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Consequences of prefrontal tDCS on inhibitory control and reactive aggression

Carmen Weidler,[1] Ute Habel,[1,2] Paul Wallheinke,[1] Lisa Wagels,[1,2] Lena Hofhansel,[1,2] Shichun Ling,[3] Julie A. Blendy,[4] and Benjamin Clemens[1]

[1]Department of Psychiatry, Psychotherapy and Psychosomatics, Faculty of Medicine, RWTH Aachen, Aachen 52074, North Rhine-Westphalia, Germany, [2]Research Center Jülich, Institute of Neuroscience and Medicine, JARA-Institute Brain Structure Function Relationship (INM 10), Jülich, 52428, North Rhine-Westphalia, Germany, [3]School of Criminal Justice and Criminalistics, California State University, Los Angeles, CA 90032, USA, and [4]Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Correspondence should be addressed to Carmen Weidler, Department of Psychiatry, Psychotherapy and Psychosomatics, Faculty of Medicine, RWTH Aachen, Pauwelsstraße 30, Aachen 52074, Germany. E-mail: cweidler@ukaachen.de

Abstract

Increased aggression and impulsivity represent a key component of several psychiatric disorders, including substance use disorder, which is often associated with deficient prefrontal brain activation. Thus, innovative tools to increase cognitive control are highly warranted. The current study investigates the potential of transcranial direct current stimulation (tDCS), a tool to modulate cortical activation and to increase cognitive control in individuals with a high potential for impulsive and aggressive behavior. In a double-blind, sham-controlled study, we applied anodal tDCS over the right dorsolateral prefrontal cortex in an all-male sample of alcohol-dependent patients (AD), tobacco users (TU) and healthy controls (HC), who completed the Taylor Aggression Paradigm and Stop Signal Reaction Time Task twice. While there were no observable effects of tDCS in controls, the results revealed altered aggressive behavior in AD following active stimulation. Specifically, these individuals did not show the standard increase in aggression over time seen in the other groups. Furthermore, improved response inhibition was found in AD and TU following active but not sham stimulation. Our study demonstrates that prefrontal tDCS improves our laboratory measure of impulse control in at-risk groups, illustrating the importance of sample characteristics such as nicotine intake and personality traits for understanding the effects of brain stimulation.

Key words: tDCS; alcohol-dependent patients; tobacco users; aggression; impulsivity

Introduction

Many mental disorders and neuro-psychopathologies are associated with heightened levels of aggression and impulsivity, which are notoriously difficult to treat. High impulsivity and pathological aggression are particularly prevalent and strongly expressed in patients with substance use disorder (Brady *et al.*, 1998). Impulsiveness does not only contribute to the likelihood

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of initial substance use, it is also a strong predictor of relapse among patients with substance use disorder (Rosvall et al., 2008; Stevens et al., 2015). Moreover, substance use is associated with an increased risk for aggressive behavior (Hawkins et al., 2000). This is further demonstrated by the fact that acute alcohol intoxication augments aggressive behavior in healthy individuals (Ito et al., 1996; Denson et al., 2008, 2011; Heinz et al., 2011) and on top of that a multitude of violent acts are committed under the influence of alcohol and other substances (Graham and Livingston, 2011; Håkansson and Jesionowska, 2018). Considering the clinical relevance and also the detrimental social and personal consequences of pathological aggression, interventions that help to increase impulse control and reduce aggressive behavior in substance users are highly warranted.

A possible strategy to reduce aggressive behavior could be to strengthen inhibition performance. Indeed, low levels of inhibitory control seem to increase aggressive behavior when emotion regulation capacities are low as well (Hsieh and Chen, 2017). Moreover, both increased impulsivity and aggression have been associated with deficient prefrontal brain activation (Asahi et al., 2004; Lane et al., 2011). Consensus among experts is that the dorsolateral prefrontal cortex (DLPFC), in collaboration with other prefrontal structures, plays a key role in executing cognitive control (Aron et al., 2004). More specifically, it was proposed that the regulation and suppression of anger and aggressive impulses is achieved by inhibitory neural signals sent from the DLPFC to the amygdala and other sub-cortical structures that are responsible for generating such aggressive impulses (Davidson et al., 2000; Kohn et al., 2014). For example, increased activation of the DLPFC is associated with better inhibition performance in the Stop Signal Reaction Time Task (SSRT) (Friehs and Frings, 2018). Similarly, increased activation of the right DLPFC has been found to reduce aggressive behavior by exerting top-down regulation (Perach-Barzilay et al., 2013; Achterberg et al., 2016). While it is unclear if this reduction of aggression is a direct result of increased inhibitory control, the DLPFC certainly presents a promising target for interventions.

In recent years, several techniques that allow researchers to alter brain activity have received increased attention. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that alters resting membrane potentials in targeted brain regions. During stimulation, a low constant current is delivered through electrodes attached to the head in a polarity-dependent manner. While it is generally assumed that cathodal current exerts inhibitory effects on the stimulated brain region, anodal tDCS is assumed to enhance neural activation by increasing cortical excitability (Nitsche and Paulus, 2000). Effects from a single session last up to 90 min following the termination of stimulation (Nitsche and Paulus, 2001) and effects of repeated sessions (e.g. 10 sessions) have been observed at 1-month (Doruk et al., 2014) and 3-month follow-ups (Forogh et al., 2017). Due to the extremely low prevalence of severe side effects and the painless, non-invasive and cost-effective characteristics of tDCS, this technique appears to be a suitable candidate for designing innovative and alternative therapeutic options for neurological and psychiatric pathologies. For instance, tDCS has already been successfully applied to increase cognitive functions in depression (Shiozawa et al., 2014) and schizophrenia (Brunelin et al., 2012). In addiction-related studies, tDCS has most frequently been applied to reduce craving (Jansen et al., 2013). Thus, tDCS could be a potential tool to enhance cognitive control.

There is emerging evidence that tDCS may have differential effects on complex behaviors based on a multitude of influences such as genetics (Plewnia et al., 2013; Nieratschker et al., 2015), nicotine intake (Grundey et al., 2018) and individual characteristics (Shen et al., 2016) and might thus depend on the study population. For instance, while decreasing risk-taking in healthy participants, the same tDCS protocol leads to increased risk-taking in marijuana users (Pascual-Leone et al., 2007; Boggio et al., 2010). It has further been proposed that tDCS effects depend on the baseline levels of the behavior of interest (Shen et al., 2016). Specifically, the effects of tDCS on risk-taking behavior are larger in highly impulsive individuals than in controls (Cheng and Lee, 2016). Rather than exerting a generalized effect, tDCS may be most appropriate for populations with behavioral impairments. A specific behavioral improvement of inhibition and a reduction of aggressive behavior after tDCS stimulation in at-risk groups, e.g. highly impulsive individuals, would increase our understanding of neural dysfunctions underlying deficient impulse control.

