.W.J., Veltman, D.J., van den Brink, W. & Goudriaan, A.E. (2013). Effects of non-invasive neurostimulation on craving: A metaanalysis. Neuroscience and
Biobehavioral Reviews 37, 2472-2480.

[50] Shahbabaie A, Golesorkhi M, Zamanian B, Ebrahimpoor M, Keshvari F, Nejati V, et al. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. Int J Neuropsychopharmacol. 2014;17(10):1591-8. doi: 10.1017/S1461145714000686. [51] Fregni F, Liguori P, Fecteau S, Nitsche MA, Pascual-Leone A, Boggio PS (2008a) Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue- provoked smoking craving: a randomized, sham-controlled study. J Clin Psychiatry 69:32–40. [52] Fregni F, Orsati F, Pedrosa W, Fecteau S, Tome FA, Nitsche MA, Mecca T, Macedo EC, Pascual-Leone A, Boggio PS (2008b) Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite 51:34–41.

[53] Falcone, M., Bernardo, L., Ashare, R.L., Hamilton, R. Faysitan, O., McKee, S.A., Loughead, J. & Lerman, C. (2016). Transcranial Direct Current Brain Stimulation Increases Ability to Resist Smoking. Brain Stimulation, 9, 191-196.

[54] Boggio, P.S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., et al., (2008b). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. Drug Alcohol Dependence 92, 55-60.

[55] Camprodon, J.A., Martínez-Raga, J., Alonso-Alonso, M., Shih, M. & Pascual-Leone, A. (2007). One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving Drug. Alcohol Depend., 86 (1) (2007), pp. 91-94.

[56] Politi E, Fauci E, Santoro A, Smeraldi E. Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. Am J Addict 2008; 17: 345-6. [57] Conti, C.L. & Nakamura-Palacios, E.M. (2014). Bilateral transcranial direct current stimulation over dorsolateral prefrontal cortex changes the drug-cued reactivity in the anterior cingulate cortex of crack-cocaine addicts. Brain Stimulation. 7, 130-132.

[58] Batista, E.K.B., Klauss, J., Fregni, F., Nitsche, M.A. & Nakamura-Palacios, E.M. (2015). A Randomized Placebo-Controlled Trial of Targeted Prefrontal Cortex Modulation with Bilateral tDCS in patients with Crack-Cocaine Dependence. International Journal of Neuropsychopharmacology, 2015,
[59] den Uyl, T.E., Gladwin, T.E. & Wiers, R.W. (2015). Transcranial direct current stimulation, implicit alcohol associations and craving. Biological Psychology 2015; 105; 3742. 

[60] Wietschorke, K., Lippold, J., Jacob, C., Polak, T., & Herrmann, M.J. (2016). Transcranial direct current stimulation of the prefrontal cortex reduces cue-reactivity in alcohol dependent patients. Journal of Neural Trans, 123 (2016), pp. 1173-1178

[61] Klauss, J., Penido Pinheiro, L.C., Silva Merlo, B.L., de Almeida CorreiaSantos, G., Fregni, F., Nitsche, M.A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. International Journal of Neuropsychopharmacology 17:1793-1803.

[62] Rêgo, G.G., Lapenta, O.M., Marques, L.M., Costa, T.L., Leite, J. & Carvalho, S. et al. (2015). Hemispheric dorsolateral prefrontal cortex lateralization in the regulation of empathy for pain. Neuroscience letters 594 (2015) 12-16.

[63] Coll, M.P., Tremblay, M.B. & Jackson, P.L. (2016). The effect of tDCS over the right temporo-parietal junction on pain empathy. Neuropsychologia 100, 110-119

[64] Hetú, S., Taschereau-Dumouchel, V. & Jackson, P.L. (2012). Stimulating the brain to study social interactions and empathy. Brain Stimulation 5, 95-102.

[65] Darby, R. R., & Pascual-Leone, A. (2017). Moral Enhancement Using Non-invasive Brain Stimulation. Frontiers in Human Neuroscience, 11.

[66] Sellaro, R., Nitsche, M. A., & Colzato, L. S. (2017). The stimulated social brain: effects of transcranial direct current stimulation on social cognition. Annals of the New York Academy of Sciences, 1369(1), 218-239.

[67] Feeser, M., Prehn, K., Kazzer, P., Mungee, A. & Bajbouj, M. (2014). Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain Stimulation 2014 Jan-Feb; 7(1): 105-12

[68] Abend, R., Sar-el, R., Gonen, T., Jalon, I., Vaisvaser. S., Bar-Haim, Y., & Hendler, T. (2017). Modulation Emotional Experience Using Electrical Stimulation of the Medial-Prefrontal Cortex: A
Preliminary tDCS-fMRI Study. Neuromodulation: Technology at the Neural Interface.

