# *Bridging the Gap Between Neurocognitive Insights and the Addiction Clinic*

***The Effects and Underlying Mechanisms of Transcranial Direct Current Stimulation in Substance Use Disorder***

**Ilse Verveer**

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## Colophon



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# Bridging the Gap Between Neurocognitive Insights and the Addiction Clinic

## The Effects and Underlying Mechanisms of Transcranial Direct Current Stimulation in Substance Use Disorder

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## Contents

# 1

# General Introduction

*"Can you imagine a pleasure so intense that you would be willing to give up everything you care about just to temporarily experience it?"*
– Nora Volkow

## Introduction

For decades it has been assumed that addictive behaviour is the result of an intense desire to experience pleasure (Berridge & Robinson, 2016). This perspective has contributed to the notion of addiction as a moral weakness and has encouraged society to treat individuals with an addiction as criminals (Volkow, Koob, & McLellan, 2016). However, addicted patients indicate that taking drugs is no longer pleasurable to them, but that they encounter difficulties in their attempts to stop taking drugs. This may sound like an excuse to continue drug use, yet scientific research has provided evidence for this concept. Neurobiological studies have found that addiction is characterized by an imbalance between the reward system of the brain that drives behaviour and the "control" system in the prefrontal cortex (PFC) that can inhibit behaviour (Goldstein & Volkow, 2002; Goldstein & Volkow, 2011; Zilverstand, Huang, Alia-Klein, & Goldstein, 2018). As a result, there is an automatic drive to pursue desires, strengthened by a substantial loss of self-control. This causes compulsive drug use, even when there is a wish to stop taking drugs (Volkow et al., 2016).

### Neurobiological insights of addiction

In order to treat addiction, it is key to understand the neural underpinnings of these processes. All drugs have in common that they initially produce a pleasurable effect, initiated by the reward system of the brain (Fig 1). The rewarding feeling reinforces continuation of drug use and causes associative learning and conditioning (Volkow et al., 2016). Environmental cues that are present during drug use will consequently become associated with experiences of drug-related rewards. These cues may represent anything that is repeatedly paired with drug use, such as the context in which the drug is taken, persons that were present during drug use or a certain state of mind before using drugs. As a result of conditioning, environmental cues become triggers that elicit rewarding

sensations before the drug is actually consumed, which is perceived as a strong desire to use drugs (i.e. craving; Volkow et al., 2006).

Prolonged exposure to drug use also leads to other adaptations in the reward circuit of the brain that can explain persistent addictive behaviour. As a result of repeated drug use, individuals with an addiction experience less euphoric feelings when taking drugs and feel less motivated to participate in everyday activities that were previously perceived as rewarding. In addition to changes in the reward circuit of the brain, repeated exposure to drugs evokes changes in the emotion circuit that lead to increased reactivity to stress and negative emotions (Goldstein & Volkow, 2011). Withdrawal from drug use therefore causes a highly dysphoric state. The fastest way to overcome these unpleasant sensations is to use drugs. Therefore, withdrawal symptoms can be viewed as added motivation for continued drug use (Volkow et al., 2016).

Finally, repeated drug use is associated with changes in the "control" system of the brain (Fig 1). The PFC plays an important role in control over behaviour because of its involvement in executive functions needed to exert top-down control over drives (Goldstein & Volkow, 2011). Dysfunction of the PFC in addiction therefore results in impaired executive control functioning, such as reduced control over inhibition and impaired decision making. Consequently, the ability to resist cravings is weakened and there is less control over decisions to stop taking drugs. This explains why individuals with an addiction can be sincerely motivated to stop using drugs while they simultaneously remain impulsive and resume drug use (Volkow et al., 2016).

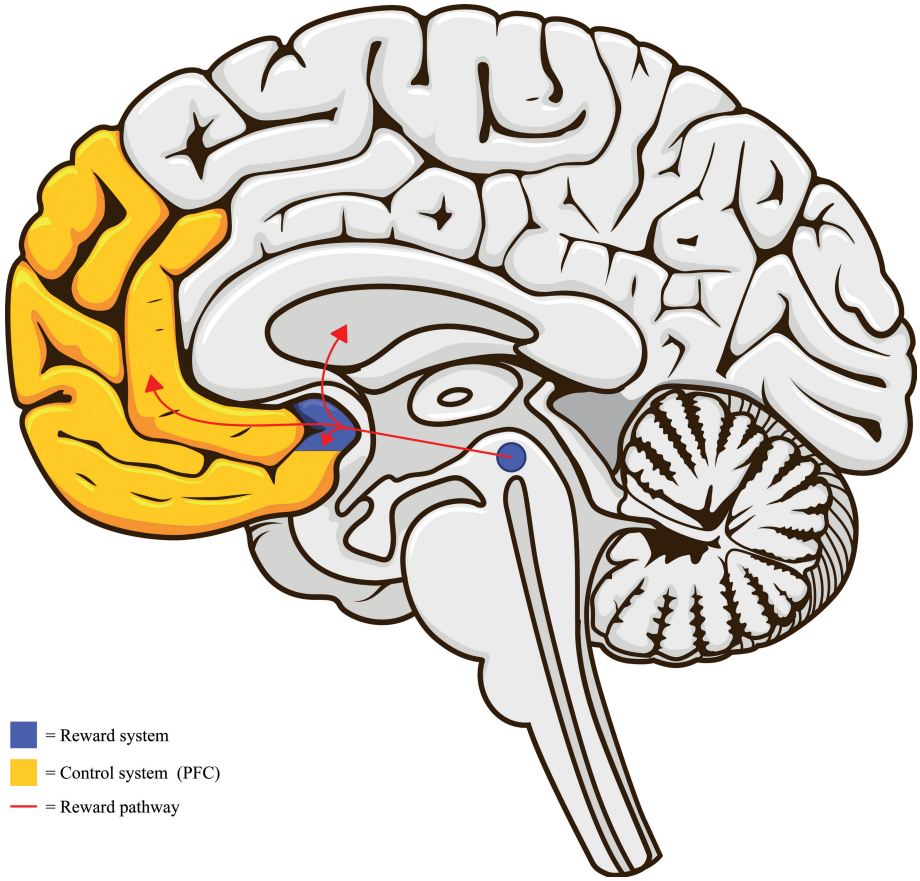


**Fig 1.** Reward pathway of the brain, including the reward and control system.

## Bridging the gap to the addiction clinic

Neurobiological knowledge about addiction could contribute to improvements and innovations in addiction treatment, but so far there have been few attempts to translate this knowledge to interventions (Luigjes, Segrave, Joode, Figee, & Denys, 2019). First-line treatment for addiction currently consists of psychosocial interventions and pharmacological treatments. To successfully engage in psychosocial therapies, certain cognitive and emotional skills are required. This can be problematic for substance users, since they often show impairments in cognitive functioning (Franken & van de Wetering, 2015) and impaired cognitive functioning has been associated with less treatment responsiveness (Winhusen et al., 2013). In addition, patients are often reluctant to take medication due to

unwanted side effects (Douaihy, Kelly, & Sullivan, 2013). Also, for some illicit drugs (e.g., cocaine) there is still little evidence for effective pharmacological treatments (De Crescenzo et al., 2018).

Psychosocial and pharmacological treatments induce brain changes in a non-selective manner, and this makes it difficult to improve these interventions with neurobiological knowledge (Luigjes et al., 2019). To bridge the gap between neurobiological insights and the addiction clinic, recent addiction studies have therefore shifted their focus towards investigating innovative methods that directly target neurocognitive mechanisms involved in the aetiology of addiction. Specifically, modulating brain activity in the PFC by means of non-invasive neurostimulation is regarded a promising intervention for addiction treatment (Nakamura-Palacios et al., 2016). It has been suggested that improved PFC functioning may affect executive control functioning and consequently reduce addictive behaviour (Lapenta et al., 2018).



## Non-invasive neurostimulation

Neuronal activity can be modulated non-invasively by means of direct electrical currents or with magnetic stimulation. Transcranial Direct Current Stimulation (tDCS) modulates membrane potentials with low-intensity electrical currents (0.5 – 2.0 mA) delivered by two electrodes that are placed on the scalp (Fig 2; Nitsche & Paulus, 2000). The currents flow in one direction, from the positive anode electrode to the negative cathode electrode. Hereby, an electrical field is produced that modulates the excitability of brain areas (Woods et al., 2016). It has been suggested that anodal stimulation enhances neuronal excitability by decreasing the sub-threshold of resting membrane potentials whereas cathodal stimulation would inhibit excitability by an increase of the sub-threshold (Nitsche & Paulus, 2000). The strength and direction of the neuromodulation effects are influenced by the intensity, duration and direction of the current flow (Feil & Zangen, 2010). In addition, multiple tDCS sessions may prolong the effects of tDCS (Nitsche & Paulus, 2001).

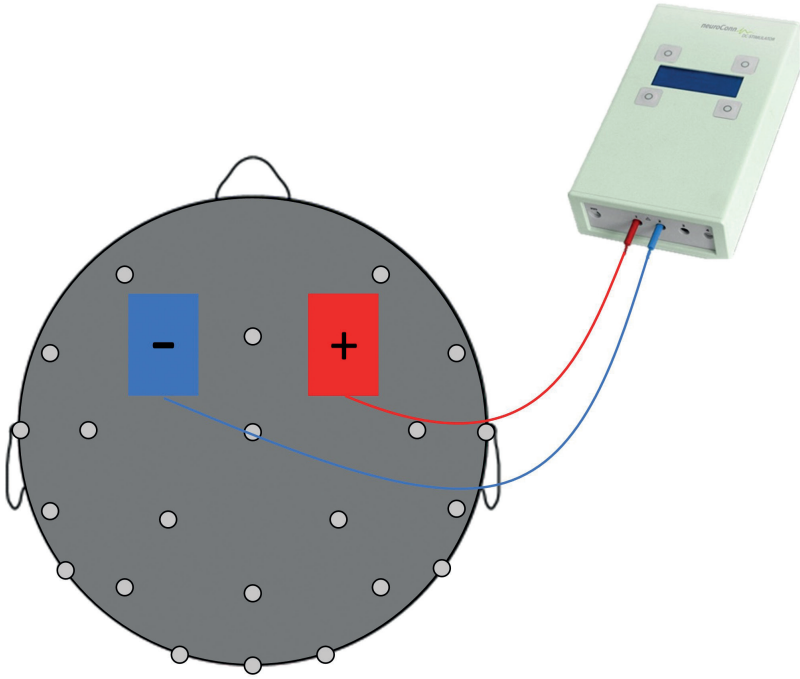


**Fig 2.** Example of tDCS montage with the anodal electrode over the dorsolateral PFC and the cathodal electrode placed over the left dorsolateral PFC.

An alternative non-invasive neurostimulation technique is Transcranial Magnetic Stimulation (TMS). This method initiates neural activity with magnetic pulses that are produced by an electromagnetic coil that is placed above the head. When TMS is delivered as a train of pulses (rTMS), it can result in prolonged excitability that outlasts the stimulation period (Pascual-Leone et al., 1998). Prolonged effects of both tDCS and rTMS has led to an increasing interest for investigating either method as therapy in neuropsychological disorders (Priori, Hallett, & Rothwell, 2009).

For addiction, it has recently been reported that tDCS and rTMS induce similar effects on addictive behaviours, such as craving and drug use (Song, Zilverstand, Gui, Li, & Zhou, 2019). Given that both techniques are also safe in use when practice guidelines are followed, several other aspects can be considered when choosing between both methods for research purposes. First, rTMS has higher focality and temporal resolution, and is less sensitive to anatomical differences

(e.g. skull thickness) as compared to tDCS (Spagnolo & Goldman, 2016). On the other hand, less severe side effects have been reported for tDCS, with minimal or no scalp sensations during stimulation and with habituation to these sensations within minutes. In contrast, rTMS is associated with strong scalp sensations accompanied by muscle twitches, and the TMS device makes a loud clicking sound. These factors make it more difficult to produce a reliable placebo (sham) for rTMS and therefore the reliability of research results is decreased (Kekic, Boysen, Campbell, & Schmidt, 2016). Furthermore, tDCS is more mobile than rTMS, because the electrical currents are induced by a battery, whereas magnetic pulses are induced by a heavier TMS device that needs a power supply. In sum, tDCS is more practical for research purposes, and therefore this technique has been the method of choice to answer the research questions of the current thesis.



## Transcranial Direct Current Stimulation in addiction

Studies on the clinical effectiveness of tDCS in addiction have primarily focused on modulating the control system of the brain by targeting a specific area in the PFC, namely the dorsolateral prefrontal cortex (DLPFC; Goldstein & Volkow, 2011). The DLPFC has often been chosen as target area because it has been implicated in top-down control over craving and in executive functions important to exert self-control over drug use (Goldstein & Vokow, 2002; Zilverstand et al., 2018). A recent meta-analysis has provided evidence that tDCS over the DLPFC can reduce craving and drug use, with similar effects for different substance use disorders (Song et al., 2019). They found that multi-session protocols were more effective than single-session protocols and that targeting the left versus the right hemisphere did not induce different effects of anodal tDCS.

These are promising findings for the implementation of tDCS as intervention in addiction treatment, however, the most important question remains unanswered. That is, can tDCS induce long-lasting effects on reducing addictive behaviours? Only few studies have attempted to answer this question by investigating long-term outcomes of tDCS in addiction. For tobacco addiction, multiple sessions of tDCS reduced cigarette consumption up to one-month follow-up (Fecteau et al., 2014; De Souza Brangioni et al., 2018). When more than five sessions were applied, cigarette consumption was even reduced beyond one-month (Behnam,

Mousavi, & Emamian, 2019). One of these studies also reported on the long-term effects of tDCS on craving, but the findings were negligible.

Long-term effects of tDCS were also studied in alcohol- and crack-cocaine use disorders, however, these studies have yielded more inconsistent results. Relapse in alcohol use disorder was reduced after multiple tDCS sessions on consecutive days (Klauss et al., 2014), but relapse rates were higher after multiple weekly sessions of tDCS (Da Silva et al., 2013). Findings were also mixed for tDCS effects on addictive behaviour in crack-cocaine use disorder. Multi-session tDCS over the DLPFC decreased craving for over four weeks (Batista, Klauss, Fregni, Nitsche, & Nakamura-Palacios, 2015), but the same research group observed no effects on craving and relapse after multiple tDCS sessions in a group of patients with more severe symptoms of crack-cocaine use disorder (Klauss et al., 2018).

To improve the application of tDCS in addiction treatment, it is important to understand the underlying mechanism of the long-term effects of tDCS over the DLPFC. It has been suggested that decreased drug use and relapse rates by modulating neuronal activity of the DLPFC is the result of reduced problems in executive functions (Lapenta et al., 2018). Several executive functions that may play a crucial role in the effects of tDCS on addictive behaviour are inhibitory control, risky decision making, and error processing. These functions have been implicated in addiction and have been related to PFC functioning (Goldstein & Volkow, 2011). Improved inhibitory control could prevent the execution of automatic behaviour driven by the reward system and substance related urges or cravings could consequently be more easily suppressed. Furthermore, better decision making would reduce risk-taking and may therefore result in better decisions regarding drug use. In addition, appropriate processing of errors after failed attempts to inhibit responses and feedback after risky decisions may improve executive functioning in future circumstances (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004).

In healthy individuals, it has generally been found that executive functions improved after anodal tDCS (Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2016; Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). However, research has been scarce regarding the effects of tDCS on executive functions in relation to the beneficial effects of tDCS on addictive behaviour (Schluter, Daans, van Holst, & Goudriaan, 2018; Naish, Vedelago, MacKillop, & Amlung, 2018).

Several addiction studies have investigated tDCS over the DLPFC for modulating decision making, and these have yielded mixed results. The effectiveness of tDCS on risky decision making may be task specific, but more research is needed in this field. Furthermore, to the best of our knowledge, the effect of this protocol on inhibitory control and error processing has not previously been explored in addiction (Naish et al., 2018; Schluter et al., 2018). In this dissertation, it was therefore investigated whether the above-mentioned executive functions are affected by tDCS in addiction, and how this would explain the effects of tDCS on addictive behaviour.



In addition, treatment effects of tDCS on craving and drug use were measured by ecological momentary assessments (EMA). EMA is a method that can be used to repeatedly measure someone's behaviour and current state in their natural environment over time by means of mobile technology (Shiffman, Stone, & Hufford, 2008). Since craving and drug use are momentary phenomena, EMA offers an ecologically valid alternative to retrospective self-reports by enabling repeated measurement of addictive behaviour at random moments of the day (Serre, Fatseas, Swendsen, & Auriacombe, 2015). EMA has not been used in tDCS studies before, despite of previous findings suggesting the use of EMA methods may result in more reliable and representative measures of craving (Serre et al., 2015), relapse (Schiffman, 2009), and possibly cognitive functioning in SUDs (Marhe, Waters, van de Wetering, & Franken, 2013). The use of EMA may therefore provide more detailed information about the duration and dynamics of tDCS effects as compared to past literature.

## Outline thesis

With the current thesis we aimed to gain more insight about tDCS as add-on treatment in addiction by exploring the short and long-term effects of tDCS on drug use, relapse, and craving. The underlying mechanisms of these tDCS effects were also investigated on a behavioural and neurophysiological level.

**Chapter 2** investigated effects of multi-session tDCS over the DLPFC on cigarette consumption and craving in smokers who had no desire to quit smoking at the start of the experiment. Participants were asked to indicate their smoking behaviour by means of EMA, multiple times a day in an app on their smartphone for three months. EMA was chosen as measurement tool to assess the primary outcome of this study in an ecologically valid manner.

**Chapter 3** investigated the effects of multi-session tDCS over the DLPFC in smokers on inhibitory control and error processing to better understand the association of these executive control functions with tDCS effects on smoking behaviour. Before, directly after and three months after multi-session tDCS inhibitory control and error processing were measured on a behavioural and neurophysiological level during the Go-NoGo task. Neurophysiological measures were recorded by electroencephalogram (EEG).

**Chapter 4** assessed how multi-session tDCS over the DLPFC would affect risky decision making in smokers during a gambling task. Risky decision making has been associated with neural correlates of feedback processing and therefore the second aim of this study was to investigate the working mechanism of tDCS by measuring feedback processing with EEG.

**Chapter 5** multi-session tDCS over the DLPFC was explored as add-on treatment in cocaine use disorder by measuring the effects of tDCS on relapse, craving and executive control functions. Relapse was determined by the number of days participants had used cocaine in the 90 days after the tDCS intervention. Craving was measured for two weeks by means of EMA. The executive functions that

were assessed included inhibitory control and risky decision making measured by the Go-NoGo task and the gambling task from chapter 3 and 4, respectively.

**Chapter 6** was a proof-of-concept study in collaboration with Monash University to investigate an innovative form of tDCS, namely high definition tDCS (HD-tDCS). HD-tDCS has improved spatial resolution as compared to traditional tDCS, enabling it to target brain areas more precisely (Alam, Truong, Khadka, & Bikson, 2016). This technique may be able to target deeper brain areas related to addiction and other mental illnesses, such as the dorsal anterior cingulate cortex (dACC; Goodkind et al., 2015). The aim of this study was to explore effects of HD-tDCS targeting the dACC on cognitive control functioning. Before, directly after and 30 minutes after one session of HD-tDCS over the dorsal Anterior Cingulate Cortex (dACC), participants with high trait impulsivity performed a Go-NoGo task while EEG was recorded. Specifically, we investigated the effects of HD-tDCS over the dACC on impulsivity by measuring outcomes of inhibitory control and error processing.

**Chapter 7** provides a summary and general discussion of this dissertation, with a focus on tDCS as add-on treatment in addiction and the working mechanism behind tDCS effects. Practical implications and recommendations for future research are also provided.

# 2

# The Effects of Multi-Session tDCS on Ad Libitum Smoking Behaviour: A Placebo-Controlled EMA study

***This chapter is in published as:***

*Verveer, I., Remmerswaal, D., Jongerling, J., van der Veen, F. M., & Franken, I. H. (2020). No effect of repetitive tDCS on daily s moking behaviour in light smokers: A placebo controlled EMA study. PloS one, 15(5), e0233414. https://doi.org/10.1371/journal.pone.0233414*

## Abstract

**Introduction:** The effectiveness of repetitive transcranial Direct Current Stimulation (tDCS) on reducing smoking behaviour has been studied with mixed results. Smoking behaviour is influenced by affect and context, therefore we choose to use mobile ecological momentary assessments (EMA) to measure changes in smoking behaviour after tDCS.

**Methods:** In a randomized, placebo-controlled, between subject study, we applied tDCS bilaterally with the anodal electrode targeting the right DLPFC (https://clinicaltrials.gov/ct2/show/NCT03027687). Smokers were allocated to six sessions of either active tDCS ($n$ = 35) or sham tDCS ($n$ = 36) and received two sessions on three different days in one week. They were asked to keep track of their daily cigarette consumption, craving and affect in an application on their mobile phones for three months starting one week before the first tDCS session.

**Results:** Number of smoked cigarettes a day progressively decreased up to one week after the last tDCS session in both conditions. Active treatment had no additional effect on cigarette consumption, craving and affect.

**Conclusions:** In this exploratory study, repetitive bilateral tDCS over the DLPFC had no effect on daily smoking behaviour. Future research needs to investigate how motivation to quit smoking and the number of tDCS sessions affect the efficacy of repetitive tDCS.

## Introduction

Smoking is associated with serious health risks and causes approximately 8 million deaths worldwide each year (WHO, 2019). Although the health risks of smoking are generally well known, 1.1 billion people of the global population are still smokers (WHO, 2019). The maintenance of tobacco addiction may be explained by an interplay of increased reward processing for smoking cues and decreased self-control over addictive behaviours (Yücel et al., 2019; Volkow et al., 2010). One brain area that plays a crucial role in this interaction is the dorsolateral prefrontal cortex (DLPFC) by its involvement in top down-control over reward processing (Goldstein & Volkow, 2011). Non-invasive neurostimulation (NIBS) is designed to directly modulate brain activity in specific brain areas. It is therefore suggested that NIBS over the DLPFC could enhance cognitive control of executive functioning, hereby reducing craving and substance use (Lapenta, Marques, Rego, Comfort, & Boggio, 2018).



Transcranical Direct Current Stimulation (tDCS) is a well-tolerable NIBS that has no known serious adverse effects (Bikson et al.,2016). tDCS modulates membrane potentials in the brain by means of small electrical currents (Nitche & Paulus, 2000). The electrical current flow from the anodal electrode to the cathodal electrode produces an electrical field that modulates the excitability of underlying brain areas (Woods et al., 2016). This modulation of excitation levels can induce changes in behaviour, mood and cognition (Vancem Fazeli, Cody, Bell, & Pope, 2016). Also, cognitive control processes related to substance use disorder can be affected by tDCS (Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2008). Importantly, several studies on addictive behaviours have shown that tDCS could reduce craving. This effect has been found for a variety of substances, such as tobacco (Fregni et al., 2008; Boggio et al., 2009), marijuana (Boggio et al., 2010), cocaine (Batista, Klauss, Fregni, Nitsche, & Nakamura-Palacios, 2015), heroin (Wang et al., 2016), and alcohol (Boggio et al., 2008). For tobacco addiction specifically it was found that tDCS could not only reduce craving, but also cigarette consumption (Fecteau et al., 2014; Falcone et al., 2016; De Souza Brangioni, 2018; Behnam, Mousavi, & Emamian, 2019; Kang, Kim, & Kim, 2019).

In a double-blind, sham-controlled, crossover study, Fecteau and colleagues (2014) found that five tDCS sessions on consecutive days could decrease cigarette consumption for up to 4 days in participants who wanted to quit smoking. In another study where smokers were not planning to quit smoking in the next three months, results showed that cigarette consumption temporarily decreased after one session of tDCS (Falcone et al., 2016). Recently, it was found that five sessions of tDCS could decrease cigarette consumption for up to 4 weeks (De Souza Brangioni, 2018). Here, motivation to quit modulated the effect of active tDCS on cigarette consumption. The results of these studies suggest that a variety of tDCS protocols could cause a decrease in cigarette consumption and craving. In addition, it was found that multiple sessions of tDCS may even provide a promising substitute to bupropion treatment in tobacco addiction (Behnam et al., 2019). Findings from a recent meta-analysis indicate that anodal tDCS over the right DLPFC with cathodal tDCS over the DLPFC had the most positive effects on smoking behaviour (Kang et al., 2019).

However, the exact parameters of the effectiveness of this specific tDCS protocol remain unknown. For example, it is unclear how many sessions are needed for tDCS to be effective in tobacco addiction and for how long the effects last beyond one-month follow-up. Recently, it was shown that 20 sessions of anodal tDCS over the left DLPFC may reduce cigarette consumption beyond one-month follow-up (Behnam et al., 2019). The current study will explore whether the protocol with anodal tDCS over the right DLPFC can also have extended effects on smoking behaviour with fewer sessions. *Ad libitum* smokers were included to pilot whether tDCS affects the natural course of smoking behaviour, without smokers being motivated to quit.

For the current study we choose to measure smoking behaviour by means of Ecological Momentary Assessment (EMA). Effects of tDCS on addictive behaviour have often been measured with retrospective self-reports in the lab. Since craving and substance use are both episodic phenomena that are associated with affect and context (Dvorak, Waters, MacIntyre, & Gwaltneym 2018; Monk, Qureshi, McNeill, Erskine-Shaw, & Heim, 2017; Wall, McKee, & Hinson, 2000), measuring these variables in daily life may lead to more reliable answers. Furthermore, retrospective measurements may be influenced by recall biases (Boniface, Kneale, & Shelton, 2014; Stockwell, Zhao, & MacDonald, 2014). EMA

therefore establishes more ecologically valid results as compared to retrospective self-reports by collecting data in real-time repeatedly.

In sum, the aim of the current study is to explore the duration of the effect of repetitive tDCS on cigarette consumption by means of EMA in a sample of *ad libitum* smokers. Following the design of Falcone and colleagues (2016), participants were included if they had no plans to actively try to quit smoking in the next three months. In line with previous studies, we expected that active tDCS can reduce the number of daily smoked cigarettes and we hypothesized that this decrease can last for up to 3 months after the last session. We also expected reduced craving after active tDCS (Jansen et al., 2013) during and after the intervention week, and at three months follow-up.



## Materials and methods

### Participants

Seventy-three participants signed the informed consent form and completed the first tDCS session. Inclusion criteria were: 1) Between the age of 18 and 65 years; 2) Currently smoking 10 cigarettes or more a day; 3) The ability to speak, read, and write in Dutch. Exclusion criteria were: 1) Current substance use disorder of a substance other than nicotine or caffeine; 2) History of neurological or psychiatric disorders; 3) Any contraindication for electrical brain stimulation procedures (i.e. electronic implants or metal implants); 4) Pregnancy or breast-feeding; 5) Intentions to actively try to quit smoking in the next three months. Participants were recruited via advertisement at Erasmus University Rotterdam from October 2016 until March 2018 and received either course credit or a financial compensation of 20 euro. Two participants dropped out during the intervention week, because of personal circumstances (n=1) and because of schedule issues (n=1). Also due to schedule issues, three participants received tDCS on only two instead of three days. Leaving these participants out of analyses had no effect on the results, therefore they were included in the final analyses. Nine participants could not be reached after three months and were therefore lost to follow-up, leaving a total of 62 participants for follow-up analyses (Fig 1).

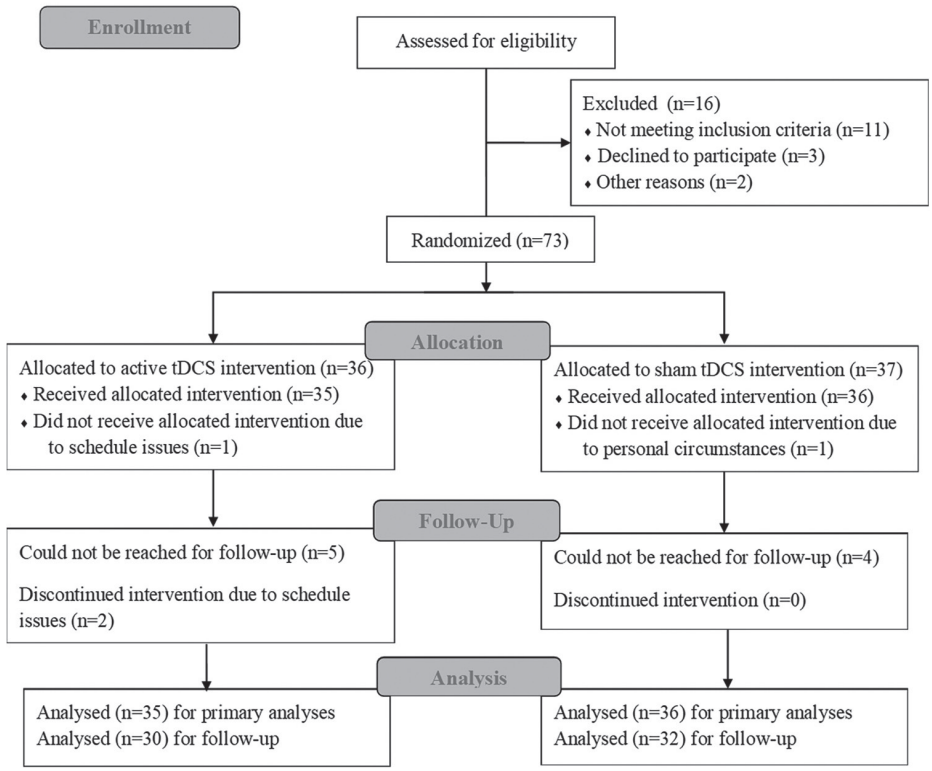


**Fig 1.** Flow Diagram

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. All procedures were carried out after participants were fully informed and had signed a written informed consent form. This report is part of the pre-registered study with identifier NCT03027687 at ClinicalTrials.gov. The complete study protocol can be found at http://dx.doi.org/10.17504/protocols.io.bcgdits6.

## Experimental design

The current study had a double-blind, randomized, sham-controlled design in which subjects received a total of six tDCS sessions (active or sham) on three days in one week with at least one day in between (Fig 2). Participants were first randomly assigned to either sham or active tDCS. Then, before the tDCS sessions and at three months follow-up, participants completed the Fagerström Test of Nicotine Dependence (FTND; (Heatherton, Kozlowski, & Frecker, 1991).

Breath carbon monoxide concentrations were also measured using a Micro+ Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) to objectively define smoking. In addition, participants completed two behavioural tasks in the Erasmus Behavioural Lab (EBL) before the first session, one day after the last tDCS session and at three months follow-up. With these tasks we measured changes in cognitive control and feedback processing by means of EEG. The results of the tasks will be discussed elsewhere, in order to remain focus on the scope of this paper (e.g. changes in smoking behaviour after tDCS).

To measure changes in smoking behaviour, participants were asked to keep track of their cigarette consumption, craving and affect in an application on their mobile phones (EMA). Questions in the application were presented at four random times a day for three weeks in total (random assessments; RA's), starting the week before the first tDCS session (T1). After three months, participants were asked to fill out the same four-time daily random assessments for one more week (T2). In addition, participants were asked to start a session every time they smoked a cigarette (user-initiated smoking assessment; SA) for three months in total. An 'end of the day' assessment (EA) was also implemented for three months, which asked participants to fill out the total number of smoked cigarettes of that day.

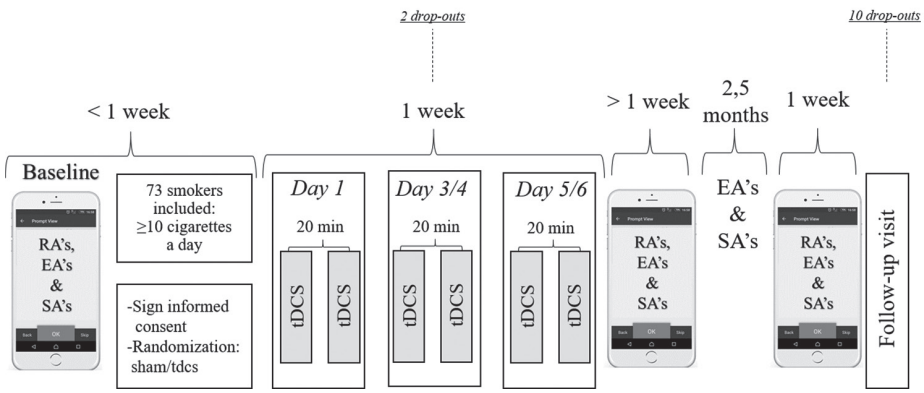


**Fig 2.** Experimental procedure. Participants are asked to fill out the following EMA assessments: Random assessments (RA's), end of the day assessments (EA's), user-initiated smoking assessment (SA's). TDCS sessions last 13 minutes each with 20 minutes in between.

### Transcranial Direct Current Stimulation (tDCS)

Participants in the active tDCS group received tDCS by an electric DC-plus stimulator (NeuroConn, Ilmenau, Germany) via a pair of carbonated silicone electrodes with a thick layer of high-conductive EEG gel underneath them (35 $cm^2$). During each session, tDCS was applied two times for 13 minutes with a 20-minute break in between, and a current intensity of 2.0 mA with a 30 sec ramp at the beginning and end of the session (Batista et al., 2015). The anodal electrode was placed over F4 area (10-20 international system) to stimulate the right DLPFC, the cathodal electrode was placed over the F3 (left DLPFC). Beneficial effects were found on smoking behaviour with this 'right anodal/left cathodal' positioning (Fecteau et al., 2014).

The control group received sham tDCS by the DC-plus stimulator. For sham, the electrodes were positioned at the same locations as active tDCS, but in this case the stimulator was gradually turned off after 30 s. Since the itching sensation of tDCS is often only experienced initially during stimulation, subjects remained blinded of the stimulation condition they received (e.g. Woods et al., 2016; Gandiga, Hummel, & Cohen, 2006). The experimenter was also blinded from the tDCS condition. That is, the codes that can automatically activate sham or active tDCS, were randomly assigned to participant numbers by an independent researcher. Then, the experimenter assigned the participant numbers.

## Ecological Momentary Assessment

### Procedure

The LifeData platform (www.lifedatacorp.com) was used to develop the application for this study and to securely collect data. Participants were instructed by email to download the LifeData application on their smartphone one week before the first tDCS session. The start-up session of the application provided general information about how to use the app. After participants had finished the start-up session, they received random prompts four times a day between 10 am and 10 pm for 21 consecutive days to complete a RA. After three months, the application automatically started prompting participants again for four times a day for seven consecutive days. All RA's that were not completed within 90 minutes after the notification disappeared and were marked as missed.