The current study

Studies investigating stimulation effects on impulsive and aggressive behavior in individuals with substance use disorder are scarce. The current study aims to fill the gap on mechanisms of impulsive and aggressive behavior in these individuals. Specifically, we aim to examine the effects of anodal tDCS over the right DLPFC on inhibitory control and reactive aggression in individuals who might have difficulties controlling their impulses. We investigate male patients diagnosed with alcohol dependence and healthy matched controls. Given the high prevalence of tobacco smoking in addictive disorders such as alcohol dependence (Guydish et al., 2016) and the indication that nicotine may affect the effects of tDCS (Grundey et al., 2018), we also include an additional group that consisted of male chronic tobacco users (TU). Using a double-blind, sham-controlled study design, performance in a modified Taylor Aggression Paradigm (mTAP) and the SSRT, two widely used and well-validated tasks, is assessed before and immediately after a single session of tDCS.

During the baseline measurement, we expect increased aggressive behavior and reduced response inhibition in alcohol-dependent patients (AD) and TU as compared to healthy controls (HC). Following anodal but not sham tDCS, we predict decreased aggressive behavior and increased response inhibition in substance users. Based on previous research, we expect to see smaller effects of anodal stimulation in healthy participants as compared with substance users.

Methods

Participants

All 51 participants were male, aged between 18 and 60, right-handed and had no history of seizures. In-patients were recruited from the psychiatry ward of the University Hospital RWTH Aachen and out-patients were recruited using public advertising. Participants who were diagnosed with alcohol dependence according to the 10th version of the International Statistical Classification of Diseases and Related Health Problems (mean time passed since initial diagnosis = 16 years) were included in the patient group (AD, $n = 18$). The diagnosis of alcohol dependence was confirmed by a trained physician during the experiment using the Structured Clinical Interview

Table 1. Personality questionnaires (mean ± SD)

	HC	AD	TU	P (HC vs AD)	P (HC vs TU)	P (AD vs TU)
N	16	18	17			
Age	40.19 ± 10.82	42.33 ± 10.77	41.47 ± 12.06	1.00	1.00	1.00
Years of education	10.88 ± 2.45	10.94 ± 2.99	10.94 ± 2.14	1.00	1.00	1.00
AQ	58.50 ± 14.13	76.00 ± 18.87	73.47 ± 16.14	0.011	0.038	1.00
BIS	56.31 ± 7.69	68.06 ± 12.50	64.12 ± 7.14	0.002	0.093	0.696
Proactive aggression	1.81 ± 2.66	2.72 ± 2.85	5.88 ± 2.18	0.99	0.0001	0.002
Reactive aggression	5.50 ± 3.93	9.72 ± 3.66	2.18 ± 1.59	0.001	0.014	0.000
SP	8.38 ± 5.52	10.17 ± 5.31	6.88 ± 4.27	1.00	1.00	0.190
SR	9.88 ± 4.15	12.89 ± 4.80	10.18 ± 3.76	0.215	1.00	0.201

HC = healthy controls; AD = alcohol-dependent patients; TU = tobacco users; AQ = Aggression Questionnaire; BIS = Barrett Impulsivity Scale; SP = sensitivity to punishment; SR = sensitivity to reward; SD = standard deviation; pairwise comparisons are Bonferroni corrected.

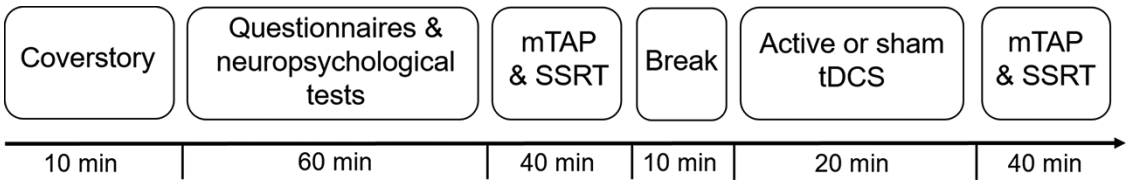

Fig. 1. Illustration of the study procedure. mTAP = modified Taylor Aggression Paradigm; SSRT = Stop Signal Reaction Time Task; tDCS = transcranial direct current stimulation.

for DSM-IV Axis I disorders [SCID I (Wittchen *et al.*, 1997)]. Patients were excluded if they were in acute withdrawal. Comorbidities with other psychiatric disorders were not exclusionary if alcohol dependence was the primary diagnosis. Individuals included in the AD group had comorbid depression ($n = 6$), posttraumatic stress disorder ($n = 2$), social anxiety ($n = 2$), specific phobia ($n = 1$), dysthymia ($n = 1$) and panic disorder ($n = 1$). Nine AD reported to also consume substances other than alcohol. Four participants had no comorbidities. Twelve individuals consumed alcohol within the last month; however, six of those were in-patients and currently abstinent. Six patients were abstinent within the last month. Medications affecting the central nervous system included atypical antidepressants ($n = 3$), benzodiazepines ($n = 2$), methadone ($n = 2$), antipsychotic medication ($n = 1$), selective serotonin reuptake inhibitors ($n = 1$) and anticonvulsants ($n = 1$). Nine patients did not take any medication.

Healthy controls (HC, $n = 16$) and TU ($n = 17$), who were age- and education-matched to the patient group (see Table 1), had no current neurological or psychiatric illnesses as confirmed by the SCID I. Both HC and TU were pre-screened for their alcohol consumption using the Alcohol Use Disorder Identification Test and included if they scored below 8 (8 = suspected alcohol abuse). HC were non-smokers and TU consumed a minimum of 10 cigarettes per day.

All participants gave written informed consent prior to the experiment and were compensated for participation. The study protocol was approved by the Internal Review Board of the medical faculty of the RWTH Aachen and in concordance with the Declaration of Helsinki.

Procedure

Prior to the experiment, all participants received the instruction to not drink alcohol on the night before the experiment and on the day of the experiment. Upon arrival, participants were informed that the experiment aimed to investigate the effects of tDCS on emotional processing and would be performed with two participants simultaneously. Each participant was introduced to his same-sex opponent, a confederate of the experimenter, and jointly listened to the instructions for the mTAP and SSRT (Coverstory). Subsequently, questionnaires and neuropsychological tests were completed. After completing these tasks but before the stimulation, the participants were given a short break (5–10 min) which the TU and AD who consumed tobacco used to smoke one cigarette. This break was provided to prevent craving effects in these participants. During the stimulation, participants completed the N-back task, a working memory task which is known to engage the DLPFC (Ragland *et al.*, 2002). The rationale here was to facilitate tDCS effects by engaging the area of the brain which was stimulated. tDCS termination was immediately followed by the second measurement of the mTAP and SSRT and subsequent debriefing about the true nature of the study. A depiction of the study design is shown in Figure 1.

Personality questionnaires and neuropsychological tests

All participants completed the Buss–Perry Aggression Questionnaire [AQ, (Buss and Perry, 1992)], the Reactive Proactive Aggression Questionnaire [RPQ, (Raine *et al.*, 2006)], the Barrett Impulsiveness Scale [BIS, (Patton *et al.*, 1995)] and the Sensitivity to Reward and Sensitivity to Punishment Questionnaire [SPSRQ, (Torrubia *et al.*, 2001)]. To examine the cognitive functioning of the participants, a battery of neuropsychological tests was performed. Participants completed the Trail Making Test (TMT) A and B (Arbuthnott and Frank, 2000), the digit span forward and backward (Wechsler, 1997) and the Wortschatz-Intelligenztest (WST) to assess lexical intelligence (Schmidt and Metzler, 1992). Questionnaire data are presented in Table 1, and performance on neuropsychological tests is provided in Table 2.

