Consequences of prefrontal tDCS on inhibitory control and reactive aggression

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**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, 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 Task twice.

While there were no observable effects of tDCS in controls, 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.

**Keywords:** tDCS, alcohol dependent patients, tobacco users, aggression, impulsivity
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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, Myrick, & McElroy, 1998). Impulsiveness does not only contribute to the likelihood 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 (Wilson et al., 2000). This is further demonstrated by the fact that acute alcohol intoxication augments aggressive behavior in healthy individuals (Denson et al., 2008, 2011; Heinz, Beck, Meyer-Lindenberg, Sterzer, & Heinz, 2011; Ito, Miller, & Pollock, 1996) and on top that a multitude of violent acts is committed under the influence of alcohol and other substances (Graham & Livingston, 2011; Häkansson & 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 seems to increase aggressive responding when emotion regulation capacities are low as well (Hsieh & Chen, 2017).

Moreover, both increased impulsivity and aggression have been associated with deficient prefrontal brain activation (Asahi, Okamoto, Okada, Yamawaki, & Yokota, 2004; Lane, Kjome, & Moeller, 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, Robbins, & Poldrack, 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 which are responsible for generating such aggressive impulses (Davidson, Putnam, & Larson,
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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 & Frings, 2018). Similarly, increased activation of the right DLPFC has been found to reduce aggressive behavior by exerting top-down regulation (Achterberg, van Duijvenvoorde, Bakermans-Kranenburg, & Crone, 2016; Perach-Barzilay et al., 2013). 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 (M. A. Nitsche & Paulus, 2000). Effects from a single session last up to 90 minutes following the termination of stimulation (M. A. Nitsche & Paulus, 2001) and effects of repeated sessions (e.g. 10 sessions) have been observed at one month (Doruk, Gray, Bravo, Pascual-Leone, & Fregni, 2014) and three month follow-ups (Foregh 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 (Nieratschker, Kiefer, Giel, Krüger,
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Plewnia, 2015; Plewnia et al., 2013), 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 (Boggio et al., 2010; Pascual-Leone et al., 2007). It has further been proposed that tDCS effects depend on baseline levels of the behavior of interest (Shen et al., 2016). Specifically, effects of tDCS on risk-taking behavior are larger in highly impulsive individuals than in controls (Cheng & 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 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. Using a double-blind, sham-controlled study design, performance in a modified Taylor Aggression Paradigm (mTAP) and the Stop Signal Reaction Time Task (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 and tobacco users as compared to healthy
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controls. 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 using public advertising. Participants that were diagnosed with alcohol dependence according to ICD-10 (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 for DSM-IV Axis I disorders (SCID I, (Wittchen, Wunderlich, Gruschitz, & Zaudig, 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 alcohol dependent patients reported to also consume other substances 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. Medication affecting the central nervous system included atypical antidepressants (n = 3), benzodiazepines (n = 2), methadone (n = 2), antipsychotic medication (n = 1), selective serotonin reuptake inhibitors (n = 1), and anticonvulsants (n = 1). Nine patients did not take any medication.
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Healthy control participants (HC, n = 16) and tobacco users (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 (AUDIT) 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 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. They were introduced to their 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, participants were given a short break (5 to 10 minutes) that tobacco users and alcohol dependent patients 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
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All participants completed the Buss Perry Aggression Questionnaire (AQ, (Buss & Perry, 1992)), the Reactive Proactive Aggression Questionnaire (RPQ, (Raine et al., 2006)), the Barrett Impulsiveness Scale (BIS, (Patton, Stanford, & Barratt, 1995)) and the Sensitivity to Reward and Sensitivity to Punishment Questionnaire (SPSRQ, (Torrubia, Ávila, Moltó, & Caseras, 2001)). To examine cognitive functioning of participants, a battery of neuropsychological tests was performed. Participants completed the Trail Making Test (TMT) A and B (Arbuthnott & Frank, 2000), the digit span forward and backward (Wechsler, 1997) and the Wortschatz-Intelligenztest (WST) to assess lexical intelligence (Schmidt & Metzler, 1992). Questionnaire data are presented in table 1, performance on neuropsychological tests are provided in table 2.

Insert Table 1

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 following screen informed participants about the opponent’s punishment selection (provocation). Upon appearance of a visual clue, 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 to 100 cents) were used for both, the decision and provocation. Similar to previous studies (Beyer, Münte, Göttlich, & Krämer, 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, 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 participants failed to inhibit the button press in stop trials, the stop signal delay was increased.
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by 33 ms, making it easier to inhibit the response in the next stop trial. Equivalently, if 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. 30% of all trials were stop trials. The task was color-balanced across participants (blue as go signal and yellow as stop signal versus the inverse). The total number of trials varied across individuals due to the adaptive stop signal delay, however, the task duration was always 15 minutes.

