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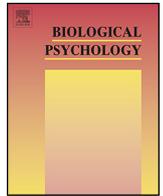
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Transcranial direct current stimulation, implicit alcohol associations and craving

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A B S T R A C T

Previous research has shown that stimulation of the left dorsolateral prefrontal cortex (DLPFC) enhances working memory (e.g. in the *n*-back task), and reduces craving for cigarettes and alcohol. Stimulation of the right inferior frontal gyrus (IFG) improves response inhibition. The underlying mechanisms are not clearly understood, nor is it known whether IFG stimulation also reduces a craving. Here, we compared effects of DLPFC, IFG, and sham stimulation on craving in heavy drinkers in a small sample ($n = 41$). We also tested effects of tDCS on overcoming response biases due to associations between alcohol and valence and alcohol and approach, using implicit association tests (IATs). Mild craving was reduced after DLPFC stimulation. Categorization of valence attribute words in the IAT was faster after DLPFC stimulation. We conclude that DLPFC stimulation can reduce craving in heavy drinkers, but found no evidence for tDCS induced changes in alcohol biases, although low power necessitates caution.

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1. Introduction

Transcranial direct current stimulation (tDCS) is a technique that can influence cortical plasticity and excitability, and it has been used to manipulate cognitive processes. With tDCS two electrodes are placed on top of the skull and a very low electrical current is transmitted through, which increases excitability under the anodal electrode and decreases excitability under the cathodal electrode (Nitsche et al., 2003). By influencing activity in certain cortical areas during relevant cognitive processes, tDCS may have beneficial effects. Anodal stimulation of the dorsolateral prefrontal cortex (DLPFC) increases performance in several cognitive domains, such as working memory (e.g. Fregni et al., 2005; Gladwin, den Uyl, Fregni, & Wiers, 2012; Ohn et al., 2008) and decision making (e.g. Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Fecteau et al., 2007). The DLPFC is involved in many processes related to addiction; mainly higher-order cognitive processes such as behaviour monitoring and attentional and memory processes (Goldstein & Volkow, 2011). The lack of control over impulses has also been proposed to constitute an important factor (Goldstein & Volkow, 2011; Jentsch & Taylor, 1999). Therefore, improving the functioning of the DLPFC could have beneficial effects in addiction.

Indeed, anodal tDCS of DLPFC has been found to reduce craving for several substances, such as alcohol, cigarettes and food (Boggio et al., 2008; Fregni et al., 2008; Goldman et al., 2011). To the best of our knowledge, effects of stimulation of other brain regions on craving have not yet been tested. Anodal stimulation of the right inferior frontal gyrus (IFG) has been found to increase inhibitory control, measured by a stop-signal task (Ditye, Jacobson, Walsh, & Lavidor, 2012; Jacobson, Javitt, & Lavidor, 2011). Therefore stimulation of this region may also decrease craving and/or increase control over impulses to use addictive substances.

The current study had two goals. First, we aimed to extend previous results of tDCS on craving. We investigated whether the effects on craving are also present in heavy drinkers and whether the IFG is also an effective target area. Second, we explored the effects of prefrontal stimulation on the ability to change or overcome biases due to automatic processing of alcohol-related information. The reduction of automatic processing biases may be a potential mediating mechanism for effects of tDCS on craving. One potentially important automatic process is the automatic activation of alcohol associations, which can be measured using an implicit association task (IAT). The IAT has been developed to measure associations between two concepts by comparing performance on a classification task when certain response-categories are grouped together (Greenwald, McGhee, & Schwartz, 1998). The grouping is congruent when the response-categories that are grouped together are associated in memory and incongruent