Modified Taylor Aggression Paradigm (mTAP). The task consisted of three separate runs with 20 trials each. In each trial (Figure 2), individuals were able to choose a punishment level ranging from 0 to 100 in steps of 10 cents (*decision*). The fol-

Table 2. Descriptives (Mean ± SD)

	HC	AD	TU	Whole sample
N	16	18	17	51
TMT-A (seconds)	30.22 ± 4.42	26.94 ± 4.17	33.76 ± 4.56	30.31 ± 2.53
TMT-B (seconds)	58.19 ± 7.44	58.38 ± 7.02	53.64 ± 7.69	56.74 ± 4.27
WST-IQ	98.75 ± 3.05	96.22 ± 2.88	100 ± 3.15	98.32 ± 1.75
Digit span forward	6.88 ± 0.51	7.22 ± 0.48	8.27 ± 0.52	7.46 ± 0.29
Digit span backward	5.69 ± 0.46	6.06 ± 0.43	6.33 ± 0.47	6.03 ± 0.26
Punishment pre tDCS	64.17 ± 34.02	62.73 ± 32.33	63.36 ± 28.12	63.44 ± 31.72
Punishment post tDCS	78.41 ± 31.87	68.53 ± 32.5	71.81 ± 25.64	73.11 ± 30.58
SSRT pre tDCS	229.85 ± 62.47	215.21 ± 69.5	223.7 ± 75.15	222.15 ± 68.42
SSRT post tDCS	214.27 ± 75.35	199.46 ± 42.93	213.88 ± 76.85	208.46 ± 64.34

SD = Standard deviation; HC = healthy controls; AD = alcohol-dependent patients; TU = tobacco users; TMT = trail making test; WST = Wortschatztest; tDCS = transcranial direct current stimulation; SSRT = Stop Signal Reaction Time.

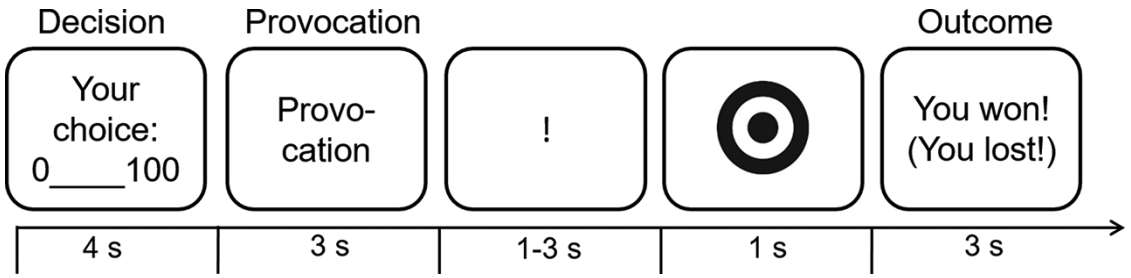

Fig. 2. Illustration of a single trial of the mTAP. In the beginning, the participants select a punishment level between 0 and 100 cents. Subsequently, they are informed about the opponent's selection. The exclamation mark signals the upcoming reaction time task. Upon the appearance of a visual cue (target), individuals are instructed to press a button as fast as possible. At the end of each trial, participants are informed whether they won or lost the reaction time task.

lowing screen informed the participants about the opponent's punishment selection (*provocation*). Upon the appearance of a visual clue, the participants were instructed to respond as fast as possible by a button press. The next screen displayed the outcome of the reaction time task (*outcome*). Monetary subtractions (0–100 cents) were used for both the decision and provocation. Similar to previous studies (Beyer *et al.*, 2015; Buades-Rotger *et al.*, 2016), provocation increased from run one (range 0–40, M = 20) to run two (range 30–70, M = 50) and three (range 60–100, M = 82). A more detailed description of the paradigm has been provided previously (Weidler *et al.*, 2019).

Stop Signal Reaction Time Task. Participants were presented pictures of colored geometric objects. In some trials, it was required to make a motor response (go trials) by pressing a button, whereas in others, the participants were asked to withhold the response (stop trials), which was indicated by a stop signal. The task was designed to be adaptive, so that if the participants failed to inhibit the button press in stop trials, the stop signal delay was increased by 33 ms, making it easier to inhibit the response in the next stop trial. Equivalently, if the participants were successful in stop trials, the delay decreased by 33 ms. An illustration of a go trial and stop trial is presented in Figure 3. Thirty percentage of all trials were stop trials. The task was color-balanced across participants (blue as go signal and yellow as stop signal *vs* the inverse). The total number of trials varied across individuals due to the adaptive stop signal delay; however, the task duration was always 15 min.

tDCS

tDCS was delivered using a battery-driven stimulator (neuroConn, Ilmenau, Germany). The anode (5 cm × 7 cm) was placed at the F4 position of the 10-20 EEG system. The cathode (10 cm × 10 cm) was used as the reference electrode and positioned over the contralateral supraorbital area with at least a 7-cm distance to the anode. Following a 20 s ramp-up phase, actively stimulated participants received a current of 1.5 mA for 20 min with a subsequent ramp-down phase of 20 s. In the sham stimulation condition, stimulation was terminated after the ramp-up phase. Both the experimenter and the participant were blind to the type of stimulation.

Statistical analysis

A multivatiate ANOVA (MANOVA) with the dependent variables AQ, BIS, the proactive and reactive aggression subscales of the RPQ and the sensitivity for punishment and sensitivity to reward subscales of the SPSRQ and the between-subject factor group (HC, TU and AD) was used to compare personality traits between groups. A second MANOVA, including the TMT-A, TMT-B, WST and digit span with the between-subject factor group, was conducted to ensure similar cognitive abilities across participants. Pairwise comparisons were used for *post hoc* tests and were corrected for multiple comparisons using Bonferroni correction. Statistical analysis was performed with SPSS (IBM SPSS Statistics 25.0; Ehningen; Germany).

Modelling aggressive and impulsive behavior: mixed effects models

Using R (R Core Team, 2014), we fitted a linear mixed effects model on a trial-by-trial basis using participants' punishment selections as the dependent variable. The model included the outcome of the prior reaction time task (won = 1, lost = 0), time

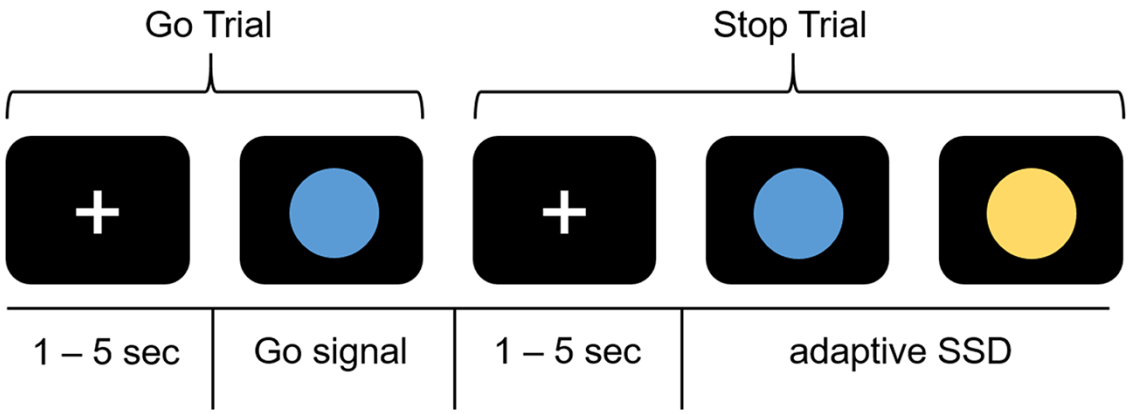

Fig. 3. Illustration of a go-trial followed by a stop-trial. In the beginning of each trial, participants are presented with a fixation cross. Participants are instructed to respond as quick and accurate as possible. The blue circle serves as the 'go-signal'. In stop-trials, the blue circle switches to a yellow circle, the 'stop-signal'. Here, individuals should withhold their response. The stop signal delay (SSD) continuously adapts to the success of the participants. That is, following successful inhibition, a 33-ms longer SSD and following unsuccessful trials, a 33-ms shorter SSD.

