Focused transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex modulates specific domains of self-regulation

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Recent neuroscience theories suggest that different kinds of self-regulation may share a common psychological mechanism. However, empirical evidence for a domain general self-regulation mechanism is scarce. The aim of this study was to investigate whether focused anodal transcranial direct current stimulation (tDCS), facilitating the activity of the dorsolateral prefrontal cortex (dlPFC), acts on a domain general self-regulation mechanism and thus modulates both affective and appetitive self-regulation. Twenty smokers participated in this within-subject sham controlled study. Effects of anodal left, anodal right and sham tDCS over the dlPFC on affective picture appraisal and nicotine craving-cue appraisal were assessed. Anodal left tDCS over the dlPFC reduced negative affect in emotion appraisal, but neither modulated regulation of positive emotion appraisal nor of craving appraisal. Anodal left stimulation did not induce any significant effects. The results of our study show that domain specific self-regulation networks are at work in the prefrontal cortex. Focused tDCS modulation of this specific self-regulation network could probably be used during the first phase of nicotine abstinence, during which negative affect might easily result in relapse. These findings have implications for neuroscience models of self-regulation and are of relevance for the development of brain stimulation based treatment methods for neuropsychiatric disorders associated with self-regulation deficits.

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1. Introduction

Recent theoretical developments suggest that different kinds of self-regulation, like regulating emotion, suppressing craving, controlling risky behavior, or delaying gratification, may share a common psychological component [for reviews see Heatherton and Wagner, 2011; Mitchell, 2011; Muraven and Baumeister, 2000] and that the neural networks subserving each of these subtypes of self-regulation may be overlapping, or even identical [Cohen and Lieberman, 2010]. Indeed, models of negative/aversive emotion regulation and of positive/appetitive emotion regulation, the domains of self-regulation examined here, have converged on an inverse relationship between top-down cognitive control from the prefrontal cortex over bottom-up affective impulses of subcortical regions involved in emotion generation and reward, respectively [for reviews see Heatherton and Wagner, 2011; Ochsner et al., 2012].

Non-invasive brain stimulation studies targeting the dorsolateral prefrontal cortex (dlPFC) further support the idea of a domain general self-regulation mechanism, because negative emotion regulation [Boggio et al., 2009b; Peña-Gómez et al., 2011], substance craving [for reviews see Feil and Zang, 2010; Wing et al., 2013], and risky decision making [and for review see Levasseur-Moreau and Fecteau, 2012; Pripfl et al., 2013] alike have been shown to be modulated by stimulating the dlPFC. Although the exact neuronal mechanisms by which these effects are driven are unknown, results are often interpreted in light of modifications of the self-regulatory top-down control function of the dlPFC induced by stimulation [for reviews see Fecteau et al., 2010; Feil and Zang, 2010; Fraser and Rosen, 2012; Levasseur-Moreau and Fecteau, 2012]. Many results

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in the literature point towards an inhibitory top-down control function of the dlPFC, i.e. that facilitating dlPFC activity by non-invasive brain stimulation results in increased inhibitory top-down control of affective and impulsive influences, respectively (Eichhammer et al., 2003; Fecteau et al., 2007; Priepfl et al., 2013). This view is further supported by results showing that diminishing activity of the dlPFC by means of non-invasive brain stimulation increases affective and impulsive influences, respectively, on behavior (Beeli et al., 2008; Knoch et al., 2006a, 2006b).

Surprisingly, very little research has directly compared different domains of self-regulation. There are a few behavioral studies comparing different forms of craving within the same sample; i.e. cue-induced craving for food and drugs of abuse, which found correlational support for the idea of a general “cue-reactive” phenotype that varies across individuals (Mahler and de Wit, 2010; Syn et al., 2013). The only neuroscience study to our knowledge studying different self-regulation domains in the same individuals used fMRI and supports the idea that motor inhibitory control and affect regulation in an emotion reappraisal task involves a common substrate in the right ventrolateral PFC (inferior frontal gyrus) (Tabibnia et al., 2011).