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when the associated response-categories are mapped to opposite responses. In a standard alcohol IAT, participants categorize alcohol and other beverages together with positive and negative attribute words. If participants have strong positive associations with alcohol they will show improved performance when "alcohol" responses are grouped with "positive" than with "negative" responses. Perhaps unexpectedly, many studies found that both heavy and light drinkers are faster to sort alcohol with negative than with positive attribute words (Meta-analysis, Rooke, Hine, & Thorsteinsson, 2008; Wiers et al., 2002). However, heavy drinkers were found to be somewhat less negative than light drinkers. When positive and negative associations were measured separately, heavy drinkers showed both positive and negative associations with alcohol, with positive and not negative associations correlating with drinking (Houben & Wiers, 2008). Implicit valence and arousal associations with alcohol have also been found to predict drinking prospectively (Wiers et al., 2002). The IAT has also been tested with approach and avoidance attribute words instead of valence or arousal words; alcohol-approach associations correlated with a higher urge to drink (Palfai & Ostafin, 2003), and with alcohol use and problems (Ostafin & Palfai, 2006). Automatic alcohol-related processes, such as those measured by the IAT, play a potentially important role in the development and maintenance of alcohol addiction. It has been demonstrated that changing alcohol-approach tendencies (and related associations) in alcohol-dependent patients helped them to remain abstinent (Eberl et al., 2013; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011).

Prefrontal tDCS could be hypothesized to influence the executive processes that allow biases due to automatic associations to be overcome. In line with this hypothesis, an fMRI study found that the DLPFC was more active during incompatible than during compatible trials (Ames et al., 2013). This leads to the possibility that prefrontal stimulation will result in a relatively negative bias, due to a shift from impulsive to reflective evaluation. This would align with findings in the context of attentional biases: several studies reported a fast alcohol-approach attentional bias while using alcohol, followed by a slow disengagement bias when patients were abstinent (Noël et al., 2006; Townshend & Duka, 2007; Vollstädt-Klein, Loeber, von der Goltz, Mann, & Kiefer, 2009).

As yet, little is known of effects of tDCS on IAT performance. A previous study with a classical IAT with insect and flower words showed that tDCS of the DLPFC did not reduce the bias, and actually selectively improved performance within congruent trials (positive-flowers and negative-insects; Gladwin, den Uyl, & Wiers, 2012). One explanation of this is that stimulation of DLPFC facilitates the recall of information but does not affect the processes leading to incongruence costs in the context of an IAT, thus only leading to a beneficial outcome in the congruent condition where the task-related response is in line with the existing bias. However, effects on alcohol-related IATs have not yet been studied. One possibility we explored is that prefrontal tDCS would enhance the ability to overcome biases, in line with previous work on the enhancement of working memory and executive function. Another possibility is that it would actually enhance performance for the congruent response-grouping, as in our previous study. Given the repeated finding that negative alcohol-associations are stronger than positive alcohol associations, tDCS could then make alcohol associations more negative. In either case, if tDCS can affect biases due to alcohol associations, this could provide clues on how tDCS is able to reduce craving.

To these aims, we tested the effects of tDCS on self-reported alcohol craving and on two variants of the IAT, one with positive and negative words (affective IAT) and one with approach/avoidance words (motivation IAT). Based on previous research, the main target area was the left DLPFC. Since addiction is associated with weakened ability to inhibit drinking behaviour (Goldstein &

Volkow, 2011), the right IFG was also explored in our setup. We hypothesized that, similar to alcohol-dependent patients, heavy drinkers would also demonstrate reduced craving after receiving DLPFC and possibly also IFG stimulation. As described above, we further explored effects of tDCS on cognitive processes indexed by the IAT.