point (pre tDCS = 1, post tDCS = 2), tDCS (sham = 0, active = 1) and group (HC = 0, AD = 1, TU = 2) as fixed factors. The model further contained provocation (0–100) of the previous trial as a fixed effect and random intercepts for participants to account for repeated measures. Following our hypotheses, we defined the interaction of time, tDCS and group in the model, so that the results would show the comparisons between the time points two and one, active and sham conditions and groups of interest (AD and TU) as compared to HC. Additionally, we fitted the same linear mixed effects model without provocation as a fixed effect. Results of this model can be found in the Supplementary Tables S1 and S2.

To measure response inhibition, the quantile method was used to acquire the estimates of the stop signal reaction time for each individual (Logan *et al.*, 1997). Three participants were excluded from the analysis due to a SSRT below 50 ms, fewer than 60% correct 'go' responses or fewer than 25% or more than 75% correctly inhibited stop trials. We fitted a linear mixed effects model using the SSRT estimates as the dependent variable and time (pre tDCS = 1, post tDCS = 2), group (HC = 0, AD = 1, TU = 2) and tDCS (sham = 0, active = 1) as fixed factors. The model further included random intercepts for the participants to account for repeated measures.

Using the R package lme4, the estimation of variance of components was performed using restricted maximum likelihood (Bates *et al.*, 2014). *Post hoc* tests were calculated with the R package emmeans. For significant interactions between categorical and continuous variables, slopes of the continuous variable were compared for all levels of the categorical variables. Results were corrected for multiple comparisons using the Tukey method.

Results

Personality traits and neuropsychological tests

The MANOVA of questionnaire scores revealed a significant effect of group for AQ ($F(2,48) = 5.380$, $P < 0.01$), proactive ($F(2,48) = 11.477$, $P < 0.001$) and reactive aggression ($F(2,48) = 24.054$, $P < 0.001$) and impulsivity (BIS) ($F(2,48) = 6.587$, $P < 0.01$). No effect of group was found for sensitivity to reward ($F(2,48) = 1.851$, $P = 0.168$) and sensitivity to punishment ($F(2,48) = 2.628$, $P = 0.083$). The associated *post hoc* tests revealed higher AQ scores for AD ($P < 0.05$) and for TU ($P < 0.05$) as compared to HC. TU also exhibited more proactive aggression than HC ($P < 0.001$) and AD ($P < 0.01$). AD scored significantly higher on reactive aggression as compared to HC ($P < 0.01$) and to TU ($P < 0.001$). Furthermore, HC revealed more reactive aggression than TU ($P < 0.01$). Impulsivity traits, as assessed by the BIS, were higher for AD than for controls ($P < 0.01$). All other comparisons did not reach significance. For detailed results see Table 1.

The MANOVA for neuropsychological tests did not reveal any significant group differences ($F(1086) = 0.646$, $P = 0.770$).

mTAP

Parameter estimates for fixed effects on participants' punishment selections of the linear mixed effects model are presented in Table 3. In the following section, the significant main effects and interactions are summarized. Variance and standard deviation of the random intercept (participants) were 321.9 and 17.94, respectively. The estimated effect size of the model was $R^2_{conditional} = 0.51$. The linear mixed effects model revealed a main effect of time ($t(5905) = 11.91$, $P < 0.001$), demonstrating higher punishment selections in the second session. Punishment selections were further heightened by increased

Table 3. Fixed effects for mTAP

Predictor	*b*	SE	*t*	*p*
Intercept	48.42	6.08	7.97	<0.001
Time2	14.82	1.24	11.91	<0.001
tDCS	−3.87	9.14	0.42	0.67
AD	−7.53	8.56	−0.88	0.38
TU	−3.04	8.56	−0.36	0.72
Provocation	0.31	0.09	33.88	<0.001
Won	2.33	0.57	4.08	<0.001
Time2 × tDCS	−6.93	1.90	−3.66	<0.001
Time2 × AD	−7.12	1.81	−3.94	<0.001
Time2 × TU	−7.69	1.81	−4.26	<0.001
tDCS × AD	11.91	12.71	0.94	0.35
tDCS × TU	3.28	12.93	0.25	0.80
Time2 × tDCS × AD	0.45	2.69	0.17	0.87
Time2 × tDCS × TU	7.37	2.74	2.69	<0.01

AD = Alcohol-dependent patients; TU = tobacco users; SE = standard error; tDCS = transcranial direct current stimulation.

Table 4. Post hoc tests of significant interactions for mTAP

Significant interaction effects	tDCS	Contrast	*b*	SE	*z ratio*	*P*
Time x tDCS	Sham	Pre-post	−9.88	0.75	−13.25	<0.001
	Active	Pre-post	−5.55	0.83	−6.68	<0.001
Time x Group	HC	Pre-post	−11.35	0.95	−11.93	<0.001
	AD	Pre-post	−4.45	0.96	−4.66	<0.001
	TU	Pre-post	−7.34	0.99	−7.41	<0.001
Time x tDCS x Group	Sham	HC $_{\text{pre-post}}$	−14.82	1.24	−11.91	<0.001
		AD $_{\text{pre-post}}$	−7.70	1.31	−5.87	<0.001
		TU $_{\text{pre-post}}$	−7.12	1.31	−5.43	<0.001
	Active	HC $_{\text{pre-post}}$	−7.88	1.44	−5.96	<0.001
		AD $_{\text{pre-post}}$	−1.21	1.39	−0.87	0.38
		TU $_{\text{pre-post}}$	−7.56	1.49	−5.09	<0.001

P values adjusted using the Tukey method; HC = Healthy controls, AD = alcohol-dependent patients; TU = tobacco users; tDCS = transcranial direct current stimulation; SE = standard error.