In addition, participants were asked to initiate an assessment whenever they started smoking a cigarette (SA). The application further alerted participants at the end of the day (22 pm) to fill out the total number of cigarettes they had smoked during the day (end-of-day assessment; EA). EA's were prompted for 90 consecutive days, starting from the day the application was downloaded.

### Measures

**Cigarette consumption.** During RA's, participants were asked how many cigarettes they had smoked since the last assessment and how many minutes had passed since they had smoked their last cigarette. Participants were also instructed to start a SA whenever they smoked a cigarette. During EA's participants filled out the total amount of cigarettes they had smoked during the day.

**Craving.** During RA's, participants were asked to indicate the urge to smoke a cigarette at that moment on a Likert scale ranging from 0 (*no urge*) to 100 (*very strong urge*).

**Mood.** General mood was measured during RA's by a prompt stating: "What is your general mood at the moment?" with response possibilities ranging from *very negative* (0) to *very positive* (5). In addition, participants were asked to evaluate the following specific affects for themselves on a 5-point Likert scale: Happiness, enthusiasm, relaxedness, irritability, sadness, stress, and how bored they felt.

## Data analyses

In order to fit the nested data structure of Time within individuals (Level 1), and Group (tDCS vs. Sham) at Level 2, the primary analysis was conducted using multilevel regression modeling, also known as hierarchical linear modeling (see Hox, 2010 for further details), in HLM 7.01. By using the maximum likelihood estimation method in multilevel modelling of the EMA data, all data points of individuals with missing data could be analyzed (Dunbar, Shiffman, & Chandra, 2018). Missing data is almost inevitable in EMA studies, since most participants miss at least some prompts due to daily activities.

For the analyses, first a baseline model was fitted to every outcome variable (cigarette consumption and craving), including random intercepts across participants. With this model, it was assessed whether multilevel analysis was required. By significant variance at Level 2, the other models were fitted. It was

confirmed that multilevel analyses could be applied in the current study, because fitting the baseline models to the data showed there was a significant amount of variance of the regression coefficients on the subject level (Level 2). The second model included the Level 1 predictor Time as fixed effect and was then extended by adding random slopes for Time. The final model included cross-level interactions between Time at Level 1 and the predictor variable Group (Active or Sham tDCS) at Level 2. The assumptions of normality and linearity were assessed by inspecting the residuals of each best fitted model. Unless otherwise reported, the assumptions were met. Further analyses examined smoking behaviour as a function of craving, and positive and negative affect on the momentary level (Level 1).

Since age and craving significantly differed for the sham and active tDCS group, multilevel analyses with cigarette consumption as outcome variable were also carried out with age and craving as covariates. Both covariates did not influence the results of tDCS on cigarette consumption. Explorative analyses were performed with the following covariates: Gender, overall FTND scores at baseline, and number of years the participant had been smoking. These variables had no influence on the effect of tDCS on cigarette consumption and craving. Finally, Spearman correlation coefficients were calculated for all three carbon monoxide scores on the one hand and mean number of cigarettes indicated by EA's in the week before each carbon monoxide concentration was measured on the other hand.

## Results

### Descriptive statistics

The final sample consisted of 71 participants (36 females, 35 males) between the age of 19 and 53 years (M = 22.3, SD = 4.7) who smoked an average of 11.3 cigarettes a day (SD = 4.2) and had a mean FTND score of 3.4 (SD = 1.9). Of these 71 participants, 35 received active tDCS and 36 received sham treatment. Because of the double-blind method the groups were not matched at baseline. As a result, the average age of the sham group (M = 23.4) was slightly higher compared to the active tDCS group (M = 21.1), $t(69) = 2.119$, $p = .038$. In addition, the active tDCS group experienced more craving at baseline ($p = .001$). For follow-up analyses, 62 participants were included ($n = 30$ Sham tDCS, $n = 32$ Active tDCS).

## Ecological Momentary Assessment: Compliance

RA's were initially prompted four times a day for 21 days, which means that the total number of possible prompts for 71 participants was 5964. The total number of completed RA's during the first 21 days was 2650. Therefore, the compliance rate for completed random assessments was 44.4%. Ninety days after the start-up session, RA's were prompted for one more week. During this follow-up week the compliance rate was 46.6%.

In addition, EA's were presented on each day for 90 days. During the first 21 days, participants completed a total of 810 out of 1491 EA's (54.3% compliance rate). During the follow-up week, 62 participants completed 242 out of 434 possible EA's, making the compliance rate 55.8%.

Additional exploratory analyses showed that 54 participants filled out at least one third of all EA's, and 38 participants filled out at least 50% of all EA's. Further analyses with these two groups showed no difference in results on the primary outcomes as compared to analyses with the entire sample. In addition, compliance on EA's did not correlate with the outcome measures for both groups.

## Primary outcome: Number of smoked cigarettes

The primary outcome measure was mean number of smoked cigarettes a day. Multilevel analysis with mean number of smoked cigarettes as dependent variable and time in days as predictor, showed that the mean number of smoked cigarettes slightly decreased over two weeks' time from the first tDCS intervention up to one week after the last tDCS session ($b$ = -.07, $t(471)$ = -2.086, $p$ =.038). This decrease over time was observed for both active tDCS and sham tDCS (Fig 3) and did not correlate with EMA compliance. Importantly, no differences were found between the groups in the amount of change over time on number of smoked cigarettes ($p$ = .745). Also at follow-up, the sham tDCS and active tDCS group did not differ in number of smoked cigarettes ($p$ = .859).

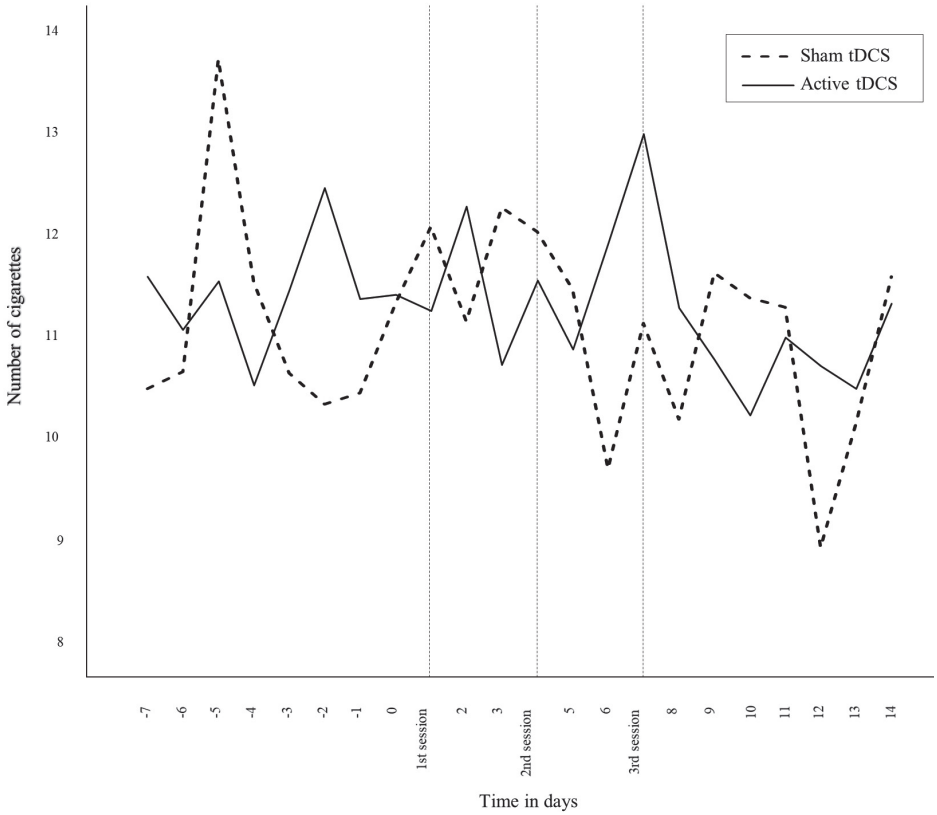


**Fig 3**. Number of smoked cigarettes on each day starting from one week before the 1st tDCS session.

## Correlational analyses: CO scores.

Additional analyses showed that number of smoked cigarettes in the week before the first tDCS session correlated with the breath concentration of carbon monoxide (CO; in parts per million) on the day of the first tDCS session ($r = .416$, $p < .001$). CO scores on the day of the last tDCS session also correlated with the mean number of cigarettes smoked during the intervention week ($r = .303$, $p = .041$). Finally, it was found that mean number of smoked cigarettes in the week before the follow-up session correlated with CO scores at follow-up ($r = .486$, $p < .001$).

## Secondary outcomes: Craving and affect

Participants in the active tDCS group experienced significantly more craving ($p < .001$) the week before the first tDCS session ($M = 56.1$, $SD = 20.7$) as compared

to the sham tDCS group (*M*= 48.7, *SD*= 19.6). Multilevel analysis with craving for cigarettes as dependent variable and time in days as predictor, showed a main effect of group in the two weeks after the first tDCS session (*b*=11.75, *t*(69)= 3.87, *p* =.003), meaning that the baseline difference in craving was maintained throughout T1. There was no main effect of time (*p* = .184) and no interaction effect of time and groups (*p* = .970) on craving at T1 (Fig 4). No differences between groups were found for overall mood at T1 (*p* = .599). For T2 at 3 months follow-up, no main effect of time and condition, or interaction effect was found for craving and overall mood.



Analyses at T1 showed that total number of smoked cigarettes was associated with craving on the same day (*b*=.035, *p* <.001). In addition, smoking behaviour was related to positive affect. Specifically, it was found that happiness was positively related to total number of smoked cigarettes on the same day (*b*=.726, *p* <.001).

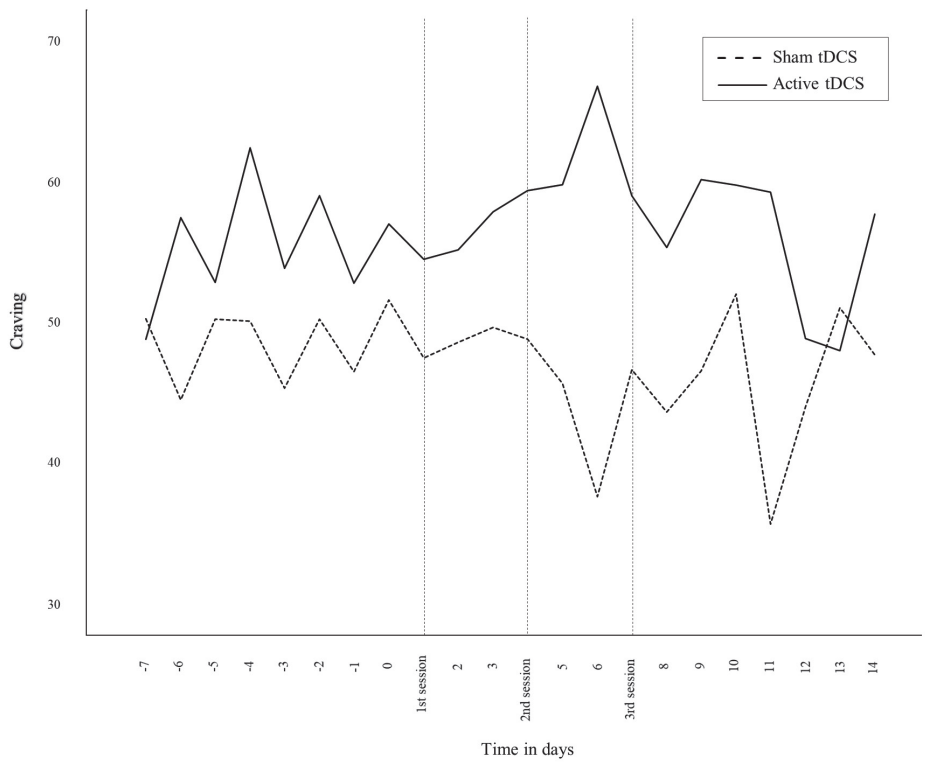


**Fig 4**. Mean craving on each day starting from one week before the 1st tDCS session

### tDCS side effects

Side effects were recorded after each tDCS session. Participants were asked to indicate the amount of itching, burning, and tingling sensations on a 5-point Likert scale, ranging from none (1) to extreme (5) sensations. In addition, we asked participants about difficulties with concentrating and whether they experienced acute mood changes during tDCS. Questions about sleepiness, neckpain and pain in the head were also rated on a 5-point Likert scale. Results showed that overall, the active tDCS group experienced significantly more itching sensations ($F$=11.379, $p$ = .001) as compared to the sham group. No other differences between the groups were observed regarding the side-effects.

## Discussion

The current study was the first to use mobile Ecological Momentary Assessments (EMA) to investigate non-invasive neurostimulation as a tool to reduce smoking behaviour. The aim of this exploratory study was to test with EMA whether tDCS over the right DLPFC could modulate cigarette consumption and craving in *ad libitum* tobacco smokers. Results showed that over the course of the intervention week, the number of smoked cigarettes decreased during the application of sham or active tDCS. This finding is consistent with observations from a previous study with multiple tDCS sessions in tobacco smokers (Fecteau et al., 2014) and may result from the participants' awareness of their smoking behaviour.

Most importantly, however, no differences were found between the sham and active tDCS group in cigarette consumption and craving. This finding is not in line with a series of previous studies that have demonstrated that tDCS is effective in reducing cigarette smoking (Fecteau et al., 2014; Falcone et al., 2016; De Souza Brangioni et al., 2018; Behnam et al., 2019) and cigarette craving (Fregni et al., 2008; Boggio et al., 2009). A possible explanation for this unexpected finding is that in the current study craving and cigarette consumption were assessed by means of EMA. With this experience sampling method, we were able to measure cigarette consumption and craving in real time. The outcomes are therefore measured in a more ecologically valid manner as compared to retrospective self-reports. This is of importance, since smoking behaviour is associated with mood and context (Monk et al., 2017; Wall et al., 2000). Individuals may for instance

smoke more during the weekend or on stressful days (Dunbar et al., 2018). This pattern of change over time is clearly illustrated in Figs 3 and 4. Moreover, with the use of momentary assessments retrospective recall biases can be avoided.

Another explanation for the lack of effect of tDCS on craving levels and cigarette consumption can be found in the study's sample that consisted of mostly light smokers who, in addition, had no desire to quit smoking. It can be suggested that motivation of smokers to quit plays an important role in the efficacy of tDCS. The current study included *ad libitum* smokers (i.e., individuals who have no intention to quit smoking at the moment of the intervention), whereas a recent study that was published after we started our data collection showed that the effect of tDCS on smoking behaviour was modulated by motivation to quit (De Souza Brangioni et al., 2018). It was also found that repetitive tDCS decreased cigarette consumption in participants who wanted to quit smoking (Fecteau et al., 0214). These findings, in combination with the results of the present study, seem to suggest that tDCS is at least effective if there is a clear motivation to quit smoking. Future studies should explore the direct relationship between motivation to quit smoking and the efficacy of tDCS on smoking behaviour.



Finally, in contrast with previous studies that applied multiple sessions of tDCS, we applied 6 tDCS sessions on three different days in one week, instead of 5 or more session on at least five different days (e.g. Fecteau et al., 2014; Behnam et al., 2019). A reduction in cigarette consumption could nevertheless be expected on the days that tDCS was applied. That is, since Falcone and colleagues (2016) found an immediate temporary effect of one tDCS session on smoking in *ad libitum* smokers. In this study, however, tDCS was applied online during cue exposure which may have influenced the effects (Falcone et al., 2016).

Besides the important improvement of using real-time assessment in the natural environment of smokers, several critical remarks can be made and therefore caution should be taken when interpreting the findings. First, while participants were randomly allocated to either the active or sham condition, groups significantly differed on baseline craving levels. That is, participants in the active condition showed higher craving levels before the intervention compared to the control group which could have affected the results of this study.

A second limitation that should be mentioned is the relatively low compliance rate, ranging from 44% to 56%, on EMA assessments. A recent meta-analysis

has shown that the average compliance rate in substance dependent samples is 69.8% (Jones et al., 2019). Even though multilevel modelling in HLM 7.01 reliably corrects for random missing data, we performed additional analyses where participants with low compliance rates were excluded to investigate whether compliance rate might have influenced the outcomes. The results of these analyses indicated no change in outcome if compliance rates are higher. Reliability of the data is further supported by the finding that carbon monoxide concentrations correlated with number of smoked cigarettes as indicated in EMA end of the day assessments. Moreover, the EMA data showed that *ad libitum* smoking was related to craving and positive affect. Specifically, the number of smoked cigarettes increased with both craving and positive affect on the same day. These findings are in accordance with the results from an earlier EMA study with a higher compliance rate (Dvorak et al., 2018). Finally, participants in the active tDCS group indicated they experienced more itching sensations during neurostimulation than the sham tDCS group. This finding is in line with observations from previous studies where participants reported tingling and itching sensations after stimulation (e.g. Fecteau et al., 2014). However, blinding can still be reliable despite of differences in comfortability between the two conditions (Russo, Wallace, Fitzgerald, & Cooper, 2013). In addition, blinding with sham tDCS is considered reliable (Gandiga et al., 2006).

This was the first exploratory investigation using EMA to study the effects of tDCS on smoking behaviour. With the use of EMA, further insights were provided on the course of smoking behaviour over time. In sum, we did not find evidence that tDCS over the DLPFC decreases cigarette consumption and cigarette craving in light smokers that have no desire to quit at the moment of intervention. These findings raise intriguing questions regarding the nature and extent of the effects of tDCS on smoking behaviour. In a previous study it was found that motivation to quit smoking modulated the efficacy of tDCS on smoking behaviour (De Souza Brangioni et al., 2018), and therefore it may be necessary for smokers to actually quit smoking or at least be motivated to quit smoking at the moment of intervention. Future studies should explore this hypothesis by investigating the effects of repetitive tDCS in a larger sample of heavier smokers who are motivated to quit.

# 3

# Long-term tDCS Effects on Neurophysiological Measures of Cognitive Control in Tobacco Smokers

***This chapter is submitted as:***

*Verveer, I., Remmerswaal, D., Jongerling, J., van der Veen, F. M., & Franken, I. H. A. (submitted). Long-term tDCS effects on neurophysiological measures of cognitive control in tobacco smokers*

## Abstract

**Introduction**: The use of transcranial Direct Current Stimulation (tDCS) has shown promising results for reducing smoking behaviour. In this study we assessed the effects of tDCS on inhibitory control and error processing to better understand tDCS modulation of smoking behaviour.

**Methods:** Smokers were allocated to six sessions of either active tDCS ($n$ = 34) or sham tDCS ($n$ = 35) (https://clinicaltrials.gov/ct2/show/NCT03027687). Immediately before, one day after, and three months after all tDCS sessions, participants performed the Go-NoGo task while we measured behavioural and neurophysiological responses.

**Results:** Active tDCS had no significant effect on early inhibitory control and error processing in tobacco smokers. However, a significant improvement in reaction times, and a decrease in No-Go P3 amplitudes for smoking cues was found three months after active tDCS.

**Conclusion:** Given the direction of the effect, we speculate that tDCS has a long-term modulatory learning effect on selective attention and motor inhibition. These findings contribute to a further understanding of tDCS as intervention for tobacco addiction, and shed light upon the mechanisms of action and duration of tDCS effects.

## Introduction

Various neurobiological models have suggested that addictive disorders are characterized by an interplay of increased activity in the subcortical reward system, and decreased activity in the prefrontal cortex (e.g. Volkow et al., 2010). The prefrontal cortex (PFC) plays a crucial role in cognitive control, because of its involvement in top-down control over reward processing. There have been at least two components of cognitive control identified that play an important role in substance use disorders, namely inhibitory control and error processing (Luijten et al., 2014). Inhibitory control can prevent the execution of (automatic) responses. As a consequence, reduced inhibitory control makes it challenging for individuals with substance dependence to suppress substance related urges or cravings that are generated by the reward system. Craving therefore often leads to compulsive substance use.



Another identified cognitive control process relevant for addictive behaviours is error processing. Harmful behaviour such as substance use can be avoided in future circumstances when individuals adaptively learn from the negative consequences of substance use. However, deficits in error processing prevents learning from past mistakes (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Consequently, diminished error processing in substance use disorder may preserve addictive behaviours. This persistence can for example be seen in tobacco addiction, for which health risks are generally well known. Still, it is estimated that 1.1 billion people of the global population are smokers (WHO, 2019).

Impaired cognitive control processing in tobacco smokers has been demonstrated by several studies using experimental paradigms that measure inhibitory control and error processing, such as the Go-NoGo task (e.g., Smith, Mattick, Jamadar, & Iredale, 2014). During the Go-NoGo task, smokers seem to make more errors on inhibition (NoGo) trials as compared to controls (Nestor et al., 2011; Smith et al., 2014; Detandt et al., 2017; Luijten, Littel, & Franken, 2011). It has furthermore been suggested that response inhibition is an important aspect of impulsivity (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001), which has been related to poorer treatment outcome (Doran, Spring, McChargue, Pergadia, & Richmond, 2004; Krishnan-Sarin et al., 2007). In addition, impaired error monitoring was displayed by slower reaction times on trials after performance

errors (i.e. post-error slowing) in tobacco smokers as compared to controls (Luijten, van Meel, & Franken, 2011; Luijten et al., 2014).

Cognitive control impairments in tobacco smokers can also be traced back in neural correlates. The N2 and P3 are two Event Related Potentials (ERPs) that have been associated with changes in brain activity related to inhibitory control (Pfefferbaum, Ford, Weller, & Kopell, 1985; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004). The N2 amplitude is a negative-going wave generated in the prefrontal cortex that peaks approximately 200-300 ms after stimulus presentation. The N2 appears to reflect early conflict detection needed to initiate inhibitory control (Nieuwenhuis, Yeung, & Cohen, 2004; Luijten et al., 2014). ERP investigations have reported that the N2 is reduced in smokers as compared to controls (Luijten et al., 2011; Buzzell, Fedota, Roberts, & McDonald, 2014), indicating impairments in early inhibitory control processes. The P3 is a positive ERP wave that emerges 300-500 ms after stimulus onset. It has been suggested that the P3 reflects the inhibition of motor processes, supported by evidence identifying the neural origin of the P3 near the motor and premotor cortices (Band & Boxtel, 1999; Smith, Johnstone, & Barry, 2008). Impaired control over inhibition as indicated by reduced P3 amplitudes has been associated with smoking relapse (Luijten, Kleinjan, & Franken, 2016).

Poorer error processing in tobacco smokers has also been reported by ERP studies. The error related negativity (ERN) is identified as a neural correlate of early and automatic error processing (Bernstein, Scheffers, & Coles, 1995). This negative going wave emerges 50-80 ms after erroneous responses and is generated by the dorsal anterior cingulate cortex (dACC) (e.g. van Veen & Carter, 2002). Reduced ERN amplitudes were found in smokers as compared to non-smokers when exposed to smoking cues (Luijten, van Meel, & Franken, 2011). In addition, impaired error processing in smokers could be related to an increase in smoking over time after an attempt to quit (Luijten et al., 2016).

Given the observed associations between substance use with impaired inhibitory control and error processing, it is reasonable to believe that interventions for tobacco addiction would be effective if they improve these cognitive control aspects. Interventions designed to directly modulate brain activity in areas related to cognitive control therefore form a promising treatment for tobacco addiction. Transcranial Direct Current Stimulation (tDCS) is a non-

invasive neurostimulation technique that modulates cortical excitability by means of small electrical currents (Nitsche & Paulus, 2000). Initial studies on tDCS in tobacco addiction have shown an efficacy of tDCS in the reduction of cue-induced craving (Fregni et al., 2008; Boggio et al., 2009), actual smoking (Fecteau et al., 2014; Falcone et al., 2016; De Souza Brangioni et al., 2018), and smoking abstinence (Behnam, Mousavi, & Emmian, 2019). However, some studies did not find an effect of tDCS on craving (Xu, Fregni, Brody, & Rahman, 2013) and cigarette consumption (Verveer et al., *Chapter 2*). Findings from a recent meta-analysis indicate that anodal tDCS over the right DLPFC with cathodal tDCS over the left DLPFC has the most positive effects on smoking behaviour (Kang, Kim, & Kim, 2019). In order to further facilitate the choice of this specific tDCS protocol for the treatment of tobacco addiction, it is important to identify the underlying effects of it on cognitive control in larger samples (Lapenta, Marques, Rego, Comfort, & Boggio, 2018).



It has been proposed that tDCS can modulate automatic responses related to impulse control, craving and substance use by modulating frontal brain areas and circuits involved in cognitive control (Lapenta et al., 2018). However, only few studies have investigated the effects of tDCS on the underlying neurophysiological aspects of cognitive control in addiction. To the authors' current knowledge, only one study evaluated this in tobacco addiction by means of functional near-infrared spectroscopy (Kroczek et al., 2016). Their results indicated a higher functional connectivity between the DLPFC and orbitofrontal cortex after anodal tDCS over the left DLPFC, but no differences in cue-induced cravings between the active and sham tDCS group were found.

Evidence from other addiction studies indicates that tDCS may modulate ERPs related to inhibitory control, e.g. the N2 and P3 (Da Silva et al., 2013). After active tDCS over the right DLPFC, a reduction in N2 amplitudes and an increase in P3 amplitudes was found for substance related cues in crack-cocaine addiction (Conti, Moscon, Fregni, Nitsche, & Nakamura-Palacios, 2014, Conti & Nakamura-Palacios, 2014). It has also been found that tDCS over the DLPFC can induce neuromodulations in other prefrontal areas, such as the dACC (Feil & Zangen, 2010; Weber et al., 2014). It is therefore expected that the ERN generated by the dACC may be modulated by tDCS.

Few electroencephalography studies have investigated the effect of tDCS on inhibitory control and error processing specifically (Sallard, Mouthon, De Pretto, & Spierer, 2018), of which non has included smokers. One study found a trend towards reduced N2 amplitudes and increased P3 amplitudes on NoGo trials after right anodal left cathodal tDCS over the DLPFC (Lapenta, Di Sierve, de Marcedo, Fregni, & Boggio, 2014). However, with a small sample size of nine female participants, results of this study are difficult to generalize. Modulated P3 amplitudes were also found on NoGo trials after active stimulation over the right inferior frontal cortex (Cunillera, Brignani, Cucurell, Fuentemilla, & Miniussi, 2016; Campanella et al., 2016). In these two studies, the N2 was not affected by tDCS. Cunillera and colleagues (2016) indicated that their online stimulation protocol might have reached the right DLPFC instead of the IFC, since the behavioural data showed that tDCS affected proactive inhibition and not reactive inhibition (Aron, 2011). A recent study with an offline tDCS protocol did however not find that tDCS over the rDLPFC could affect P3, N2, and ERN amplitudes, whereas active stimulation over the left DLPFC was associated with increased P3 amplitudes and reduced N2 amplitudes on incongruent trials during a flanker task (Dubreuil-Vall, Chau, Ruffini, Widge, & Camprodon, 2019).

In this study we assessed the behavioural and physiological effects of anodal tDCS over the DLPFC on inhibitory control and error processing to better understand the association of these signatures with adaptive tDCS modulation of smoking behaviour. It was expected that cognitive control is improved on a behavioural and physiological level after active tDCS over the DLPFC. Since only few studies have investigated physiological effects of tDCS, we were also interested in the correlation between these outcomes and behavioural outcomes of tDCS. The duration of the effect was also explored, since repeated tDCS can induce longer lasting effects (Monte-Silva, Kuo, & Hessenthaler, 2013), and previous addiction studies have shown that the effects of multiple tDCS sessions can last for 1 month up to 6 months in tobacco, alcohol and cocaine addiction (De Souza Brangioni et al., 2018; Klauss et al., 2014; Batista, Klauss, Fregni, Nitsche, & Nakamura-Palacios et al., 2015).

## Materials and Methods

### Experimental Design

The present study, which was part of a larger study on the effects of tDCS on smoking behaviour (Verveer et al., *Chapter 2*), employed a between-subject, double-blind, randomized, sham-controlled design in which subjects received a three-day regimen of either active or sham tDCS over the DLPFC (Flowchart; see Figure 1). Participants performed the Go-NoGo task and a gambling task before and one day after the tDCS protocol, and at three months follow-up. Only the Go-NoGo task will be discussed in the current paper, since the focus of this paper is on cognitive control.



In addition, subjects were asked to fill out subjective craving and number of smoked cigarettes via ecological momentary assessments (EMA) for three months starting one week before the first tDCS session. The results of the EMA data are discussed in Chapter 2.

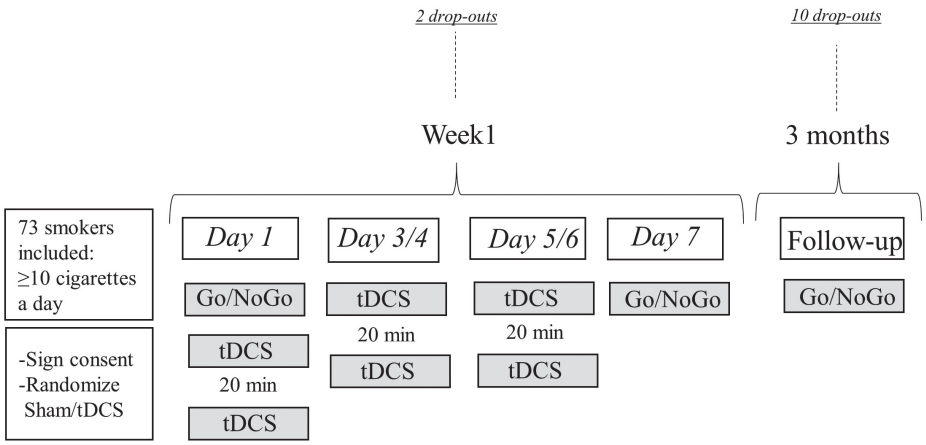


***Figure 1.*** Flowchart of experimental design.

### Participants

The sample consisted of 73 smokers (36 females, age: $M = 22.3$, $SD = 4.7$) who smoked an average of 11.2 cigarettes a day and had a mean score of 3.4 on the Fagerström Test for Nicotine Dependence (FTND). Exclusion criteria were: 1) Current substance use disorder of a substance other than nicotine or caffeine;

2) History of neurological or psychiatric disorders; 3) Any contraindication for electrical brain stimulation procedures (i.e. electronic implants or metal implants); 4) Pregnancy or breast-feeding; 5) Intentions to actively try to quit smoking in the next three months.

Participants were recruited via advertisement at Erasmus University Rotterdam, and received either course credit or a financial compensation of 20 euro. Two participants dropped out during the intervention week, because of personal circumstances (n=1) and because of schedule issues (n=1). In addition, two more participants were excluded because of too many performance errors. Also due to schedule issues, three participants received tDCS on only two instead of three days. Leaving these participants out of analyses had no effect on the results, therefore they were included in the final analyses. Of the 69 participants, 34 received active tDCS and 35 received sham treatment. Nine participants could not be reached after three months and were therefore lost to follow-up, leaving a total of 60 participants for follow-up analyses.

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. All procedures were carried out after participants were fully informed and had signed a written informed consent form. This report is part of the pre-registered study with identifier NCT03027687 at ClinicalTrials.gov.

## Measures

### Breath CO measures and Questionnaires

Breath carbon monoxide concentration was measured using a Micro+ Smokerlyzer (Bedfort Scientific Ltd., Rochester, UK) before each test session. The FTND was used to measure nicotine dependence (Heatherton, Koxlowski, Frecker, & Fagerstrom, 1991). We assessed subjective cigarette craving before and after the Go-NoGo task with the Questionnaire of Smoking Urges (SQU) (Cox, Tiffany, & Christen, 2001). In addition, responses to the following questionnaires will be discussed elsewhere: behavioural inhibition and reward responsiveness were measured with the BIS-BAS plus Reward Responsiveness (RR), and the Brief Sensation Seeking Scale (BSSS) was used to measure sensation seeking.

**Go-NoGo task**

A smoking related Go-NoGo task was used to measure inhibitory control, based on the paradigm used in the study of Luijten, Littel and Franken (2011). During this task, participants were presented with a series of smoking-related and neutral pictures. Go and NoGo trials were indicated by the coloured frame of pictures (blue or yellow). The attribution of the frame colour to Go versus NoGo trials was counterbalanced across participants.

Each picture was presented for 200 ms, followed by a black screen displayed for a randomly varying duration between 1020 and 1220 ms. The paradigm involved 112 different smoking-related pictures and 112 matched neutral pictures that were presented one time as NoGo trials and three times as Go trial (see figure 2 for an example of a smoking and neutral trial). The order of picture content (smoking versus neutral) was completely randomized and the order of trial type (Go versus NoGo) was quasi randomized such that at most four Go and two NoGo trials were presented consecutively.

Participants were instructed to press a button with their index finger as fast as possible for Go trials, and to inhibit their response for the unexpected NoGo trials (25% of all trials). The task included a practice phase containing 23 practice trials with a neutral content. Participants were also given the opportunity to take a short break four times during the task. The total duration of the task was about 25 minutes, depending on the length of the breaks.

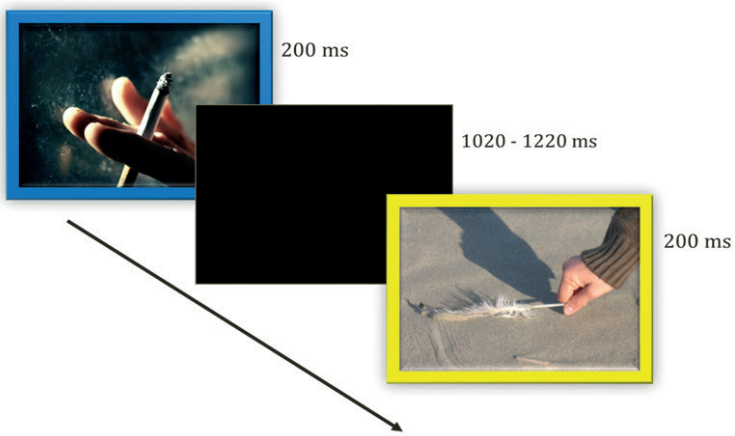


***Figure 2.*** Example of a neutral and smoking related picture in the Go-NoGo task. The blue and yellow frames indicate Go and NoGo trials.

## EEG Acquisition

Brain activity was recorded with EEG using a Biosemi ActiveTwo System amplifier (10-20 International System). EEG recordings were done at 32 scalp sites and one additional electrode at FCz. In addition, one electrode was placed on each mastoid to serve as reference electrode. Vertical ocular movements were measured by electrodes placed above and below the left eye (VEOG). To measure horizontal ocular movement, one electrode was placed at the outer canthi of each eye (HEOG).