2. Methods

2.1. Participants

Forty-eight students (age: $M = 21.7$, SD = 2.8; gender: 17M/31F) were included. The study focused on hazardous drinkers (AUDIT > 8 at screening via email). On the testing day six participants scored lower than 8 when retaking the AUDIT, and were excluded from the final sample. One participant did not perform the experiment as required and was also excluded. The final analytical sample therefore consisted of 41 participants (age: $M = 21.7$; SD = 3.0; gender: 15M/26F). All were right handed and were Dutch speaking healthy participants. As is common in a Dutch student population approximately 60% were occasional drug-users (cannabis/other). They did not meet any tDCS exclusion criteria to ensure the safety of the stimulation (exclusion criteria were; central nervous system disorders (e.g. epilepsy, meningitis), or other neurological damage (stroke, severe concussion), the use of psychopharmacological medication, a pacemaker, metal in the head, pregnancy, claustrophobia, regular headaches/nausea/panic attacks, direct family with epilepsy, skin conditions (e.g. eczema)). Participants gave written informed consent and the study was approved by the faculty's ethics committee.

2.2. Materials

Participants performed two different versions of the alcohol implicit association test (IAT), one with approach and avoidance words (motivation IAT; similar as Ostafin & Palfai, 2006) and one with positive words and negative words (affective IAT; similar as Houben, Nosek, & Wiers, 2010). In the IAT, participants are required to categorize words into a category shown on the left or right of the screen. Two categories (target vs. attribute) are represented with two subcategories (target: alcoholic drinks vs. regular drinks and attribute: positive vs. negative words or in 2nd IAT attribute: approach vs. avoidance words). In a single category block only target (or attribute) words were shown on the screen (one subcategory left and one right). Words were presented in the middle of the screen and must be categorized as alcoholic or non-alcoholic beverage (or approach/avoid; or pleasant/unpleasant). In combined blocks, target and attribute category-words were alternated, thus two categories were associated with the same response-key. In one combined block pleasant words were coupled with alcohol words and unpleasant with non-alcohol words (alcohol-positive block) and in another block unpleasant words were to be categorized with alcohol words (alcohol-negative block) (see Supplementary Materials). The IAT consisted of 7 blocks; with 3 single (with a total of 30 trials) and 4 combined (with a total of 120 trials) blocks (see online Supplementary Materials). The order (first alcohol-positive, then alcohol-negative or vice versa) of the blocks was randomized across subjects (due to a randomization error the distribution was slightly askew; 63% received the alcohol-negative and 61% the alcohol-avoidance block first, there was no difference in the distribution of order per group, (respectively, $\chi^2(2) = 1.53$, $p = 0.47$; $\chi^2(2) = 0.25$, $p = 0.88$). Participants received the IAT in the same order before and after tDCS. Each subcategory had five different words (see online Supplementary Materials); in the combined practice each word was presented once. In order to minimize exemplar learning, different sets of words were used for each IAT session (approach/avoid or pleasant/unpleasant and pre- and post-tDCS). Order and combination of words were randomized across subjects.

Craving was measured with the alcohol approach and avoidance questionnaire (AAAQ, McEvoy, Stritzke, French, Lang, & Ketterman, 2004). The AAAQ consists of 14 questions on a 9-Likert scale on attitudes towards alcohol at a specific moment. Three subscales were used; measuring mild inclinations to drink (inclined/indulgent scale), strong inclinations to drink (obsessed/compelled scale), and inclination to avoid drinking (resolved/regulated scale) (McEvoy et al., 2004). Students scored relatively high on the Inclined scale and this scale was most predictive of drinking behaviour. Participants also filled out the alcohol use disorder identification questionnaire (AUDIT, Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) and a retrospective 1 week alcohol diary before testing. The AUDIT assessed alcohol use (first three multiple choice questions) and alcohol related problems (seven multiple choice questions).

2.3. Transcranial direct current stimulation

The current was administered by using two 35 cm² (7 × 5) electrodes that were placed on the head and kept in place with rubber straps. The current strength used was 1 mA and the stimulation was kept constant for 10 min for active stimulation and for 30 s for sham stimulation. In the sham stimulation condition the tDCS apparatus stopped automatically without notification of the participant. For the stimulation of the left dorsolateral prefrontal cortex the anodal electrode was placed on F3. For right inferior frontal gyrus stimulation the electrode was placed on the crossing of

Table 1
Demographic variables and baseline scores.