Insert Table 2

tDCS

TDCS was delivered using a battery-driven stimulator (neuroConn, Ilmenau, Germany). The anode (5cm x 7cm) was placed at the F4 position of the 10-20-EEG system. The cathode (10cm x 10cm) was used as the reference electrode and positioned over the contralateral supraorbital area with at least 7cm distance to the anode. Following a 20 second ramp-up phase, actively stimulated participants received a current of 1.5 mA for 20 minutes with a subsequent ramp-down phase of 20 seconds. 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

Multivariate 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, 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).
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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 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 results would show the comparisons between time point two and one, active and sham conditions, and groups of interest (AD and TU) as compared to healthy controls. 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 material (S1 and S2).

To measure response inhibition, the quantile method was used to acquire estimates of the stop signal reaction time for each individual (Logan, Schachar, & Tannock, 1997). Three participants were excluded from the analysis due to a SSRT below 50ms, 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 participants to account for repeated measures.

Using the R package lme4, the estimation of variance of components was performed using restricted maximum likelihood (Bates, Mächler, Bolker, & Walker, 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.
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Results

Personality traits and neuropsychological tests

The MANOVA of questionnaire scores revealed a significant effect of group for AQ ($F(2,48) = 5.380, p < .01$) for proactive ($F(2,48) = 11.477, p < .001$) and reactive aggression ($F(2,48) = 24.054, p < .001$) and impulsivity (BIS) ($F(2,48) = 6.587, p < .01$). No effect of group was found for sensitivity to reward ($F(2,48) = 1.851, p = .168$) and sensitivity to punishment ($F(2,48) = 2.628, p = .083$). Associated post hoc tests revealed higher AQ scores for AD ($p < .05$) and for TU ($p < .05$) as compared to HC. TU also exhibited more proactive aggression than HC ($p < .001$) and AD ($p < .01$). Alcohol dependent patients scored significantly higher on reactive aggression as compared to HC ($p < .01$) and to TU ($p < .001$). Furthermore, HC revealed more reactive aggression than TU ($p < .01$). Impulsivity traits, as assessed by the BIS, were higher for AD than for controls ($p < .01$). 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 ($F(10,86) = .646, p = .770$).

mTAP

Parameter estimates for fixed effects on participants’ punishment selections of the linear mixed effects model are presented in table 3. In the following, 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 $R^2_{\text{conditional}} = 0.51$. The linear mixed effects model revealed a main effect of time ($t(5905) = 11.91, p < .001$), demonstrating higher punishment selections in the second session.

Punishment selections were further heightened by increased provocation ($t(5918) = 33.88, p < .001$) and won competitions ($t(5912) = 4.08, p < .001$). 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
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description of these results and associated post hoc tests. A significant three-way interaction was found for time, tDCS, and TU ($t(5905) = 2.69, p < .01$). 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 punishment selections in the second session. The results are depicted in figure 4. Boxplots for each time point, group and stimulation condition can be found in the supplementary material (S3). For the descriptive statistics, please refer to table 2.

*Insert Table 3 and 4*

**SSRT**

Parameter estimates for fixed effects on participants’ stop signal reaction times are presented in table 5. In the following, 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 $R^2_{\text{conditional}} = 0.76$. The linear mixed effects model revealed a significant tDCS x time x TU interaction ($t(41.27) = -2.11, p < .05$). All other effects were not significant. Associated post hoc comparisons showed improved SSRTs for AD and TU following active but not sham stimulation. All other comparisons did not reach significance. 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 material (S4). To investigate whether improved SSRTs following active tDCS seen in alcohol dependent patients and chronic tobacco users 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. Results revealed a significant interaction of time and tDCS ($F(1, 41) = 7.23, p = .01$). Associated post hoc comparisons revealed an increased number of successfully inhibited stop trials following active but not sham stimulation ($p = .05$) for all three groups. For the descriptive statistics please refer to table 2.
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Insert Table 5 and 6

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, tobacco users and healthy controls. Indeed, our results support the assumption that anodal stimulation of the right DLPFC reduced impulsive behavior in alcohol dependent patients and tobacco users. Additionally, results implicate a beneficial effect of anodal tDCS on aggressive behavior in alcohol dependent patients. 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 individual characteristics of participants. Specifically, researchers are recommended to consider alcohol and/or tobacco use and personality traits as influencing factors.