In order to directly test the hypothesis whether different domains of self-regulation are supported by a common regulatory mechanism in dlPFC, our study examined the effect of focused transcranial direct current stimulation (tDGS) applied over the dlPFC on appraisal processes of negative and positive affective stimuli, and appetitive craving-cues. If tDGS over the dlPFC acts on a domain general inhibitory top-down regulation mechanism, then (1) tDGS induced facilitation of activity in this area should decrease negative as well as positive cue-induced affective experience, as well as cue-induced craving and (2) the stimulation induced modulations should be positively correlated across the self-regulation domains.

2. Methods

2.1. Participants

Twenty university students participated in the study. Analysis was performed on a final sample of 17 smokers (11 females; mean age 22.2 years, S.D. = 2.0 years, range 19–25 years) because three participants had to be excluded for not finishing all three sessions.

Participants met ICD-10 criteria for tobacco dependence (F17.2), had been smoking at least 10 cigarettes per day for at least one year and had a mean score of 2.3 ± 1.4 in the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) which indicates a low level of dependence. Participants were all right handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), with normal or corrected-to-normal vision, and had been screened for the absence of present or past neurological or psychiatric conditions and use of psychoactive medication. Participants gave informed written consent and received course credits for participation. The study was conducted in conformity to the Declaration of Helsinki and approved by the ethics committee of the University of Vienna.

2.2. Experimental design

In a within-subjects design, each participant joined three tDGS sessions with different stimulation conditions (anodal left, anodal right, sham; see Section 2.4 and Fig. 1), with at least one week between sessions. The sequence of stimulation conditions was counter-balanced across participants. For sham stimulation electrode positions of both verum stimulations (anodal left, anodal right) were balanced across participants.

Participants had to abstain from smoking at least 6 h before the tDGS session started, as the level of craving intensifies over 3–6 h after the last cigarette (Jarvik et al., 2000). To assure compliance participants were informed that smoking sensitive urine drug tests will be randomly conducted.

After electrode application, participants were seated in a comfortable chair in a sound-attenuated, dimmed room equipped with an intercom to the experimenter. Before starting the stimulation participants were given a training session to familiarize them with the task, which was presented on a 19-Zoll-CRT-Monitor placed in 60 cm viewing distance. Participants were instructed to sit quietly with eyes open for the first 5 min of stimulation, after which task presentation started. Stimulation of the verum sessions was terminated after 15 min. Processing of the tasks lasted a few (one to two) minutes longer, depending on the individual reaction times. Note that anodal verum poststimulation effects at the motor cortex for a stimulation duration of 13 min have been documented to last for about 90 min (Nitsche and Paulus, 2001). After electrode removal,
Similarly, craving was assessed by a graphic figure with a neutral facial expression equipped with a lit cigarette, varying from very small, indicating very low craving, to very big, indicating very strong craving.

Craving was assessed analogously: for this reason the graphic figure with a neutral facial expression was equipped with a lit cigarette, varying from very small, indicating very low craving, to very big, indicating very strong craving (see Fig. 2). This procedure allowed for quickly assessing appraisal of craving, valence, and arousal for each picture category, enabling the assessment of different self-regulation domains within a single task.