	DLPFC group		IFG group		Sham group		*p*-value
Gender (F/M)	8/6		10/5		8/4		0.84
Age	21.1	±2.9	21.6	±3.2	22.4	±2.7	0.52
AUDIT	15.2	±3.3	13.9	±5.5	13.9	±3.3	0.66
Drinks last week	20.1	±11.8	15.7	±9.1	18.1	±13.9	0.59
AAAQ inclined	5.5	±1.2	4.9	±1.8	5.0	±1.8	0.56
% used drugs this month	57%		73%		50%		0.45

Note. The alcohol use disorder identification questionnaire (AUDIT), total amount of drinks in past week, approach avoidance alcohol questionnaire (AAAQ) Inclined scale. The '% used drugs this month', refers to the percentage of participants per group that had used any sort of drugs (cannabis, XTC, etc.) at least once in the previous month.

F7 and Cz and Fz and T3 (Jacobson et al., 2011). The reference electrode (cathodal) was placed on the contralateral supraorbital region. The experimenter was blind to the sham or real stimulation type (a function incorporated in the neuroConn DC-stimulator Plus). One third of the DLPFC stimulations and one third of the IFG stimulations were sham, creating three equal groups.

2.4. Design and procedure

The study used a mixed repeated measures design with tDCS type as between subject variable. Participants were informed of the in- and exclusion criteria beforehand. All testing sessions were done in the afternoon as it was expected that craving in a student population would be less likely in the morning. Participants first filled out several questionnaires, performed a practise version of the IAT and then completed both IATs once.[1] After the task, the tDCS electrodes were strapped to the head and subjects received 10 min of stimulation while they read a student psychology magazine. Participants also filled out the AAAQ before and after tDCS. Participants were randomly assigned to receive either DLPFC, IFG or sham stimulation. After stimulation they completed both IATs again in the same order. The experiment took approximately 1 h.

2.5. Statistical analysis

A repeated measures ANOVA was used to test the effects of tDCS on craving in heavy drinkers. TDCS was the between-subjects factor and pre- and post-measurement of the Inclined score was the within-subjects factor. We primarily considered the subscale Inclined of the AAAQ, since students scored highest on this scale (McEvoy et al., 2004). Difference scores were calculated (pre- minus post-tDCS), to do planned comparisons with sham stimulation as control condition, and test the specific hypothesis that DLPFC stimulation would decrease craving compared to sham, and inspect the effect of IFG stimulation. For the affective IAT a bias score was calculated (in order to check for correlations with behaviour) by subtracting combined alcohol-positive trials (or alcohol-approach trials) from combined alcohol-negative trials (or alcohol-avoid trials), for both reaction time and accuracy. This bias score was also compared to zero with a one-sample *t*-test to look at the baseline bias in the sample. The reliability of the IAT was tested with Cronbach alpha, by taking the bias scores for each separate word category (positive/negative/alcohol/soda). Effects of tDCS on the IAT were tested with a repeated measures ANOVA with tDCS as between subject variable and within-subject factors time (pre- and post-tDCS), block-type (alcohol-positive vs. alcohol-negative), target-type (target vs. attribute), and word-type (target (alcohol vs. non-alcohol) and attribute (negative vs. positive)) (baseline data were also assessed by excluding the factor time and only looking at the pre-tDCS data). Interactions involving time and (between-subject factor) Group were relevant for an effect of tDCS. Significant interactions were followed by single group comparisons with sham stimulation. Analogous analyses were performed for the motivation IAT.