[69] Gilam, G., Abend, R., Gurevitch, G., Erdman, A., Baker, H., Ben-Zion, Z., & Hendler, T. (2018). Attenuating anger and aggression with neuromodulation of the vmPFC: A simultaneous tDCS-fMRI Study. Cortex. 2018 Dec;109:156-170.

[70] Riva, P, Lauro, L.J.R., DeWall, C.N., Chester, D.S. & Bushman, B.J. (2015) Reducing aggressive responses to social exclusion using transcranial direct current stimulation. SCAN, 10, 352-356. Published by Oxford University Press.

[71] Riva, P., Gabbiadini, A., Romero Lauro, L.J., Andrighetto, L., Volpato, C. & Bushman, B.J. (2017). Neuromodulation can reduce aggressive behavior elicited by violent video games. Cognitive Affective Behavioral Neuroscience (2017). 17: 452-459.

[72] Choy, O., Raine, A., & Hamilton, R.M. (2018). Stimulation of the Prefrontal Cortex Reduces Intentions to Commit Aggression: A Randomized, Double-Blind, Placebo-Controlled, Stratified, Parallel-Group Trial.

[73] Dambacher, F., Schuhmann, T., Lobbestael, J. Arntz, A., Brugman, S. & Sack, A.T. (2015). Reducing proactive aggression through non-invasive brain stimulation. SCAN (2015) 10, 1303-1309.

[74] Van Dongen, J.D.M., Brazil, I.A., Van der Veen, F.M., & Franken, I.H.A. (2018). Electrophysiological Correlates of Empathic Processing and its Relation to Psychopathic Meanness. Cognitive Affective and Behavioural Neuroscience.

[75] Tillem, S., Van Dongen, J.D.M., Brazil, I., & Baskin-Sommers, A. (2018). Interpersonal-Affective Traits of Psychopathy are Associated with Less Efficient Neural Communication during Resting-State EEG.

[76] Santarnecchi, E., Fox, M. D., Almquist, J., Brem, A. K., Kadosh, R. C., Dillard, M., ... & Levenbaum, E. Predicting the outcome of computerized cognitive training using resting-state functional connectivity patterns.

[77] Minhas P, Bansal V, Patel J, Ho JS, Diaz J, Datta A, Bikson A. Electrodes for high-definition transcranial DC stimulation for application in drug delivery and electrotherapy, including tDCS. Journal of Neuroscience Methods. 2010;190:188-197.
[78] Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., ... & Marangolo, P. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clinical Neurophysiology, 128(1), 56-92.

[79] Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Götzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200-207.

[80] Spreen, M., Brand, E., Ter Horst, P., & Bogaerts, S. (2014). Handleiding en Methodologische Verantwoording HKT-R, Historisch, Klinische en Toekomstige-Revisie.

[81] Cherek, D.R. (1992). Point subtraction aggression paradigm (PSAP). Houston, University of Texas.

[82] Fox, M. D., Buckner, R. L., Liu, H., Chakravarty, M. M., Lozano, A. M., and Pascual-Leone, A. (2014). Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. Proc. Natl. Acad. Sci. U.S.A. 111, E4367–E4375. doi: 10.1073/pnas.1405003111.

[83] Baxter, B.S., Edelman, B.J., Sohrabpour, A., & He, B. (2017). Anodal Transcranial Direct Current Stimulation Increases Bilateral Direct Brain Connectivity during Motor-Imagery Based Brain-Computer Interface Control. Front. Neurosci, 07 December 2017.

[84] Buch, E. R., Santarnecchi, E., Antal, A., Born, J., Celnik, P. A., Classen, J., et al. (2017). Effects of tDCS on motor learning and memory formation: a consensus and critical position paper. Clin. Neurophysiol. 128, 589–603. doi: 10.1016/j.clinph.2017.01.004

[85] Fisher, D. B., Fried, P., Ruffini, G., Ripolles, O., Ketchabaw, T., Santarnecchi, E., et al. (2017). Network-targeted non-invasive brain stimulation with multifocal tDCS. Brain Stimul. 10, 411–412. doi: 10.1016/j.brs.2017.01.219

[86] Nissim, N.R., O’Shea, A., Indahlastari, A., Telles, R., Richards, L., Porges, E., Cohen, R., & Woods, A.J., (2019). Effects of in-Scanner Bilateral Frontal tDCS on Functional Connectivity of the Working Memory Network in Older Adults. Front. Aging Neurosci., 15 March 2019
[87] Dziobek, I., Rogers, K., Fleck, S., Bahnemann, M., Heekeren, H.R., Wolf, O.T., & Convit, A. (2008). Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET). J Autism Dev Disord. 2008 Mar;38(3):464-73.

[88] Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The “Reading the Mind in the Eyes” Test Revised Version: A Study with Normal Adults, and Adults with Asperger Syndrome or High-functioning Autism. J. Child Psychol. Psychiat. Vol. 42, No.2., pp 241-255, 2001

[89] Gandiga, P.C., Hummel, F.C., & Cohen, L.G. (2006). Transcranial DC Stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol. 2006 Apr;117(4):845-50.