All signals were digitized with a sampling rate of 512 Hz and 24-bit analog-to-digital conversion. EEG and EOG data was filtered with a band filter of .1-30 Hz (24 dB/octave slope). Data were segmented in epochs from 200 ms before to 800 ms after response or stimulus presentation. After ocular correction was performed (Gratton, Coles, & Donchin, 1983), artefacts were excluded from the average for amplitudes smaller than -100 μV and larger than 100 μV. The mean 200 ms pre-response or pre-stimulus period served as baseline. After baseline correction, the average waveform was calculated separately for epochs locked to correct and incorrect responses. Segments with incorrect responses (miss for Go trials and false-alarms for NoGo trials) were excluded from EEG analyses.

The N2 amplitude was defined as the average wave within a 200–300 ms window following stimulus onset, and studied at a cluster of frontocentral electrodes, including Fz, FC1, FC2, FCz and Cz (Luijten, Littel, & Franken, 2011). The P3 component was defined as the average positive going amplitude within 300–400 ms following stimulus onset. P3 amplitude effects are largest at central electrodes, hence the P3 was measured at a cluster FCz, Cz, C3, C4, and CPz electrodes (Luijten, Littel, & Franken, 2011). The ERN amplitude was defined as the mean value within 25-75 ms after incorrect NoGo responses, and measured at a cluster of Fz, FCz, and Cz electrodes (Luijten, van Meel, & Franken, 2011).

## Transcranial Direct Current Stimulation

Participants in the active tDCS group received tDCS by an electric DC-plus stimulator (NeuroConn, Ilmenau, Germany) via a pair of carbonated silicone electrodes with a thick layer of high-conductive EEG gel underneath them (35 $cm^2$). During each session, tDCS was applied two times for 13 minutes with a 20 minute break in between, and a current intensity of 2.0 mA with a 30 sec ramp

at the beginning and end of the session (Batista et al., 2015). The anodal electrode was placed over the F4 area (10-20 international system), and the cathodal electrode was placed over the F3. Beneficial effects were found on smoking behaviour and craving with this right anodal/left cathodal positioning over the DLPFC (Kang, Kim, & Kim, 2019; Fecteau et al., 2014; Jansen et al., 2013).

The control group received sham tDCS by the DC-plus stimulator. For sham, the electrodes were positioned at the same locations as active tDCS, but in this case the stimulator was gradually turned off after 30 s. Since the itching sensation of tDCS is often only experienced initially during stimulation, subjects remained blinded of the stimulation condition they received (e.g. Gandiga, Hummel, & Cohen, 2006; Woods et al., 2016). The experimenter was also blinded from the tDCS condition. That is, the codes that can automatically activate sham or active tDCS, were randomly assigned to participant numbers by an independent researcher.



## Statistical Analyses

Multilevel analysis were performed in R (R Core Team, 2018) using the lme4 package (Bates, Maechler, Bolker, & Walker, 2014) in order to include participants who had missed the follow-up session and to fit the nested data structure. For accuracy on the Go-NoGo task the variables Time (day1, day7, and follow-up) and Inhibition (Go vs. NoGo trials) were defined at Level 1. Picture type (Neutral vs. smoking pictures) was used as crossed random factor (Judd, Westfall, & Kenny, 2012; Volpert-Esmond, Merkle, Levsen, Ito, & Bartholow, 2017). Reaction times for go trials were analysed with Time and Picture Type as Level 1 variables. Post reaction times included the variables Time and Correct vs Incorrect at Level 1. N2 and P3 analyses was based on NoGo trials, since these represent response inhibition. The ERN included amplitudes related to incorrect NoGo trials. Time and Picture Type were included at Level 1 for all electrophysiological outcomes. Electrode (Fz, FC1, FC2, FCz, Cz for N2, FCz, Cz, C3, C4, and CPz for P3, and Fz, FCz, and Cz for the ERN) was used as crossed random factor (see Volpert-Esmond et al., 2017 for more details). Participants were defined at Level 2 with Group (sham tDCS vs active tDCS) as predictor variable for all outcome variables.

For every outcome variable, first an intercept-only model predicting every outcome variable from only the intercept was created (M0). With this model, it was assessed whether multilevel analysis was required. By significant variance

at Level 2, the other models were fitted. In the second model, random intercepts across participants were fitted to the data (M1). The third model included the Level 1 predictors as fixed effects (M2). This model was further extended by adding random slopes for Time (M3). Then, the Level 2 predictor Group was added to the model (M4). The final model (M5) included cross-level interactions between Level 1 variables and Group at Level 2. The fit of the models was compared using a significance test on the deviance statistics. Parameter estimates of the best fitted models are reported in Table 2. Finally, Spearman correlation analyses were performed between behavioural performances, and the N2, P3 and ERN.

## Results

### Breath CO measures and Craving

There was no difference between the sham and active tDCS group on breath concentrations of Carbon Monoxide before each Go-NoGo session. Subjective craving for cigarettes significantly increased over time from before the Go-NoGo task ($M$ = 30.05, $SD$ = 9.14) to after the Go-NoGo task ($M$ = 39.95, $SD$ = 9.16), $t(63)$ = -12.33, $p < .001$. The groups did not differ in their increase in craving on each session.

### Behavioural Data

The relationship between Time and Accuracy showed significant variance in intercepts across participants, $X^2(1) = 71.26$, $p < .001$. The model showed that there was a significant main effect of Inhibition for accuracy, $b$ = -.22, $p < .001$, indicating reduced accuracy for NoGo trials (75.9%) as compared to Go Trials (97.7%). No significant main and interaction effects were found for Time and Group.

For the outcome measure reaction time on Go trials, the model where Time was added as random effect showed the best fit. Significant variance in intercepts across participants was found for the relationship between Time and the reaction time for Go trials, $X^2(1) = 34965$, $p < .001$. Also, slopes for Time were significantly different across participants, $X^2(7) = 6766.60$, $p < .001$. There was a significant main effect of Time, with slower reaction times on Go trials during the second session (M=294.8 ms, $b$ = 13.52, $p$ = .005) and during the follow-up session (M=300.6 ms, $b$ = 20.65, $p < .001$) as compared to the first session (M=281.1 ms).

No significant main effects were found for Group and Picture Type. There was a trend towards a significant interaction effect for Time x Group, with a smaller difference in reaction times at follow-up as compared to baseline in the active tDCS group, $b$ = -19.22, $p$ = .072 (Figure 3).

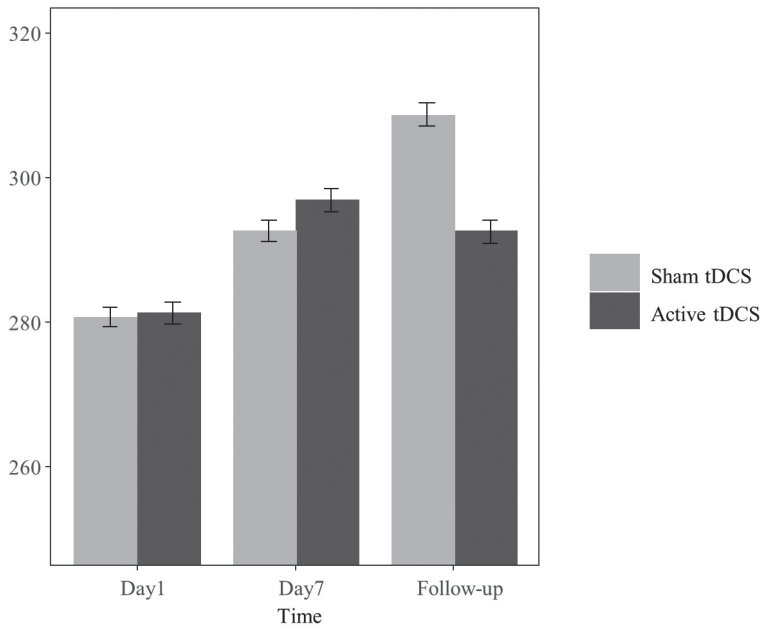


**Figure 3.** Mean reaction Time on Go trials for Sham and Active tDCS over time.

There was a significant amount of variance for intercepts across participants in the relationship between Time and post reaction times, $X^2$ (1) = 645.06, $p$ < .001. For this model, slopes for Time were significantly different across participants, $X^2$ (8) = 264.26, $p$ < .001. There was no difference between reaction times post correct responses and reaction times post erroneous responses (i.e. post-error slowing). For post reaction times there was a significant main effect of Time (figure 4), with significantly slower reaction times after responses at follow-up as compared to the first session, $b$ = 40.21, $p$ < .001. A small but significant interaction effect of Time x Correct vs Incorrect x Group was found, with faster reaction times after correct responses for the active tDCS group at follow-up ($M$ = 272.5 ms) as compared to the Sham tDCS group ($M$ = 315.4 ms), $b$ = 22.44, $p$ = .020 (Figure 4).

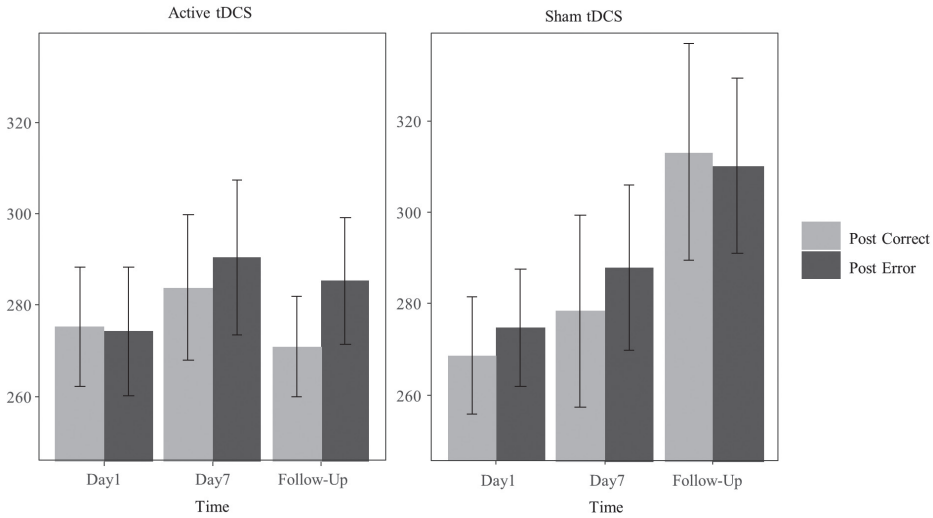


**Figure 4.** Mean reaction time for trials following erroneous responses for the sham and active tDCS group over time.

## Event related potentials

All ERP amplitude values are presented in Table 1.

**Table 1.** Descriptive data for electrophysiological measures.

| | Day1 | | Day7 | | Follow-up | |
|---|---|---|---|---|---|---|
| | Active tDCS | Sham tDCS | Active tDCS | Sham tDCS | Active tDCS | Sham tDCS |
| **N2** | n=32 | n=34 | n=32 | n=35 | n=28 | n=27 |
| Fz | -8.81 (3.69) | -7.75( 4.03) | -9.13 (3.64) | -8.31 (4.32) | -8.38 (3.68) | -8.99 (3.68) |
| FCz | -9.14 (3.86) | -8.32 (4.00) | -9.38 (3.89) | -9.11 (4.52) | -8.75 (3.87) | -9.38 (4.17) |
| Cz | -7.71 (3.78) | -7.32 (4.06) | -7.87 (3.62) | -7.84 (4.45) | -7.40 (4.05) | -8.18 (4.00) |
| **P3** | n=32 | n=34 | n=32 | n=35 | n=28 | n=27 |
| FCz | 2.39 (4.82) | 4.15 (5.06) | 1.77 (4.87) | 2.62 (5.03) | 1.61 (4.84) | 2.63 (4.56) |
| Cz | 3.61 (5.08) | 4.97 (5.28) | 2.83 (5.14) | 3.66 (4.99) | 2.36 (5.08) | 3.67 (5.08) |
| CPz | 3.84 (4.91) | 4.81 (5.10) | 3.07 (5.00) | 3.77 (4.85) | 2.47 (4.89) | 3.58 (4.66) |
| **ERN** | n=25 | n=25 | n=25 | n=24 | n=21 | n=19 |
| Fz | -6.40 (4.64) | -6.28 (4.16) | -7.47 (4.73) | -7.28 (3.89) | -5.39 (4.68) | -5.52 (4.60) |
| FCz | -7.53 (5.10) | -8.13 (5.24) | -9.06 (6.06) | -8.58 (5.98) | -6.64 (5.57) | -6.16 (5.48) |
| Cz | -5.83 (4.49) | -7.45 (6.55) | -7.34 (6.28) | -6.66 (5.06) | -5.14 (5.49) | -5.05 (5.78) |

*Note.* Mean (SD) for N2, P3, and ERN amplitudes (μV) at each relevant electrode side: Fz (Frontal); FCz (fronto-central); Cz (central); CPz (centro-parietal).

**N2 Amplitudes**

The intercept only model for the relationship between Time and N2 amplitudes showed significant variance in intercepts across participants, $X^2$ (1) = 1905.53, $p < .001$. Adding Time as random slopes significantly improved the fit of the model, $X^2$ (5) = 757.33, $p < .001$, suggesting that the effect of time on the N2 differed across participants.

In the best fitted model, N2 amplitudes were slightly larger for Neutral pictures as compared to smoking pictures, $b$ = -0.36, $p$ =.041. There was also a main effect of Time, with larger N2 amplitudes at Day 7, $b$ = -0.94, $p$ = .015, and at follow-up, $b$ = -1.33, $p$ = .023, as compared to baseline (table 1). No interaction effect was found for Time and Group.



**P3 Amplitudes**

There was significant variance in intercepts across participants for P3 amplitudes over Time, $X^2$ (1) = 1897.32, $p < .001$. Slopes for Time were also significantly different across participants for P3 amplitudes, $X^2$ (5) = 1116.6, $p < .001$. The best fitted model showed that P3 amplitudes measured over a cluster of central electrodes were larger for smoking related pictures as compared to neutral pictures, as shown by a robust main effect for Picture Type, $b$ = -0.96, $p < .001$. There was also a main effect of Time, showing smaller P3 amplitudes at Day 7, $b$ = -1.31, $p$ = .014, and at follow-up, $b$ = -1.67, $p$ = .027, as compared to Day 1 (Table 1). In addition, a significant interaction between Time at follow-up, Picture Type and Group was observed, $b$ = 1.11, $p$ = .004, indicating a larger decrease in NoGo P3 amplitudes for smoking related pictures for the active tDCS group (Figure 5) as compared to sham tDCS (Figure 6).

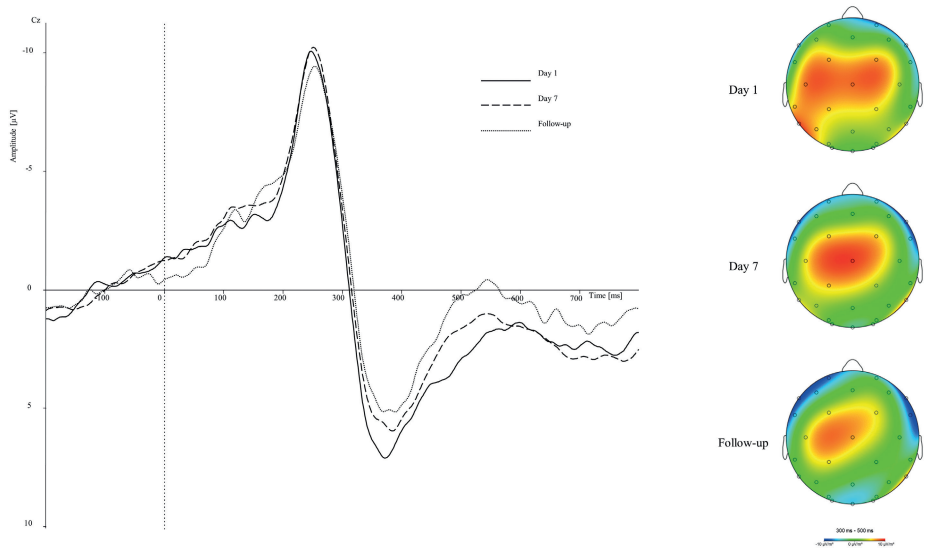


**Figure 5.** P3 activity during smoking related NoGo trials for Active tDCS.

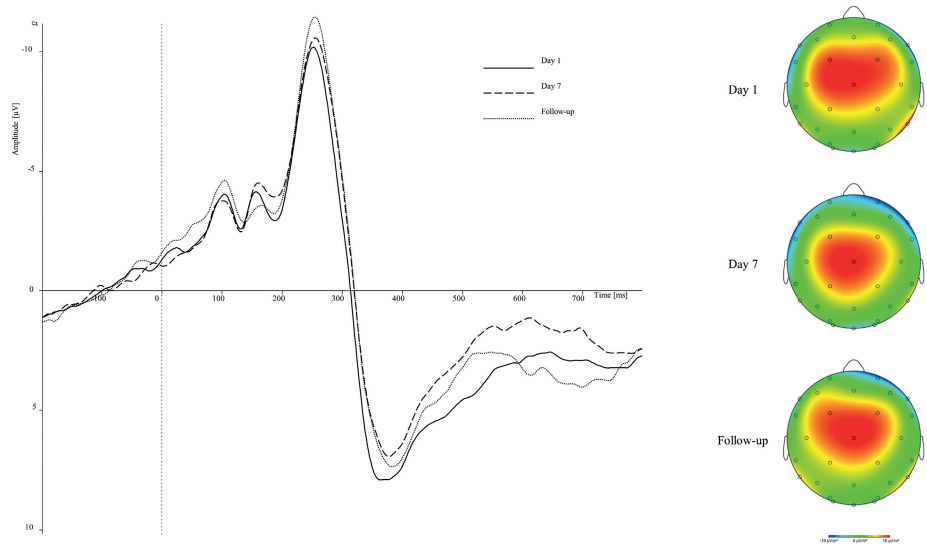


**Figure 6.** P3 activity during smoking related NoGo trials for Sham tDCS.

**ERN Amplitudes**

The relationship between Time and the ERN showed significant variance in intercepts across participants, $X^2(1) = 241.18$, $p < .001$. Also, the slopes for Time varied across participants $X^2(7) = 307.36$ , $p < .001$. There was a trend for Picture Type, with smaller ERN amplitudes for smoking related pictures as compared to neutral pictures, $b = -1.01$, $p = .065$. There were no significant main effects or interaction effects of Time and Group for the ERN.

**Table 2.** Multilevel models for the outcome variables of the Go-NoGo task.

| *Outcome* | *Model* | *b* | *SE b* | *95% CI* |
|---|---|---|---|---|
| **N2** | | | | |
| | Time Day7 | -0.94 | 0.38 | -1.68 to -0.20 |
| | Time Follow-up | -1.33 | 0.57 | -2.45 to -0.21 |
| | Picture Type | -0.36 | 0.18 | -0.71 to -0.01 |
| | Group | -0.45 | 0.88 | -2.17 to 1.27 |
| | Time Day7 * Picture Type * Group | 0,00 | 0.36 | -0.71 to 0.71 |
| | Time Follow-up * Picture Type * Group | -0.21 | 0.37 | -0.94 to 0.52 |
| **P3** | | | | |
| | Time Day7 | -1.31 | 0.52 | -2.33 to -0.29 |
| | Time Follow-up | -1.67 | 0.74 | -3.12 to -0.22 |
| | Picture Type | -0.96 | 0.18 | -1.31 to -0.61 |
| | Group | -1.07 | 1.08 | -3.19 to 1.05 |
| | Time Day7 * Picture Type * Group | 0.37 | 0.37 | -0.36 to 1.10 |
| | Time Follow-up * Picture Type * Group | 1.11 | 0.39 | 0.35 to 1.87 |
| **ERN** | | | | |
| | Time Day7 | -0.49 | 1.15 | -2.74 to 1.76 |
| | Time Follow-up | -0.29 | 1.60 | -3.43 to 2.85 |
| | Picture Type | -1.01 | 0.55 | -2.09 to 0.07 |
| | Group | -0.15 | 1.38 | -2.85 to 2.55 |
| | Time Day7 * Picture Type * Group | 1.30 | 1.11 | -0.88 to 3.48 |
| | Time Follow-up * Picture Type * Group | 0.34 | 1.18 | -1.97 to 2.65 |
| **Accuracy** | | | | |
| | Time Day7 | 0.00 | 0.01 | -0.02 to 0.02 |
| | Time Follow-up | 0.00 | 0.01 | -0.02 to 0.02 |
| | Inhibition | -0.22 | 0.01 | -0.24 to -0.20 |
| | Group | -0.00 | 0.02 | -0.04 to 0.04 |
| **RT Go Trials** | | | | |
| | Time Day7 | 13.52 | 4.60 | 4.50 to 22.54 |
| | Time Follow-up | 20.65 | 5.30 | 10.26 to 31.04 |
| | Picture Type | -0.84 | 0.53 | -1.88 to 0.20 |
| | Group | -10.39 | 12.21 | 34.32 to 13.54 |
| **RT Post Response** | | | | |
| | Time Day7 | 10.30 | 8.46 | -6.28 to 26.88 |
| | Time Follow-up | 40.21 | 8.57 | 23.41 to 57.01 |
| | Correct vs Incorrect | 6.07 | 4.60 | -2.95 to 15.09 |
| | Group | 10.05 | 11.69 | -12.86 to 32.96 |
| | Time Day7 * Correct vs Incorrect * Group | 7.62 | 9.15 | -10.31 to 25.55 |
| | Time Follow-up * Correct vs Incorrect * Group | 22.44 | 9.59 | 3.64 to 41.24 |

*Note*. RT indicates reaction times.

## Correlations

Correlations between neurophysiological and behavioural outcomes of the Go-NoGo task are displayed in Table 3. The results show that larger N2 amplitudes are correlated with larger P3 amplitudes and larger ERN amplitudes. There was a small correlation between N2 amplitudes and the percentage of correct NoGo trials, $r = .242$, $p = .046$. The results also show a negative relationship between P3 amplitudes and reaction times on Go trials and reaction times after incorrect NoGo trials. Reaction times for Go trials were also correlated with ERN amplitudes. Also important to note is that accuracy on NoGo trials correlated with reaction times, indicating that slower reaction times are associated with more accuracy on the Go-NoGo task. Finally, there was a trend for a correlation between the ERN and post error slowing, $r = .259$, $p = .054$. Exploratory analyses showed that the ERN correlated with post error slowing at day 1, $r = .266$, $p = .050$, and day 7, $r = .350$, $p = .009$, but not with post error slowing at follow-up, $r = .086$, $p = .561$. The outcome measures on the Go-NoGo task were not correlated with nicotine dependence as measured by the FTND at baseline and follow-up.



**Table 3.** *Correlations between neurophysiological and behavioural outcomes on the task.*

| Outcome | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1. N2 Amplitude | - | | | | | | |
| 2. P3 Amplitude | .333** | - | | | | | |
| 3. ERN Amplitude | .426** | .131 | - | | | | |
| 4. % Correct Go Trials | .183 | .197 | -.097 | - | | | |
| 5. % Correct NoGo Trials | .242* | -.107 | .098 | .498** | - | | |
| 6. RT Correct Trials | .212 | -.377** | .353** | -.079 | .579** | - | |
| 7. RT Post Incorrect Trials | .126 | -.301* | .259 | -.025 | .568** | .867** | - |

Note. RT indicates Reaction Times. * indicates $p < .05$. ** indicates $p < .01$.

## tDCS side effects

Side effects were recorded after each tDCS session. Participants were asked to indicate the amount of itching, burning, and tingling sensations on a 5-point Likert scale, ranging from none (1) to extreme (5) sensations. In addition, we asked participants about difficulties with concentrating and whether they experienced acute mood changes during tDCS. Questions about sleepiness, neckpain and pain in the head were also rated on a 5-point Likert scale. Results showed that

overall, the active tDCS group experienced significantly more itching sensations ($F$=11.379, $p$ = .001) as compared to the sham group. No other differences between the groups were observed regarding the side-effects.

## Discussion

The present study assessed the effect of tDCS on cognitive control, a fundamental mechanism responsible for the maintenance of tobacco addiction. The aim of this study was to investigate the effects of tDCS on inhibition- and error related brain and performance measures, including the duration of these effects. To the best of our knowledge, the current study is the first to explore the effect of tDCS on neurophysiological outcomes in tobacco addiction.

### Effects of tDCS

Active stimulation did not seem to affect neurophysiological outcomes of early inhibitory control processes and error processing. The results for the N2 are in line with previous studies that did not find a modulation of neurophysiological measures of inhibitory control after stimulation of the right DLPFC (Lapenta et al., 2014; Dubreuil-Vall et al., 2019). The results for error processing were also compatible with previous findings in a general population that found no effect of tDCS on the ERN (Dubreuil-Vall et al., 2019). It was expected that ERN amplitudes would be affected by tDCS, since it has been shown that the brain area related to the ERN (e.g. dACC) was indirectly modulated by tDCS over the rDLPFC (Weber et al., 2014). It should be noted that sample sizes for the ERN are often smaller, since participants cannot be included if they make too few errors. Therefore, the power can be low which may lead to incorrect conclusions. It could also well be that more tDCS sessions over the DLPFC are needed to effectively modulate the dACC and have an effect on error processing.

Interestingly, we observed changes in inhibitory control over motor responses at follow-up, but not right after the tDCS sessions. We found a larger decrease in P3 amplitudes for smoking related NoGo trials as compared to neutral pictures for participants that received active tDCS. In addition, active stimulation was associated with faster reaction times at follow-up as compared to sham tDCS. The delayed effects are somewhat difficult to explain in terms of neurophysiology,

but the tDCS protocol used in the current study might give an explanation. That is, Monte-Silva and colleagues (2013) suggested that two tDCS sessions with a duration of 13 minutes and a 20 minute break in between may be associated with delayed after effects.

Smaller NoGo P3 amplitudes at follow-up may also be the result of a tDCS effect on learning. The P3 is prone to a test-retest effect, with smaller P3 amplitudes at retest after a short period (Kompatsiari, Candrian, & Mueller, 2016), as was also found in the current study for both groups. Smaller NoGo P3 amplitudes were furthermore correlated with faster reaction times on Go trials, but not with accuracy. The delayed effect of tDCS on NoGo P3 amplitudes may therefore indicate a long-term learning effect on inhibition over motor responses, rather than a real improvement in inhibition. It has been shown that electrical brain stimulation could modulate long-term synaptic plasticity in the context of (motor) learning more than performance (Stagg & Nitsche, 2011; Simonsmeier, Grabner, Hein, Krenz, & Schneider, 2018). In the current study, learning would indicate smaller NoGo P3 amplitudes as found at retest, and therefore tDCS may have resulted in enhanced learning effects, hence the larger decrease of P3 amplitudes at follow-up. Since accuracy for NoGo trials at follow-up was not affected by tDCS, it can be hypothesized that less brain activity was required to achieve the same level of motor inhibitory control.



The relatively smaller test-retest effect we found for N2 amplitudes did, however, not lead to N2 differences between groups at follow-up. Since the N2 is correlated with accuracy on NoGo trials, this amplitude may be more related to inhibitory control performance instead of motor learning. This may explain why there was no effect of tDCS for the N2 at follow-up.

Importantly, NoGo P3 amplitudes only decreased for smoking related pictures after tDCS. This result may indicate that the tDCS effect for motor learning was specific for cues that draw motivational attention. P3 amplitudes have been mainly related to motor inhibition, but they are also known to be associated with motivational attention towards smoking cues (Littel, Euser, Munafo, & Franken, 2012; Piasecki, Fleming, Trela, & Barthlow, 2017; Deweese, Codispoti, Robinson, Cinciripini, & Versace, 2018). This hypothesis is also supported by our finding of larger NoGo P3 amplitudes for smoking related cues.

Differences between smoking related pictures and neutral pictures were also found for the N2, ERN, and for accuracy on NoGo trials. Our results suggest smaller N2 and ERN amplitudes for smoking related pictures. Smaller N2 amplitudes for smoking cues may indicate a preparedness for smoking (Oliver, Jentink, Drobes, & Evans, 2016), and diminished error processing in smokers was particularly found when exposed to smoking cues (Luijten, van Meel, & Franken, 2011). Future studies should therefore specifically focus on enhancing cognitive control for smoking related cues.

## Limitations

It should be noted that this study has been primarily concerned with light smokers who continued smoking throughout the study. Therefore, the results cannot be generalized to a population of heavy or abstinent smokers. Secondly, the active tDCS group experienced more itching sensations as compared to the sham tDCS group. This finding is in line with observations from previous studies where participants reported tingling and itching sensations after stimulation (e.g. Falcone et al., 2016; De Souza Brangioni et al., 2018). Despite of differences in comfortability between the two conditions, blinding has been found to be reliable (Russo, Wallace, Fitzgerald, & Cooper, 2013).

Finally, considering that the effect of tDCS was most prominent for motor responses, it is possible that anodal currents reached the premotor cortex more than the DLPFC. P3 amplitudes were however not significantly decreased directly after tDCS, but this is in line with the results from a study where tDCS was applied over the primary motor cortex (Conley, Fulham, Marquez, Parsons, & Karayanidis, 2016). The two electrode tDCS montage may have caused electrical fields to diffuse to non-targeted brain areas (Nitsche et al., 2007; Datta, Elwassif, Battaglia, & Bikson, 2008). However, the findings suggest that we also stimulated the rDLPFC, since P3 amplitudes were particularly reduced for smoking related pictures. This suggests that motor inhibition was particularly affected for cues that require motivational attention, and it was shown that no-go activity in the rDLPFC is associated with attentional resources (Criaud & Boulinguez, 2013). Future studies may consider using HD-tDCS as alternative to the original tDCS. This 4x1 montage with 1 anodal electrode surrounded by 4 cathodal electrodes results in better spatial precision by modulating the part of the brain directly

underneath the center electrode (Alam, Truong, Khadka, & Bikson, 2016). It's effectiveness on smoking behaviour has yet to be investigated.

## Conclusions

The findings of the current study suggest that there is not a direct effect of tDCS on early inhibitory control and error processing in smokers. The underlying mechanism of the effect of tDCS on smoking behaviour may be explained by neurophysiological changes of other cognitive processes, such as risky decision making (e.g. Fecteau et al., 2014). The results further indicate that tDCS might have a long-term modulatory effect on motor inhibitory learning processes, specifically for cues that draw attention. This is the first study to investigate the long-term effect of tDCS on physiological responses, therefore more research is needed in this field. Nevertheless, this finding implies the importance of taking into account learning processes for drug related cues in the treatment of addiction when tDCS is used as additional treatment.

# 4

# Neuromodulation Effects on Risky Decision Making and Feedback Processing During a Gambling Task in Tobacco Smokers: A tDCS-EEG Study

***This chapter is submitted as:***

*Verveer, I., van der Veen, F. M., & Franken, I. H. A. (submitted). Neuromodulation effects on risky decision making and feedback processing during a gambling task in tobacco smokers: A tDCS-EEG study*

## Abstract

Beneficial effects of transcranial Direct Current Stimulation (tDCS) on smoking behaviour may be associated with decreased risky decision making. However, mixed results of tDCS have been reported when different risk-taking tasks were used in addiction studies. Here, we therefore investigated feedback processing as underlying mechanism of tDCS effects on risk-taking in smokers, as feedback processing plays an important role in shaping future decisions by processing the outcomes of previous choices. First, we explored how smokers ($n$ = 71) differed from non-smokers ($n$ = 58) on a probabilistic two-choice gambling task (TCGT). Risk-taking was defined by the number of gained points and by the percentage of high-risk choices participants made on the TCGT. Feedback processing was assessed by event related potentials (i.e. the feedback related negativity (FRN) and feedback P3) after positive or negative feedback for wins and losses, respectively. Smokers performed the TCGT for a second time, one day after receiving six sessions of either active tDCS ($n$ = 35) or sham tDCS ($n$ = 35). The results indicated that **s**mokers more often chose high risk options than non-smokers. This may be associated with impaired early feedback processing as reflected by blunted FRN amplitudes in smokers. In addition, the feedback P3 for low rewards was larger in smokers. Moreover, active tDCS was associated with increased risk taking in smokers as compared to sham but we found no effect of tDCS on feedback processing. We suggest that risky decision making as measured by gambling tasks may increase after tDCS in smokers.

***Keywords:*** Tobacco addiction, Smoking, Risky Decision Making, Gambling, Feedback Processing, FRN, Feedback P3, tDCS

## Introduction

Transcranial Direct Current Stimulation (tDCS) is a promising non-invasive neuromodulation technique with regard to reducing smoking behaviour when modulating activity of the dorsolateral prefrontal cortex (DLPFC; Kang, Kim, & Kim, 2019). The DLPFC is the apex neural node in the prefrontal control hierarchy, and of crucial importance for successful inhibition of behavioural (smoking) or cognitive (craving) responses when faced with conflicting options (Badre & Nee, 2018; Song, Zilverstand, Gui, Li, & Zhou., 2019). In substance use disorders, the DLPFC has been implicated in impaired inhibitory control, showing hypoactivation when attempting to inhibit motor responses and during cognitive self-regulation (Luijten et al., 2014; Zilverstand, Huang, Alia-Klein, & Goldstein, 2018). The lack of inhibitory control in combination with a hyperactive reward system often leads to risky decision making in addiction by a preference for immediate rewards that cannot be inhibited, despite of well-known negative consequences. In support of this notion, individuals with an addiction perform worse during decision making tasks, as shown by a tendency to choose more risky options (Zilverstand et al., 2018). During loss anticipation specifically, it has consistently been demonstrated that individuals with addiction show hypoactivity in several networks, including the DLPFC (Zilverstand et al., 2018). Moreover, risky decision making has been associated with decisions to smoke and smoking relapse (Ert, Yechiam, & Arshavsky, 2013; González-Roz, Secades-Villa, Pericot-Valverde, Weidberg, & Alonso-Pérez, 2019).