3. Results

All participants tolerated the stimulation well and none asked for the stimulation to be terminated. Groups did not differ on baseline characteristics (Table 1). The interaction between tDCS and time on Inclined scores was significant ($F(2,38) = 4.13$, $p = 0.024$, $\eta^2 = 0.18$; Fig. 1). Planned contrasts with difference scores (post–pre) showed that craving decreased after DLPFC stimulation compared to sham stimulation ($t(38) = -1.88$, p (one-sided) = 0.034,
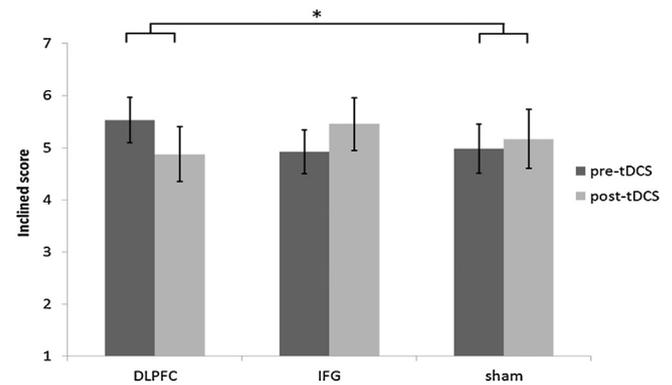
Fig. 1. Effects of tDCS on craving. Mean score on Inclined scale (Likert scale 1–9) before and after stimulation. Error bars represent standard errors. There is a significant decrease in craving after DLPFC stimulation compared to sham stimulation.

$d = 0.762$). Craving did not change significantly after IFG stimulation compared to sham stimulation ($t(38) = 0.79$; $p = 0.43$).

The affective IAT showed good internal reliability for each word category (Cronbach alpha; pre-test = 0.90, post-test = 0.80). The bias scores, however, did not correlate significantly with AUDIT, TLFB, or AAAQ Inclined scores.[2] Bias score did correlate strongly with the order of the blocks (-0.59, $p < 0.001$), showing that performance was dependent on time-on-task, adding extra variance to the bias scores. At baseline the bias score differed significantly from zero; there was a negative bias in the sample ($t(40) = -3.19$, $p = 0.003$; when the bias score was corrected for order effects this effect remained, $t(40) = -2.67$, $p = 0.01$). The ANOVA with tDCS and the affective IAT showed only one interaction effect involving group and time; the three-way interaction including target-type ($F(2,38) = 4.00$, $p = 0.027$, $\eta^2 = 0.17$). Further analysis showed that this interaction was significant when comparing DLPFC stimulation to sham ($F(1,24) = 7.0$, $p = 0.014$); there was a significant decrease in reaction times for attribute words after DLPFC (and not IFG or sham) stimulation ($F(1,13) = 12.60$, $p = 0.004$, Fig. 2). There was also a trend for an interaction with block-type ($F(1,13) = 4.11$, $p = 0.063$); but follow-up analysis showed that there were no significant differences compared to sham stimulation ($p > 0.3$). There were no stimulation effects on accuracy.

The motivation IAT showed good internal reliability for each word category (Cronbach's alpha 4 items; pre-test = 0.83, post-test = 0.82). The bias score did not correlate with AUDIT, craving, or explicit measures ($p > 0.3$). There was no significant bias at baseline ($p > 0.8$). No effects of tDCS on the motivation IAT were found (Fig. 3). There was a significant interaction with target-type and time ($F(1,38) = 4.5$, $p = 0.04$, $\eta^2 = 0.11$), indicating that participants, regardless of group (the interaction with group was not-significant,

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[1] Participants also performed an approach avoidance task (AAT), but due to problems (high error rates/low reliability) with this specific version of the task it is excluded from this paper.