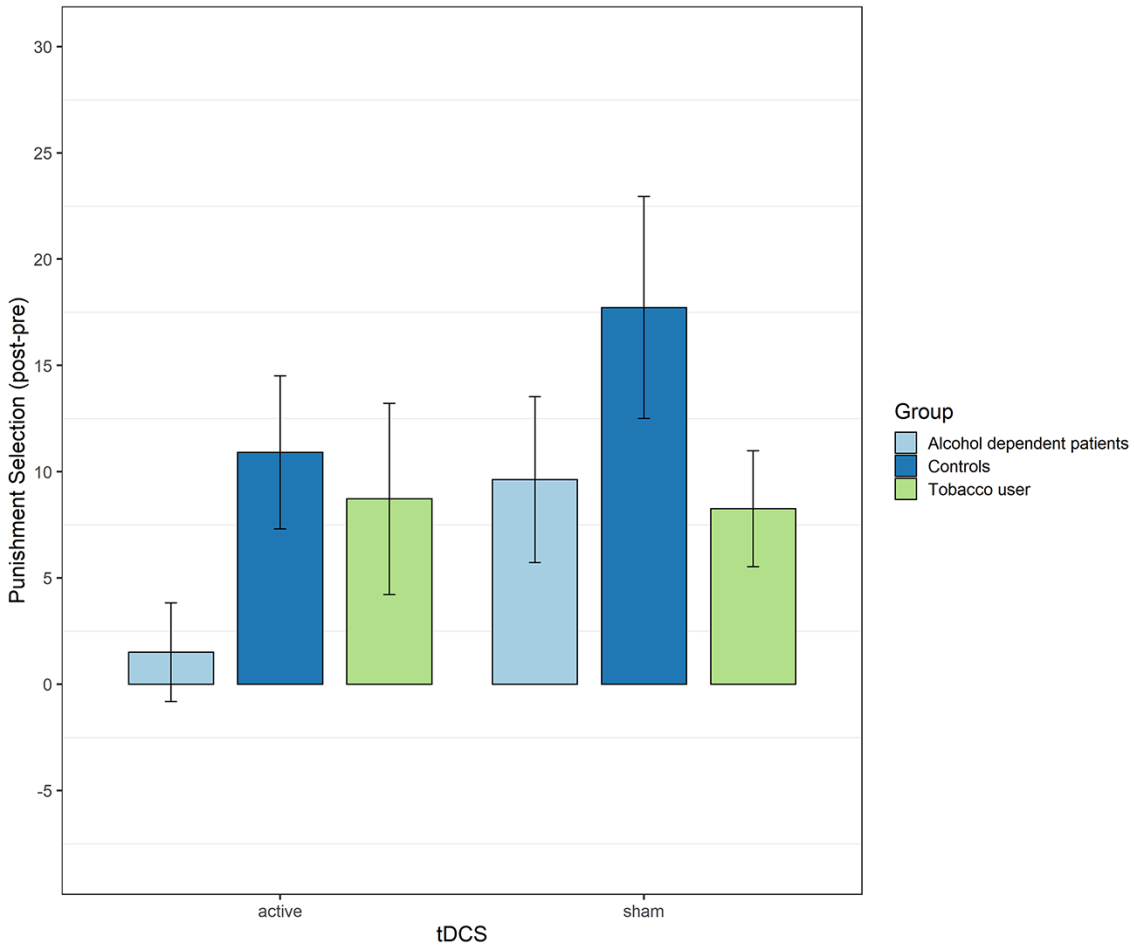

Fig. 4. Results of the liner mixed effects model for the mTAP. The difference (post stimulation − pre stimulation) in punishment selections (0–100 cents) are shown for HC, AD and chronic TU. All participants who received sham stimulation (right) significantly increased their punishment selections in the second session ($P < 0.001$). HC and TU also subtracted significantly more money following active stimulation (left; $P < 0.001$). Only AD who received active tDCS did not alter their punishment selections in the second session ($P < 0.38$). Error bars represent the standard error. *Post hoc* pairwise comparisons are corrected for multiple comparison using the Tukey method.

provocation ($t(5918) = 33.88$, $P < 0.001$) and won competitions ($t(5912) = 4.08$, $P < 0.001$). For details of all fixed effects and *post hoc* tests, please refer to Tables 3 and 4. As our hypotheses were mainly focusing on the three-way interaction of time, tDCS and group, we will limit the following section to the description of these results and the associated *post hoc* tests. A significant three-way interaction was found for time, tDCS and TU ($t(5905) = 2.69$, $P < 0.01$). The associated *post hoc* tests revealed that all but one group selected higher punishment levels in session two: only AD who received active tDCS did not increase the punishment selections in the second session. The results are depicted in Figure 4. Boxplots for each time point, group and

Table 5. Fixed effects for SSRT

Predictor	*b*	SE	*t*	*P*
Intercept	242.53	22.49	10.78	<0.001
Time	−19.62	16.93	−1.16	0.25
tDCS	−44.66	37.63	−1.19	0.24
AD	−40.73	31.80	−1.28	0.21
TU	−40.53	31.80	−1.27	0.21
Time × tDCS	13.48	27.42	0.49	0.63
Time × AD	25.58	23.35	1.10	0.28
Time × TU	37.78	23.35	1.62	0.11
tDCS × AD	71.50	49.27	1.45	0.15
tDCS × TU	94.25	50.71	1.86	0.07
Time × tDCS × AD	−56.92	35.62	−1.60	0.12
Time × tDCS × TU	−77.44	36.65	−2.11	<0.05

P values calculated using Satterthwaite degrees of freedom; AD = Alcohol-dependent patients; TU = tobacco users; tDCS = transcranial direct current stimulation; SE = standard error.

stimulation condition can be found in the Supplementary Table S3. For the descriptive statistics, please refer to Table 2.

SSRT

Parameter estimates for fixed effects on the participants' stop signal reaction times are presented in Table 5. In the following section, the significant main effects and interactions are summarized. Variance and standard deviation of the random intercept (participants) were 3388 and 58.21, respectively. The estimated effect size of the model was $R^2_{conditional} = 0.76$. The linear mixed effects model revealed a significant tDCS × time × TU interaction ($t(41.27) = -2.11$, $P < 0.05$). All other effects were not significant. The associated *post hoc* comparisons showed improved SSRTs for AD and TU following active but not sham stimulation. All other comparisons did not reach significance. The detailed results are presented in Table 6 and Figure 5. Boxplots for each time point, group and stimulation condition can be found in the Supplementary Table S4. To investigate whether the improved SSRTs following active tDCS seen in AD and chronic TU are also accompanied by an increased number of successfully inhibited stop trials, we additionally compared the percentage of successful trials in a repeated measures ANOVA using time (pre, post) as within-subject factor and tDCS (sham, active) and group (AD, TU, HC) as between-subject factors. The results revealed a significant interaction of time and tDCS ($F(1, 41) = 7.23$, $P = 0.01$). Associated *post hoc* comparisons revealed an increased number of successfully inhibited stop trials following active but not sham stimulation ($P = 0.05$) for all three groups. For the descriptive statistics, please refer to Table 2.

Discussion

The current study aimed to upregulate the right DLPFC, a brain region that has frequently been implicated in impulse control and aggression regulation. This right prefrontal upregulation by anodal tDCS was expected to reduce impulsivity and aggression. The innovative aspect of this particular study was that our comprehensive design enabled us to observe and compare these effects between alcohol-dependent individuals, TU and HC. Indeed, our results support the assumption that anodal stimulation of the right DLPFC reduced impulsive behavior in AD and TU. Additionally, the results implicate a beneficial effect of anodal tDCS on aggressive behavior in AD. The implications of these results will be discussed in the remainder of this section, but we already would like to point out the importance of the observed group differences for future studies: due to different responsivity to tDCS in the three groups, forthcoming experimental designs using tDCS are strongly encouraged to incorporate the individual characteristics of participants. Specifically, researchers are recommended to consider alcohol and/or tobacco use and personality traits as the influencing factors.