2.4. tDSCS

Anodal tDSCS was delivered over three sintered Ag/AgCl electrodes (sized 5.3 cm² in total), which were connected by an electrode splitter cable (one to three) to the anodal output of a battery-driven, constant-current stimulator (DC-STIMULATOR PLUS, neuroConn GmbH, Erlangen, Germany) (see Fig. 1). Small electrodes were used for anodal stimulation to improve focality and to emphasize the facilitating effect on neuronal activity of tDSCS (Datta et al., 2009; Faria et al., 2009; Marshall et al., 2004; Minhas et al., 2010; Miranda et al., 2009; Nitsche et al., 2007). Positions F1, F3 and AF1 according to the international 10-20 electrode system (Jasper, 1958) were used for left hemisphere anodal stimulation (“anodal left” hitherto). For right hemisphere anodal stimulation (“anodal right”), electrodes were positioned at F2, F4 and AF2. Electrodes were positioned and kept in place by using an elastic and individually fitted electroencephalography (EEG) cap (EASY-CAP Ges.m.b.H., Herrsching, Germany). The 7 cm × 5 cm cathodal reference electrode was centered contralateral at positions F3 and
F4, respectively, with the short side running in parallel to the imaginary Cz-Fz connecting line. Stimulation electrodes were filled with degassed electrode gel (Electro-Cap International, Inc., Eaton, USA), and the skin under the electrodes had been cleaned with alcohol and slightly scratched to decrease skin resistance (Bauer et al., 1989). This method assured electrode impedance values of ≤3 kΩ, as individually measured by an impedance meter (Ing. Zickler Ges.m.b.H., Paffstätten, Austria). At the side of the surface sponge electrode the skin was only cleaned with alcohol, but not scratched, since this might have created unwanted focal cathodal stimulation effects.

A direct current of 0.45 mA intensity, resulting in an anodal current density of 0.085 mA/cm², was induced for 15 min in the verum sessions, and for 30 s with 30 s fade-in and 30 s fade-out in the sham session. Modeling studies showed that 0.45 mA delivered via an electrode of about 5 cm² induces a comparable current intensity at the surface of the cortex than 1 mA via a 35 cm² electrode (Miranda et al., 2009). At the cathode a direct current density of 0.013 mA/cm² was induced. Because a minimum current density of 0.017 mA/cm² was previously shown to be necessary to modify motor cortex excitability by tDCS (Nitsche and Paulus, 2000), current density at the reference electrode might be considered as functionally irrelevant.

2.5. Data analysis

The main outcome measures were CCAPAT ratings for craving, valence, and arousal, which were subjected as dependent variables to separate repeated measures ANOVAs with the within-subjects factors stimulation condition (anodal left, anodal right, sham) and picture category (craving, positive, negative, neutral). Each dichotomized scale (absent, present) of the adverse effects questionnaire was subjected to a Cochran-Q test comparing the three stimulation conditions.

Significance was evaluated at *p < 0.05*. All data are reported as means ± standard error of the mean (SEM). Greenhouse-Geisser correction was used to adjust the degrees of freedom for the repeated measures ANOVA calculations. Bonferroni corrected post hoc linear comparisons were used to examine interactions and omnibus main effects. Statistical analyses were performed using IBM® SPSS® Statistics 20 (IBM Corporation, Chicago, IL, US).

3. Results

Adverse effects: Frequencies of reported adverse effects did not differ between the three stimulation conditions (all *p*-values >0.097). The three most frequent reported adverse effects were sleepiness (49%), tingling (37%), and itching (20%).

3.1. Cue induced Craving and Affective Picture Appraisal Task (CCAPAT)

The repeated measures ANOVAs revealed significant differences for each of the assessed dependent variables for the main effect picture category (craving: *F*(3,48) = 25.833, *p* < 0.001, partial *η²* = 0.618; valence: *F*(2,36) = 49.718, *p* < 0.001, partial *η²* = 0.757; arousal: *F*(3,48) = 25.175, *p* < 0.001, partial *η²* = 0.611). Bonferroni corrected post hoc test revealed that (i) smoking cues induced higher craving than each other picture category (all *p*-values ≤0.001), but that positive, negative, and neutral pictures did not differ in their craving ratings (see Fig. 3A). (ii) Smoking cues and neutral pictures did not differ in their valence ratings (*p* = 1.000). Positive pictures were appraised as more positive than any other category (all *p*-values <0.001), and negative pictures were rated more negative than any other category (all *p*-values <0.001) (see Fig. 3B). (iii) Arousal ratings did not differ between smoking cues.
4.1. Appraisal of craving cues and affective stimuli

As expected, craving-cues elicited higher ratings on the craving scale than any other picture category, positive pictures received the most positive ratings, and negative pictures the most negative ones. The valence of craving-cues was rated to be neutral, with no difference to ratings of neutral pictures, which is in agreement with previous research (e.g. Geier et al., 2000). Negative pictures induced highest arousal, followed ex-equo by positive pictures and smoking-cues, and neutral pictures. These results confirm earlier studies which showed the importance of arousal in addictive and tobacco dependence phenomena (e.g. Khazaal et al., 2012).