[2] There were also no significant correlations when the D600 (Greenwald et al., 2003) score was used.
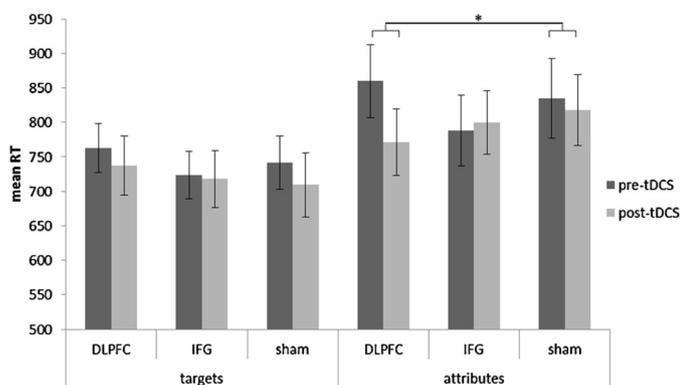
Fig. 2. Effects of tDCS on categorizing target-type. Mean reaction times for categorizing targets and attribute words before and after (DLPFC/IFG/sham) tDCS. Error bars represent standard errors. After DLPFC stimulation (compared to sham) participants respond faster to attribute words compared to target words.

$p = 0.19$) were faster at attribute words the second time. There were no effects on accuracy, although there was a trend for accuracy to increase after sham stimulation ($F(2,38) = 2.66$, $p = 0.083$, $\eta^2 = 0.12$).

4. Discussion

This study examined the effects of anodal tDCS over the DLPFC and IFG on craving and two implicit association tests. It gives new support for the possibility for tDCS of the DLPFC to also influence mild craving in heavy drinkers, in line with earlier studies indicating reductions in stronger forms of craving in alcohol-dependent patients (Boggio et al., 2008). In the present sample of heavy
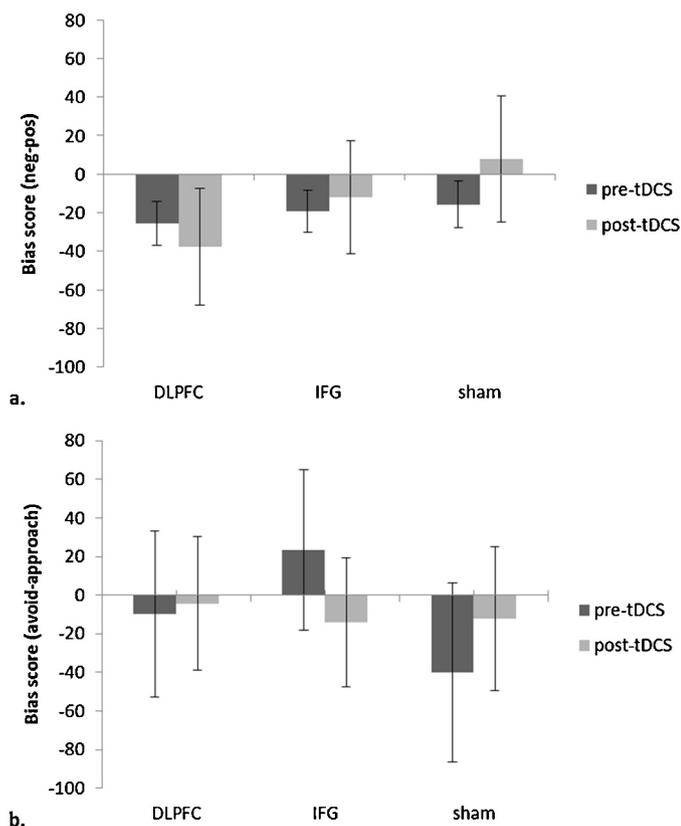
Fig. 3. tDCS effects on IAT bias score. (a) Bias score for affective IAT per group, before and after tDCS. (b) Bias score for motivation IAT per group, before and after tDCS. Error bars represent standard errors. There are no significant effects of tDCS on bias scores.

drinking students, effects were found on a scale that measured inclinations to drink; somewhat weaker feelings of craving. Stimulation of the IFG did not decrease craving. Previously this form of stimulation has been shown to increase response inhibition in a stop-signal task (Jacobson et al., 2011). Although inhibition of motor responses is conceptually different from craving related inhibition of thoughts and desires, similar effects could be expected when inhibiting craving-related thoughts. However, whether the IFG solely plays a role in response inhibition is debated; some areas might also be related to attention processes (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2010; Nikolaou, Field, Critchley, & Duka, 2013). It may be the enhanced attention to stop-stimuli in an inhibition task that improves performance, however, enhanced attention to alcohol without inhibition instructions might not lead to decreased craving.