Aggression

Our results revealed that HC and TU selected higher punishment levels in the mTAP during the post-stimulation session, regardless of whether they received active or sham stimulation. This confirms the previous findings of null effects of anodal tDCS in healthy individuals (Dambacher *et al.*, 2015). Also, AD who received sham stimulation selected higher punishment levels after the stimulation. In contrast, following active tDCS, the latter did not apply higher punishments during the post-stimulation session. It can be assumed that the participants exhibit less control in the course of the experiment due to repeated provocation. This absence of an increase in punishments in AD during the second session could indicate a beneficial effect of anodal tDCS over the right DLPFC, resulting in the maintenance of top-down regulation. Yet, one has to be cautious as the baseline measurement revealed slightly higher punishment selections for the subsequently actively stimulated as compared to sham stimulated AD. However, HC in the sham stimulation group demonstrated similarly high selections and still significantly increased punishment in the post-stimulation session. Hence, we consider a ceiling effect to be unlikely and would rather attribute this effect to the stimulation. While the absence of an effect of tDCS on reactive aggressive behavior in healthy participants is in line with previous research (Dambacher *et al.*, 2015), we would have expected to observe similar effects in TU and AD. In our study, both groups were characterized by higher aggressive traits than HC. However,

Table 6. Post hoc tests of significant interactions for SSRT

Group	tDCS	Contrast	*b*	SE	*t ratio*	*P*
Healthy controls	Sham	Pre-post	19.62	16.9	1.16	0.25
	Active	Pre-post	6.14	21.6	0.28	0.78
Alcohol-dependent patients	Sham	Pre-post	−5.96	16.1	−0.37	0.71
	Active	Pre-post	37.48	16.1	2.33	<0.05
Tobacco users	Sham	Pre-post	−18.16	16.1	−1.13	0.27
	Active	Pre-post	45.79	18.2	2.51	<0.05

P values calculated using Kenward–Roger degrees of freedom method; tDCS = Transcranial direct current stimulation; SE = standard error.

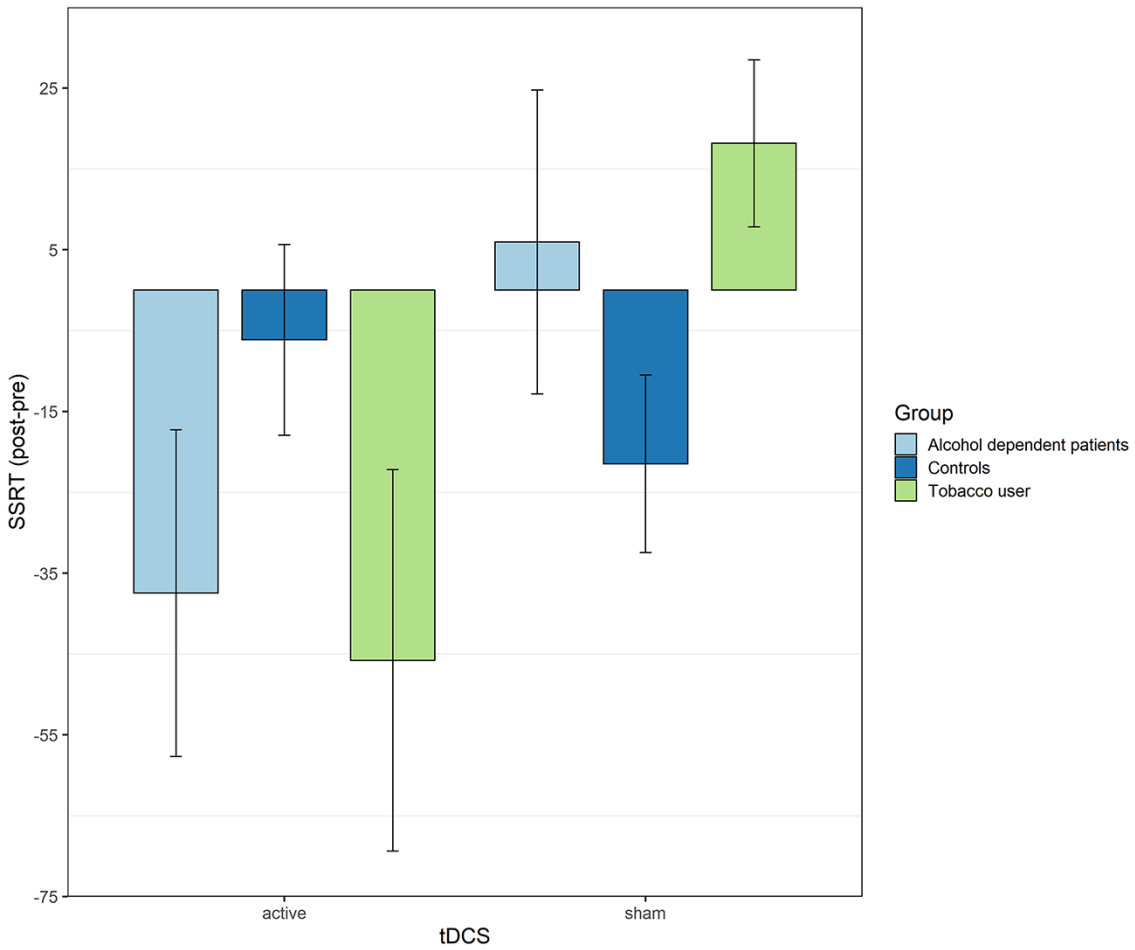

Fig. 5. Results of the liner mixed effects model for the SSRT. The difference (post stimulation−pre stimulation) SSRTs are shown for HC, AD and chronic TU. For all participants who received sham stimulation (right), no significant difference in SSRTs between the first and second sessions were observed. AD and TU had significantly shorter SSRTs following active stimulation (left; $P < 0.05$). No effect of active stimulation was seen in HC. Error bars represent the standard error. *Post hoc* pairwise comparisons are corrected for multiple comparison using the Tukey method.

looking more deeply into proactive and reactive trait aggression in tobacco users, we found them to be characterized by a low reactive but high proactive aggression. Since the mTAP measures reactive aggressive behavior and does not provide a measure of proactive aggression in our implementation, the absence of an effect might be attributable to these characteristics of TU. Hence, the findings from our study could potentially point toward a beneficial but selective tDCS effect on aggressive behavior in AD.

Impulsivity

This study demonstrated that AD and chronic TU showed improved response inhibition following active but not sham tDCS over the right DLPFC, whereas no differences between stimulation conditions were seen in HC. It is important to note that, contrary to our hypothesis, all groups showed similar performance in response inhibition measured by the SSRT during the baseline measurement. However, chronic TU as well as AD were characterized by higher impulsivity traits than the matched controls. Previous research suggests that these traits might facilitate tDCS effects (Cheng and Lee, 2016). Moreover, even though the SSRT was performed after the mTAP (approximately 30 min after termination of the stimulation), it showed the strongest effect of tDCS. This provides evidence that the protocol was suited to induce behavioral changes that outlast the stimulation.