Considering the role of the DLPFC in risky decision making, it has been suggested that beneficial tDCS effects on smoking behaviour are the result of improved decision making (Fecteau et al., 2014). This hypothesis has been supported by findings indicating that tDCS over the DLPFC reduced risky decision making during the Risk Task and the Balloon Analogue Risk Task (BART) in healthy participants (Fecteau et al., 2007 a,b). In addition, it has been reported that risky decision making was decreased in smokers after tDCS, as shown by more rejected offers during the ultimatum game when the reward is cigarettes (Fecteau et al., 2014). The tDCS protocol that was used in this study, with the anodal electrode over the right DLPFC and the cathodal electrode over the left DLPFC, seems to generally have a positive effect on decision making in

addiction (see Schluter, Daams, van Holst, & Goudriaan, 2018 for a systematic review). For example, risky decision making decreased on the BART task and the 'Hot' version of the Columbia Card Task after tDCS (Pripfl, Neumann, Köhler, & Lamm, 2013; Gorini, Lucchiari, Russell-Edu, & Pravettoni, 2014). However, some addiction studies were unable to find significant beneficial effects of tDCS over the DLPFC on risk-taking (e.g. Boggio et al., 2010; Fecteau et al., 2014). Inconsistent findings were reported when addiction studies had used the Risk Task to measure changes in risk-taking related to tDCS effects. For instance, Fecteau and colleagues (2014) who found reduced risky decision making during the ultimatum game, reported no significant changes in risk-taking using the Risk Task after tDCS in smokers. Also, more risk-taking behaviour during the Risk Task was reported in marijuana users after active tDCS (Boggio et al., 2010).

To gain further insights about tDCS effects on risky decision making, we investigated the working mechanism behind these effects in smokers by investigating neurophysiological measures of feedback processing. Feedback processing plays an important role in shaping future decisions by processing the outcomes of previous choices (Verdejo-Garcia, Chong, Stout, Yücel, & London, 2018). Prior studies have reported altered neurophysiological measures of feedback processing during decision making tasks in addiction. We therefore hypothesized that changes in decision making after tDCS would be associated with altered feedback processing. Feedback processing is reflected by Event Related Potentials (ERPs) that are elicited when feedback (win or loss) for decisions is presented. Two ERPs related to feedback processing are the feedback related negativity (FRN; Miltner, Braun, & Coles, 1997) and the feedback P3 (Yeung & Sanfey, 2004).

The FRN is a negative wave generated in the ACC that peaks within 200-300 ms after feedback onset (Gehring & Willoughby, 2002; Luft, 2014). The FRN is larger for negative feedback as compared to positive feedback (Chandrakumar, Feuerriegel, Bode, Grech, & Keage, 2018), and is sensitive to the expectancy of an outcome, with larger FRN amplitudes for unexpected outcomes (Hauser et al., 2014). The FRN is therefore assumed to reflect an early, fast evaluation of whether outcomes are better or worse than expected. How much better or worse an outcome is than expected is more reflected by the feedback P3 (e.g. Morie, Landi, Potenza, Mayes, & Crowley, 2018). The feedback P3 is a later positive component that peaks between 300 to 500 ms after feedback onset. Feedback

P3 amplitudes are larger for unexpected outcomes (Hajcak, Moser, Holroyd, & Simons, 2007) and for choices with larger magnitude outcomes (Polezzi, Sartori, Rumiati, Vidotto, & Daum, 2010; Schuermann et al., 2012; Endrass, Schuermann, Roepke, Kessler-Scheil, & Kathmann, 2016). Although we are aware that difference waves (reward vs. non-rewards/losses) have also been investigated in risky decision-making, such as the reward positivity (RewP; Proudfit, 2015), we will use averaged FRN and P3 components to be able to examine feedback processing for rewards and losses separately (Luft, 2014), and to compare our results with previous studies in this research domain.

Specific hypotheses about how tDCS would affect feedback processing may be formulated based on how feedback processing is altered in addiction. It has been reported that the FRN was smaller after negative feedback in alcohol use disorder (Kamarajan et al., 2010; Sehrig, Weiss, Miller, & Rockstroh, 2019), and in treatment-naive problem drinkers (Fein & Chang, 2008). Decreased FRN amplitudes were also found in patients with cocaine use disorder for reward outcomes and for outcomes with a large magnitude as compared to healthy controls (Morie, De Sanctis, Garavan, & Foxe, 2016). For unexpected rewards, however, the FRN was larger for smokers as compared to non-smokers (Potts, Bloom, Evans, & Drobes, 2014).



Findings have been more inconsistent regarding the feedback P3 in addiction studies. Similar to the FRN, the feedback P3 was blunted for non-drug related rewards in individuals with cocaine use disorder (Goldstein et al., 2008; Morie et al., 2016). Reduced feedback P3 amplitudes were also reported in individuals with alcohol use disorder (Kamarajan et al., 2010), and in adolescents with a parental history of substance use disorder (SUD; Euser et al., 2013). However, in a more recent study feedback P3 amplitudes did not differ between individuals with alcohol use disorder and healthy controls (Sehrig et al., 2019), and this component was even increased in methamphetamine users after reward outcomes (Wei et al., 2018).

To sum up, mixed results have been reported on feedback processing of decisions in individuals with SUD. Overall, it has been found that feedback processing is altered in addiction, however, the direction in which this process is altered remains unclear. A limitation of previous studies is that decision making tasks were not designed to independently control for expectancy, magnitude, and valence of decision outcomes. As mentioned above, these aspects can affect the FRN and feedback P3. To address these issues, we used the two-choice gambling

task (TCGT: Schuermann et al., 2012; Endrass et al., 2016) to investigate tDCS effects on feedback processing and risk-taking in smokers. In this task, participants are instructed to choose between a high-risk option yielding high rewards or losses, and a low risk option with less points to win or lose. The probability of earning a reward is indicated in each option before any decision is made, hereby controlling for expectancy. Since this gambling task has not been used in addiction studies before, we first investigated TCGT differences between smokers and non-smokers in feedback processing and risky decision making. It was expected that smokers take more risks than non-smokers as reflected by a higher percentage of high-risk choices on the TCGT. In addition, smaller FRN were expected for smokers as compared to non-smokers, as blunted FRN amplitudes have generally been related to increased risk-taking (e.g. Schuermann et al., 2011). For the feedback P3, we suggested that differences between smokers and non-smokers would depend on the magnitude and valence of the decision outcome. As the TCGT can be considered a gambling task like the Risk task, we hypothesized that tDCS might increase the percentage of risky decisions in smokers. It was expected that this would be associated with a decrease in feedback related ERP amplitudes.

## Methods

### Participants

The sample consisted of 73 smokers (36 females, age: $M = 22.3$, $SD = 4.7$) and 58 non-smokers (36 females, age: $M = 21.0$, $SD = 2.6$). Smokers had to smoke a minimum of 10 cigarettes a day and had a mean score of 3.4 (SD = 1.9) on the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Koxlowski, Frecker, & Fagerstrom, 1991). Exclusion criteria for both groups were: 1) Current substance use disorder of a substance other than nicotine or caffeine; 2) History of neurological or psychiatric disorders. Additional exclusion criteria for smokers for the brain stimulation they received were: 1) Any contraindication for electrical brain stimulation procedures (i.e. electronic implants or metal implants); 2) Pregnancy or breast-feeding; 3) Intentions to actively try to quit smoking in the next three months.

Participants were recruited via advertisement at Erasmus University Rotterdam and received either course credit or a financial compensation of 20 euro. All participants completed the first EEG session. Smokers were only

included for the final analyses if they had also completed the task after the tDCS intervention week. Two smokers dropped out during the tDCS intervention week because of personal circumstances (n=1) and schedule issues (n=1), and one smoker completed the task only once because of software problems. In the end, 70 smokers were included for final analyses, of which 35 received active tDCS and 35 received sham treatment. Non-smokers did not receive neurostimulation.

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. All participants gave written informed consent after the purpose and procedures of the study were fully explained. The current report is part of the pre-registered study with identifier NCT03027687 at ClinicalTrials.gov.



## Procedure

Participants were recruited from the population of Rotterdam via advertisement and were reimbursed with course credits after participating. At the start of the experiment, a thorough verbal explanation of the research procedure and the purpose of the investigation was provided. Participants were then given the opportunity to ask any study related questions. Following provision of informed consent, participants were seated in a comfortable chair in a light and sound-attenuated room. After the EEG electrodes were applied, both smokers and non-smokers engaged in the Two Choice Gambling Task (TCGT) while EEG was recorded. This was the only part of the study that non-smokers participated in.

Smokers continued with the rest of the study. Following the TCGT, EEG electrodes were removed and tDCS was applied, with the battery strategically placed behind the chair. The intervention was double-blind; therefore, smokers were randomly allocated to either sham or active tDCS. During tDCS, participants were asked to stay alert and awake while they watched a neutral movie. Both groups received a total of six tDCS on three different days in one week, with at least one day in between tDCS sessions. One day after the intervention week, smokers performed the TCGT for the second time while EEG was recorded (Flowchart; see Fig 1). Smokers also performed a Go-NoGo task at baseline and after the intervention week and filled out subjective craving and number of smoked cigarettes via ecological momentary assessments (EMA). The results of these data were discussed in Chapter 3 of this dissertation.

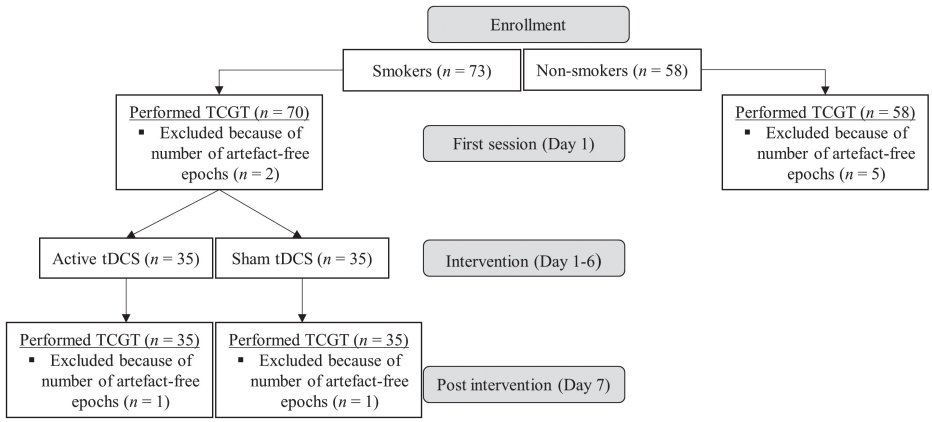


**Fig 1 . Flow chart of experimental design**

## TCGT Task

An adjusted version of the computerized probabilistic two-choice gambling task was used for the current study (Scheurmann et al., 2012; Endrass et al., 2016). Participants were instructed to gain as many points as possible by choosing between two options that were presented on a computer screen. The risk of the options was determined by the number of points participants could win or lose (magnitude) and the chance of losing (chance) as displayed in each stimulus (Fig 2). One option always had a larger magnitude (high risk) than the other option (low risk). Additionally, the size of the green bar within each option indicated the chance of winning, whereas the size of the red bar indicated the chance of losing. Hereby, an additional risk factor was added with more risk if there was a higher chance of losing points. The chance of winning (75%, 65%, or 55%) was always larger than the chance of losing (25%, 35%, or 45%) within each option. The variability in chance of winning and losing was different from the original TCGT, where the chance of winning was always 75% and the chance of losing always 25%.

Choices were made by pressing the corresponding response button. Directly after pressing the button, participants were shown the outcome of their choice for 750 ms. When participants won, a green happy face appeared on the screen, together with the amount of points they had gained (positive feedback). For losses, participants were shown a red frowny face with the amount of points they had lost (negative feedback). In addition to the feedback stimuli, the total

account balance across trials was presented. The next trial was presented after an intertrial interval of 500 ms (Fig 2).

After participants had read the standardized instructions, they performed ten practice trials. The actual experiment consisted of 168 trials that were presented 4 times over 3 blocks, and lasted for about 40 minutes. One third of the trials (224) contained a high magnitude option with a higher chance of losing than the low risk option (trial A; Fig 2). Another 224 trials contained equal chances of losing for the high and low magnitude option (trial B; Fig 2). And finally, one third of the trials contained a low magnitude option with a higher chance of losing than the high magnitude option (trial C; Fig 2). High risk choices were determined by the percentage of times the left option was chosen in Trial A and B (Fig 2). Trial C can be considered as control trial, since both options represent low risk options. Positions of options on the computer screen changed across trials in pseudo-random order.



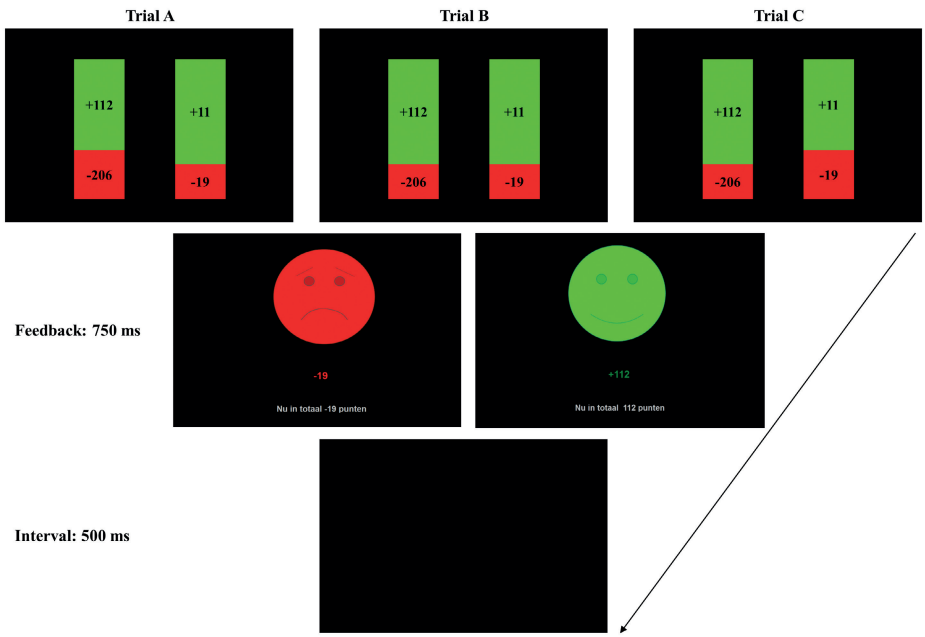


**Fig 2 .** Example of the probabilistic two choice gambling task. Trial A represents a high magnitude option (left) with a higher chance of losing than the low magnitude option (right). Trial B depicts two options with equal chances of losing for the high magnitude (left) and low magnitude option (right). Trial C presents a low magnitude option (right) with a higher chance of losing than the high magnitude option (left).

## EEG acquisition

Brain activity was recorded with EEG using a Biosemi ActiveTwo System amplifier (10-20 International System). EEG recordings were done at 32 scalp sites and two additional electrodes at FCz and CPz with Ag/AgCl active electrodes mounted in an elastic cap. In addition, one electrode was placed on each mastoid to serve as reference electrode. To be able to correct for ocular artefact, ocular movements were recorded by four additional electrodes. Vertical ocular movements were measured by electrodes placed above and below the left eye (VEOG). To measure horizontal ocular movement, one electrode was placed at the outer canthi of each eye (HEOG).

All signals were digitized with a sampling rate of 512 Hz and 24-bit analog-to-digital conversion. EEG and EOG data were filtered with a band filter of .1-30 Hz (24 dB/octave slope). Data were segmented in epochs from 200 ms before to 800 ms after feedback onset. After ocular correction was performed (Gratton, Coles, & Donchin, 1983), epochs with voltages smaller than -100 μV and larger than 100 μV were rejected as artefacts and excluded from further processing. The mean 200 ms pre-response or pre-stimulus period served as baseline. After baseline correction, the average waveforms were computed for high and low risk rewards, and high and low risk losses.

The FRN was defined as the average amplitude within a 200–300 ms window following feedback onset based on a similar approach and visual inspection of the grand-average waveforms. The feedback P3 was defined as the average positive going amplitude within 300–500 ms following feedback onset. For both components, statistical analyses were performed on frontocentral electrodes (Fz, FCz, and Cz; Euser, van Meel, Snelleman, & Franken, 2011).

## Transcranial Direct Current Stimulation

Participants in the active tDCS group received tDCS by an electric DC-plus stimulator (NeuroConn, Ilmenau, Germany) via a pair of carbonated silicone electrodes with a thick layer of high-conductive EEG gel underneath them (35 $cm^2$). During each session, tDCS was applied two times for 13 minutes with a 20-minute break in between, and a current intensity of 2.0 mA with a 30 sec ramp at the beginning and end of the session (Klauss et al., 2014). The anodal electrode was placed over the F4 area (10-20 international system), and the cathodal electrode was placed over the F3. Effects on risk-taking and smoking

behaviour were found with this right anodal/left cathodal positioning over the DLPFC (e.g. Fecteau et al., 2014).

The control group received sham tDCS by the DC-plus stimulator. For sham, the electrodes were positioned at the same locations as active tDCS, but in this case the stimulator was gradually turned off after 30 s. Since the itching sensation of tDCS is often only experienced initially during stimulation, subjects remained blinded of the stimulation condition they received (e.g. Gandiga, Hummel, & Cohen, 2006; Woods et al., 2016). The experimenter was also blinded from the tDCS condition. That is, the codes that can automatically activate sham or active tDCS, were randomly assigned to participant numbers by an independent researcher.

## Data analyses



### Smokers vs. non-smokers

All analyses were performed in IBM SPSS 24.0. To assess risk-taking, the percentages of high risk choices (left option on Trial A and B; Fig 2) were determined. Trial C (Fig 2.) can be considered as control trial, as both options are low risk choices. A repeated measures ANOVA was performed to analyse whether the percentage of high risk choices varied as a function of group and trial. In addition, smokers were compared to non-smokers on the average amount of gained points on the TCGT using a repeated measures ANOVA with Trial as within subject factor.

To statistically analyse the ERP data, repeated measurement ANOVAs were used. Separate analyses for the FRN and feedback P3 were conducted with the between-subject factor Group (smokers vs. non-smokers) and within subject factors Electrode (Fz, FCz, and Cz), Feedback Valence (reward vs. loss), and Feedback Magnitude (low-risk vs high-risk).

### Active vs. sham tDCS

Repeated measures ANOVAs were performed to explore the effect of tDCS on risky decision making and feedback processing in smokers. Behavioural outcome measures of risky decision making were again the percentage of risky choices (left option on Trial A and B; Fig 2) and the average number of gained points per trial. The between subject factor was Group (active tDCS vs. sham tDCS) and the

within subject factors were Time (pre vs. post intervention) and Trial. The ERP analyses for the effect of tDCS on FRN and feedback P3 amplitudes included the between-subject factor for tDCS Group (active tDCS vs. sham tDCS), and the within subject factors Time (pre- vs. post-intervention) Electrode (Fz, FCz, and Cz), Feedback Valence (reward vs. loss), and Feedback Magnitude (low points vs. high points).

## Results

### Behavioural results

#### Smokers vs. non-smokers

There was trend towards a significant difference between smokers and non-smokers for percentage of high-risk choices on Trials A and B ($F(1,126) = 3.37$, $p = .069$, $\eta^2_p = .03$); Table 1). Smokers choose the high-risk option on 59% of all trials, and non-smokers on 52% of all trials. In addition, smokers gained significantly more points per trial than non-smokers, as indicated in Table 1 by a significant main effect of Group for ($F(1,126) = 11.99$, $p = .001$, $\eta^2_p = .09$). There were no significant interaction effects between Group and Trial on the percentage of high-risk choices and the average number of gained points.

**Table 1 .** Means for Behavioural results on TCGT before the tDCS intervention for smokers and for non-smokers

| | Smokers: | Non-smokers: |
|---|---|---|
| Win per trial (SE) | 57.6 (1.52) | 49.8 (1.67) |
| % High risk trial A (SD) | 39.7 (25.8) | 34.9 (21.2) |
| % High risk trial B (SD) | 77.6 (16.4) | 70.0 (21.4) |

*Note*: Percentages are calculated based on the number of times the left option was chosen as compared to the right option on the same trial (A, B or C).

#### Active vs. sham tDCS

There was a significant interaction effect for Group (active vs. sham tDCS) x Time (pre vs. post intervention) on high-risk choices ($F(1, 68) = 6.67$, $p = .012$, $\eta^2_p = .09$). The active tDCS group showed a higher percentage of high risk choices after the tDCS intervention as compared to before, while the percentage of high

risk choices for smokers in the sham group did not change from pre- to post intervention (Table 2). The type of Trial (A or B) did not significantly interact with this effect.

There was also a significant interaction effect for Group with Time on the average number of gained points per trial ($F(1, 68) = 10.12$, $p = .002$ , $\eta^2_p = .13$). The active tDCS group gained more points per trial post intervention as compared to before the intervention, as indicated by the amount of average gained points per trial (Table 2).

**Table 2 .** Means for behavioural results on TCGT before and after the tDCS intervention (Active or Sham) for smokers.

| | Pre intervention | | Post-intervention | |
|---|---|---|---|---|
| | Active | Sham | Active | Sham |
| Win per trial (SE) | 53.9 (2.12) | 61.3 (2.12) | 58.9 (2.12) | 54.5(2.12) |
| % High Risk trial A (SD) | 33.0 (24.3) | 46.3 (25.8) | 41.6 (28.9) | 41.8 (25.9) |
| % High Risk trial B (SD) | 75.6 (17.4) | 79.6 (15.4) | 81.0 (13.5) | 79.6 (16.5) |

*Note*: Percentages are calculated based on the number of times the left option was chosen as compared to the right option on the same trial (A, B or C).



## ERP Results

ERP amplitude values are presented in Table 3 and Table 4 for the FRN and feedback P3 as recorded during the TCGT pre- and post-intervention respectively.

**Table 3** Descriptive data for electrophysiological responses during TCGT at baseline

| | Non-Smokers | | Smokers Active tDCS | | Smokers Sham tDCS | |
|---|---|---|---|---|---|---|
| | FRN | P3 | FRN | P3 | FRN | P3 |
| Low Gain | 2.48 (3.64) | 4.84 (4.31) | 4.87 (5.84) | 7.28 (7.45) | 5.14 (5.64) | 6.16 (5.13) |
| High Gain | 4.12 (4.06) | 8.29 (4.83) | 5.18 (6.30) | 9.67 (8.46) | 5.98 (5.63) | 8.87 (5.51) |
| Low Loss | 1.58 (5.19) | 8.83 (5.24) | 3.90 (6.67) | 9.70 (9.70) | 4.90 (5.98) | 9.70 (6.06) |
| High Loss | 3.10 (4.52) | 11.49 (5.82) | 5.03 (6.95) | 12.30 (8.55) | 5.29 (5.08) | 12.49 (5.79) |

Note. Mean (SD) for FRN and Feedback P3 amplitudes (μV) at electrode side FCz

**Table 4 .** Descriptive data for electrophysiological responses during TCGT post intervention.

| | Smokers Active tDCS | | Smokers Sham tDCS | |
|---|---|---|---|---|
| | FRN | P3 | FRN | P3 |
| Low Gain | 2.54 (5.05) | 3.54 (5.07) | 2.93 (6.25) | 4.66 (6.06) |
| High Gain | 1.63 (3.12) | 4.54 (4.43) | 4.49 (7.43) | 7.39 (7.99) |
| Low Loss | 0.48 (5.07) | 3.73 (7.19) | 2.53 (7.25) | 6.94 (8.46) |
| High Loss | 0.92 (3.83) | 6.61 (5.36) | 2.57 (7.59) | 9.43 (9.80) |

Note. Mean (SD) for FRN and Feedback P3 amplitudes (μV) at electrode side FCz

**FRN: Smokers vs. non-smokers**

A significant main effect of valence was observed for the FRN, with larger amplitudes for negative feedback as compared to positive feedback ($F(1, 123) = 8.74$, $p = .004$, $\eta^2_p = .07$). The FRN was also larger for small magnitude outcomes as compared to large magnitude outcomes ($F(1, 123) = 23.17$, $p < .001$, $\eta^2_p = .16$). Finally, a main effect of group was found with smaller FRN amplitudes in smokers as compared to non-smokers (Figure 3; $F(1, 123) = 6.72$, $p = .011$, $\eta^2_p = .05$). More specifically, the FRN was smaller for rewards ($F(1, 119) = 5.49$, $p = .021$, $\eta^2_p = .04$) as well as for losses ($F(1, 118) = 6.88$, $p = .010$, $\eta^2_p = .06$) in smokers than in non-smokers. Interaction effects with Group were not significant.

**Feedback P3: Smokers vs. non-smokers**

Again, a significant main effect for valence was observed, with larger amplitudes for negative feedback as compared to positive feedback ($F(1, 123) = 148.75$, $p < .001$ , $\eta^2_p = .55$). The feedback P3 was also larger for high magnitude outcomes, as shown by a significant main effect of magnitude ($F(1, 123) = 53.55$, $p < .001$, $\eta^2_p = .30$). In addition, we found a significant interaction effect of Valence x Magnitude x Group ($F(1, 123) = 4.03$, $p = .047$ , $\eta^2_p = .03$). The difference between smokers and non-smokers for the feedback P3 was larger for low rewards as compared to high rewards, low losses, and high losses. In particular, smokers showed larger feedback P3 amplitudes for low rewards as compared to non-smokers ($F(1, 119) = 3.97$, $p = .049$ , $\eta^2_p = .03$); Figure 3).

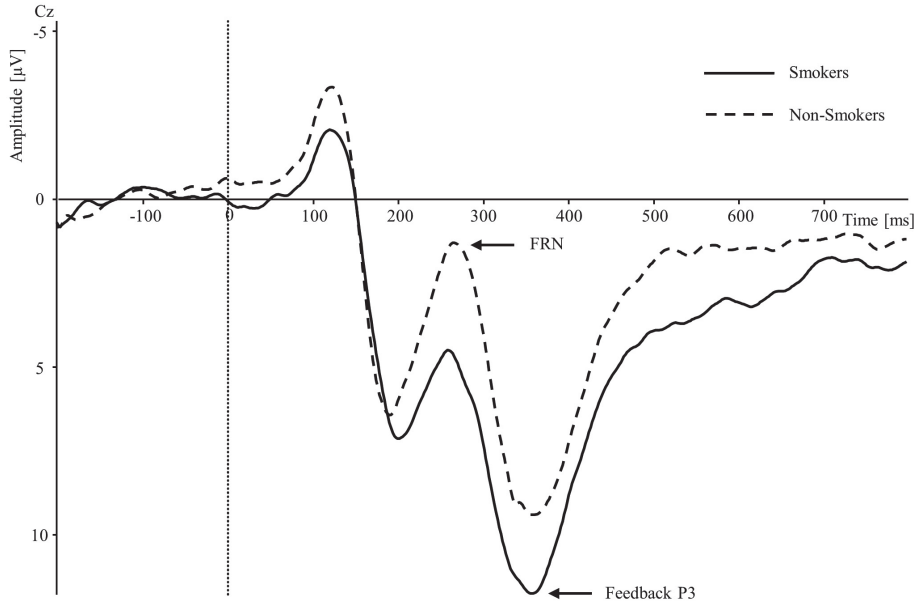


**Fig 3 .** FRN and Feedback P3 for low rewards in smokers and non-smokers.



### FRN: Active vs. sham tDCS

There was a main effect of Time for the FRN, with larger FRN amplitudes after the intervention week as compared to baseline ($F(1, 63) = 18.42$, $p < .001$, $\eta^2_p = .23$). No significant interaction effects were found with tDCS Group and Time. Hence, there was no difference between the active and sham tDCS group for the FRN after the intervention.

### Feedback P3: Active vs. sham tDCS

The feedback P3 was smaller post intervention as compared to baseline, as shown by a significant main effect of Time ($F(1, 63) = 20.40$, $p < .001$, $\eta^2_p = .25$). Interaction effects including the tDCS group and Time were not significant.

## Discussion

In the current study, we investigated feedback processing as underlying mechanism of the effects of tDCS on risky decision making in smokers. The TCGT was used as decision making task, as it was designed to independently

control for expectancy, magnitude, and valence of decision outcomes, which are important aspects that can affect feedback processing. As the TCGT was not used in addiction studies before, we first explored how smokers differed from non-smokers in behavioural and neurophysiological responses on the TCGT. In line with previous studies, smokers more frequently choose high-risk options over low-risk options as compared to non-smokers. As expected, early feedback processing was significantly decreased for smokers as compared to non-smokers in the current study, as shown by blunted FRN amplitudes. Interestingly, the feedback P3 was larger for smokers than non-smokers, but only for low rewards. After we validated how the TCGT differentiated between smokers and non-smokers, it was explored how tDCS over the DLPFC would affect decision making and feedback processing in smokers on the TCGT. Active neurostimulation was associated with increased risky decision making in smokers as compared to sham and seemed to have no effect on neurophysiological measures of feedback processing.

## TCGT in smokers and non-smokers

Regarding FRN amplitudes, the results are in line with previous studies that have reported impaired early feedback processing in individuals with SUD for decisions unrelated to drugs or cigarettes (Kamarajan et al., 2010; Sehrig et al., 2019; Fein & Chang, 2008; Morie et al., 2016). Larger FRN amplitudes are suggested to reflect better reinforcement learning (Luft, 2014). The finding of reduced FRN amplitudes in smokers therefore supports the notion that individuals with SUD show impaired reinforcement learning (e.g. Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017). In addiction, this may particularly be reflected in impaired processing of unexpected feedback to decisions unrelated to drugs or cigarettes (Sehrig et al., 2019). Also, the pattern of blunted FRN amplitudes in smokers is in line with the notion that the ACC is dysfunctional in SUD patients (Volkow, Wang, Fowler, Tomasi, & Telang, 2010).

Larger feedback P3 amplitudes for low rewards in smokers may be explained by the view that the feedback P3 reflects an adaptation for future decision making by learning from particularly surprising feedback (Fischer & Ullsperger, 2013; Endrass et al., 2016). In line with this view, the feedback P3 has been found to be larger for more unexpected outcomes (Hajcak et al., 2007). Since smokers chose high magnitude options over low magnitude options more often than non-smokers,

feedback for low rewards was presented less frequently to smokers as compared to non-smokers. This less frequent, and therefore more unexpected, reward outcome may have consequently led to larger feedback P3 amplitudes in smokers. The expectancy of certain feedback outcomes may also explain why results for the feedback P3 in addiction have been mixed. We would therefore recommend future studies to control for the effect of expectancy on feedback processing.

### Effects of tDCS in smokers

The tDCS intervention in smokers resulted in more risk-taking on the TCGT, similar to findings from another addiction study that used a gambling task to measure the effects of tDCS on decision making (Boggio et al., 2010). Yet, other addiction studies have found decreased risky decision making after active tDCS on tasks where reinforcement learning was involved in the decision making process (Pripfl et al., 2013; Gorini et al., 2014; Hajcak et al., 2007).We suggest that the mixed findings on tDCS effects on risky decision making in addiction result from the type of task used. Modulation of decision making after tDCS may result in increased gambling behaviour on gambling tasks and improved reinforcement learning during reinforcement learning tasks.

The effects of tDCS on feedback processing may also be task dependent. That is, the FRN is affected by subjective expectancy of a decision outcome, however, it has been found that this construct does not necessarily correspond with overt probabilities (Hajcak et al., 2007). This may explain why the FRN was blunted for smokers as compared to non-smokers in general, but not specifically for any of the four conditions. The TCGT controls for expectancy by indicating the chance of winning and losing before any decision is made, but subjective expectancies of decision outcomes were not explicitly tested in the current study. Therefore, it is difficult to draw conclusions about the effects of tDCS on feedback processing. Future studies could control for expectancy more directly by asking participants after their decision what outcome they expect. Herewith, it can also be tested whether increased confidence for reward outcomes is a possible explanation increased risk-taking after active tDCS during gambling tasks.

Alternatively, electrical currents induced by tDCS may not have reached brain areas involved in feedback processing, such as the ACC. Although it has been suggested that tDCS targeting the DLPFC could alter brain activity in

the ACC (Weber et al., 2014), the diffusion of electrical currents could reduce the possibility to reach this deeper brain structure (Nitsche et al., 2007; Datta, Elwassif, Battaglia, & Bikson, 2008). Innovative forms of tDCS, with increased focality such as high definition tDCS (HD-tDCS), may be able to target brain areas related to feedback processing more precisely (To et al., 2018).

## Limitations

The findings of this study need to be interpreted with several limitations in mind. First, tobacco smokers in this study were primarily light smokers who continued smoking throughout the study. The results can therefore not be generalized to a population of heavy or abstinent smokers. Furthermore, contrary to previous studies where tasks were performed directly after the neurostimulation session, here the TCGT was performed one day after the last tDCS session. This study design was chosen to ensure that the effect of all tDCS sessions, instead of only the last session, was examined. Even though effects may slightly fade out, which may explain why feedback processing was not affected by tDCS, it has been reported that the effects of the current tDCS protocol last longer than 24 hours (Monte-Silva et al., 2013). Moreover, there is no indication of reversed effects after one day. Therefore, it would be arbitrary to suggest that this delayed task administration may have resulted in the contradicting findings for risky decision-making.

## Conclusion

In conclusion, early feedback processing was altered in smokers as compared to non-smokers as reflected by blunted FRN amplitudes. Interestingly, the feedback P3 was larger for low rewards in smokers than in non-smokers. We suggest this may result from the low expectancy of smokers for low reward feedback. The tDCS findings confirm the notion that the DLPFC is involved in risky decision making in individuals with SUD. We propose that tDCS may increase risky decision making in addiction for gambling tasks. To further explore how tDCS affects risky decision making and underlying mechanisms such as feedback processing, future addiction studies may compare the effects of tDCS on gambling and reinforcement tasks directly.

# 5

# Multi-Session Electrical Neuromodulation Effects on Craving, Relapse and Cognitive Functions in Cocaine Use Disorder: A Randomized, Sham-Controlled tDCS Study

***This chapter is submitted as:***

*Verveer, I., van der Veen, F. M., Shababaie, A., Remmerswaal, D., & Franken, I. H. A. (submitted). Multi-Session Electrical Neuromodulation Effects on Craving, Relapse and Cognitive Functions in Cocaine Use Disorder: A Randomized, Sham-controlled tDCS Study*

## Abstract

**Background**: The use of transcranial Direct Current Stimulation (tDCS) has previously shown promising results for reducing craving in cocaine use disorder. In this study we assessed therapeutic and behavioural effects of multi-session tDCS to further explore the potential of tDCS as add-on intervention in the treatment of cocaine use disorder.

**Methods:** In a randomized, placebo-controlled, between subject study, we applied tDCS bilaterally with the anodal electrode targeting the right DLPFC (https://clinicaltrials.gov/ct2/show/NCT03025321). Patients with cocaine use disorder were allocated to ten sessions of either active tDCS ($n$ = 29) or sham tDCS ($n$ = 30) on five consecutive days. Inhibitory control and risky decision-making were measured via a Go-NoGo task and a two-choice gambling task, respectively, each at baseline, one day after all tDCS sessions and a follow up after three months. In addition, relapse at follow-up and craving were measured.