Craving requires cognitive processing, by elaboration and imagination of the substance and situation (Kavanagh, Andrade, & May, 2005). DLPFC stimulation has been suggested to interfere with a craving response by interrupting the processes normally leading to craving (Boggio et al., 2008; Fregni et al., 2008). However, the precise mechanisms are still unclear. These results showed that even small inclinations towards alcohol, that are likely prompted by the processing of alcohol related stimuli or alcohol related imaginative questions, may be reduced by anodal tDCS in heavy drinkers. This suggests that tDCS of the DLPFC does not only interrupt a maladaptive craving process, but affects common reward processing pathways in a continuous matter.

No clear effects of tDCS were found on alcohol association biases in the two IATs. DLPFC stimulation did improve reaction times when categorizing attribute words. This might be interpreted as an improvement of general emotional processing, which has previously been found as a result of DLPFC stimulation (Nitsche et al., 2012). However, attributes was also the category participants performed the worst on at baseline, hence the one in which they could improve the most; another alternative explanation for this effect is a facilitation of performance on relatively difficult trials, which has also been found in previous studies (Cerruti & Schlaug, 2009; Gladwin, den Uyl, & Wiers, 2012; Meiron & Lavidor, 2012). However, neither an overall reduction in bias nor a shift to a more negative association was found.

In contrast with previous research none of the bias scores correlated with drinking behaviour. This may have been due to the low variance in the sample, since we only included hazardous drinkers and no light drinkers. The absence of a specific bias does make it more difficult to draw conclusions on whether tDCS can influence the bias score that exists in this population. The results did not precisely match the results found in Gladwin, den Uyl, Fregni, et al. (2012); Gladwin, den Uyl, and Wiers (2012). In that study, as in the current study, no decrease in bias was found; DLPFC tDCS was in fact found to selectively result in an improvement in congruent trials. However, in this previous classical flowers-and-insects IAT experiment three repetitions of the seven blocks were used, giving a more reliable IAT score and more opportunity to optimize performance, which could have given rise to the detection of more subtle learning effects. Since bias scores can diminish after frequent testing, we chose to limit the testing to one block in this design (where the tasks were done within a short amount of time of each other opposed to at least a day apart). Also compared to a classical insect IAT (Greenwald et al., 1998), in an alcohol-IAT, no universal preference is assessed and many people are ambivalent, which indicates they may have both positive (/approach) associations and negative (/avoidance) associations, which may differ in relative strength, depending on context (Houben & Wiers, 2006; cf. Roefs et al., 2006). The target categories are also not necessarily straightforward, since high sugary (unhealthy) soda drinks might also activate negative associations. The lack of a significant result

on these biases could also be due to the lack of power to find smaller effects; with these ambiguous biases we would need a much larger sample to be able to detect all the different facets that underlie these bias scores. It might also be of interest in further research to classify people beforehand as to which bias they have and in such a way create groups, who might react differently to a bias manipulation.

This is the first study to show similar trends for DLPFC stimulation in hazardous drinkers as previously found in dependent subjects. However, the context of craving questions for heavy drinkers is somewhat different than the craving questions for alcoholics and it is still an open question whether tDCS will lead to reduction in drinking behaviour in the long run. In line with the general finding that anodal DLPFC simulation can enhance cognition; reaction times were reduced on the slowest trials on an IAT. However, no evidence was found suggesting that alcohol-related automatic associative processes measured by the IAT, or biases due to them, are affected by tDCS. Thus, further study is needed to understand the mechanisms underlying the potentially important effect of tDCS on craving and hence aid its potential clinical applications.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2014.12.004.

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