Implications and future directions

TDCS is a promising non-invasive brain stimulation technique that enables researchers to modulate brain activity for acute (e.g. up to 90 min following one session of tDCS) or extended (e.g. up to 3 months following repeated sessions of tDCS) periods of time (Nitsche and Paulus, 2001; Doruk *et al.*, 2014; Forogh *et al.*, 2017). Despite a number of encouraging results, there is increasing evidence that a multitude of parameters—such as nicotine intake (Grundey *et al.*, 2018), stimulation parameters (Nitsche *et al.*, 2005; Tergau *et al.*, 2007; Cohen *et al.*, 2008) and genetic (Plewnia *et al.*, 2013; Nieratschker *et al.*, 2015) or psychopathological traits (Dedoncker *et al.*, 2016) may affect tDCS outcomes. Due to these complex interactions, the exact mechanisms through which tDCS affects brain activity and behavior still remain to be fully understood.

In the current study, a majority of AD smoked prior to the stimulation, as did chronic TU. In contrast, all HC were non-smokers. Hence, we were not able to delineate whether stimulation effects on response inhibition seen in these groups are attributable to impulsivity traits (similar to research mentioned previously) or might be affected by prior nicotine consumption. There is evidence for similar molecular mechanisms of nicotine and tDCS, both potentially inducing long-term potentiation like synaptic modulation (Dani *et al.*, 2001; Stagg and Nitsche, 2011). In non-smoking healthy individuals, acute nicotine administration cancelled the stimulation effects, possibly due to calcium overflow (Grundey *et al.*, 2018). Despite this known interaction between nicotine and tDCS, little is known about the possible interactions in individuals who developed a tolerance, such as in chronic TU. Future studies should consider the influence of nicotine on tDCS effects.

Considering that several AD patients reported comorbid drug use, with cannabis being the most commonly used illicit drug in the population, it is worth mentioning that previous tDCS and neuroimaging studies also revealed alterations in decision-making neural networks among chronic cannabis users (Boggio *et al.*, 2010). Such changes might have, in addition to alterations related to chronic alcohol consumption, influenced the present results to a certain degree, given that the cognitive deficits related to attention, memory and decision-making are also commonly observed in chronic cannabis users. Thus, more pronounced improvements in the AD group might have been due to a-priori lower efficacy and reduced functionality within decision-making networks related to both chronic alcohol consumption and cannabis use in some of the AD.

The current study is limited by an all-male sample. There is some evidence that there may be gender differences in the tDCS effects (Fumagalli *et al.*, 2010; Dambacher *et al.*, 2015). Furthermore, the mixed findings for AD might be partly explained by the heterogeneity of the group. Future studies should consider to recruit patients currently being in the same stage (e.g. abstinence). Although demonstrated on a small sample size, the results point toward the relevance of sample characteristics on stimulation success, which might be further investigated by future studies using larger samples.

Conclusion

Overall, this study demonstrated differential and specific effects of anodal stimulation over the right DLPFC concerning target populations as well as targeted functions. We detected reduced impulsive behavior as measured by the SSRT in both alcohol-dependent and tobacco users following active but not sham stimulation, whereas the beneficial effects of tDCS on aggression measured by the Taylor Aggression Paradigm were limited to AD. Both AD and TU were found to exhibit higher aggressive and impulsive traits than HC and smoked prior to the stimulation, which might contribute to the differential effects of tDCS on the observed behaviors. Future research should consider how sample characteristics may alter the effects of brain stimulation.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary data

Supplementary data are available at SCAN online.

References

Achterberg, M., van Duijvenvoorde, A.C.K., Bakermans-Kranenburg, M.J., Crone, E.A. (2016). Control your anger! The neural basis of aggression regulation in response to negative social feedback. *Social Cognitive and Affective Neuroscience*, *11*(5), 712–20.

Arbuthnott, K., Frank, J. (2000). Trail Making Test, Part B as a measure of executive control: validation using a set-switching paradigm. *Journal of Clinical and Experimental Neuropsychology*, *22*(4), 518–28.

Aron, A.R., Robbins, T.W., Poldrack, R.A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, *8*, 170–77.

Asahi, S., Okamoto, Y., Okada, G., Yamawaki, S., Yokota, N. (2004). Negative correlation between right prefrontal activity during response inhibition and impulsiveness: a fMRI study. *European Archives of Psychiatry and Clinical Neuroscience*, *254*(4), 245–51.

Bates, D., Mächler, M., Bolker, B., Walker, S. (2014). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48.

Beyer, F., Münte, T.F., Göttlich, M., Krämer, U.M. (2015). Orbitofrontal cortex reactivity to angry facial expression in a social interaction correlates with aggressive behavior. *Cerebral Cortex*, *25*(9), 3057–63.

Boggio, P.S., Zaghi, S., Villani, A.B., Fecteau, S., Pascual-Leone, A., Fregni, F. (2010). Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). *Drug and Alcohol Dependence*, *112*(3), 220–25.

Brady, K.T., Myrick, H., McElroy, S. (1998). The relationship between substance use disorders, impulse control disorders, and pathological aggression. *American Journal on Addictions*, *7*(3), 221–30.

Brunelin, J., Mondino, M., Gassab, L., et al. (2012). Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *American Journal of Psychiatry*, *169*(7), 719–24.

Buades-Rotger, M., Engelke, C., Beyer, F., Keevil, B.G., Brabant, G., Krämer, U.M. (2016). Endogenous testosterone is associated with lower amygdala reactivity to angry faces and reduced aggressive behavior in healthy young women. *Scientific Reports*, *6*(1), 38538.

Buss, A.H., Perry, M. (1992). The Aggression Questionnaire. *Journal of Personality and Social Psychology*, *63*(3), 452–59.

Cheng, G.L.F., Lee, T.M.C. (2016). Altering risky decision-making: influence of impulsivity on the neuromodulation of prefrontal cortex. *Social Neuroscience*, *11*(4), 353–64.

Cohen, L.G., Hummel, F., Paulus, W., et al. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimulation*, *1*, 206–23.

Dambacher, F., Schuhmann, T., Lobbestael, J., Arntz, A., Brugman, S., Sack, A.T. (2015). Reducing proactive aggression through non-invasive brain stimulation. *Social Cognitive and Affective Neuroscience*, *10*(10), 1303–09.

Dani, J.A., Ji, D., Zhou, F.M. (2001). Synaptic plasticity and nicotine addiction. *Neuron*, *31*, 349–52.

Davidson, R.J., Putnam, K.M., Larson, C.L. (2000). Dysfunction in the neural circuitry of emotion regulation - a possible prelude to violence. *Science*, *289*, 591–94.

Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.A. (2016). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain Stimulation*, *9*(4), 501–17.

Denson, T.F., Aviles, F.E., Pollock, V.E., Earleywine, M., Vasquez, E.A., Miller, N. (2008). The effects of alcohol and the salience of aggressive cues on triggered displaced aggression. *Aggressive Behavior*, *34*(1), 25–33.

Denson, T.F., Spanovic, M., Aviles, F.E., Pollock, V.E., Earleywine, M., Miller, N. (2011). The effects of acute alcohol intoxication and self-focused rumination on triggered displaced aggression. *Journal of Aggression, Maltreatment & Trauma*, *20*(2), 128–47.

Doruk, D., Gray, Z., Bravo, G.L., Pascual-Leone, A., Fregni, F. (2014). Effects of tDCS on executive function in Parkinson's disease. *Neuroscience Letters*, *582*, 27–31.