**Results:** There was no significant effect of active tDCS on the number of relapse days and craving. Relapse was frequent among patients who had received either active or sham tDCS (48.0% and 69.2%, respectively), despite an overall decrease in craving during the first two weeks of treatment. An additional analysis revealed that active tDCS significantly reduced relapse rates for crack cocaine use only ($n$ = 36). No effects were found on cognitive functions.

**Conclusions:** Although somewhat promising results were obtained regarding relapse among cocaine users, we believe that further research is required to consolidate the use of tDCS as a complementary treatment in cocaine use disorder.

**Keywords:** Cocaine use disorder, tDCS, EMA, cognitive control, Go-NoGo, risky decision-making

## Introduction

Psychosocial interventions are currently recommended as first-line treatment for cocaine addiction, and there is still little evidence for effective pharmacological treatments (De Crescenzo et al., 2018). In order to successfully follow psychosocial therapies, certain cognitive and emotional skills are required. This can be problematic for substance users, since they often show impairments in cognitive control functioning (Franken & van de Wetering, 2015), as a result of prefrontal cortex (PFC) dysfunction (Goldstein & Volkow, 2011). Impaired cognitive control has been associated with less treatment responsiveness (Winhusen et al., 2013) and with relapse in substance use disorders (SUDs; Volkow et al., 2016). Therefore, research on addiction treatment has recently shifted towards interventions focusing on modulating brain activity in the PFC by means of non-invasive brain stimulation (NIBS; Nakamura-Palacios et al., 2016).



Transcranial Direct Current Stimulation (tDCS) over the dorsolateral PFC has been one of the protocols of choice in studies on the clinical effectiveness of NIBS in addiction (Kekic et al., 2016; Lapenta et al., 2018). Promising results have been found for tDCS over the DLPFC on craving in a variety of SUDs (Jansen et al., 2013). For cocaine addiction specifically, five sessions of active bilateral tDCS with the anodal electrode over the right DLPFC reduced craving (Batista et al., 2015). However, no effects on craving and relapse were observed after ten tDCS sessions in a group of patients with cocaine use disorder that reported more craving at baseline and more years of substance use (Klauss et al., 2018a). Few other studies have attempted to explore the effect of tDCS on relapse in addiction. More specifically, studies with similar stimulation protocols have reported a reduction in risk of relapse in alcohol use disorder (Klauss et al., 2014; Klauss et al., 2018b), and cigarette consumption in smokers (Kang et al., 2019).

Investigating the underlying mechanism of the therapeutic effects of tDCS could help improve the application of NIBS in addiction treatment. It has been suggested that therapeutic effects on craving and relapse by modulating neuronal activity of the DLPFC is the result of reduced inhibitory control and risky decision-making (Brevet-Aeby et al., 2016; Lapenta et al., 2018; Naish et al., 2018; Schluter et al., 2018). Bilateral tDCS with the anodal electrode over the right DLPFC has been associated with less risky decision-making in addiction (Fecteau

et al., 2014; Pripfl et al., 2013). Also, risky decision-making was reduced in patients with cocaine use disorder when the same tDCS protocol was applied (Gorini et al., 2014). However, only few studies have investigated tDCS for modulating decision-making in addiction and to the best of our knowledge, the effect of tDCS on inhibitory control has not previously been explored in addiction.

The current study explored inhibitory control and risky decision-making in relation to beneficial effects of tDCS on craving and relapse in a representative sample of patients with cocaine use disorder. We decided not to exclude patients with additional substance use disorders, since cocaine addiction is rarely a stand-alone SUD. It has been reported that approximately two-third of patients with cocaine use disorder report seeking help for secondary substance use disorders (WDR, 2019). In addition, craving was measured by ecological momentary assessments (EMA) to collect detailed information about the duration and dynamics of the beneficial effects of tDCS (Shiffman et al., 2008). Since craving is a momentary phenomenon, EMA offers an ecologically valid alternative to retrospective self-reports by enabling repeated measurement of craving at random moments of the day (Serre et al., 2015).

We expect that the multi-session tDCS protocol employed in the current study as add-on treatment in cocaine use disorder will decrease the number of relapse days within three months after the intervention. In addition, we hypothesize that beneficial effects of multiple sessions of tDCS on relapse will be established by its effects on craving and cognitive functions, as shown by less craving, improved inhibitory control and reduced risky decision-making after active tDCS.

## Materials and methods

This clinical trial was pre-registered with identifier NCT03025321 at ClinicalTrials.gov. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. Detailed information about the materials is provided at dx.doi.org/10.17504/protocols.io.bdrzi576.

### Participants

All participants were fully informed by the principal investigator before they signed the written informed consent and entered the study. Seventy-eight patients

(61 males, 17 females) who met the DSM-5 criteria for cocaine use disorder were recruited between February 2017 and November 2018 from one specialized clinic for SUD treatment in Rotterdam (Antes) within one week after arrival. In total, fifty-nine patients (active tDCS $n$ = 29, sham tDCS $n$ = 30) completed the intervention week. Reasons for drop-out did not differ between groups (e.g. relapse, high load of experiment, tDCS side effects).

The inclusion criteria for the current study were: 1) Males and females aged between 18 and 65 years; 2) Meeting the DSM-5 criteria for cocaine use disorder; 3) The ability to speak, read, and write in Dutch at an eight-grade literacy level; 4) Owner of a smartphone. Exclusion criteria were: 1) Any withdrawal signs or symptoms at baseline; 2) Unstable mental or medical disorder as assessed by a physician; 3) A diagnosis of epilepsy, convulsions or *delirium tremens* during abstinence of cocaine; 4) Any contraindication for electrical brain stimulation procedures (i.e. electronic implants or metal implants); 5) The intake of medications for psychiatric conditions; 6) Pregnancy or breast-feeding. In addition, all participants received treatment as usual in the clinic, including psychosocial therapies conducted by professional practitioners – sometimes combined with adjunctive pharmacotherapy including benzodiazepines and disulfiram.



## Experimental design

The current study had a double-blind, randomized, sham-controlled design in which patients with cocaine use disorder received a total of ten tDCS sessions (active or sham) on five consecutive mornings in the week after arrival in the clinic (Fig 1). Participants were first randomly assigned to either sham or active tDCS. Then, before the tDCS sessions, participants completed questionnaires regarding demographics and past drug use. In addition, they performed two behavioural tasks (i.e., an inhibitory control and risky decision-making task) before the first session and one day after the last tDCS session. Participants were furthermore asked to answer questions about craving in an application on their mobile phones (EMA) for two weeks, starting the day of the first tDCS session.

Three months after the tDCS intervention, participants returned to the clinic in order to verify cocaine use in the past three months. Upon follow-up, participants completed the same behavioural tasks as at baseline.

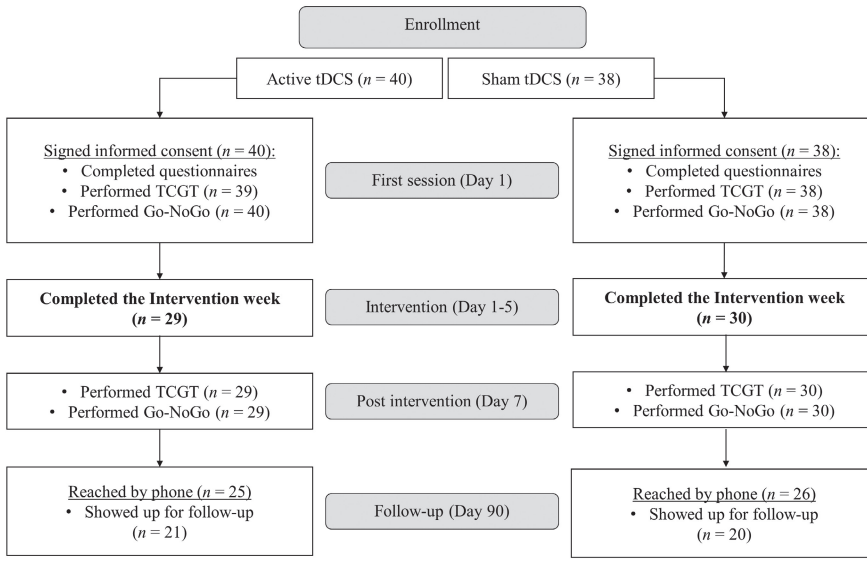


**Fig 1.** Flow-chart of the experimental procedure. Participants were recruited from the addiction clinic, signed the informed consent, and were randomized to receive either sham or active transcranial Direct Current Stimulation (tDCS). The intervention week comprised 10 sessions of bilateral tDCS with the anodal electrode over the right DLPFC (2mA, 2x 13 min stimulation with a 20-minute rest interval in between) on five consecutive days.

## Measures

### Relapse

Patients were followed-up 90 days after the last tDCS session regarding cocaine use relapse. Relapse was defined as the number of self-reported days that patients had used cocaine in the past 90 days. This information was gathered by a telephone call, during which an appointment was made for the follow-up session in the clinic. If patients could not be reached by telephone, they were contacted by email. In case of no response, we contacted a family member, to request further information on how to reach the patient. During the follow-up session in the clinic, patients were asked again how many days in the past 90 days they had used cocaine, which was then verified with urine control samples.

### EMA: Craving

The LifeData platform (www.lifedatacorp.com) was used to develop the application for this study and to securely collect data. After participants had

downloaded the application on their smartphone during the first session, they received random prompts three times a day between 10 AM and 10 PM for 14 consecutive days to complete a random assessment (RA). During RAs, participants were asked to indicate their craving for cocaine at that moment on a Likert scale ranging from 0 to 100.

**Inhibitory control: Go-NoGo task**

Previous studies have indicated that patients with cocaine use disorder perform worse on the Go-NoGo task as compared to healthy controls (e.g. Hester et al., 2013). The current study used a cocaine related Go-NoGo task to measure inhibitory control, based on the paradigm used in Luijten and colleagues (2011). During this task, participants were presented with a series of cocaine-related and neutral pictures. Participants were instructed to press a button with their index finger as fast as possible for Go trials, and to inhibit their response for the unexpected NoGo trials (25% of all trials). See Fig 2 and Materials in dx.doi.org/10.17504/protocols.io.bdrzi576 for more details about the task.



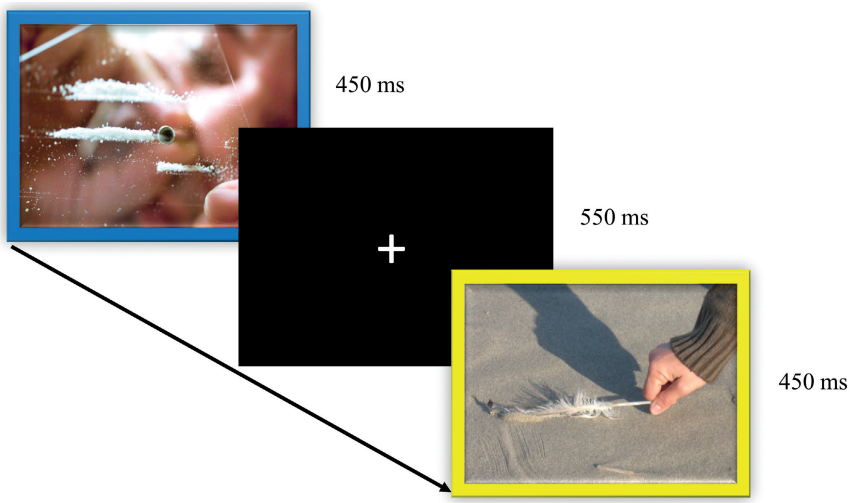


**Fig 2.** Example of a cocaine related and neutral picture in the Go-NoGo task. The blue and yellow frames indicate Go and NoGo trials. Each picture was presented for 450 ms, followed by a black screen displayed for a randomly varying duration between 550 and 650 ms. The paradigm involved 112 different cocaine-related pictures and 112 matched neutral pictures that were presented two times. The order of picture content (cocaine versus neutral) was completely randomized and the order of trial type (Go versus NoGo) was quasi randomized such that at most four Go and two NoGo trials were presented consecutively.

### Risky Decision-making: Two Choice Gambling Task (TCGT)

An adjusted version of the computerized probabilistic two-choice gambling task (TCGT) was used for the current study (Scheurmann et al., 2012). Participants were instructed to gain as many points as possible by choosing between a high-risk and a low-risk option that was presented on a computer screen (Fig 3). See dx.doi.org/10.17504/protocols.io.bdrzi576 for further details about the task.

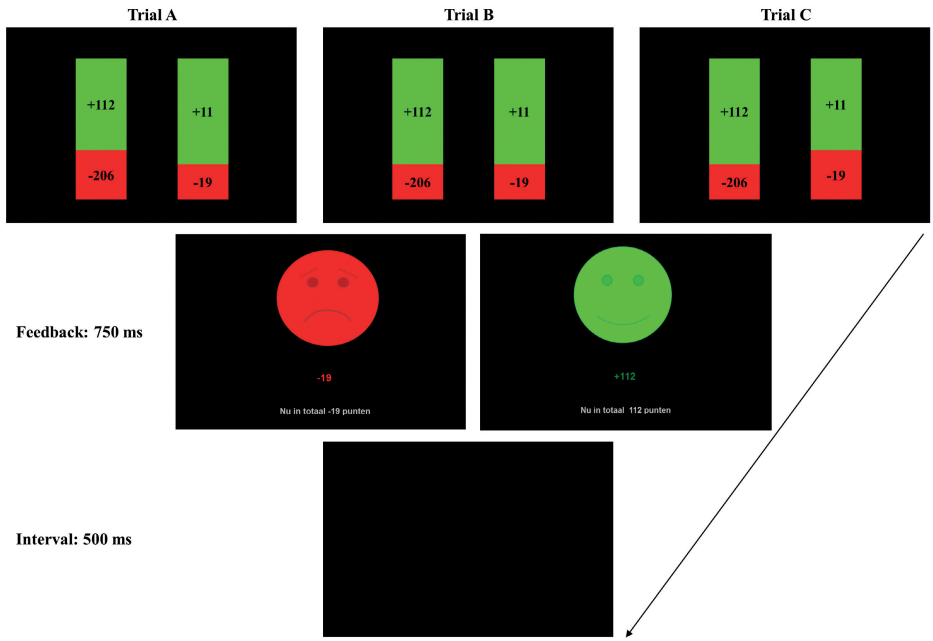


**Fig 3.** Example of the probabilistic two choice gambling task. Trial A represents a high-risk option (left) with a higher chance of losing than the low-risk option (right). Trial B depicts two options with equal chances of losing for the high (left) and low-risk option (right). Trial C presents a low-risk option (right) with a higher chance of losing than the high-risk option (left). Choices were made by pressing the corresponding response button. Directly after pressing the button, participants were shown the outcome of their choice for 750 ms. When participants won, a green happy face appeared on the screen, together with the amount of points they had gained (positive feedback). For losses, participants were shown a red frowny face with the amount of points they had lost (negative feedback). In addition to the feedback stimuli, the total account balance across trials was presented. The next trial was presented after an intertrial interval of 500 ms.

## Transcranial Direct Current Stimulation

Participants received tDCS by an electric DC-plus stimulator (NeuroConn, Ilmenau, Germany) via a pair of carbon silicon electrodes with a thick layer

of high-conductive EEG gel underneath them (35 $cm^2$). During each session, tDCS was applied two times for 13 minutes (2mA) with a 20-minute rest interval between the stimulations (Klauss et al., 2014; Shahbabaie et al., 2018). Each 13-minute stimulation included a 30 sec ramp up at the beginning and ramp down at the end. Monte-Silva and colleagues (2013) have reported that this protocol can extend after-effects of tDCS. The anodal electrode was placed over the F4 and the cathodal electrode was placed over the F3 based on 10-20 international system. Beneficial effects were found on relapse and craving with this right anodal/left cathodal positioning over the DLPFC (Klauss et al., 2014; Jansen et al., 2013; Shahbabaie et al., 2014).

The control group received sham tDCS by the DC-plus stimulator. In the sham condition, the electrodes were positioned at the same locations as in the active tDCS condition, but in this case the stimulator was gradually turned off after 30 s. Since the itching sensation of tDCS is often only experienced initially during stimulation, it was expected subjects remained blinded of the stimulation condition they received (e.g. Gandiga et al., ; Woods et al., 2016). The experimenter was also blinded from the tDCS condition. That is, the codes that can automatically activate sham or active tDCS, were randomly assigned to participant numbers by an independent researcher.



## Data analyses

### Relapse

An independent samples t-test was performed in SPSS to analyse the average number of days participants had relapsed in the 3 months after the tDCS intervention. An additional analysis was performed to test whether relapse rates differed for the active and sham tDCS group using the chi-square fisher exact test.

### Craving

Multilevel analysis was performed in R (R Core Team, 2018) using the lme4 package (Bates et al., 2014) to fit the nested data structure of Time within individuals (Level 1), and Group (sham vs. active tDCS) at Level 2. Multilevel modelling also allowed us to include data points of individuals with missing

data. Missing data is almost inevitable in EMA studies, since most participants miss at least some prompts.

The outcome variable in this analysis was average craving a day. Time (day 1 to 14) was defined at Level 1 and patients at Level 2, with Group (sham vs. active tDCS) as a Level 2 predictor variable (see Hox, 2010). For the analyses, first a baseline model (M0) was fitted to the data with random intercepts. The baseline model was used to assess whether multilevel analysis was required, by testing if the variance at Level 2 was significant. In the second model (M1) the Level 1 predictor Time was added to the model. In the third model (M2) random slopes were added for Time. The fourth model (M3) included the Level 2 predictor Group. Finally, the fifth model (M4) was extended by a cross-level interaction of Time at Level 1 and Group at Level 2 to assess whether the effect of time varied across groups. The fit of the models was analyzed by testing the difference in deviance across models. In addition, the assumptions of normality and linearity were assessed by inspecting the residuals of each best fitted model. Unless otherwise reported, the assumptions were met.

**Behavioural tasks**

For behavioural data generated during the Go-NoGo task and the TCGT, multilevel analyses were again performed in R using the lme4 package . For all outcome measures, Time (pre, post, and follow-up) was defined at Level 1 and patients were defined at Level 2 with Group (sham tDCS vs active tDCS) as predictor variable. Similar to the outcome of craving, models M0, M1, M2, M3 and M4 were fitted to behavioural outcomes.

For the outcome measures of the Go-NoGo task, different models were fitted to accuracy scores, reaction times on Go trials, and post error reaction times. Accuracy was defined as the percentage of correct NoGo trials. For both accuracy and reaction times on Go trials, Picture Type (cocaine vs. neutral) was defined as Level 1 variable in addition to Time. The main outcome variable of the TCGT was the average number of points won per trial. In addition, separate models were built for trials A and B of the TCGT (see fig. 3), with risk-taking calculated as the percentage of times that participants choose high-risk options over low-risk options. Trial C (see fig 3.) can be considered as control trial, since both options contain a low level of risk-taking.

**Adverse effects tDCS**

After each tDCS session, participants were asked to indicate how much they experienced any of the following adverse effects on a 5-point Likert scale (ranging from none (1) to extreme (5) sensations): itching, burning, or tingling sensations, difficulties with concentrating, acute mood changes, sleepiness, neck pain, and headache. An independent samples t-test with Group (Active vs. Sham tDCS) as between-subject factor was performed for average intensity of adverse effects experienced by each participant. No differences between the groups (active tDCS vs sham) were observed regarding adverse effects.

## Results

Demographical data and patterns of drug use are presented in Table 1. The sham and active tDCS group did not differ in baseline characteristics. It was furthermore confirmed that multilevel analyses could be performed for all outcomes, since results showed that baseline models (M0) with random intercepts fitted the data (i.e., variance at Level 2 was significant).

**Table 1.** Socio-demographic characteristics of the total sample of cocaine users (n = 59), subdivided in subjects that received the transcranial Direct Current Stimulation intervention (active tDCS: n=29) or the sham intervention (sham tDCS: n=30)

| | | Groups | | | |
|---|---|---|---|---|---|
| | | Sham tDCS | Active tDCS | | p-value |
| Age [mean (SD)] | | 41.9 (9.7) | 37.6 (10.7) | t(57) = 1.62 | 0.11 |
| Gender (% male) | | 70.0 | 89.7 | Fisher = 1.0 | 0.10 |
| Years of Education (%) | 0-8 years | 6.7 | 17.2 | X2 = 3.04 | 0.22 |
| | 9-14 years | 46.7 | 27.6 | | |
| | above 14 years | 46.7 | 55.2 | | |
| Age of onset cocaine use [mean (SD)] | | 22.1 (6.9) | 20.8 (5.6) | t(57) = 0.80 | 0.43 |
| Number of years cocaine use [mean (SD)] | | 17.1 (8.3) | 13.6 (10.5) | t(57) = 1.42 | 0.16 |
| Days of abstinence before study [mean (SD)] | | 14.3 (10.1) | 18.2 (8.5) | t(57) = -1.63 | 0.11 |
| OCDUS cocaine thoughts and interference | | 15.53 (6.71) | 16.66 (6.34) | t(57) = -0.66 | 0.51 |
| OCDUS cocaine desire and control | | 10.60 (3.78) | 10.52 (3.69) | t(57) = 0.09 | 0.93 |
| OCDUS cocaine resistance | | 5.67 (2.60) | 5.48 (1.82) | t(57) = 0.32 | 0.75 |
| How cocaine is used (%) | Snorting | 23.3 | 37.9 | X2 = 1.80 | 0.41 |
| | Smoking | 63.3 | 55.2 | | |
| | Both | 13.3 | 6.7 | | |
| Number of Other Substances Used (%) | No other substance | 20.0 | 24.1 | X2 = 0.15 | 0.93 |
| | One other substance | 36.7 | 34.5 | | |
| | Multiple | 43.3 | 41.4 | | |
| Type of other substances used (%) | Alcohol | 33.3 | 36.7 | X2 = 3.85 | 0.43 |
| | Cannabis | 26.7 | 28.3 | | |
| | Heroine | 10.0 | 10.0 | | |

## Relapse

There were no mismatches between urine controls and answers patients gave to the question whether they had relapsed or not. The number of days that

participants had relapsed did not differ between groups ($t(27) = 0.60$, $p = 0.55$). Overall, relapse rates within 90 days after the 10 tDCS sessions were high for both the active (48.0%) and sham (69.2%) tDCS group. There was no significant difference in relapse rates between both groups for the 90 days follow-up (odds-ratio = 0.42, $X^2(1) = 2.37$, $p = 0.12$).

Since previous studies had merely analysed relapse rates for patients who use crack-cocaine, we decided to perform an exploratory analysis including only crack cocaine users (table 3). These results show that relapse was lower for the active tDCS group (41.2%) as compared to the sham tDCS group (73.7%). The odds-ratio for the group of crack cocaine users was 0.26 ($X^2(1) = 3.90$, $p = 0.05$).

The group of patients who used cocaine in the form of crack were older as compared to the group who used powder ($t(57) = -2.48$, $p = 0.02$). Also, 11 out of 12 female participants from our sample were crack-cocaine users. Taking these variables into account did not affect the results for relapse.



## EMA

### Compliance

The total number of completed RAs for day 1 to day 14 was 1250 out of 2775 RAs. Therefore, the compliance rate for completed random assessments was 45.0%. As shown in Table 4, the compliance rate was higher for the active tDCS group (49.6%) as compared to the sham tDCS group (40.5%), with an odds ratio of 0.69 ($X^2(1) = 22.95$, $p < .001$).

### Craving

The third model (M2) with random intercepts and slopes for time, including Time as Level 1 predictor, was the best fitted model for average craving a day (Table 2). There was an overall decrease of craving over time observed in the 14 days after the first tDCS or sham session, with an average decrease of 1.29 ($t(52) = -5.00$, $p < .001$). The results show no indication of significant differences between the sham and active tDCS group in craving over time. Additionally, the results for craving did not differ for participants who had relapsed or not three months after active or sham tDCS. Finally, there was no difference between the active and sham tDCS group in craving over time if only crack-cocaine users were included for analyses.

## Inhibitory control

For all behavioural measures of inhibitory control as measured by the Go-NoGo task, the results indicate that the third model (M2) was the best fitted model for the data. The third model for accuracy on NoGo trials (Table 3) indicates that accuracy increases over time from baseline to follow-up with an average of 5.36 ($t(58) = 2.89$, $p < .01$). In addition, M2 for reaction times during Go trials (Table 3) suggests an average decrease of 15 ms from pre- to post intervention ($t(57) = -2.92$, $p < .01$). Finally, there was evidence of a general post-error slowing: reaction times post error trials were on average 27 ms slower than reaction times post correct trials ($t(154) = -11.90$, $p < .001$), as shown by the results of M2 in Table 3. The final model (M4) was never the best fitted model, and therefore no significant differences over time between groups were found for all inhibitory control outcomes.

## Risky decision-making

The baseline model was the best fit for the average number of points won per trial (Table 4) and for risk-taking on Trial A (Table 4). For risk-taking on trial B, the second model (M1) with Time as fixed effect was the best fitted model (Table 4). However, when random slopes for time were added to the model (M2), the effect of Time was no longer significant. The lack of significant cross-level interaction effects indicates that risky decision-making was unaffected by tDCS.

**Table 2.** Parameter estimates (se between brackets) and model fit statistics per model for craving.

| Outcome | Fixed part | | | | Random part | | | Likelihood ratio test2 |
|---|---|---|---|---|---|---|---|---|
| Craving | Intercept | Time | Group | Group * Time | $\sigma^2_e$ | $\sigma^2_{u0}$ | $\sigma^2_{u1}$ | |
| M0 | 15.71 (2.78)*** | | | | 191.7 | 382.6 | | 387.37*** |
| M1 | 24.53 (2.91)*** | -1.31 (0.15)*** | | | 166.4 | 372.9 | | 70.90*** |
| M2 | 24.44 (3.63)*** | -1.29 (0.26)*** | | | 131.21 | 629.74 | 2.18 | 61.29*** |
| M3 | 27.18 (4.68)*** | -1.28 (0.26)*** | -5.00 (5.34) | | 131.26 | 639.19 | 2.16 | 0.90 |
| M4 | 25.23 (5.45)*** | -1.08 (0.38)** | -1.43 (7.36) | -0.36 (0.51) | 131.33 | 642.13 | 2.16 | 0.52 |

M0: baseline model with random intercepts and Level 1 predictor time. M1: M0 + fixed effects for time.
M2: M1 + random slopes for time. M3: M2 + Level 2 predictor group.
M4:M3 + cross-level interaction effect of time and group. *p < 0.05. **p < 0.01. ***p<.001.

**Table 3.** Parameter estimates (se between brackets) and model fit statistics per model for behavioural measures of the Go-NoGo task.

| Outcome | Fixed part | | | | | | | Random part | | | | Likelihood ratio test2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Accuracy: | Intercept | Pre-Post | Pre-FollowUp | Picture Type | Group | Group * Pre-Post | Group * Pre-FollowUp | $\sigma^2_e$ | $\sigma^2_{u0}$ | $\sigma^2_{u1}$ | $\sigma^2_{u2}$ | |
| M0 | 75.77 (0.02)*** | | | | | | | 86.5 | 169.7 | | | 203.09*** |
| M1 | 73.35 (1,96)*** | 2.10 (1.19) | 5.79 (1,38)*** | 0.64 (1.03) | | | | 81.6 | 171.5 | | | 17.58*** |
| M2 | 73.35 (2.22)*** | 2.11 (1.88) | 5.36 (1.85)** | 0.64 (0.61) | | | | 29.2 | 269.5 | 175.7 | 145.0 | 105.14*** |
| M3 | 75.63 (2.79)*** | 2.13 (1.88) | 5.33 (1.86)** | 0.64 (0.61) | -4.62 (3.50) | | | 29.2 | 264.5 | 175.7 | 146.0 | 1.76 |
| M4 | 76.19 (3.07)*** | 1.35 (2.67) | 4.56 (2.60) | 0.64 (0.62) | -5.77 (4.36) | 1.58 (3.79) | 1.58 (3.75) | 29.2 | 265.9 | 178.7 | 148.5 | 0.21 |
| RT Go trials: | | | | Picture Type | | | | | | | | |
| M0 | 326.34 (5.26)*** | | | | | | | 975.8 | 1438.1 | | | 150.16*** |
| M1 | 331.77 (5.97)*** | -14.66 (4.06)*** | -5.91 (4.69) | 2.94 (3.49) | | | | 935.7 | 1441.0 | | | 13.64** |
| M2 | 331.83 (6.81)*** | -14.74 (5.05)** | -7.05 (6.05) | 2.94 (2.58) | | | | 512.7 | 2364.9 | 930.9 | 1233.3 | 52.41*** |
| M3 | 337.10 (8.19)*** | -14.71 (5.05)** | -7.17 (6.06) | 2.94 (2.58) | -10.72 (9.45) | | | 512.7 | 2313.9 | 931.7 | 1236.9 | 1.29 |
| M4 | 341.11 (9.35)*** | -20.28 (7.00)** | -10.92 (8.37) | 2.94 (2.58) | -19.06 (0.16) | 11.54 (10.06) | 7.87 (12.22) | 512.7 | 2314.5 | 919.9 | 1257.4 | 1.38 |
| RT post errors: | | | | Correct vs. Error | | | | | | | | |
| M0 | 312.45 (5.09)*** | | | | | | | 890 | 1352 | | | 156.61*** |
| M1 | 327.79 (5.61)*** | -1.70 (3.42) | -5.58 (3.97) | -26.94 (2.95)*** | | | | 669.5 | 1391.3 | | | 74.39*** |
| M2 | 327.77 (5.81)*** | -1.69 (4.02) | -5.87 (5.50) | -26.90 (2.26)*** | | | | 393.8 | 1717.5 | 533.9 | 948.5 | 36.37*** |
| M3 | 331.46 (7.63)*** | -1.68 (4.02) | -5.89 (5.51) | -26.89 (2.26)*** | -7.50 (10.09) | | | 393.8 | 1712.2 | 534.1 | 948.7 | 0.56 |
| M4 | 333.63 (8.06)*** | -3.74 (5.68) | -10.23 (7.62) | -26.90 (2.26)*** | -11.91 (11.39) | 4.13 (8.10) | 9.06 (11.09) | 393.8 | 1714.3 | 546.2 | 960.3 | 0.73 |

M0: baseline model with random intercepts and Level 1 predictor time. M1: M0 + random slopes for time. M2: M1 + Level 2 predictor group.
M3:M2 + cross-level interaction effect of time and group. Stand.: Standardized coefficients of fixed effects. ***p < 0.001. **p < 0.01. *p<.05.

**Table 4.** Parameter estimates (se between brackets) and model fit statistics per model for behavioural measures of the TCGT.

| Outcome | Fixed part | | | | Random part | | | Likelihood ratio test2 |
|---|---|---|---|---|---|---|---|---|
| Win per trial: | Intercept | Time | Group | Group * Time | $\sigma^2_e$ | $\sigma^2_{u0}$ | $\sigma^2_{u1}$ | |
| M0 | 40.20 (1.79)*** | | | | 172.2 | 118.8 | | 20.90*** |
| M1 | 36.21 (3.11)*** | 2.19 (1.40) | | | 170.0 | 118.7 | | 2.45 |
| M2 | 36.35 (2.95)*** | 2.08 (1.47) | | | 158.4 | 82.0 | 13.8 | 1.75 |
| M3 | 35.51 (3.43)*** | 2.07 (1.47) | 3.53 (1.71) | | 158.3 | 86.2 | 14.0 | 0.24 |
| M4 | 35.98 (4.19)*** | 0.78 (5.97) | 1.77 (2.10) | 0.58 (2.98) | 158.1 | 93.3 | 16.4 | 0.04 |
| % high-risk Trial A | | | | | | | | |
| M0 | 38.93 (2.43) *** | | | | 135.7 | 294.1 | | 66.91*** |
| M1 | 38.29 (3.35)*** | 0.35 (1.27) | | | 136.9 | 294.2 | | 0.08 |
| M2 | 38.11 (3.34)*** | 0.49 (1.41) | | | 105.2 | 360.1 | 35.8 | 2.47 |
| M3 | 37.68 (4.12)*** | 0.50 (1.41) | 0.87 (4.90) | | 105.2 | 364.9 | 35.9 | 0.03 |
| M4 | 36.31 (4.73)*** | 3.63 (6.74) | 1.35 (2.02) | -1.71 (2.86) | 104.5 | 373.6 | 38.3 | 0.06 |
| % high-risk Trial B | | | | | | | | |
| M0 | 63.34 (2.54)*** | | | | 147.6 | 319.6 | | 67.31*** |
| M1 | 58.44 (3.46)*** | 2.71 (1.30)* | | | 142.0 | 323.6 | | 4.29* |
| M2 | 58.30 (3.52)*** | 2.81 (1.41) | | | 115.2 | 407.7 | 29.2 | 1.69 |
| M3 | 58.21 (4.34)*** | 2.81 (1.41) | 0.18 (5.14) | | 115.2 | 414.8 | 29.2 | 0.00 |
| M4 | 58.81 (4.98)*** | -1,03 (7.10) | 2.46 (2.01) | 0.70 (2.84) | 115.4 | 420.6 | 31.0 | 0.06 |

M0: baseline model with random intercepts and Level 1 predictor time. M1: M0 + random slopes for time. M2: M1 + Level 2 predictor group.
M3:M2 + cross-level interaction effect of time and group. Stand.: Standardized coefficients of fixed effects. *p < 0.05. **p < 0.01. ***p<.001.

## Discussion

The present study explored multi-session tDCS over the DLPFC as add-on treatment for cocaine use disorder and its effects on cognitive functions. There was no indication of a decrease in the number of relapse days after three months for patients with cocaine use disorder who had received active tDCS as compared to sham. In line with the non-significant findings of tDCS on relapse in cocaine use disorder, no beneficial effects of tDCS on craving and cognitive functions were found in the present study.