Hence, the procedure used to assess affective and craving appraisal worked well and is in line with our predictions as well as previous research (e.g. Geier et al., 2000; Lang et al., 2008).

4.2. Effects of tDCS stimulation

Anodal tDCS over the right dlPFC reduced negative affect in emotion appraisal, but neither modulated regulation of positive emotion appraisal, nor of craving appraisal. Anodal stimulation over the left dlPFC did not induce any significant modifications, neither on affective picture appraisal, nor on craving ratings.

Involvement of the right dlPFC in regulation of negative affect is in agreement with neuroimaging studies dealing with different kinds of emotion regulation strategies, like voluntary suppression and reappraisal (Goldin et al., 2008), as well as voluntary attentional control during the inhibition of responses to negative, but not positive, emotional stimuli (Goldstein et al., 2007). Furthermore, this result is in accordance with the findings of a recent tDCS study (Feeser et al., 2014), showing that anodal tDCS over the right dlPFC (left dlPFC not studied) facilitates cognitive reappraisal of pictures with negative valence.

However, tDCS studies in healthy subjects with anodal stimulation over the left dlPFC (in which right anodal stimulation was not assessed) showed modulation of negative picture evaluations as well (Boggio et al., 2009b; Peña-Gómez et al., 2011). Furthermore, anodal tDCS stimulation over the right (Fregni et al., 2008a) as well as left dlPFC (Boggio et al., 2009a; Fregni et al., 2008a) has been shown to modulate cue-induced cigarette craving in smokers. Those findings could not be replicated in our study.

We propose to attribute these mixed results to differences in the stimulation procedures used, and in particular the different electrode sizes. All previous studies that had found stimulation effects of negative picture evaluation when stimulating the left prefrontal cortex, used a big sized anode (7 cm × 5 cm) placed over the left dlPFC with the cathode of the same size placed contralateral supraorbital (Boggio et al., 2009b), or contralateral at position C4 (right motor cortex. Peña-Gómez et al., 2011). Similarly, studies which found significant effects on cigarette craving used a 7 cm × 5 cm anode placed over the left and right dlPFC, respectively, and an even bigger sized cathode (100 cm²) placed over the contralateral dlPFC (Boggio et al., 2009a; Fregni et al., 2008a).

Hence, the differences between those studies and our own are probably due to the much smaller scalp area covered by our anodal electrode setting (about 1/7) which consisted of three connected EEG electrodes sized 5.3 cm² in total. Our rationale for the use of this very small anode in combination with a big, i.e. 35 cm², cathode was to increase the focality of tDCS, which improves the interpretation of the functional effects of stimulation because it probably restricts its effects to more clearly defined cortical areas. Moreover, we intended to avoid unwanted reversed effects of tDCS under the reference electrode. Nitsche et al. (2007) showed that reducing the...
size of the anodal DC-stimulation electrode (3.5 cm²) focalizes the respective tDCS-induced excitability changes in the motor cortex, while increasing the size of the cathode (10-fold of the anode, i.e. 35 cm²) renders the stimulation over the motor-cortex functionally inefficient. Although this has never been shown for areas other than the motor-cortex, and the exact distribution of the current flow through the brain is unknown (Datta et al., 2009; Dmochowski et al., 2011; Faria et al., 2013), it seems plausible that the much smaller electrode in our study exerts its influence on a smaller area of the cortex (Datta et al., 2009; Miranda et al., 2006; Nitsche et al., 2007),