Aggression

Our results revealed that healthy controls and tobacco users selected higher punishment levels in the mTAP during the post-stimulation session, regardless of whether they received active or sham stimulation. This confirms previous findings of null effects of anodal tDCS in healthy individuals (Dambacher et al., 2015). Also, alcohol dependent patients who received sham stimulation selected higher punishment levels after stimulation. In contrast, following active tDCS, the latter did not apply higher punishments during the post-stimulation session. It can be assumed that participants exhibit less control in the course of the experiment due to...
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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 alcohol dependent patients. However, healthy controls 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 tobacco users and alcohol dependent patients. In our study, both groups were characterized by higher aggressive traits than healthy controls. However, looking more deeply into proactive and reactive trait aggression in tobacco users, we found them to be characterized by low reactive but high proactive aggression. Since the mTAP measures reactive aggressive behavior and in our implementation does not provide a measure of proactive aggression, the absence of an effect might be attributable to these characteristics of tobacco users. Hence, findings from our study could potentially point toward a beneficial but selective tDCS effect on aggressive behavior in alcohol dependent patients.

Impulsivity

This study demonstrated that alcohol dependent patients and chronic tobacco users showed improved response inhibition following active but not sham tDCS over the right DLPFC, whereas no differences between stimulation conditions were seen in healthy controls. 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 tobacco users as well as alcohol dependent patients were characterized by significantly higher impulsivity traits than matched controls. Previous research suggests that these traits might facilitate tDCS effects (Cheng & Lee, 2016). Moreover, even though the
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SSRT was performed after the mTAP (approximately 30 minutes 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 minutes following one session of tDCS) or extended (e.g., up to three months following repeated sessions of tDCS) periods of time (Doruk et al., 2014; Forogh et al., 2017; M. A. Nitsche & Paulus, 2001). 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 (Cohen et al., 2008; Michael A. Nitsche et al., 2005; Tergau et al., 2007), genetic (Nieratschker et al., 2015; Plewnia et al., 2013) or psychopathological traits (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 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 alcohol dependent patients smoked prior to the stimulation, as did chronic tobacco users. In contrast, all healthy controls 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, Ji, & Zhou, 2001; Stagg & Nitsche, 2011). In non-smoking healthy individuals, acute nicotine administration cancelled stimulation effects, possibly due to calcium overflow (Grundey et al., 2018). Despite this known interaction between nicotine and tDCS, little is known about possible interactions in individuals that developed a tolerance, such as in chronic tobacco users. Future studies should consider the influence of nicotine on tDCS effects.
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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 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 alcohol dependent patients.

The current study is limited by an all-male sample. There is some evidence that there may be gender differences in tDCS effects (Dambacher et al., 2015; Fumagalli et al., 2010). Furthermore, mixed findings for alcohol dependent patients 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, 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 Stop Signal Reaction Time Task in both alcohol dependent and tobacco users following active but not sham stimulation, whereas beneficial effects of tDCS on aggression measured by the Taylor Aggression Paradigm were limited to alcohol dependent patients. Both, alcohol dependent patients and tobacco users were found to exhibit higher aggressive and impulsive traits than healthy controls and smoked prior to the stimulation, which might contribute to the differential effects of tDCS on
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the observed behaviors. Future research should consider how sample characteristics may alter the effects of brain stimulation.

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Declaration of Interest

The authors declare no conflict of interest.

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Figure Captions

**Figure 1.** Illustration of the study procedure. mTAP = modified Taylor Aggression Paradigm; SSRT = Stop Signal Reaction Time Task; tDCS = transcranial direct current stimulation.
Figure 2. Illustration of a single trial of the modified Taylor Aggression Paradigm. In the beginning, 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.

Figure 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 participants. That is, following successful inhibition, a 33ms longer SSD and following unsuccessful trials, a 33ms shorter SSD.
Figure 4. Results of the linear mixed effects model for the modified Taylor Aggression Paradigm. The difference (post stimulation – pre stimulation) in punishment selections (0-100 Cents) are shown for healthy controls, alcohol dependent patients and chronic tobacco users. All participants who received sham stimulation (right) significantly increased their punishment selections in the second session ($p < .001$). Healthy controls and tobacco users also subtracted significantly more money following active stimulation (left; $p < .001$). Only alcohol dependent patients who received active transcranial direct current stimulation did not alter their punishment selections in the second session ($p < .38$). Error bars represent the standard error. Post hoc pairwise comparisons are corrected for multiple comparison using the Tukey method.
Figure 5. Results of the linear mixed effects model for the Stop Signal Reaction Times Task. The difference (post stimulation – pre stimulation) Stop signal reaction times (SSRTs) are shown for healthy controls, alcohol dependent patients and chronic tobacco users. For all participants who received sham stimulation (right), no significant difference in SSRTs between first and second session were observed. Alcohol dependent patients and tobacco users had significantly shorter SSRTs following active stimulation (left; \( p < .05 \)). No effects of active stimulation was seen in healthy controls. Error bars represent the standard error. Post hoc pairwise comparisons are corrected for multiple comparison using the Tukey method.
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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 | <.05     | <.05         | 1.00         |
| BIS              | 56.31 ± 7.69  | 68.06 ± 12.50 | 64.12 ± 7.14  | <.01     | .093         | .696         |
| Proactive Aggression | 1.81 ± 2.66   | 2.72 ± 2.85   | 5.88 ± 2.18   | .99      | <.001        | <.01         |
| Reactive Aggression | 5.50 ± 3.93  | 9.72 ± 3.66  | 2.18 ± 1.59   | <.01     | <.01         | <.001        |
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|       | 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