## Relapse rates

Relapse rates after three months were high for both the active tDCS (48.0%) and sham tDCS group (69.2%). Klauss and colleagues (2018a) found similar relapse rates of 52.9% for active tDCS and 66.7% for sham tDCS, 60 days after discharge from the clinic. However, an additional analysis on relapse rates including only patients that used cocaine in the form of crack (Batista et al., 2015; Klauss et al., 2018a), did reveal a significant effect of multiple sessions of tDCS on relapse rates in the current study (41.2% active tDCS vs. 73.7% sham). It is unclear why tDCS may be more effective in crack-cocaine users, but the motivation to quit and severity of crack-cocaine addiction may have played an important role (De Souza Brangioni et al., 2018). Arguably, crack-cocaine users in the Netherlands have more severe addiction and related problems and might be more motived for change. In addition, relapse rates are still high after active tDCS for patients who used cocaine in the form of crack. Therefore, further research is needed to explore and improve the effectiveness of non-invasive brain stimulation techniques in addiction.



## Craving

While no significant difference between the two groups was found on craving levels, both groups showed a decrease in craving from the first tDCS session until 14 days after. This finding is in line with observations from previous studies investigating similar tDCS protocols in cocaine use disorder (Batista et al., 2015; Klauss et al., 2018a). One of these studies also found a larger decrease in craving after active tDCS as compared to sham (Batista et al., 2015). However, another study was unable to replicate this finding in a sample of slightly older patients who showed more severe patterns of cocaine use and who indicated more craving at baseline (Klauss et al., 2018a). It can be hypothesized that effects of tDCS on craving are larger when the intervention takes place at an earlier stage of cocaine use disorder.

## Cognitive Functions

To the best of our knowledge, this is the first time that the effect of multi-session tDCS on inhibitory control has been investigated in addicted patients (Naish et al., 2018; Schluter et al., 2018). Inhibitory control improved for both groups over time, as indicated by increased accuracy and faster reaction times on the Go-

NoGo task. Yet, tDCS had no additional effect on improved inhibitory control. Previous studies that investigated effects of tDCS on inhibitory control in healthy populations have revealed that tDCS over the right inferior frontal gyrus (rIFG) might improve reactive response inhibition as measured by inhibitory control on the stop signal task (Brevet-Aeby et al., 2016). They suggested that the DLPFC would be more involved in proactive response inhibition on the Go-NoGo task. However, so far there is little evidence for this hypothesis.

We also found no effect of multiple tDCS sessions on risky decision-making in patients with cocaine use disorder. For both healthy and addicted individuals it has been reported that risky decision-making decreased after bilateral tDCS with the anodal electrode over the right DLPFC. However, there have been exceptions where tDCS over the DLPFC did not effectively reduce risky decision-making. In fact, active tDCS even increased risk-taking behaviour in marijuana users during the Risk Task (Boggio et al., 2010), and in smokers during the TCGT (Verveer et al., *Chapter 4*). Also, smokers showed no changes in risk-taking on the Risk Task after active tDCS (Fecteau et al., 2014). In contrast, when the BART task and the 'Hot' version of the Columbia Card Task were used, risky decision-making after tDCS was decreased in addiction (Gorini et al., 2014; Pripfl et al., 2013). Both the Risk Task and TCGT involve a gambling aspect, and the reward probability is indicated before any decision is made. In contrast, the BART and 'Hot' Columbia Card Task may reflect reinforcement learning more than gambling, since participants can learn from previous decisions to optimize the probability of receiving rewards (Hajcak et al., 2007). Inconsistent findings may therefore depend on task characteristics. Clearly, more research is needed to better understand how risky decision-making is involved in therapeutic effects of tDCS.

## Limitations

The current results should be interpreted with several limitations in mind. Although the sample size was slightly larger as compared to previous studies on tDCS in cocaine use disorder, the drop-out rate for follow-up sessions reduced the power for relapse outcomes. Another limitation is the relatively low EMA compliance rate. This may not come as a surprise, given the marginalized population of patients with (crack) cocaine use disorder, but other addiction studies have reported a higher average compliance of 69.8% (Jones et al., 2019).

The strength of using EMA is that individual patterns of craving over time can be estimated in an ecologically valid manner, however it remains unclear how EMA compliance can be increased, particularly in challenging populations (Jones et al., 2018). Nevertheless, the current results are in line with previous studies that suggest a general decrease in craving in the first weeks of addiction treatment (e.g. Klauss et al., 2018a). Furthermore, multilevel analysis reliably corrects for missing data. Therefore, the EMA results on craving can still be used, but caution should be taken when interpreting the results.

## Conclusions

The findings thus imply that multiple sessions of bilateral tDCS with the anodal electrode over the right DLPFC has no significant beneficial effects on relapse and craving, or on cognitive control functions in patients with cocaine use disorder. However, some preliminary evidence was provided that relapse rates decrease after tDCS for crack-cocaine users specifically. We suggest that motivation to quit plays an important role in beneficial effects of tDCS (De Souza Brangioni et al., 2018). Future investigations should examine different effects of tDCS depending on type of substance use, age, severity of substance use, and motivation to quit.

# 6

# Modulation of Control: Can HD-tDCS Targeting the dACC Reduce Impulsivity?

***This chapter is submitted as:***

*Verveer, I., Hill, A. T., Franken, I. H. A., Yücel, M., van Dongen, J. D. M., & Segrave, R. (submitted). Modulation of control: Can HD-tDCS targeting the dACC reduce impulsivity?*

## Abstract

**Background:** The dorsal anterior cingulate cortex (dACC) and its neurocircuits are central in impulsivity, and maladaptive dACC activity has been implicated in psychological disorders characterized by high trait impulsivity. High-Definition transcranial Direct Current Stimulation (HD-tDCS) is a non-invasive neuromodulation tool that has promising potential to innervate deep subcortical structures, like the dACC, with spatial precision.

**Objectives:** Using behavioural and electrophysiological measures we investigated whether HD-tDCS targeting the dACC could modulate two key components of impulsivity, inhibitory control and error processing.

**Methods:** Twenty-three healthy adults with high trait impulsivity, as indicated by a score of $\geq$47 on the SUPPS-P questionnaire, were invited for two experimental sessions. Participants received active or sham HD-tDCS in counterbalanced order with a wash-out period of at least 3 days, as part of a single-blind, cross-over design. EEG was recorded during the Go-NoGo task before, directly after, and 30 minutes after HD-tDCS.

**Results**: HD-tDCS targeting the dACC did not affect inhibitory control performance on the Go-NoGo task, but there was evidence for a delayed change in underlying neurophysiological components of motor inhibition (NoGo P3) and error processing (error related negativity; ERN) after one session of HD-tDCS.

**Conclusion:** HD-tDCS has potential to modulate underlying neurophysiological substrates of impulsivity. Future studies should explore whether multi-session HD-tDCS has the capacity to also induce behavioural changes, particularly in clinical samples characterized by high trait impulsivity.

## Introduction

Impulsivity is a multidimensional construct that predisposes an individual to a range of maladaptive behaviours (Evenden, 1999; Whiteside & Lynamm, 2001). More generally defined, it refers to the tendency to act prematurely without adequate forethought about the consequences (Dalley, Everitt, & Robbins, 2011; Evenden, 1999). Impulsivity varies across healthy individuals and can be adaptive in some circumstances (Dickman, 1990). For example, impulsive entrepreneurs tend to be less sensitive to negative consequences and are therefore more persistent in completing entrepreneurial actions that are necessary to keep their business running (Wikland, Yu, & Patzelt, 2018). However, impulsivity is more generally regarded as a maladaptive personality trait associated with inappropriate or harmful behaviour towards oneself or others, such as recklessness and aggression (Verdejo-García, Lawrence, & Clark, 2008). High trait impulsivity also plays a key role in a broad range of mental illnesses, such as substance use disorders (SUD), attention deficit/hyperactivity disorder (ADHD), and antisocial personality disorder (ASPD; Zisner & Beauchaine, 2016).



Two components of cognitive functioning particularly involved in high trait impulsivity are inhibitory control and error processing (Luijten et al., 2014). Inhibitory control is the ability to suppress the execution of automatic responses, while error processing reflects the ability to monitor performance in order to detect errors and adaptively learn from them (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Ruchsow, Spitzer, Grön, Grothe, & Kiefer, 2005). Deficits in these functions can have substantial negative consequences. For example, when strong desires are no longer inhibited it can lead to problematic patterns of substance use or antisocial behavior in SUD and ASPD, respectively. Diminished error processing in turn prevents learning from negative outcomes, and thus perpetuating dysfunctional behaviour.

The dorsal anterior cingulate cortex (dACC) is a critical node in neurocircuits that support the robust cognitive functions contributing to impulsivity (Botvinick & Cohen, 2014). More specifically, it has been proposed that dACC activity is related to processes that determine the expected costs and benefits of exercising control over automatic behaviour (Shenhav, Cohen, & Botvinick, 2016). The degree of exerted inhibitory control can therefore be regarded as the product of

dACC processes, while error processing has a more direct connection with dACC activity, by the association of the dACC with conflict detection and error-related responses (Hester, Fassbender, & Garavan, 2004; Ridderinkhof et al., 2004).

Because of the involvement of the dACC in inhibitory control and error processing, this area represents a potential target for non-invasive neuromodulation aimed at modifying impulsivity. High-Definition transcranial Direct Current Stimulation (HD-tDCS) has potential to target brain structures with high focality through the placement of multiple compact gel-based electrodes on the scalp (DaSilva et al., 2015). These electrodes deliver low-intensity electrical currents (typically 0.5 – 2 mA) that cause sub-threshold modulation of neuronal membrane potentials (Woods et al., 2016), resulting in excitability changes within the brain. Importantly, certain electrode configurations allow HD-tDCS montages to be optimized for targeting deeper sub-cortical brain structures (Faria, Hallett, Miranda, 2011; To et al., 2018).

To date, only one study has investigated whether HD-tDCS targeting the dACC could modify cognitive functioning. To et al (2018) used a HD-tDCS montage comprising four return electrodes positioned across the forehead and one target electrode placed over Fz according to the International 10-20 System. This configuration was based on computational current flow models indicating that with this HD-tDCS montage the electrical field would peak at the dACC and exit at the forehead. To the best of our knowledge, the study by To et al (2018) is the first and only proof-of-concept study to target the dACC with HD-tDCS and the results indicated that anodal stimulation was associated with improved reaction times and neurophysiological changes in the dACC as measured with source-localized resting-state EEG. However, it is unclear whether the observed behavioural changes were specific to modulation of dACC activity, as EEG was not recorded during task performance. In addition, faster reaction times after HD-tDCS may partially be attributed to changes in pre-supplementary motor area (pre-SMA) activity, given that electrical currents induced by HD-tDCS targeted at the dACC will also pass through the pre-SMA (To et al., 2018). Finally, it is questionable whether HD-tDCS with 1 mA intensity is sufficient to produce adequate stimulation at the depth of the dACC.

The aim of the current study was to further investigate cognitive changes induced by HD-tDCS over the dACC with an increased current intensity of 1.5

mA. Specifically, we investigated this montage as potential neuromodulation technique to change impulsivity, as measured by inhibitory control and error processing on the Go-NoGo task, in individuals with high trait impulsivity. The Go-NoGo task is a gold-standard paradigm to assess error processing and inhibitory control (Luijten et al., 2014). ERPs that reflect inhibitory control during the Go-NoGo task are the N2 and P3 (Bokura, Yamaguchi, & Kobayashi, 2001). It is assumed that the N2 emerges from the dACC and reflects early conflict detection needed to initiate inhibitory control during NoGo trials (Luijten et al., 2014; Nieuwenhuis, Yeung, & Cohen, 2004; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; van Veen & Carter, 2002), while the P3 is more a reflection of the actual motor inhibition of not pressing a button during NoGo trials, as it is identified near the motor and premotor cortices (Band & Boxtel, 1999; Smith, Johnstone, & Barry, 2008). The error related negativity (ERN) is generated by the dACC after non-inhibited NoGo trials and can be regarded as a neurophysiological measure of error processing (e.g. Ridderinkhof et al., 2004).

The current study is the first to investigate the effects of HD-tDCS targeting the dACC on measures of impulsivity. It extends upon the work of To et al (2018) by utilising a stronger current intensity, assessing the impact of stimulation on behavioural measures of impulsivity and EEG measures of inhibitory control and error processing, tested in a cohort of individuals with high trait impulsivity. As self-reported impulsivity has generally been related to worse performance on the Go-NoGo task (Keilp, Sackeim, & Mann, 2005; Littel et al., 2012), it was hypothesised that anodal HD-tDCS stimulation would result in improved performance on the Go-NoGo task, indicative of an acute reduction in impulsivity. In addition, healthy populations with high trait impulsivity and individuals with externalizing disorders often show decreased neurophysiological responses related to inhibitory control and error processing (Littel et al., 2012; Ruchsow et al., 2005; Ruchsow et al., 2008; Shen, Lee, & Chen, 2014). We therefore hypothesized that N2, P3, and ERN amplitudes would become stronger after HD-tDCS over the dACC.

## Materials and methods

### Participants

Twenty-three healthy right-handed adults (7 males, 16 females) were recruited from Melbourne, Australia (n = 14) and Rotterdam, The Netherlands (n = 9) via online advertisements. All participants scored $\geq$47 (M = 53.0, SD = 4.6) on the Short Version of the Urgency, Premeditation, Perseverance, Sensation Seeking and Positive Urgency Impulsive behaviour scale (SUPPS-P; Smith, McCarthy, & Zapolski, 2009; Cyders, Littlefield, Coffey, & Karyadi, 2014), indicative of high trait impulsivity (see SUPPS-P below for cut-off score rational). All participants were aged between 18 – 55 years (M = 20, SD = 2.5), and educated for an average of 14 $\pm$ 2 years. Study exclusion criteria were: 1) any contraindications to HD-tDCS; 2) current or lifetime history of DSM-5 defined mental illness as determined by the Mini Neuropsychiatric Interview 7.1 (Sheehan et al., 1998); 3) self-reported history of traumatic brain injury, neurological illness or diagnosis of ADHD or learning disorder and; 4) current use of psychoactive medications. Eligibility was assessed by a researcher trained for standardised clinical interviewing. Written informed consent was obtained from participants before they entered the study and the protocol was approved by the Monash University Human Research Ethics Committee (MUHREC) and the Ethics Review Committee DPECS at Erasmus University. The study was pre-registered with identifier NCT04290533 at ClinicalTrials.gov.

### Experimental design

The study employed a single-blind, cross-over design, with each participant undergoing two experimental sessions (see Fig 1). For participants from Melbourne, the sessions took place at BrainPark Monash University, and in Rotterdam at the Erasmus Behavioural Lab. In each session, participants received either active or sham HD-tDCS administered in counter-balanced order. Before (Baseline), directly after (Post 1), and 30-minutes after HD-tDCS (Post 2), participants performed the Go-NoGo task whilst EEG was recorded. Post 2 data was collected, as maximal excitation following HD-tDCS can occur temporally downstream from stimulation delivery (Kuo et al., 2012). The first session had a total duration of approximately two hours. The second session took place after

a wash-out period of at least 3 days (M = 7.1 days, SD = 3.9 days), and had a duration of approximately 1.5 hours.

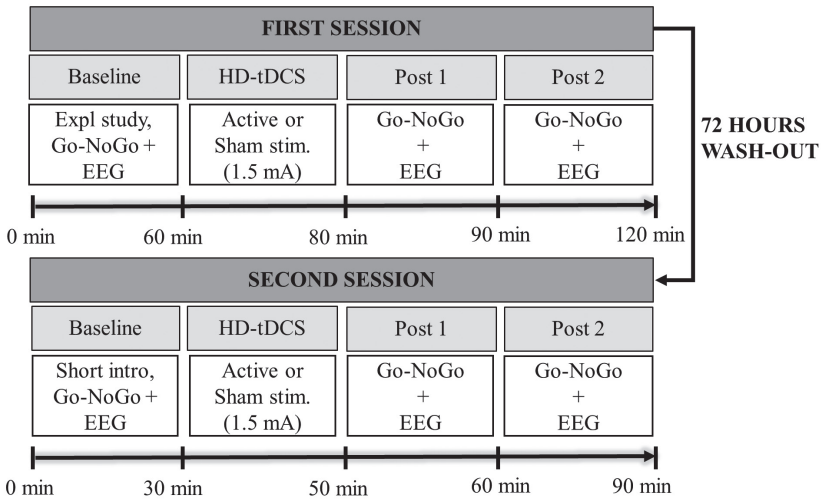


**Fig 1.** Study design. Individuals with high trait impulsivity received either active or sham HD-tDCS targeted to the dACC (1.5mA, 20 min stimulation) during the first session. At baseline, directly after (Post 1) and 30 minutes after HD-tDCS (Post 2) the Go-NoGo task was performed while EEG was recorded. During the second session, participants received the alternate HD-tDCS condition (session order counterbalanced).



## Materials and Measures

### High-Definition trancranial Direct Current Stimulation

HD-tDCS was delivered by a battery-driven, wireless, multichannel Starstim neurostimulator system (Neuroelectrics, Barcelona, Spain). Direct currents were transmitted through five circular Ag/AgCl PiStim electrodes (1 cm radius) that were applied with conductive gel and embedded within an actiCAP (Brain Products, Munich, Germany). The placement of the electrodes was determined by the International 10-20 System, with the anodal electrode placed over the scalp region overlying the dACC (Fz) and four return electrodes montaged over the forehead (Fp1, Fp2, F7, and F8; To et al., 2018). HD-tDCS stimulation duration was 20-minutes, with a 60-second ramp at the beginning and end of the session.

Before commencement of the study, the HD-tDCS montage was modelled with both 1 mA and 1.5 mA intensities to compare the associated electric field strengths

used in this study with the one previously used to target the dACC (To et al., 2018). Computational electric field models were conducted using the SimNIBS software (www.simnibs.org; Thielscher, Antunes, & Saturnino, 2015) incorporating the extended MNI head model ('MNIhead') included with the software. The model indicated that 1.5 mA would achieve greater impact on brain regions approximating the dACC compared with the 1 mA intensity, which was shown to achieve only minimal current flow across this region (see Fig 2). After additional piloting, which confirmed the tolerability and potential for blinding of stimulation at 1.5mA, we deemed this intensity preferable for use in the present protocol.

For the sham-condition, the placement of the electrodes were identical to active HD-tDCS condition. To assist with participant blinding, a 60-second active ramp-up phase was applied, identical to the active HD-tDCS condition, however at conclusion of this ramp-up when the current reached 1.5mA current intensity was gradually ramped down again to 0 mA over the next 60 seconds (To et al., 2018). The current was then held at 0 mA for the remaining 18-minutes. These sham procedures mimic the transient skin sensation frequently reported at the beginning of active HD-tDCS without producing any conditioning effects on the brain (e.g. Gandiga, Hummel, & Cohen, 2006; Woods et al., 2016).

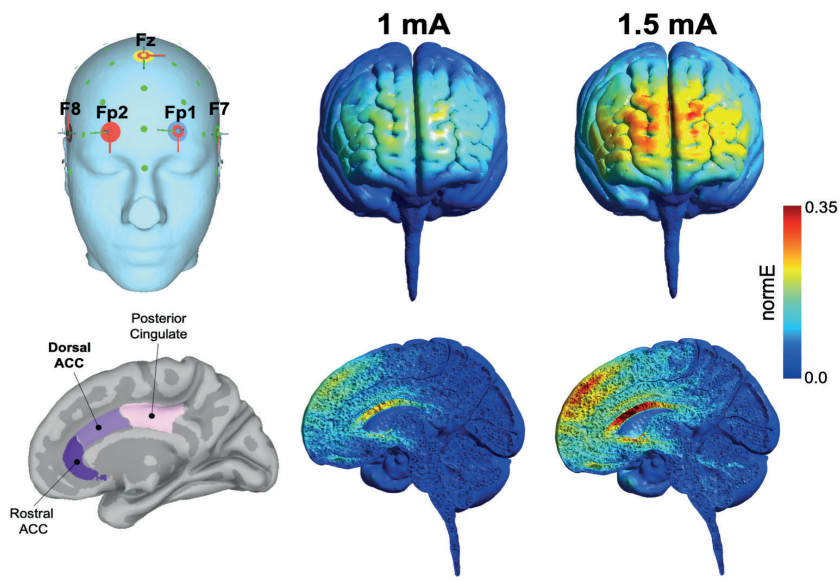


**Fig 2.** Computational model of HD-tDCS stimulation with 1mA and 1.5mA intensity using the SimNIBS software (www.simnibs.org; Thielscher, Antunes, & Saturnino, 2015).

**HD-tDCS tolerability**

Immediately following the stimulation period, the intensity of any cutaneous sensations associated with HD-tDCS administration was assessed on a 5-point Likert scale (1 = no sensation, 5 = extreme sensation). The following sensations were rated: itching, burning, or tingling sensations, difficulties with concentrating, acute mood changes, sleepiness, neck pain, and headache. A paired samples t-test with Condition (Active vs. Sham tDCS) as within-subject factor was performed for the average intensity of adverse effects experienced by each participant. No differences between the conditions were observed regarding adverse effects.

**SUPPS-P**

The SUPPS-P (Smith et al., 2009; Cyders et al., 2014) was used to measure trait impulsivity. The SUPPS-P is a widely used validated 20-item scale that measures five dimensions of impulsive behavior: negative urgency, premeditation, perseverance, sensation seeking and positive urgency. Participants are asked to indicate how strongly they agree or disagree on a 4-point Likert scale (1 = agree strongly to 4 = disagree strongly) with statements that relate to impulsive tendencies, such as "When I feel bad, I will often do things I later regret in order to make myself feel better now" and "I tend to lose control when I am in a great mood". The SUPPS-P demonstrates strong internal consistency coefficients and a factor structure comparable to the widely used full 64-item version of the UPPS-P (Cyders et al., 2014).

The cut-off score of 47 applied in the current study to indicate high trait impulsivity was determined following analysis of a large database (n = 485) of impulsivity, compulsivity and mental health questionnaires completed by a healthy community sample as part of an ongoing unrelated research study at Monash University BrainPark. For this dataset the mean SUPPS-P score was 38.7 $\pm$ 8.4. Thus, the current cut off score represents 1 SD above the mean of a large community sample, indicating the upper end of the community population distribution. We subsequently collected SUPPS-P data from a local community sample in Rotterdam (n = 387) and found comparable SUPPS-P scores (M = 42.3, SD = 7.5).

### Go-NoGo task

The Go-NoGo task is one of the most commonly used cognitive tasks to measure inhibitory control processes (Luijten et al, 2014). Three different stimuli are presented in this Go-NoGo task, namely Go stimuli (grey circle), IfGo stimuli (purple circle) and NoGo stimuli (blue circle; see Fig 3). IfGo stimuli are basically go stimuli with a different colour, added in this version of the Go-NoGo task to control for attentional processes. The rational is that NoGo stimuli are more attentionally demanding compared to Go stimuli (Gao, Qi, & Zhang, 2017), and may therefore evoke larger brain responses which are not merely related to response inhibition (Hong, Wang, Sun, Li, & Tong 2017).

During the task, participants must press a button as fast as possible for Go stimuli and IfGo stimuli. For NoGo stimuli, participants are instructed to withhold their response. The task starts with 10 practice trials and comprises a total of 383 trials. Of all trials, 249 (65%) are Go stimuli, 67 (17.5%) are IfGo stimuli and 67 (17.5%) are NoGo stimuli. Stimuli are displayed for 600 ms, followed by a black screen with a duration varying between 900 ms and 1100 ms. The total duration of the task is about ten minutes, including two short breaks.

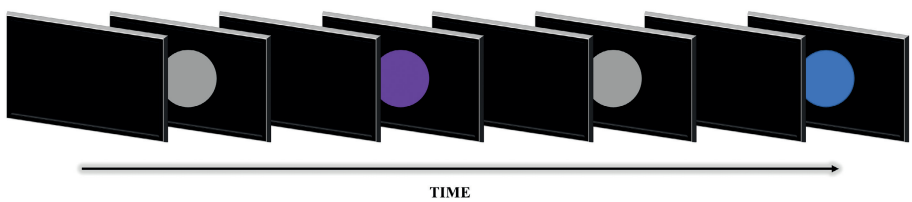


**Fig 3.** Example of the Go-NoGo task. Grey circles represent Go trials, purple circles reflect IfGo trials, and blue circles are NoGo trials.

## EEG recording and processing

EEG activity was recorded using a Brain Products recorder (BrainProducts GmBH, Munich, Germany). Silver chloride (Ag/AgCl) active electrodes were positioned according to the International 10-20 system (F3, F4, FC1, FCz , FC2, FC5, FC6, C3, Cz, C4, CP1, CP2, CP5, CP6, T7, T8, P3, Pz, P4, P7, P8, O1, Oz, O2). Note that brain activity was not recorded over electrode sites Fz, Fp1, Fp2, F7, and F8 since these were used for HD-tDCS electrodes. Two EOG electrodes, above and below the left eye, measured eye movements and two additional external

electrodes were placed over the mastoids. All signals were digitized with a sampling rate of 5000 Hz, a 16-bit A/D conversion and a low pass filter of 28 Hz.

Data were processed offline using BrainVision Analyzer 2 (Brain Products GmbH, Munich, Germany). The data were first re-referenced to the mastoids. EEG and EOG data were filtered using a low cutoff of .10 Hz and high cutoff of 30 Hz (24 dB/octave slope). Data were segmented into epochs from 200 ms before to 800 ms after response or stimulus presentations. The Gratton and Coles algorithm was used for ocular correction (Gratton, Coles, & Donchin, 1983). All ERPs were baseline corrected, with the mean 200 ms pre-stimulus period serving as baseline. Artefact rejection was performed with the criterion minimum and maximum baseline-to-peak –100 to +100 μV.

For response inhibition, grand averages were obtained from the correct NoGo trials (segments with incorrect responses were excluded). The N2 was defined as the average negative waveform within the 225–325 ms interval post-stimulus onset and the P3 was determined as the average value within 325–425 ms after stimulus onset. The time intervals for the N2 and P3 were based on previous literature and verified via visual inspection (e.g. Luijten, Littel, Franken, 2011). For error processing, grand averages were calculated for incorrect button presses. The ERN was quantified as the mean amplitude measure in a time window of 0 to 75 ms (Littel et al., 2012). All ERP components in the current study peak over frontocentral sites, therefore the main analyses of ERP data were restricted to electrodes FCz and Cz (Kiefer, Marzinzik, Weisbrod, Scherg, & Spitzer, 1998; Overbeek et al., 2005).



## Data analyses

To include participants with missing data and to fit the nested data structure, multilevel analyses were performed in R (R Core Team, 2018) using the lme4 package (Bates, Maechler, Bolker, & Walker, 2014). Multilevel modelling has also been recommended as an approach to investigate change in ERPs across the course of an experiment (see Volpert-Esmond, Merkle, Levsen, Ito, & Bartholow, 2017 for further detail).

Baseline, Post 1, and Post 2 measurements of performance outcomes and ERPs were defined at Level 1, and Participants at Level 2, with Condition (sham HD-tDCS vs. active HD-tDCS) as predictor variable (e.g., Hox, 2010; for a general

overview of multilevel analysis procedures). Consistent with previous literature, electrode (FCz and Cz) was added as crossed random factor (Judd, Westfall, & Kenny, 2012; Volpert-Esmond et al., 2017). With this procedure it cannot be tested whether effects of HD-tDCS vary across different electrode sites. Therefore, we conducted additional multilevel analyses for ERPs measured over single electrode sites FCz and Cz.

Separate multilevel analyses were conducted for every outcome variable. Performance on the Go-NoGo task was assessed by the percentage of accurate inhibited NoGo trials, reaction times on Go trials, and reaction times post errors. For ERP analyses, sperate models were fitted to NoGo N2 and P3 amplitudes and to the ERN. EEG data that resulted in too few analyzable ERP segments were excluded from analyses.

First, a baseline model was fitted to every outcome variable, including random intercepts across participants (M0). With this model, it was assessed whether multilevel analysis was required. The intraclass correlation (ICC = $\rho = \frac{\sigma^2_{u0}}{\sigma^2_{u0} + \sigma^2_{\hat{e}}}$) was consequently calculated using the baseline models' results as an indication of the proportion of total variance explained by the subject variation at Level 2. By significant variance at Level 2, the other models were fitted. The second model included the Level 1 predictors as fixed effects (M1). This model was further extended by adding random slopes for Time (M2). Next, the Level 2 predictor Condition was added to the model (M3). The final model (M4) included cross-level interactions between Level 1 variables and the predictor variable Condition at Level 2. The fit of the models was compared using a significance test on the deviance statistics. The assumptions of normality and linearity were assessed by inspecting the residuals of each best fitted model. Unless otherwise reported, the assumptions were met.

## Results

### Behavioural outcomes

For all behavioural outcomes on the Go-NoGo task a multilevel model with random intercepts fitted the data (i.e. variance at Level 2 was significant), where $ICC_{Accuracy} = 0.79$, $ICC_{RT\_GO} = 0.79$ and $ICC_{RT\_post} = 0.60$ (Table 1). Comparing the fitted models on the percentage of correct NoGo trials (accuracy) indicated that

the baseline model (M0) was the best fitted model. Consequently, there was no significant change for accuracy across the three time points. In addition, the main effect of Condition was not significant, indicating that accuracy did not differ between the active HD-tDCS and sham HD-tDCS conditions.

For both reaction times on Go trials and reaction times post erroneous trials, the first model with Time as fixed effect (M1) fitted the data best (Table 2). In these models, there was a significant main effect of Time (Baseline to Post 1 and Baseline to Post 2). As shown in Fig. 4, reaction times on Go trials decreased with an average of 8 ms from Baseline to Post 1 and with an average of 7 ms from Baseline to Post 2. Reaction times post erroneous responses also changed across measurement moments, with an average post reaction time decrease of 24 ms from Baseline to Post 1 and an average decrease of 20 ms from Baseline to Post 2 (Fig 5). There was no significant difference between the active HD-tDCS and sham HD-tDCS condition on reaction times.

**Table 1.** Parameter estimates (se between brackets) and model fit statistics per model for behavioural measures of the Go-NoGo.

| Outcome | Fixed part | | | | | | Random part | | | | Likelihood ratio test[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Accuracy: | Intercept | Pre-Post1 | Pre-Post2 | Group | Group * Pre-Post1 | Group * Pre-Post2 | $\sigma^2_e$ | $\sigma^2_{u0}$ | $\sigma^2_{u1}$ | $\sigma^2_{u2}$ | |
| M0 | 31.06 (3.23) *** | | | | | | 61.3 | 228.9 | | | 135.39*** |
| M1 | 31.07 (3.37)*** | -0.44 (1.66) | 0.41 (1.68) | | | | 62.3 | 228.5 | | | 0.26 |
| M2 | 31.04 (3.61)*** | -0.40 (1.83) | 0.42 (1.68) | | | | 58.8 | 268.8 | 17.6 | 3.8 | 2.49 |
| M3 | 30.75 (3.66)*** | -0.40 (1.83) | 0.41 (1.68) | 0.60 (1.34) | | | 59.4 | 268.1 | 17.0 | 3.6 | 0.21 |
| M4 | 31.40 (3.78)*** | -1.36 (2.42) | -0.56 (2.35) | -0.72 (2.33) | 1.99 (3.27) | 1.99 (3.30) | 60.4 | 268.2 | 16.2 | 3.4 | 0.51 |
| RT Go trials: | | | | | | | | | | | |
| M0 | 318.82 (5.86)*** | | | | | | 196.4 | 756.2 | | | 138.43*** |
| M1 | 323.62 (6.10)*** | -8.28 (2.85)** | -6.21 (2.88)* | | | | 184.7 | 757.9 | | | 8.91* |
| M2 | 323.70 (6.75)*** | -8.36 (3.60)* | 6.20 (3.47) | | | | 148.9 | 971.9 | 146.8 | 121.8 | 7.81 |
| M3 | 323.15 (6.83)*** | -8.35 (3.61)* | -6.21 (3.47) | 1.13 (2.13) | | | 150.1 | 972.7 | 146.1 | 120.9 | 0.29 |
| M4 | 320.07 (7.00)*** | -3.30 (4.36) | -2.05 (4.29) | 7.50 (3.62)* | -10.49 (5.08)* | -8.53 (5.14) | 145.6 | 980.4 | 150.0 | 123.4 | 4.88` |
| RT post errors: | | | | | | | | | | | |
| M0 | 305.28 (7.86)*** | | | | | | 849.5 | 1274.5 | | | 70.85*** |
| M1 | 319.18 (8.53)*** | -21.92 (5.73)*** | -19.69 (5.80)*** | | | | 745.7 | 1291.0 | | | 16.63*** |
| M2 | 319.20 (9.98)*** | -22.10 (6.46)** | -19.78 (5.81)** | | | | 692.9 | 1935.4 | 258.9 | 59.5 | 7.61 |
| M3 | 320.51 (10.22)*** | -22.12 (6.48)** | -19.74 (5.83)** | -2.73 (4.59) | | | 697.1 | 1934.3 | 259.1 | 60.3 | 0.36 |
| M4 | 321.51 (10.71)*** | -25.28 (8.46)** | -19.45 (8.11)* | -4.80 (7.97) | 6.54 (11.17) | -0.50 (11.29) | 707.0 | 1931.4 | 258.4 | 60.7 | 0.51 |

*M0: baseline model with random intercepts and Level 1 predictor time. M1: M0 + random slopes for time. M2: M1 + Level 2 predictor group. M3:M2 + cross-level interaction effect of time and group. RT: Reaction Time. *p < 0.05. **p < 0.01. ***p<.001.*

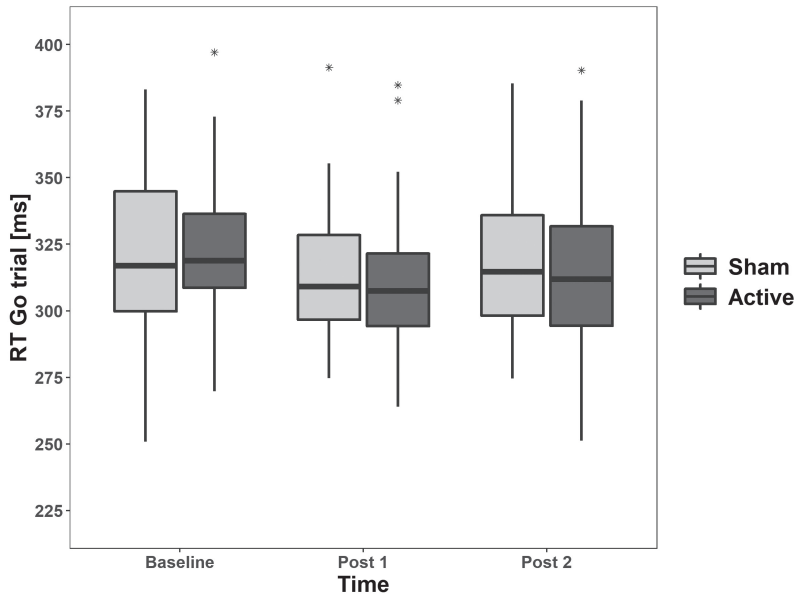


**Figure 4.** Box plots representing reaction times (RT) on Go trials for Sham and Active HD-tDCS at baseline, directly after HD-tDCS (Post 1) and 30 minutes after HD-tDCS (Post 2). RT significantly decreased from Baseline to Post 1 and from Baseline to Post 2.