A large stimulated area comprises various neuronal systems with different functions and behavioral effects. Thus, the reported effects of tDCS stimulation over the dIPFC across different domains of self-regulation, i.e. craving reduction (Boggio et al., 2008, 2009a; Fregni et al., 2008a, 2008b; Goldman et al., 2011) and affective picture appraisal in healthy (Boggio et al., 2009b; Peña-Gómez et al., 2011) as well as depressive samples (Wolkenstein and Plemnia, 2013), might be a result of the big electrodes used. Alternatively, settings with big sized electrodes might have modulated an area critical for domain general self-regulation mechanism (e.g. the ventrolateral PFC; Cohen and Lieberman, 2010; Tabibnia et al., 2011), which was not influenced by our small electrodes. Further studies, in particular ones providing information on the precise neural effects such as combinations of tDCS with fMRI, are therefore necessary to clarify if the influence of different electrode settings on tDCS activity and whether other areas are also stimulated and therefore might contribute to the reported effects (Keeser et al., 2011).

However, our observation that anodal stimulation of the right dIPFC reduces negative affect in smokers could be of relevance for the use of non-invasive brain stimulation as smoking cessation therapy. Negative affect has been shown to increase substantially during the first days of abstinence (Bidwell et al., 2013) and is a predictor of relapse (Shiffman et al., 2007). A therapeutic intervention which is able to reduce negative affect might thus be of high value in supporting nicotine cessation therapy.

4.3. Limitations

Some limitations to this study exist. Only smokers were included in this study. Smokers, reliably differ from non-smokers in traits associated with self-regulation, like impulsivity and sensation seeking (for reviews see Baker et al., 2004; Ryan et al., 2013), and behave highly risky in a variety of real life situations (Hirschi and Viscusi, 1998). Furthermore, long term smoking is associated with decreased gray matter volume of the PFC which is correlated with greater life time exposure to cigarettes (for reviews see Domino, 2008; Frase and Rosen, 2012; Kober and DeLeon, 2011), smokers show less cortical activity in cognitive control tasks (Nestor et al., 2011) and chronic nicotine use can result in alterations on neuronal excitability (for review see Feil and Zangén, 2010). Thus, it remains to be determined if a similar domain specific tDCS induced modulation mechanism of negative emotion regulation is existent in healthy non-smokers. Furthermore, like most brain stimulation studies in this domain (but see, Feeser et al., 2014), our results are limited to “automatic” self-regulation mechanisms, i.e. appraisal of affective and craving cues without the voluntary engagement of regulatory processes (Phillips et al., 2008). Please note that most reported results and many models in the area of self-regulation are based on the deliberate deployment of an emotion regulation strategy in the service of explicit goals to change one’s emotions, like reappraisal or selective attention (for reviews see Koole, 2009; Ochsner et al., 2012).

Future studies will show if non-invasive brain stimulation helps to improve self-regulation based on voluntary strategies, perhaps in a domain general manner.

4.4. Conclusion

The present study demonstrates that focused anodal tDCS applied over the right dIPFC reduces negative affect in affective picture appraisal, but does neither change positive affect nor smoking craving-cue appraisal in smokers. Anodal stimulation over the left dIPFC had no effect on self-regulation. Thus, our results demonstrate that within the prefrontal cortex domain specific self-regulation networks are at work. Focused tDCS modulation of this specific self-regulation network could probably be used during the first phase of nicotine abstinence, during which negative affect might easily result in relapse. Future studies have to find out if stimulation with bigger electrodes can modify both affective and appetitive self-regulation at the same time, which might be even more effective in the treatment of nicotine dependence. These findings have implications for neuroscience models of self-regulation and are of relevance for the development of brain stimulation based treatment methods for a variety of neuropsychiatric disease states marked by self-regulation deficiencies.

Conflicts of interest

The authors declare no conflicts of interest.

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