Forogh, B., Rafiei, M., Arbabi, A., Motamed, M.R., Madani, S.P., Sajadi, S. (2017). Repeated sessions of transcranial direct current stimulation evaluation on fatigue and daytime sleepiness in Parkinson's disease. *Neurological Sciences*, *38*(2), 249–54.

Friehs, M.A., Frings, C. (2018). Pimping inhibition: anodal tDCS enhances stop-signal reaction time. *Journal of Experimental Psychology. Human Perception and Performance*, *44*(12), 1933–45.

Fumagalli, M., Vergari, M., Pasqualetti, P., et al. (2010). Brain switches utilitarian behavior: does gender make the difference? *PLoS One*, *5*, 1.

Graham, K., Livingston, M. (2011). The relationship between alcohol and violence: population, contextual and individual research approaches. *Drug and Alcohol Review*, *30*(5), 453–57.

Grundey, J., Barlay, J., Batsikadze, G., Kuo, M.F., Paulus, W., Nitsche, M. (2018). Nicotine modulates human brain plasticity via calcium-dependent mechanisms. *Journal of Physiology*, *596*(22), 5429–41.

Guydish, J., Passalacqua, E., Pagano, A., et al. (2016). An international systematic review of smoking prevalence in addiction treatment. *Addiction*, *111*(2), 220–30.

Hawkins, J.D., Herrenkohl, T.I., Farrington, D.P., Brewer, D., Catalano, R.F., Harachi, T.F. (2000). Predictors of youth violence. In: Wilson, J.J., editor. *Juvenile Justice Bulletin: Predictors of Youth Violence*, Washington, DC: US Department of Justice, 1–12. Available: https://www.ncjrs.gov/pdffiles1/ojjdp/179065.pdf/.

Håkansson, A., Jesionowska, V. (2018). Associations between substance use and type of crime in prisoners with substance use problems – a focus on violence and fatal violence. *Substance Abuse and Rehabilitation*, *9*, 1–9.

Heinz, A.J., Beck, A., Meyer-Lindenberg, A., Sterzer, P., Heinz, A. (2011). Cognitive and neurobiological mechanisms of alcohol-related aggression. *Nature Reviews Neuroscience*, *12*(7), 400–13.

Hsieh, I.J., Chen, Y.Y. (2017). Determinants of aggressive behavior: interactive effects of emotional regulation and inhibitory control. *PLoS One*, *12*, 4.

Ito, T.A., Miller, N., Pollock, V.E. (1996). Alcohol and aggression: a meta-analysis on the moderating effects of inhibitory cues, triggering events, and self-focused attention. *Psychological Bulletin*, *122*(1), 60–82.

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 meta-analysis. *Neuroscience and Biobehavioral Reviews*, *37*, 2472–80.

Kohn, N., Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., Habel, U. (2014). Neural network of cognitive emotion regulation - an ALE meta-analysis and MACM analysis. *NeuroImage*, *87*, 345–55.

Lane, S.D., Kjome, K.L., Moeller, F.G. (2011). Neuropsychiatry of aggression. *Neurologic Clinics*, *29*, 49–64.

Logan, G.D., Schachar, R.J., Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science*, *8*(1), 60–64.

Nieratschker, V., Kiefer, C., Giel, K., Krüger, R., Plewnia, C. (2015). The COMT Val/Met polymorphism modulates effects of tDCS on response inhibition. *Brain Stimulation*, *8*(2), 283–88.

Nitsche, M.A., Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology*, *527*(3), 633–39.

Nitsche, M.A., Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899–901.

Nitsche, M.A., Seeber, A., Frommann, K., et al. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *Journal of Physiology*, *568*(1), 291–303.

Pascual-Leone, A., Knoch, D., Fregni, F., Boggio, P., Sultani, N., Fecteau, S. (2007). Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *Journal of Neuroscience*, *27*(46), 12500–05.

Patton, J.H., Stanford, M.S., Barratt, E.S. (1995). Factor structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology*, *51*(6), 768–74.

Perach-Barzilay, N., Tauber, A., Klein, E., Chistyakov, A., Ne'eman, R., Shamay-Tsoory, S.G. (2013). Asymmetry in the dorsolateral prefrontal cortex and aggressive behavior: a continuous theta-burst magnetic stimulation study. *Social Neuroscience*, *8*(2), 178–88.

Plewnia, C., Zwissler, B., Längst, I., Maurer, B., Giel, K., Krüger, R. (2013). Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT Val/Met polymorphism. *Cortex*, *49*(7), 1801–07.

R Core Team (2014). *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. Available: http://www.R-project.org/.

Ragland, J.D., Turetsky, B.I., Gur, R.C., et al. (2002). Working memory for complex figures: an fMRI comparison of letter and fractal n-back tasks. *Neuropsychology*, *16*(3), 370–79.

Raine, A., Dodge, K., Loeber, R., et al. (2006). The reactive-proactive aggression questionnaire: differential correlates of reactive and proactive aggression in adolescent boys. *Aggressive Behavior*, *32*(2), 159–71.

Rosvall, T., Adinoff, B., Schepis, T.S., et al. (2008). Impulsivity, neural deficits, and the addictions. *Journal of Addictive Diseases*, *26*(sup1), 25–39.

Schmidt, K.-H., Metzler, P. (1992). *Wortschatztest (WST)*. Weinheim: Beltz Test GmbH.

Shen, B., Yin, Y., Wang, J., Zhou, X., McClure, S.M., Li, J. (2016). High-definition tDCS alters impulsivity in a baseline-dependent manner. *NeuroImage*, *143*, 343–52.

Shiozawa, P., Fregni, F., Benseñor, I.M., et al. (2014). Transcranial direct current stimulation for major depression: an updated

systematic review and meta-analysis. *International Journal of Neuropsychopharmacology*, *17*(9), 1443–52.

Stagg, C.J., Nitsche, M.A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist*, *17*, 37–53.

Stevens, L., Goudriaan, A.E., Verdejo-Garcia, A., Dom, G., Roeyers, H., Vanderplasschen, W. (2015). Impulsive choice predicts short-term relapse in substance-dependent individuals attending an in-patient detoxification programme. *Psychological Medicine*, *45*(10), 2083–93.

Tergau, F., Karaköse, T., Antal, A., et al. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of Neurophysiology*, *97*(4), 3109–17.

Torrubia, R., Ávila, C., Moltó, J., Caseras, X. (2001). The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. *Personality and Individual Differences*, *31*(6), 837–62.

Wechsler, D. (1997). Manual for the Wechsler Adult Intelligence Scale. In: *Psychological Corporation*, 3rd edn, San Antonio, TX: The Psychological Corporation. Available: https://doi.org/Thesis_references-Converted#317.

Weidler, C., Wagels, L., Regenbogen, C., et al. (2019). The influence of the OPRM1 (A118G) polymorphism on behavioral and neural correlates of aggression in healthy males. *Neuropharmacology*, *156*, 107467.

Wittchen, H.-U., Wunderlich, U., Gruschitz, S., Zaudig, M. (1997). *Strukturiertes Klinisches Interview für DSM-IV, Achse I (SKID-I)*. Göttingen: Hogrefe.