[90] Geniole, S.N., MacDonell, E.T., & McCormick, C.M. (2016). The Point Subtraction Paradigm as a laboratory tool for investigating the neuroendocrinology of competition. Hormones and Behavior, Online First.

[91] Taylor, S.P. (1967). Aggressive behavior and physiological arousal as a function of provocation and the tendency to inhibit aggression. Journal of Personality, 35(2), 297-310.

[92] Gordts, S., Uzielbo, K., Neumann, C., Van den Bussche, E., & Rossi, G. (2017). Validity of the Self-Report Psychopathy Scales (SRP-III full and short versions) in a community sample. Assessment, 24(3), 308-325.

[93] Cima, M., Raine, A., Meesters, C., & Popma, A. (2013). Validation of the Dutch Reactive Proactive Questionnaire (RPQ): Differential Correlates of Reactive and Proactive Aggression From Childhood to Adulthood. Aggressive Behavior, 39(2), 99-113.

[94] de Corte, K., Buysse, A., Verhofstadt, L., Roeyers, H., Ponnet, K., & Davis, M. (2007). Measuring empathic tendencies: Reliability and validity of the Dutch version of the Interpersonal Reactivity Index. Psychologica Belgica, 47(4).

[95] Bagby, R. M., Taylor, G. J., & Parker, J. D. A. (1994). The twenty-item Toronto Alexithymia Scale: II. Convergent, discriminant, and concurrent validity. Journal of Psychosomatic Research, 38(1), 33-40.

[96] Van Dongen, J.D.M., Sergiou, C.S., Godor, B., & Franken, I.H.A., 2018. Risky, Impulsive, and Self-Destructive Behavior Questionnaire (RISQ) (in prep.)
[97] Patton, J.H., Stanford, M.S., & Baratt, E.S. (1995). Factor structure of the Baratt Impulsiveness Scale. Journal of Clinical Psychology, 51, 768-7.

[98] Babor, T.F., Higgins-Biddle, J.C., Saunders, J.B. & Monteiro, M.G. (2001). The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care World Health Organization (WHO Publication Februari 2014. Diagnostische instrumenten. Kenniscentrum Kinder- en Jeugdpsychiatrie No. 01.6a), World Health Organization, Geneva, Switzerland.

[99] Drug Use Disorder Identification Test (DUDIT) Berman, A. H., Bergman, H., Palmstierna, T., & Schlyter, F. (2005). Evaluation of the Drug Use Disorders Identification Test (DUDIT) in Criminal Justice and Detoxification Settings and in a Swedish Population Sample. European Addiction Research, 11(1), 22-31.?

[100] Franken, I.H.A, Hendriks, V.M. & van den Brink, W. (2002). Initial validation of two opiate craving questionnaires the obsessive compulsive drug use scale and the desires for drug questionnaire.

[101] Schippers GM, De Jong CAJ, Lehert Ph, Potgieter A., Deckers F, CasselmanJ, & Geerlings. PJ (1997). The Obsessive Compulsive Drinking Scale: Translation into Dutch and possible modifications. European Addiction Research, 3, 116-122.

[102] Ouellet, J., McGirr, A., Van den Eynde, F., Jollant, F., Lepage, M., & Berlim, M.T. (2015). Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): A randomized and sham-controlled exploratory study. J Psychiatr Res. 2015 Oct; 69: 27-34.

Figures
Relationship between the impaired brain areas, impaired processes and behavior. The highlighted brain area, impaired process and behavior are discussed in this paper. *DLPFC= Dorsolateral Prefrontal Cortex, vmPFC= Ventromedial Prefrontal Cortex

Figure 1

Flowchart of the trial

Figure 2
### SPIRIT Schedule of Enrollment, Interventions and Assessments

#### Figure 3

| TIMEPOINT | Enrollment | Pre-Intervention | Intervention (Modulation) | Post-Intervention | Follow-up |
|-----------|------------|------------------|---------------------------|-------------------|-----------|
| T-1       |            | T0               | T1                        | T2                | T3        | T4        | T5        | T6        | T7        |

**ENROLMENT:**
- Eligibility screen: X
- Informed consent: X
- HKT-R: X
- Allocation: X

**INTERVENTIONS:**
- tDCS Active Stimulation + TAU
- Sham Stimulation + TAU
- MET, rMET, Movies

**ASSESSMENTS:**
- Resting state EEG: X
- Passive Viewing Empathy Task (EEG): X
- PSAP: X
- Self-report Questionnaires: X

---

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRIT_Fillable-checklist-C.Sergiou.25-04-2019.pdf
- Positive decision NL65209.078.18v2_S_METC359766 METC.pdf
- Budget KFZ.English Version.pdf