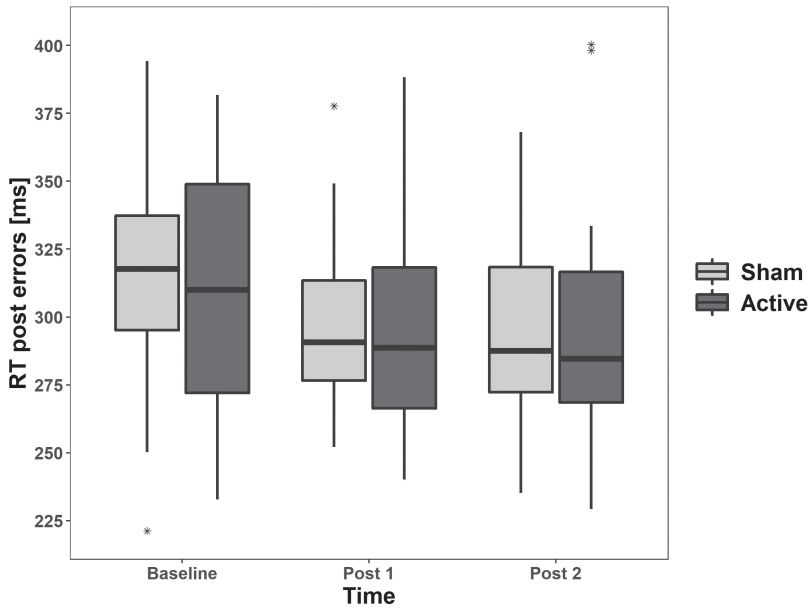


**Figure 5.** Box plots representing reaction times (RT) on post erroneous trials for Sham and Active HD-tDCS at baseline, directly after HD-tDCS (Post 1) and 30 minutes after HD-tDCS (Post 2). RT significantly decreased from Baseline to Post 1 and from Baseline to Post 2.

## Event related potentials

**Table 2.** Descriptive data for electrophysiological measures.

| | Baseline | | Post1 | | Post2 | |
|---|---|---|---|---|---|---|
| | Active tDCS | Sham tDCS | Active tDCS | Sham tDCS | Active tDCS | Sham tDCS |
| **N2** | n=21 | n=21 | n=21 | n=19 | n=20 | n=20 |
| FCz | -6.45 (3.65) | -6.55 (3.23) | -5.97 (4.72) | -6.52 (3.99) | -5.76 (3.41) | -6.74 (2.94) |
| Cz | -1.65 (2.31) | -1.93 (2.29) | -2.13 (1.93) | -1.91 (2.39) | -2.07 (2.21) | -1.65 (2.38) |
| **P3** | n=20 | n=21 | n=21 | n=19 | n=19 | n=20 |
| FCz | 6.41 (5.69) | 5.80 (3.96) | 5.82 (6.68) | 5.06 (5.04) | 5.79 (5.25) | 4.04 (4.78) |
| Cz | 1.67 (3.89) | 1.15 (3.42) | 1.12 (4.20) | 0.40 (3.66) | 0.96 (2.81) | 0.34 (3.92) |
| **ERN** | n=18 | n=19 | n=18 | n=15 | n=20 | n=16 |
| FCz | -7.38 (3.07) | -8.58 (5.14) | -7.07 (5.34) | -7.16 (4.63) | -6.36 (4.71) | -6.30 (4.79) |
| Cz | -1.89 (2.49) | -0.35 (2.56) | -1.46 (1.91) | -0.85 (2.59) | -1.10 (1.97) | -1.04 (2.07) |

*Note*: Mean (SD) for NoGo N2, NoGo P3, and ERN amplitudes (μV) at each relevant electrode side: FCz and Cz.
Table 2 shows the descriptive statistics for relevant ERP amplitude values.

The baseline models with random intercepts (M0) fitted the ERP data, where $ICC_{NoGo\_N2}$ = 0.40, $ICC_{NoGo\_P3}$ = 0.40 and $ICC_{ERN}$ = 0.41 (Table 2). It was therefore confirmed that multilevel analyses could be performed for all ERP outcomes. For the ERP cluster analyses, the baseline model was the best fit for the data indicating that there were no significant main effects for Time and Condition, nor was there a significant cross-level interaction effect for the NoGo N2, NoGo P3 and ERN components.

Multilevel analyses for FCz again revealed that M0 was the best fitted model for NoGo N2 and NoGo P3 amplitudes, with no change over measurement moments and no difference between conditions (active HD-tDCS vs. sham HD-tDCS). For the ERN component as measured over electrode site FCz, M1 was the best fitted model. This model indicated that there was a significant main effect of Time (Baseline to Post 2), with reduced ERN amplitudes 30 minutes after stimulation with both active and sham HD-tDCS ($b$ = 2.27, $p < 0.001$). There was no significant main effect of Condition or cross-level interaction effect.

M0 was also the best fitted model for NoGo N2 amplitudes measured over Cz, indicating no change over time and no significant difference between conditions. In contrast, M4 was the best fitted model for NoGo P3 and ERN components as

measured over Cz. In both models, there was a significant cross-level interaction effect of Condition with Time (Baseline – Post2), indicating smaller amplitudes after active HD-tDCS at Post 2 for the NoGo P3 ($b$ = -1.29, $p$ = 0.045; Fig 6) and for the ERN ($b$ = 1.31, $p$ = 0.032; Fig 7). In sum, these findings show that HD-tDCS over the dACC modulates both the NoGo P3 and ERN measured over central electrode sites (Cz) 30 minutes after stimulation.

**Table 3.** *Parameter estimates (se between brackets) and model fit statistics per model for electrophysiological measures of the Go-NoGo task.*

| Outcome | Fixed part | | | | | | Random part | | | | Likelihood ratio test[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NoGo N2: | Intercept | Pre-Post1 | Pre-Post2 | Group | Group * Pre-Post1 | Group * Pre-Post2 | $\sigma^2_e$ | $\sigma^2_{u0}$ | $\sigma^2_{u1}$ | $\sigma^2_{u2}$ | |
| M0 | -4.08 (2.27) | | | | | | 5.4 | 3.6 | | | 79.98*** |
| M1 | -4.12 (2.28) | 0.01 (0.37) | 0.11 (0.37) | | | | 5.5 | 3.6 | | | 0.11 |
| M2 | -4.12 (2.28) | 0.02 (0.37) | 0.10 (0.37) | | | | 5.4 | 3.7 | 0.04 | 0.10 | 1.88 |
| M3 | -4.25 (2.28) | 0.01 (0.37) | 0.10 (0.37) | 0.24 (0.31) | | | 5.4 | 3.7 | 0.04 | 0.10 | 0.62 |
| M4 | -4.23 (2.29) | 0.02 (0.53) | 0.05 (0.53) | 0.21 (0.52) | -0.02 (0.74) | 0.11 (0.74) | 5.5 | 3.7 | 0.04 | 0.10 | 0.03 |
| NoGo P3: | | | | | | | | | | | |
| M0 | 2.25 (3.22) | | | | | | 10.1 | 6.6 | | | 74.69*** |
| M1 | 2.57 (3.24) | -0.37 (0.50) | -0.60 (0.50) | | | | 10.1 | 6.5 | | | 1.51 |
| M2 | 2.57 (3.23) | -0.39 (0.50) | -0.60 (0.50) | | | | 10.0 | 6.3 | 0.2 | 0.1 | 1.85 |
| M3 | 2.31 (3.24) | -0.41 (0.50) | -0.60 (0.50) | 0.53 (0.41) | | | 10.0 | 6.3 | 0.2 | 0.1 | 1.61 |
| M4 | 2.28 (3.25) | -0.42 (0.72) | 0.51 (0.71) | 0.58 (0.70) | 0.02 (1.00) | -0.18 (0.99) | 10.1 | 6.3 | 0.2 | 0.1 | 0.05 |
| ERN: | | | | | | | | | | | |
| M0 | -4.15 (3.06) | | | | | | 8.0 | 5.5 | | | 65.34*** |
| M1 | -4.66 (3.07) | 0.45 (0.48) | 1.08 (0.47)* | | | | 7.8 | 5.7 | | | 5.37 |
| M2 | -4.66 (3.08) | 0.45 (0.48) | 1.08 (0.47)* | | | | 7.8 | 5.9 | 0.0 | 0.0 | 0.08 |
| M3 | -4.63 (3.08) | 0.45 (0.48) | 1.09 (0.47)* | -0.06 (0.40) | | | 7.8 | 5.9 | 0.0 | 0.0 | 0.02 |
| M4 | -4.53 (3.09) | 0.40 (0.70) | 0.80 (0.69) | -0.28 (0.67) | 0.12 (0.98) | 0.55 (0.95) | 7.9 | 5.9 | 0.0 | 0.0 | 0.38 |

*M0: baseline model with random intercepts and Level 1 predictor time. M1: M0 + random slopes for time. M2: M1 + Level 2 predictor group. M3:M2 + cross-level interaction effect of time and group. Stand.: Standardized coefficients of fixed effects. *p < 0.05. **p < 0.01. ***p<.001.*

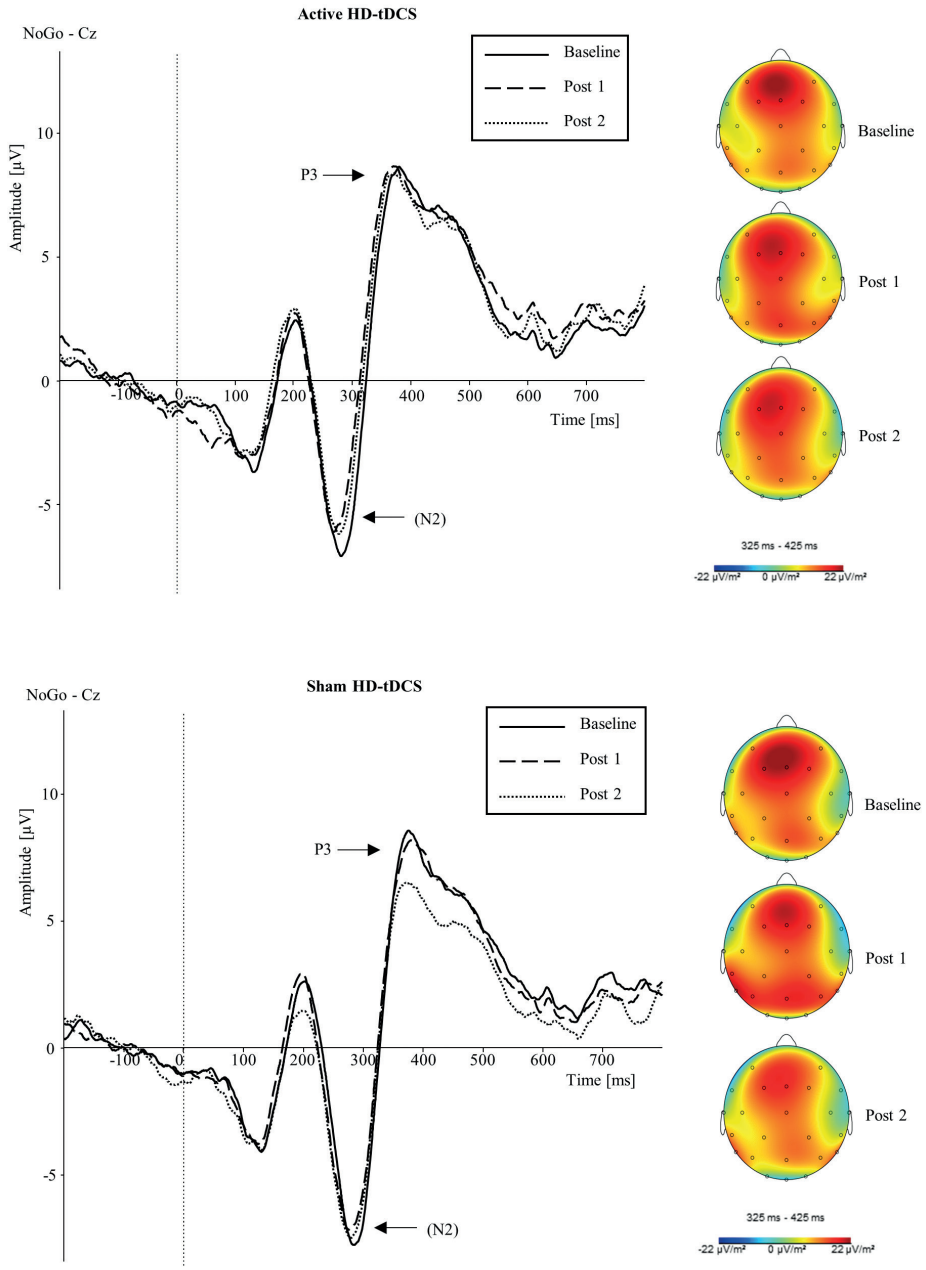


**Figure 6.** NoGo P3 activity for Active and Sham HD-tDCS at baseline, directly after HD-tDCS (Post 1) and 30 minutes after HD-tDCS (Post 2).

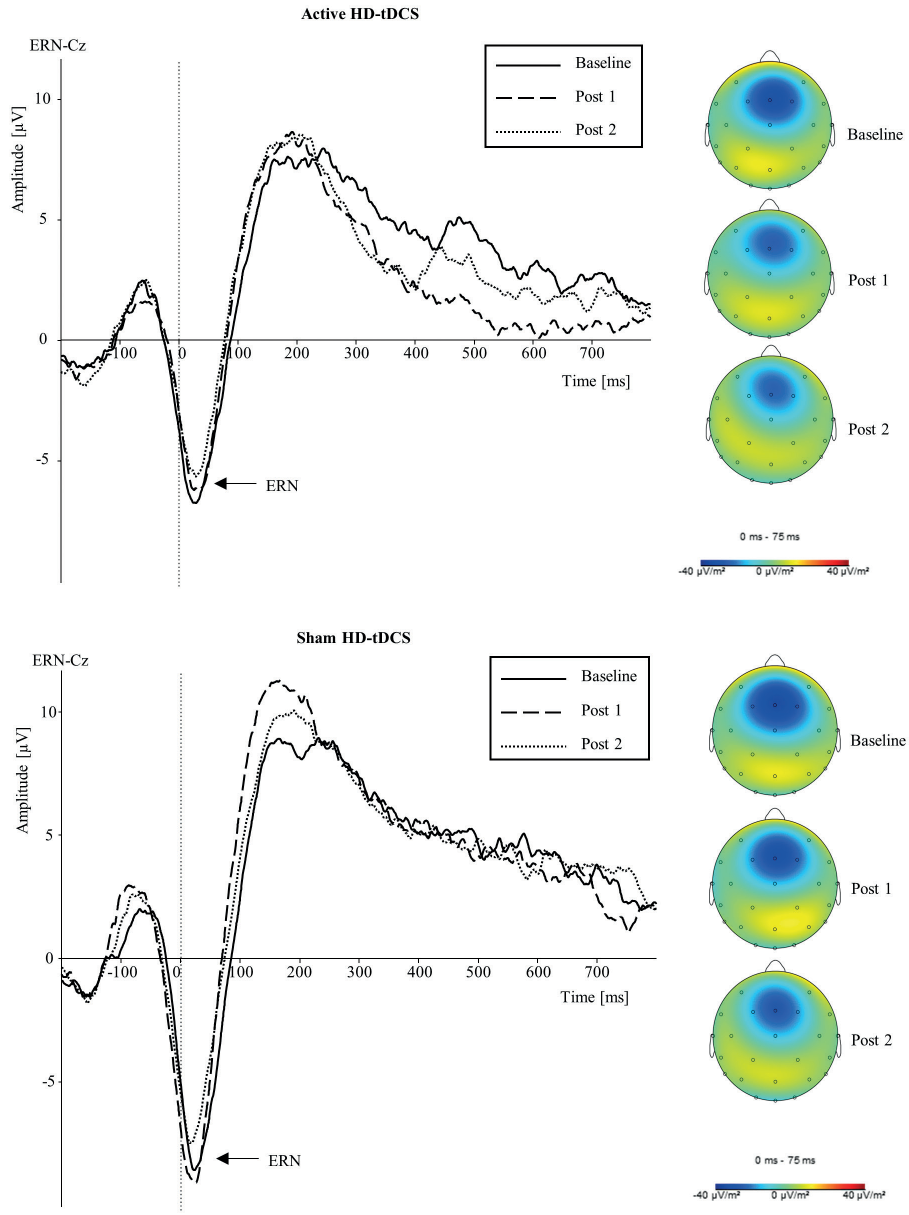


**Figure 7.** ERN activity for Active and Sham HD-tDCS at baseline, directly after HD-tDCS (Post 1) and 30 minutes after HD-tDCS (Post 2).

## Discussion

To the best of our knowledge, this is the first proof-of-concept study to explore whether HD-tDCS over the dACC can modulate two key components of impulsivity, namely inhibitory control and error processing, in individuals with high trait impulsivity. While behavioural performance on the Go-NoGo task was unaffected by HD-tDCS, 30-minutes after stimulation a reduction in ERP amplitudes indexing motor inhibition (P3) and error processing (ERN) were observed, consistent with prior reports indicating maximal response to HD-tDCS temporally downstream from the cessation of stimulation (Kuo et al., 2012). These findings indicate that our implemented HD-tDCS montage, designed to direct current flow to the dACC, may successfully modulate the underlying neurobiological substrates of impulsivity, but that these changes are not associated with observable behavioural modifications after a single dose of stimulation.

Past findings on the effects of prefrontal non-high definition tDCS montages are consistent with the current results indicating no change in inhibitory control performance by the absence of behavioral accuracy enhancement on the Go-NoGo task, despite of subtle brain modifications (Campanella et al., 2017; Cunillera, Brignani, Cucurell, Fuentemilla, & Miniussi, 2016; Lapenta Di Sierve, de Macedo, Fregni, & Boggio, 2014; Sallard, Mouthon, De Pretto, & Spierer, 2018; Verveer et al., *Chapter 3*). The effects of tDCS on proactive inhibitory control, as measured by reaction times on Go trials, have been more mixed. In line with our findings, some studies have observed no change in reaction times on Go trials after tDCS (Campanella et al., 2017; Lapenta et al., 2014), whereas others have reported significant changes in reaction times after tDCS (Cunillera et al., 2016; Verveer et al., *Chapter 3*). In addition, a recent study reported a larger increase in prefrontal cortex activity as measured by fMRI on Go trials than on NoGo trials after anodal tDCS, while no effects on performance and reaction times were found (Sallard et al., 2018). Inconsistent findings on proactive inhibitory control after tDCS have been attributed to the difficulty of the Go-NoGo task. It was proposed that reaction times do not improve for simple Go-NoGo tasks because of a floor effect (Campanella et al., 2017; Sallard, Mouthon, De Pretto, & Spierer, 2018). However, this explanation does not apply to the

current data, as we observed faster reaction times at later time points as compared to baseline. Alternatively, 'online' HD-tDCS protocols, where stimulation is applied concurrently with task performance, might result in larger effects on Go-NoGo performance than 'offline' HD-tDCS, whereby stimulation is applied in the absence of any cognitive engagement. However, it should be noted that online HD-tDCS protocols have also reported neurophysiological changes in the absence of behavioural modulation (Hill, Rogash, Fitzgerald, & Hoy, 2019).

The lack of behavioural performance enhancement after HD-tDCS does not render neurophysiological modifications irrelevant as a reflection of changes in impulsivity. Few studies to date have investigated the effects of prefrontal tDCS on the NoGo P3 ERP. In line with the current results, prior research has shown decreased NoGo P3 amplitudes after anodal tDCS, without related changes in accuracy on inhibitory control trials (Campanella et al., 2017; Cunillera et al., 2016; Verveer et al., *Chapter 3*). It has been suggested that the P3 reflects the inhibition of motor processes (Band & Boxtel, 1999; Smith, Johnstone, & Barry, 2008), and therefore lower P3 amplitudes after (HD-)tDCS may indicate that less neural resources are needed to reach similar motor response inhibition levels as before neurostimulation (Cunillera et al., 2016). Of note, the electrical currents induced by HD-tDCS travel through other brain areas before reaching the dACC. One of these areas is the pre-supplementary motor area (pre-SMA; To et al., 2018); a brain region involved in motor response inhibition during simple Go-NoGo tasks (Mostofky et al., 2003; Garavan et al., 2006). We therefore argue that the modulation of neurophysiological correlates of motor response inhibition might be the result of our HD-tDCS montage affecting motor areas.

Modulation of the ERN component after HD-tDCS may be more directly linked to modulation of the dACC (e.g. Ridderinkhof et al., 2004). We are unaware of any previous studies reporting tDCS-induced changes in the ERN amplitude, however, modulation of this component has recently been reported following high frequency repetitive transcranial magnetic stimulation (rTMS) over the dACC (Carmi et al., 2018). By the lack of behavioural changes in error processing, we again speculate that smaller amplitudes after HD-tDCS indicate improved efficiency regarding the use of neural resources for error processing. It may also be that HD-tDCS caused a shift in brain activity, focalized towards

the dACC, resulting in decreased NoGo P3 and ERN amplitudes over central electrode sites.

HD-tDCS targeting the dACC did not result in significant modulations of NoGo N2 amplitudes. As the NoGo N2 is reflective of early conflict detection needed to initiate inhibitory control, the lack of changes is in line with the absence of behavioural performance modulations. It was somewhat surprising that we observed no change in the NoGo N2 ERP, as it is generally assumed the NoGo N2 is generated from the dACC. Yet, it has also been proposed that the inferior frontal cortex (IFC) may contribute to the initiation of N2 amplitudes (Huster, Enriquez-Geppert, Lavallee, Falkenstein, & Herrmann, 2013). However, when the IFC was targeted with conventional tDCS in previous studies, N2 amplitudes were also not modulated (Campanella et al., 2017; Cunillera et al., 2016). Regarding these results, it is important to keep in mind that the current investigation was a proof-of-concept study. Although our computational models indicated that the present HD-tDCS montage could induce electric fields within deeper brain regions corresponding to the dACC, it remains uncertain whether one session of HD-tDCS with 1.5 mA intensity is sufficient to modulate dACC activity. Future studies should investigate this HD-tDCS montage with fMRI to further verify dACC modulation. In addition, larger samples may be needed to find relatively small effects, if present. Yet, while our sample size was moderate, the cross-over design was a strength as it assists with controlling for the many factors that influence interindividual differences in response to HD-tDCS.



In sum, results of the current study indicate that when delivered to individuals with high trait impulsivity a single session of HD-tDCS over the dACC can modulate ERPs reflecting motor inhibition and error processing, which form two core constructs of impulsivity. We therefore conclude that HD-tDCS has potential to affect neurobiological components related to impulsivity. HD-tDCS was not sufficient, however, to modulate behavioural performance on the GoNoGo task. Multi-session HD-tDCS may have a better capacity to induce behavioural changes in impulsivity and warrant future investigation. This proof-of-concept study may be the first step towards an innovative HD-tDCS intervention in clinical samples characterized by high trait impulsivity (e.g. ADHD, SUD, ASPD).

# 7

# General Discussion

Individuals with a substance use disorder often report difficulties to stop using drugs despite the obvious negative consequences and a strong willingness to quit this use. This concept has been explained by a hyperactive reward system and hypoactive control system of the brain (i.e. prefrontal cortex; PFC), as the result of repeated and prolonged drug use (Volkow et al., 2011). The central aim of this dissertation was to investigate whether non-invasive electrical brain stimulation, in the form of transcranial Direct Current Stimulation (tDCS), applied over the PFC would be beneficial in the treatment of addiction by reducing substance use and craving. Furthermore, this dissertation explored if tDCS modulates behavioural and neurophysiological measures of executive functions associated with the control system, to get better insights in the working mechanism of tDCS in addiction treatment. In order to examine these research topics, we tested the effects of multiple tDCS sessions in *ad libitum* smokers (i.e. smokers who were not motivated to quit smoking at the start of the study) and in patients with cocaine use disorder. We additionally investigated an innovative form of tDCS, namely high-definition tDCS (HD-tDCS), in individuals with high trait impulsivity, as impulsivity is a key characteristic of addiction.

## Summary of Results

When *ad libitum* smokers received multiple sessions of tDCS, we found that tDCS had no additional effect on reducing craving and cigarette consumption as measured by ecological momentary assessments (EMA; chapter 2). In the same group of smokers, we investigated behavioural and neurophysiological measures of executive functions after multi-session tDCS. Inhibitory control and error processing as measured during the Go-NoGo task (chapter 3), as well as feedback processing measured after decisions on the two-choice gambling task (TCGT; chapter 4), seemed unaffected immediately after tDCS. However, behavioural measures of risky decision making changed after multi-session tDCS (chapter 4). In addition, tDCS was associated with faster reaction times and changes in the neurophysiological measure of motor inhibitory control (NoGo P3) at three months follow-up (chapter 3).

In chapter 5, multi-session tDCS was tested as add-on treatment in a sample of cocaine addicted patients. Also, tDCS effects on performance during the

Go-NoGo task and TCGT were assessed in chapter 5. It was hypothesized that patients would be more susceptible to change after tDCS by a higher motivation to quit drug use as compared to *ad libitum* smokers. Yet, there was no effect of multi-session tDCS on craving as measured by EMA and on number of relapse days at three months follow-up. In addition, no changes in inhibitory control and risky decision making were observed. Interestingly, exploratory analysis revealed that multisession tDCS seemed more effective in a subgroup of the sample, who particularly smoked crack cocaine. That is, for these patients relapse rates were significantly lower three months after active tDCS as compared to sham tDCS.

An innovative form of tDCS that has better spatial precision, namely HD-tDCS, was investigated as potential tool to modulate deeper brain regions associated with executive control functions in chapter six. More specifically, we explored the effects of HD-tDCS over the dACC on an important characteristic that is associated with addiction, namely impulsive behaviour, as measured by inhibitory control and error processing on the Go-NoGo task. Although one session of HD-tDCS in individuals with high trait impulsivity did not result in behavioural changes on the Go-NoGo task, we did observe a delayed effect of 30 minutes on neurophysiological measures of motor inhibitory control (NoGo P3) and error processing (error related negativity; ERN).



## Discussion

### Substance Use

Few studies have investigated (immediate and longer-term) tDCS effects on substance use. A recent meta-analysis suggests that tDCS over the dorsolateral prefrontal cortex (DLPFC) has potential to reduce drug use in various substance use disorders (Song et al., 2019). In contrast, we were generally unable to find any significant beneficial effects of tDCS on cigarette consumption and cocaine use in the current dissertation.

### Cigarette consumption

Findings from a recent meta-analysis indicated that the tDCS protocol used in chapter two, with anodal tDCS over the right DLPFC and cathodal tDCS over the left DLPFC, had the most positive effects on smoking behaviour (Kang, Kim,

& Kim, 2019). In order to improve tDCS interventions for tobacco addiction, it is therefore important to understand why we found no effects of tDCS on number of smoked cigarettes in the current dissertation. An important difference is that most previous addiction studies on the effects of tDCS have performed neurostimulation sessions on at least five consecutive days (Fecteau et al., 2014; De Souza Brangioni et al., 2018; Behnam, Mousavi, & Amamian, 2019), whereas in chapter two there was a break of at least two days between each intervention day. It could be speculated that a wash-out effect may have taken place, and that tDCS sessions should be provided on consecutive days in order to obtain a cumulative effect of all tDCS sessions. However, we would have at least expected a short-lasting effect on smoking intake after one tDCS session, as was found by Falcone and colleagues (2016), but this was not the case either. In addition, we found changes in behavioural and neurophysiological measures of inhibitory control at three months follow-up after active tDCS, which could unlikely have occurred in the absence of cumulative long-term tDCS effects.

A more feasible explanation for the non-significant effect of tDCS on cigarette consumption might be the lack of motivation for *ad libitum* smokers to quit smoking. Several motivation models have suggested that addiction treatment in general is most successful when an individual is truly willing to change (Hiller, Knight, Leukefeld, & Simpson, 2002). Individual differences in motivation to quit smoking or drug use may therefore play an important role in the effectiveness of tDCS in addiction treatment. More direct evidence for this hypothesis was provided by a study showing that the effect of tDCS on cigarette consumption was moderated by the motivation to quit smoking (De Souza Brangioni et al., 2018). It was then suggested that the enhanced likelihood of spontaneous neural firing induced by tDCS may particularly impact behaviour that participants are motivated to engage in, whether this is an attempt to quit smoking or a cognitive task they are performing (De Souza Brangioni et al., 2018; Di Rosa et al., 2019; Jones, Gözenman, & Berryhil, 2015). This could explain why smoking behaviour was unaffected by tDCS in our *ad libitum* smokers, who were not necessarily motivated to quit at the start of the study (chapter 2). Also, the finding in chapter five showing that tDCS is particularly promising for patients with crack-cocaine addiction may support this view. It can be speculated that crack-cocaine users may be more motived to change addictive behaviour once they finally decide to

get treatment, as they have more severe addiction related problems than powder-cocaine users. Future addiction studies should take the motivation to quit into account as moderator of tDCS effects.

### Relapse in cocaine addiction

An interesting observation regarding the tDCS effects in cocaine use disorder is that relapse rates three months after sham and active tDCS were similar to previously reported relapse rates in a sample of patients with crack-cocaine use disorder (Klauss et al., 2018). The combined findings show that relapse rates ranged from 41% to 53% after active tDCS as compared to relapse rates ranging from 67% and 74% after sham tDCS. The difference in relapse rates was only significant for the crack-cocaine users in the current dissertation, and not for the powder-cocaine users. Perhaps, tDCS has better treatment success in patients who use cocaine in the form of crack instead of powder, although the difference in relapse rates after active vs. sham tDCS did not reach significance in a previous study with crack-cocaine users (Klauss et al., 2018). Arguably, larger sample sizes are needed, with an equal number of patients who use cocaine in the form of crack and powder, to increase the power and to be able to better detect an effect of tDCS on both crack- and powder cocaine addiction, if present.

The timing of the intervention is another important aspect to take into consideration in research on tDCS in addiction treatment. We started the intervention after the first week of cocaine detoxification, whereas Klauss and colleagues (2018) performed tDCS after 30 days of regular treatment. Abstinent cocaine users go through different stages of neurocognitive recovery (Hanlon, Beverridge, & Porrino, 2013). For example, during the first week of abstinence elevated cerebral metabolism in the PFC have been reported, whereas activity in the PFC was decreased after this first week (Volkow et al., 1991). It can be suggested that the impact of tDCS on synaptic plasticity interacts with the different stages of neurocognitive recovery. Alternatively, tDCS as add-on addiction treatment may strengthen the effectiveness of behavioural treatment by a general increase in neuroplasticity, particularly when patients are highly engaged in available treatment programmes. Therefore, the timing of tDCS treatment and the motivation of patients to actively engage in treatment programmes should be considered in future research.

## Craving

Craving has a strong association with substance use and relapse and was therefore assessed as secondary outcome measure of tDCS effects on addictive behaviour. Both smokers and patients with cocaine use disorder were asked to indicate their craving for the addictive substance (i.e. cigarettes or cocaine) multiple times a day by means of EMA on their own smartphone for two weeks starting from the first tDCS session. Craving was also measured during lab sessions by means of the most commonly used multi-item craving questionnaires, namely the questionnaire for smoking urges (QSU; Cox, Tiffany, & Christen, 2001) and the Obsessive and Compulsive Drug Use Scale (OCDUS; Franken, Hendriks, & van den Brink, 2002) for cocaine craving (Tiffany & Wray, 2012). Lab sessions took place on the day of the first tDCS session, one day after completion of the tDCS intervention and at three months follow-up. We found no beneficial effects of tDCS on craving as measured by EMA and as measured by questionnaires in both smokers (chapter 2) and cocaine users (chapter 5).

While no significant effects of tDCS on craving were found in this dissertation, other studies have reported predominantly positive results on craving (Jansen et al., 2013). In general, retrospective self-reports have been used to assess craving after tDCS, while craving was primarily measured by EMA in the current dissertation. Craving is an episodic phenomenon influenced by environmental cues and internal factors such as stress (e.g. Jones, Rose, Cole, & Field, 2013; Sinha et al., 2009). Self-reported craving may therefore heavily depend on the moment of measurement, making EMA particularly suitable to measure craving, as it captures real-time data multiple times a day in naturalistic settings (Shiffman, Stone, & Hufford, 2008). Consequently, retrospective recall biases can be avoided, which improves the accuracy of assessments. The use of EMA as measurement tool may therefore explain the discrepancy between the results in the current dissertation and previous literature. That is, EMA data may have revealed that for smokers who are not motivated to quit smoking, craving may not decrease after tDCS. However, this may not be the best explanation for the lack of tDCS effects on cocaine craving.

Craving levels for patients with cocaine use disorder were measured with EMA inside the addiction clinic. It could well be the case that there was a floor effect of craving levels by the lack of environmental cues or stress inside the

clinical setting (den Uyl, Gladwin, Rinck, Lindenmeyer, & Wiers, 2017). Our results support this view, as we observed a general decrease of craving over time after both active and sham tDCS, with very low craving levels by the end of the intervention week (chapter 5). This pattern was also found in a study by Klauss and colleagues (2018). Alternatively, these findings may indicate a strong placebo effect of sham tDCS in (cocaine) addicted patients. Future studies may consider including a control group that receives treatment as usual, to test the placebo effect of tDCS in individuals with substance use disorder.

## Executive Functions

Objective neurophysiological and behavioural outcomes of executive functions may constitute a closer mapping to neural abnormalities in addiction than the currently classified symptoms of addiction such as craving (Luigjes et al., 2019). To investigate the underlying mechanism of tDCS in order to improve interventions for addiction treatment we therefore also investigated the effects of tDCS on executive functions associated with addiction and brain areas affected by tDCS targeting the DLPFC, namely inhibitory control, risky decision making, and the (neurophysiological) processing of feedback and errors.