Table 3: Fixed effects for modified Taylor Aggression Paradigm

| Predictor       | b    | SE   | t     | p      |
|-----------------|------|------|-------|--------|
| Intercept       | 48.42| 6.08 | 7.97  | <.001  |
| Time2           | 14.82| 1.24 | 11.91 | <.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 | <.001  |
| Won             | 2.33 | 0.57 | 4.08  | <.001  |
| Time2 x tDCS    | -6.93| 1.90 | -3.66 | <.001  |
| Time2 x AD      | -7.12| 1.81 | -3.94 | <.001  |
| Time2 x TU      | -7.69| 1.81 | -4.26 | <.001  |
| tDCS x AD       | 11.91| 12.71| 0.94  | 0.35   |
| tDCS x TU       | 3.28 | 12.93| 0.25  | 0.80   |
| Time2 x tDCS x AD | 0.45 | 2.69 | 0.17  | 0.87   |
| Time2 x tDCS x TU | 7.37 | 2.74 | 2.69  | <.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 modified Taylor Aggression Paradigm

| Significant interaction effects | tDCS   | Contrast |   | SE   | z ratio | p     |
|---------------------------------|--------|----------|---|------|---------|-------|
| Time x tDCS                     | sham   | Pre-post | -9.88 | 0.75 | -13.25 | <.001 |
|                                 | active | Pre-post | -5.55 | 0.83 | -6.68  | <.001 |
| Time x Group                    | HC     | Pre-post | -11.35 | 0.95 | -11.93 | <.001 |
|                                 | AD     | Pre-post | -4.45  | 0.96 | -4.66  | <.001 |
|                                 | TU     | Pre-post | -7.34  | 0.99 | -7.41  | <.001 |
| Time x tDCS x Group             | sham   | HC pre-post | -14.82 | 1.24 | -11.91 | <.001 |
|                                 | AD pre-post |         | -7.70  | 1.31 | -5.87  | <.001 |
|                                 | TU pre-post |       | -7.12  | 1.31 | -5.43  | <.001 |
|                                 | active | HC pre-post | -7.88  | 1.44 | -5.96  | <.001 |
|                                 | AD pre-post |         | -1.21  | 1.39 | -0.87  | 0.38  |
|                                 | TU pre-post |       | -7.56  | 1.49 | -5.09  | <.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
Table 5: Fixed effects for Stop Signal Reaction Time Task

| Predictor   | b    | SE   | t     | p     |
|-------------|------|------|-------|-------|
| Intercept   | 242.53 | 22.49 | 10.78 | <.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 x tDCS | 13.48  | 27.42 | 0.49  | 0.63  |
| Time x AD   | 25.58  | 23.35 | 1.10  | 0.28  |
| Time x TU   | 37.78  | 23.35 | 1.62  | 0.11  |
| tDCS x AD   | 71.50  | 49.27 | 1.45  | 0.15  |
| tDCS x TU   | 94.25  | 50.71 | 1.86  | 0.07  |
| Time x tDCS x AD | -56.92 | 35.62 | -1.60 | 0.12  |
| Time x tDCS x TU | -77.44 | 36.65 | -2.11 | <.05  |

*p values calculated using Statterthwaite degrees of freedom; AD = Alcohol dependent patients; TU = Tobacco users; tDCS = transcranial direct current stimulation; SE = Standard error

Table 6: Post-hoc tests of significant interactions for Stop Signal Reaction Time Task

| Group                  | tDCS | contrast | b    | SE   | t ratio | p     |
|------------------------|------|----------|------|------|---------|-------|
| Healthy controls       | sham | pre-post | 19.62 | 16.9 | 1.16    | .25   |
|                        | active| pre-post | 6.14  | 21.6 | 0.28    | .78   |
| Alcohol dependent patients | sham | pre-post | -5.96 | 16.1 | -0.37   | .71   |
|                        | active| pre-post | 37.48 | 16.1 | 2.33    | <.05  |
| Tobacco users          | sham | pre-post | -18.16 | 16.1 | -1.13   | .27   |
|                        | active| pre-post | 45.79  | 18.2 | 2.51    | <.05  |

*p values calculated using Kenward-Roger degrees of freedom method; tDCS = transcranial direct current stimulation; SE = standard error