### Inhibitory control

To the best of our knowledge, this is the first time that the effect of multi-session tDCS - targeting the DLPFC - on inhibitory control has been investigated in individuals with addiction (chapter 3 and 5). In smokers and patients with cocaine use disorder, tDCS had no significant effect on improving accuracy during inhibitory control trials on the Go-NoGo task. We were also unable to observe an immediate effect of tDCS on reaction times during the Go-NoGo task (chapter 3 and 5). However, at three months follow-up, we found slightly faster reaction times for smokers who had received active tDCS. In addition, smokers showed a change in the neurophysiological measure of motor inhibitory control (NoGo P3) for smoking related pictures at three months follow-up as compared to baseline.

Considering that the effect of tDCS was most prominent for motor responses, it is possible that the electrical currents reached the premotor cortex in addition to the DLPFC. That is, since the two electrode tDCS montage may cause electrical

fields to diffuse to non-targeted brain areas (Nitsche et al., 2007; Datta, Elwassif, Battaglia, & Bikson, 2008). However, NoGo P3 amplitudes were particularly reduced for smoking related pictures. These pictures require more motivational attention as compared to neutral pictures, and it has been reported that NoGo activity in the right DLPFC is associated with attentional resources (Criaud & Boulinguez, 2013). The findings therefore suggest that at least some currents reached the right DLPFC, but further neuroimaging research is needed to test this hypothesis.

The delayed effects of tDCS on motor inhibitory control are more difficult to explain in terms of neurophysiology. The tDCS protocol we used, with a 20-minute break between two tDCS sessions, may result in delayed after-effects (Monte-Silva et al., 2013). Evidence also suggests that multi-session electrical brain stimulation could modulate long-term synaptic plasticity in the context of (motor) learning (Stagg & Nitsche, 2011; Simonsmeier et al., 2018). The delayed effect of tDCS on NoGo P3 amplitudes may therefore indicate a long-term learning effect on inhibition over motor responses. In this context, the direction of the change in NoGo P3 amplitudes makes sense as well. The P3 is prone to a test-retest effect, with smaller P3 amplitudes at retest after a short period (Kompatsiari, Candrian, & Mueller, 2016), as was also found in chapter three after both active and sham stimulation. Smaller NoGo P3 amplitudes were correlated with faster reaction times, and therefore learning in the context of motor inhibition may indicate the use of less brain activity to achieve the same or an improved level of motor inhibitory control. We suggest that our results could be interpreted as an increased learning effect as a result of tDCS.

There was no tDCS effect on an earlier neurophysiological component related to inhibitory control (NoGo N2). The NoGo N2 was correlated with accuracy on NoGo trials and less related to motor learning than the NoGo P3. More specifically, the N2 reflects early conflict detection needed to initiate inhibitory control (Nieuwenhuis, Yeung, & Cohen, 2004; Luijten et al., 2014), and evidence has indicated that the N2 emerges from the dACC (van Veen & Carter, 2002; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003). Although it has been suggested that tDCS targeting the DLPFC could alter brain activity in the ACC (Weber et al., 2014), the diffusion of electrical currents could reduce the possibility to reach this deeper brain structure. In chapter six, we therefore

decided to use an innovative form of tDCS (HD-tDCS) with increased focality targeting the dACC to investigate the modulatory effects on inhibitory control.

In chapter six we described the first proof-of-concept study to explore whether HD-tDCS targeting the dACC (1.5 mA) can affect inhibitory control, as measure of impulsivity. Impulsivity is an important characteristic associated with addiction, and therefore individuals with high trait impulsivity were recruited for this study. Again, inhibitory control performance was unaffected by one session of HD-tDCS, and again, there was evidence for a delayed change in neurophysiological outcomes of motor inhibition (NoGo P3). Regarding this finding, it should be noted that with the use of this protocol we can be certain that the electrical currents induced by HD-tDCS also travelled through the pre-supplementary motor area (pre-SMA) before reaching the dACC (To et al., 2018). The pre-SMA is involved in motor response inhibition during simple Go-NoGo tasks (Mostofky et al., 2003; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006), and this could very well explain the change in NoGo P3 amplitudes. In addition, a delayed effect of 30 minutes after one session of HD-tDCS is very common and in line with previous literature (Kuo et al., 2012).



**Risky decision making**

In chapter four and five we investigated whether multi-session tDCS could affect risky decision-making in individuals with an addiction. It was previously suggested that tDCS would reduce addictive behaviour by improved decision making (e.g. Fecteau et al 2014). However, after critically reviewing past literature on this topic, we found that tDCS effects on risky decision making in addiction were very inconsistent. While some addiction studies have reported decreased risky decision making after tDCS on several decision making tasks (Fecteau et al., 2014; Gorini et al., 2014; Pripfl et al., 2013), risk-taking on other decision making tasks was unaffected or even increased after tDCS (Boggio et al., 2010; Fecteau et al., 2014). In chapter four we also found that risky decision making was increased after active tDCS on the TCGT, whereas decision making was unaffected after tDCS in patients with cocaine use disorder (chapter 5).

The underlying mechanism of how decisions are made during different risk-taking tasks may explain the mixed results for tDCS effects on risk-taking. Risk taking was particularly decreased after tDCS on decision making tasks where

participants could learn from previous decisions to optimize the probability of receiving rewards. Decreased risk-taking induced by tDCS on these tasks may therefore reflect improved reinforcement learning (Hajcak et al., 2007). In contrast, risk-taking was unaffected or increased after tDCS on decision making tasks where decisions are based on gambling with some degree of certainty about how much risk is taken, since the reward probability is indicated before any decision is made. Arguably, reinforcement learning and gambling constitute different cognitive functions that may be affected differently by tDCS.

**Feedback and error processing**

Another goal of chapter four was to gain further insight into the working mechanism of tDCS on risky decision making by investigating neurophysiological measures of feedback processing. Feedback processing plays an important role in shaping future decisions by processing the outcomes of previous choices (Verdejo-Garcia, Chong, Stout, Yücel, & London, 2018). Prior studies have reported altered neurophysiological measures of feedback processing during decision making tasks in addiction. We therefore hypothesized that beneficial changes in decision making after tDCS would be associated with improved feedback processing. However, despite of changes in risky decision making, feedback processing (i.e. FRN and feedback P3 amplitudes) remained unchanged after active tDCS (chapter 4). Particularly, for the early neurophysiological measure of feedback processing (FRN) we expected an effect of tDCS during the TCGT, since smokers showed blunted FRN amplitudes as compared to non-smokers on the TCGT. It has been assumed that the FRN is generated by the ACC (Gehring & Willoughby, 2002; Luft, 2014), therefore HD-tDCS targeting the dACC may be more effective in changing FRN amplitudes.

The same was hypothesized for the lack of tDCS effects on error processing when tDCS was applied over the DLPFC (chapter 3). Therefore, error processing was also investigated in chapter six with HD-tDCS targeting the dACC. In this study, the active HD-tDCS group showed smaller ERN amplitudes after HD-tDCS as compared to the sham group. We are unaware of any previous studies reporting tDCS-induced changes in the ERN amplitude, however, modulation of this component has recently been reported following high frequency repetitive transcranial magnetic stimulation (rTMS) over the dACC (Carmi et al., 2018).

By the lack of behavioural changes in error processing, we speculate that smaller amplitudes after HD-tDCS indicate improved efficiency regarding the use of neural resources for error processing. Multi-session HD-tDCS may have a better capacity to induce behavioural changes and warrant future investigation

## Limitations and Future Directions

### Outcome measures of treatment success

In clinical trials, it is both challenging and important to select the appropriate primary outcome measure to investigate treatment success. The assessment of complete abstinence has been the golden standard to measure treatment efficacy; however, relapses often occur after treatment and a reduction of drug use to less harmful levels can already be a positive outcome (Ekhtiari et al., 2019). Instead of binary relapse rates, we therefore decided to define relapse by a more informative outcome measure, namely the number of days participants had used cocaine in the three months following tDCS treatment. Yet, in order to compare the results of chapter five to previous reported treatment efficacy of tDCS in cocaine addiction (Klauss et al., 2018), we also determined binary relapse rates. We only found an effect of tDCS for binary relapse rates in crack-cocaine users. This may be because patients were released from the addiction clinic at different moments after the tDCS intervention, introducing divergence in the number of days that participants had the opportunity to use drugs. However, since we preregistered our studies, the primary outcome measure was unchanged to remain credibility of the study protocol and analyses. Future investigations may use the percentage of relapse days and the time until the first relapse as (additional) informative primary outcome measures of treatment success. We would also recommend assessing relapse by means of more objective measures, such as urine controls (chapter 5). Alternatively, self-set treatment goals of patients could be considered to determine individual definitions of treatment success, since these goals may differ per patient depending on the preference and obtainability of treatment outcomes.

### EMA

The use of EMA as measurement tool presents some notable challenges. For example, the experimenter is unable to control variables outside the laboratory

that might be of interest. In addition, occupations in everyday life can have a negative impact on compliance with EMA. Participants may for instance have other priorities when at work, studying, or when out with friends. Because of non-compliance, missing data increases and this can have a significant effect on statistical power. In addition, most non-compliance to EMA questions is systematic and not at random (Stone & Shiffman, 2002). Participants more often miss specific assessments, for example during working hours, rather than random prompts at different times, and this introduces bias.

The compliance rates in chapter two and five were also relatively low, ranging from 44% to 56%, as compared to the average compliance rate of 69.8% in samples with a substance dependence (Jones et al., 2019). Participants in chapter two were mostly students and therefore it can be suggested that activities in their daily life might have affected their compliance. However, this explanation does not apply to the sample of patients with cocaine use disorder from chapter five, who were in the clinic during the study, with only few short-lasting programmes to attend during the day. Some participants indicated technical difficulties with the app we used, and this may explain part of the non-compliance. Other suggested predictors of compliance have been prompt frequency, the total duration of assessments, the type of reimbursement offered and individual differences, such as age and gender. Yet, a recent meta-analysis revealed there was limited evidence that any of these variables were associated with compliance rates (Jones et al., 2019).

Despite low compliance rates, there is reason to believe that the EMA data could still be interpreted, be it with caution. First, we have used the maximum likelihood estimation method in multilevel modelling of the EMA data. Instead of listwise deletion of cases with missing data, the maximum likelihood method allows the inclusion of incomplete data and consequently all data that was available has been analysed (Hox, Moerbeek, & van de Schoot, 2018). Second, the patterns in the data were in line with previous research and other (more objective) measures of the same outcomes. For example, smokers showed a decrease in cigarette consumption starting from the first tDCS session until two weeks later. This main effect of time for smoking intake was also observed in a previous tDCS study with smokers who were motivated to quit smoking (Fecteau et al., 2014). The pattern of change over time in craving measured by EMA in individuals with

cocaine use disorder was also similar to previous research. There was a decrease in craving from the start of the tDCS intervention until two weeks later (chapter 5), regardless of the tDCS condition (sham or active) they received, and this change in craving over time was also found in a sample of crack-cocaine users (Klauss et al., 2018). Finally, excluding participants with low compliance rates did not change the observed effects.

In the future, craving could best be measured with EMA outside the clinic, as craving is often induced by environmental cues or stress. Alternatively, if one decides to measure craving in the clinic after all, it would be recommended to induce craving by means of cue-exposure, as a reflection of craving levels outside the clinic. Moreover, to increase the reliability of induced craving measures, it could be considered to biologically verify cue-reactivity, for instance with EEG, eye-tracking/pupillometry, startle response, heart rate measurements and blood pressure (Ekhtiari et al., 2019).

### Go-NoGo Task and Two Choice Gambling Task

In the chapters where we investigated the effects of tDCS on inhibitory control, we made use of the Go-NoGo task (chapter 3, 5, and 6). This task is one of the most commonly used paradigms to assess behavioural and neurophysiological outcomes of inhibitory control (Luijten et al., 2014). Although we found changes in measures of motor inhibitory control (i.e. reaction times and NoGo P3), no changes in inhibitory control performance (i.e. accuracy on NoGo trials) were observed. One suggestion is that changes in inhibitory control performance after tDCS depend on targeted brain areas and the task involved. For example, it has repeatedly been reported that inhibitory control on the stop signal task was improved after tDCS over the right inferior frontal gyrus (rIFG; Jacobson et al., 2011; Ditye et al., 2012; Stramaccia et al., 2015; Castro-Meneses et al., 2016). However, inhibitory control on the stop-signal task may be more a reflection of reactive response inhibition which is related to rIFG activity, whereas the DLPFC would be more involved in proactive response inhibition on the Go-NoGo task (Brevet-Aeby et al., 2016). Alternatively, tDCS may be more effective when applied during the task instead of before or after. It has been reported that the effects of anodal tDCS may be particularly increased after online stimulation

as compared to offline stimulation for response accuracy in neuropsychiatric patients (Dedocker, Brunoni, Baeken, & Vanderhasselt, 2016).

To measure the effects of tDCS on risky decision making we used the two-choice gambling task (TCGT) in chapter four and five (Schuermann et al., 2012; Endrass et al., 2016). In this task, participants are instructed to choose between a high-risk option yielding high rewards or losses, and a low risk option with less points to win or lose. The probability of earning a reward is indicated in each option before any decision is made, hereby controlling for expectancy. The TCGT was chosen since it was deemed to be particularly well-suited to measure important components underlying decision making, namely neurophysiological measures of feedback processing (FRN and feedback P3). However, the TCGT was not previously used in substance use populations. Therefore, we first compared smokers and non-smokers on their performance and feedback processing during the TCGT (chapter 4). We found that smokers won more points in total on the TCGT than non-smokers, which was interpreted as higher risk-taking. In addition, smokers showed blunted FRN amplitudes as compared to non-smokers as expected. It was surprising, however, that decreased FRN amplitudes were not specific for high or low rewards or losses. The FRN is affected by subjective expectancy of a decision outcome, however, it has been found in previous studies that this construct does not necessarily correspond with overt probabilities (Hajcak et al., 2007) such as indicated in the TCGT. Subjective expectancy of decision outcomes should be explicitly tested in future studies, to be able to draw firm conclusions about the effects of tDCS on feedback processing. Herewith, it can also be tested whether increased confidence for reward outcomes is a possible explanation for increased risk-taking after active tDCS during gambling tasks.

A limitation of the TCGT is that more risk-taking on this task results in higher rewards as reflected by the total number of points at the end of the task. At the start of the task, participants received the instruction to win as many points as possible. If they discovered that increased risk-taking led to higher rewards, an increase in the total number of points at the end of the task, as was found after active tDCS but not after sham tDCS (chapter 4), may reflect increased reinforcement learning rather than increased risky decision making. This could also explain why risk-taking was not increased after tDCS for patients with cocaine use disorder (chapter 5). That is, a certain cognitive level is needed

to learn that risky decision making leads to higher rewards in the long run. Since participants are told that every decision is a gamble, they might not discover this pattern unless they are highly educated like the smokers in chapter two. Together, these results underline the importance of choosing the appropriate task for reliably measuring the executive functions of interest.

### Transcranial Direct Current Stimulation

It has generally been assumed that anodal stimulation by tDCS enhances cortical excitability whereas cathodal stimulation inhibits excitability of neural networks targeted by tDCS. Consequently, we suggested that anodal tDCS over the DLPFC would increase DLPFC activity. However, the underlying mechanism of tDCS may be far more complex than this proposed model. The effects of anodal and cathodal stimulation have varied considerably, depending on current brain state, inter-individual differences in neurophysiology, clinical status, cognitive capacity, and stimulation parameters such as the duration and intensity of tDCS stimulation (Ekhtiari et al., 2019; Jamil et al., 2017; Luigjes et al., 2019). Although it has recently been reported that multi-session tDCS over the right DLPFC would be beneficial in reducing addictive behaviour (Song et al., 2019), very little is known about the contribution of other parameters to the clinical effectiveness of tDCS in addiction.



A particularly promising way forward may be to consider individual differences in order to optimize stimulation parameters for addiction treatment. Although speculative, certain genetic polymorphisms may for example predict the effect of tDCS on inhibitory control (Wiegand, Nieratschker, & Plewnia, 2016), which may translate to effects on addictive behaviour. Another approach could be to fit the tDCS protocol to the patients' cognitive profile (Luigjes et al., 2019). Patients with high trait impulsivity may for instance particularly benefit from tDCS over prefrontal regions. Furthermore, tDCS treatment outcomes may be predicted by baseline EEG measures (Al-Kaysi et al., 2017).

Another field of interest for improving tDCS interventions is the duration between sessions and the total number of sessions. Whereas increasing the duration of one tDCS session might be counterproductive since it can change the direction of excitability (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013), performing a second session during the after-effects of the first tDCS session

(within 20 minutes) could increase the duration of combined after-effects beyond one day (Monte-Silva et al., 2013). That is why we decided to apply two tDCS sessions with a 20-minutes break on each intervention day (chapter 2, 3, 4, and 5). However, more than a total of ten sessions may be needed to induce long-term after-effects beyond three months follow-up. For example, typically 20-30 neurostimulation sessions are considered for the treatment of major depression (Luigjes et al., 2019). Additionally, a recent study in smokers showed that 20 sessions of tDCS resulted in similar abstinence rates as bupropion treatment (Benham et al., 2019). Moreover, they compared two active tDCS conditions where both groups received ten tDCS sessions in two weeks, but the remaining sessions were spread over two weeks for one group and over ten weeks for the other group. The tDCS intervention was significantly more effective for reducing abstinence rates at six months follow-up for the group that had received 20 tDCS sessions spread out over 12 weeks. Perhaps, weekly boosting sessions after the actual tDCS intervention may increase the effectiveness of tDCS.

Finally, it is important to consider alternative and innovative tDCS montages, since the typical two electrode tDCS montage is limited to modulating brain areas near the scalp, and electrical currents induced by this montage may diffuse to non-targeted areas (Nitsche et al., 2007). In chapter six, we showed that HD-tDCS may be a promising alternative to tDCS, since it has the potential to target brain structures with increased focality by placing multiple smaller "high definition" electrodes on the scalp (DaSilva et al., 2015). Besides better spatial precision, HD-tDCS may reach deeper brain structures, particularly when four return electrodes are placed at a certain distance from one target electrode (Faria, Hallett, Miranda, 2011). Consequently, deeper brain areas in the control system, such as the dACC, or networks related to harm-avoidance and reward processing may be targeted.

We provided preliminary evidence that one session of HD-tDCS over the dACC has the capacity to alter neurophysiological activity related to addiction as evidenced by changes in ERPs related to error processing (ERN) and (motor) inhibitory control (NoGo P3). Behavioural changes in inhibitory control were not observed, possibly because of a ceiling effect considering the healthy, highly educated sample in chapter six. Nevertheless, this sample scored high on measures of impulsivity, a core characteristic of addiction. Therefore, future studies should investigate whether neurophysiological modulations after (multi-

session) HD-tDCS over the dACC has potential to affect addictive behaviour and inhibitory control in clinical samples.

### Good research practice

TDCS is specifically practical for research purposes because of its tolerability, mobility, affordability, and reliable placebo (sham) procedure (Priori, Hallett, & Rothwell, 2009). Furthermore, the tDCS system is programmed in a way that active and sham tDCS can be started by filling out a code on the machine. Consequently, a reliable double-blind procedure can be used for the tDCS interventions. This can obviously be regarded as a strength, considering that both the experimenter and participants are oblivious of who receives the actual intervention instead of the placebo. Although the blinding with sham tDCS has been proven reliable, it would still be recommended to explicitly test blinding by asking participants at the end of the experiment to guess whether they have received active or sham stimulation.

Another strength is that all studies in this dissertation were pre-registered. Both researchers and research in general can benefit from preregistration. That is, researchers will have a more elaborate thought process about the study design by describing hypotheses, methods, and analyses before a data collection. In addition, it increases the credibility, transparency and reproducibility of reported results and reduces publication bias. It is also very easy to pre-register by the greatly facilitated online tools. Therefore, we highly recommend performing good research practice, while at the same time improving the quality of psychology research, by means of pre-registration.



## General Conclusion

In general, there was a lack of support for beneficial tDCS effects in the treatment of substance use disorders. Based on the results of this dissertation and past research we suggest that the motivation to quit drug use might be an important modulator for the effects of tDCS on reducing substance use and craving, but further research is needed to investigate this hypothesis. Furthermore, the underlying mechanism of tDCS in addiction remains yet to be discovered. We found evidence that (HD-)tDCS could induce neurophysiological modulations

related to motor inhibitory control and error processing, but how this impacts addictive behaviour and inhibitory control performance remains unclear due to the lack of behavioural changes after (HD-)tDCS. In addition, tDCS may modulate decision making on gambling tasks in smokers. However, it is uncertain whether this tDCS effect reflected increased gambling behaviour, improved reinforcement learning, or changes in any other underlying mechanism.

Future research may particularly focus on the personalization of tDCS treatment by investigating predictors of treatment outcome, such as genetic make-up, EEG measures and age. Also, preliminary evidence suggests that HD-tDCS targeted at the dACC might be a promising innovative intervention for reducing addictive behaviour. Taken together, the overall conclusion of this dissertation is that more research is needed on the application and underlying processes of tDCS to ultimately be able to improve addiction treatment.

# 7

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# Samenvatting

## Samenvatting

*"Kun je je een genot voorstellen dat zo intens is dat je er alles wat je liefhebt voor zou opgeven, alleen maar om het tijdelijk te kunnen ervaren?"* – Nora Volkow

Decennialang werd er aangenomen dat verslavend gedrag voortkomt uit een intens verlangen om genot te ervaren. Hierdoor werd verslaving gezien als een morele zwakte, wat eraan heeft bijgedragen dat individuen met een verslaving door de maatschappij werden behandeld als criminelen. Patiënten met een verslaving geven echter aan dat het gebruik van drugs niet langer plezierig is, maar dat ze desondanks grote moeilijkheden ervaren bij hun pogingen om te stoppen met drugsgebruik. Neurobiologisch onderzoek heeft bewijs geleverd voor dit concept. Er is namelijk aangetoond dat verslaving wordt gekenmerkt door een disbalans tussen het beloningsysteem van het brein, die de drijfveer vormt achter gedrag, en het controlesysteem in de prefrontale cortex (PFC), die gedrag kan inhiberen. Als gevolg hiervan is er een automatische impuls om verlangens naar drugsgebruik te vervullen, die lastig te onderdrukken is door een substantieel verlies over zelfcontrole. Zelfs als er een wens is om te stoppen met het gebruiken van drugs kan deze disbalans hierdoor zorgen voor compulsief drugsgebruik.

Neurobiologische kennis over verslaving zou bij kunnen dragen aan verbeterde en vernieuwende behandelingen binnen de verslavingszorg, maar tot dusver zijn er weinig pogingen gedaan om deze kennis te vertalen naar de kliniek. Het verbeteren van de huidige psychosociale en farmaceutische behandelingen is ingewikkeld, omdat deze interventies non-selectieve veranderingen in de hersenen teweegbrengen. Daarom heeft recent verslavingsonderzoek zich gefocust op onderzoek naar innovatieve methodes die direct invloed kunnen uitoefenen op neurocognitieve mechanismen die betrokken zijn bij de etiologie van verslaving. Een van deze methodes is non-invasieve elektrische neurostimulatie, in de vorm van *transcranial Direct Current Stimulation* (tDCS). Met name de modulatie van hersenactiviteit in de PFC door middel van tDCS lijkt veelbelovend in de behandeling van verslaving.

In voorgaand verslavingsonderzoek werd gevonden dat tDCS, aangebracht over een specifiek gebied van de PFC, namelijk de dorsolaterale PFC (DLPFC), op korte termijn drugsgebruik en trek naar drugs kan verminderen. Een belangrijkere vraag die onbeantwoord bleef was of tDCS ook langdurig effectief

kan zijn voor het verminderen van verslavend gedrag. Er zijn maar weinig studies geweest die hier onderzoek naar gedaan hebben en de resultaten bleken inconsistent. De centrale doelstelling van het huidige proefschrift was daarom om de langere termijneffecten van tDCS als interventie bij de behandeling van verslaving verder te onderzoeken door te kijken naar de effecten van meerdere tDCS sessies op het gebruik van- en de trek naar drugs. Ook is onderzocht hoe tDCS neurofysiologische- en gedragsmaten van cognitief functioneren kan beïnvloeden, om zo meer inzicht te verkrijgen in het onderliggende werkingsmechanisme van tDCS als behandeling bij verslaving.

In hoofdstuk 2 van het proefschrift werd onderzoek gedaan naar de effecten van meerdere tDCS sessies, aangebracht over de DLPFC, op sigarettenconsumptie en trek naar sigaretten in rokers die niet specifiek de wens hadden om te stoppen met roken bij de start van de tDCS interventie. Het rookgedrag werd door de participanten voor drie maanden bijgehouden in een app op hun smartphones, door middel van zogenoemde *Ecological Momentary Assessments* (EMA). Uit de resultaten bleek dat tDCS geen toegevoegde waarde had voor het verminderen van roken en de trek naar sigaretten.

In dezelfde groep rokers onderzochten we veranderingen in neurofysiologische- en gedragsmaten van cognitief functioneren na meerdere tDCS sessies. Controle over inhibitie, foutverwerking, en feedback verwerking leken onveranderd direct na de tDCS interventie (Hoofdstuk 3 en 4). Wel werden er meer risicovolle beslissingen genomen tijdens een goktaak direct na de tDCS interventie (Hoofdstuk 4). Ook werd drie maanden na de interventie gevonden dat de groep die actieve tDCS had ontvangen, in vergelijking met de groep die sham (placebo) tDCS ontvangen had, snellere reactietijden vertoonden en significante veranderingen lieten zien in neurofysiologische maten van motor controle over inhibitie (NoGo P3; Hoofdstuk 3).

In hoofdstuk 5 werd vervolgens onderzoek gedaan naar meerdere tDCS sessies als extra interventie bij de behandeling van cocaïneverslaving. Verder werd in deze groep patiënten onderzocht wat de effecten van tDCS zijn op cognitief functioneren. De verwachting was dat patiënten met een cocaïneverslaving vatbaarder zouden zijn voor tDCS effecten door een hogere motivatie om te stoppen met het gebruik van drugs in vergelijking met rokers (Hoofdstuk 2, 3 en 4). Uit de resultaten bleek echter dat tDCS geen effect had op trek naar

cocaïne, gemeten met EMA, en op het aantal dagen cocaïnegebruik (terugval) gemeten drie maanden na de tDCS interventie. Ook werden er na de interventie geen veranderingen geobserveerd in controle over inhibitie en het maken van risicovolle beslissingen. Wel bleek voor een subgroep van de patiënten, die cocaïne in de vorm van crack gebruikten, dat de kans op terugval was afgenomen drie maanden na actieve tDCS in vergelijking met sham tDCS.

Het uitblijven van voordelige tDCS effecten op gebruik van- en trek naar middelen betekent niet automatisch dat tDCS geen potentie heeft als behandeling bij verslaving. Er zijn een aantal verklaringen waarom de onderzoeken in de huidige dissertatie geen significante effecten van tDCS laten zien. Zo kan er bijvoorbeeld een kritische blik geworpen worden op de gebruikte meetmethoden en de timing van de interventie, en is het van belang om in de toekomst rekening te houden met de motivatie van deelnemers om te stoppen met middelengebruik. Ook de werking van tDCS kan de resultaten beïnvloed hebben. Bij conventionele tDCS kan de elektrische gelijkstroom namelijk gemakkelijk naar andere hersengebieden verspreiden, waardoor het gebied dat daadwerkelijk gestimuleerd moet worden wellicht minder gelijkstroom ontvangt. Ook kunnen alleen hersengebieden dichtbij de schedel gemoduleerd worden met tDCS.

Een innovatieve tDCS methode met betere precisie, namelijk HD-tDCS, werd daarom in een pilotstudie onderzocht als potentiele techniek om diepere hersengebieden te moduleren die geassocieerd zijn met verminderd cognitief functioneren bij verslaving (Hoofdstuk 6). Specifiek werd onderzoek gedaan naar de effecten van HD-tDCS, aangebracht over de *dorsal anterior cingulate cortex* (dACC), op een belangrijke eigenschap van verslaving, namelijk impulsiviteit, bij gezonde individuen die hoog scoorden op een impulsiviteit vragenlijst. Eén HD-tDCS sessie zorgde niet voor significante gedragsveranderingen. Desondanks werd er wel een effect van HD-tDCS gevonden op neurofysiologische maten van motor controle over inhibitie (NoGo P3) en foutverwerking (*Error Related Negativity*; ERN) 30 minuten na de actieve HD-tDCS sessie.

Samengevat leveren de resultaten van deze dissertatie geen sterk bewijs voor voordelige effecten van meerdere tDCS sessies in de behandeling van verslaving. Hoewel (HD-)tDCS veranderingen teweegbracht in neurofysiologische maten van motor controle over inhibitie en foutverwerking, is het nog onduidelijk of en hoe deze modulaties verslaving gerelateerd gedrag beïnvloeden. Uit

de pilotstudie van deze dissertatie blijkt dat HD-tDCS, aangebracht over dACC, wellicht een veelbelovend alternatief is voor conventionele tDCS in de behandeling van verslaving, door het verminderen van impulsiviteit. Om hier meer duidelijkheid over te krijgen zal deze methode onderzocht moeten worden bij een patiëntenpopulatie. Een andere focus voor toekomstig onderzoek is het personaliseren van tDCS interventies aan de hand van voorspellers van behandelingsuitkomsten, zoals genetische opmaak, eeg-metingen, motivatie om te stoppen en leeftijd. Concluderend is er meer onderzoek nodig naar de effecten en onderliggende processen van tDCS om de behandeling van verslaving met tDCS interventies te verbeteren.

# Dankwoord

## Dankwoord

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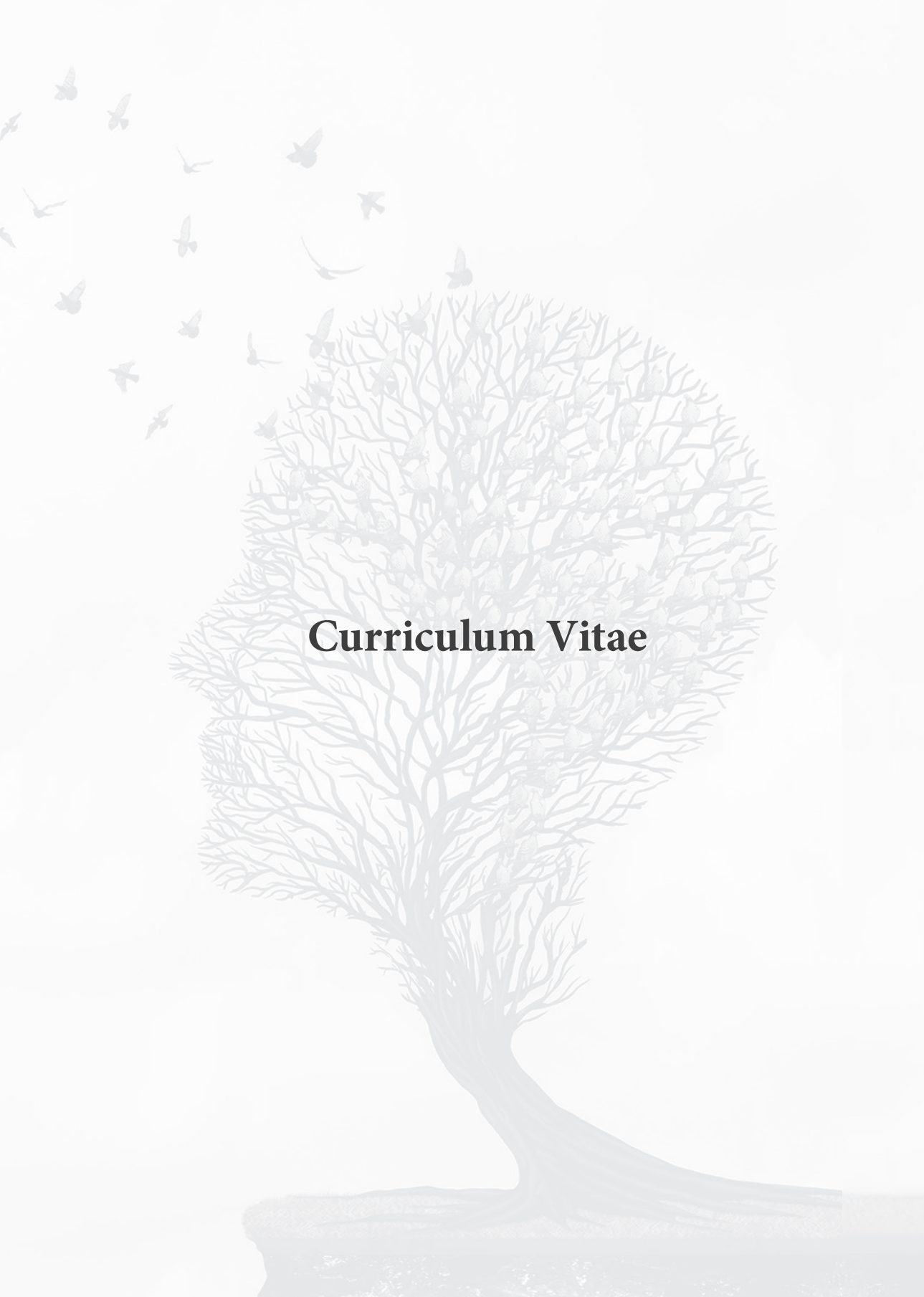

# Curriculum Vitae

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Ilse Verveer was born in Rotterdam on June 17th, 1991. She completed secondary education (VWO) in 2009 at the Calvijn Groene Hart in Barendrecht. In 2012, she obtained her bachelor's degree in Psychology (Brain & Cognition), during which time she worked as a student-assistant for the ERGO sleep research at Erasmus MC. She obtained her Master's degree in Psychology (Brain & Cognition) at Erasmus University Rotterdam in 2014, while simultaneously completing the Advanced Research Program. After obtaining her master's degree, she worked as an academic teacher (tutor) at Erasmus University Rotterdam. In 2016, she started her PhD project on the effects and underlying mechanisms of transcranial Direct Current Stimulation in substance use disorder under supervision of prof. dr. Ingmar Franken, dr. Frederik van der Veen and dr. Danielle Remmerswaal. During this time she was an active member of the PhD council of the Erasmus Graduate School of Social Sciences and the Humanities. In addition, Ilse supervised several Bachelor and Master theses, reviewed articles for international journals, and presented her work at several conferences. For her research visit to Brainpark in Melbourne, Australia, she received a travel grant from ZonMw Translational Research as well as funding from *Stichting Volksbond Rotterdam*.