

Electrical stimulation reduces smokers' craving by modulating the coupling between dorsal lateral prefrontal cortex and parahippocampal gyrus

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Abstract

Applying electrical stimulation over the prefrontal cortex can help nicotine dependents reduce cigarette craving. However, the underlying mechanism remains ambiguous. This study investigates this issue with functional magnetic resonance imaging. Thirty-two male chronic smokers received real and sham stimulation over dorsal lateral prefrontal cortex (DLPFC) separated by 1 week. The neuroimaging data of the resting state, the smoking cue-reactivity task and the emotion task after stimulation were collected. The craving across the cue-reactivity task was diminished during real stimulation as compared with sham stimulation. The whole-brain analysis on the cue-reactivity task revealed a significant interaction between the stimulation condition (real vs sham) and the cue type (smoking vs neutral) in the left superior frontal gyrus and the left middle frontal gyrus. The functional connectivity between the left DLPFC and the right parahippocampal gyrus, as revealed by both psychophysical interaction analysis and the resting state functional connectivity, is altered by electrical stimulation. Moreover, the craving change across the real and sham condition is predicted by alteration of functional connectivity revealed by psychophysical interaction analysis. The local and long-distance coupling, altered by the electrical stimulation, might be the underlying neural mechanism of craving regulation.

Key words: nicotine dependence; addiction; craving; brain stimulation; tDCS; DLPFC

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Introduction

Cigarette consumption is a worldwide health problem. A majority of smokers attempting traditional interventions, based on psychotherapy and pharmacotherapy, relapse within 1 year of quitting (Szasz et al., 2012). Craving, especially cue-elicited craving, is a trigger of relapse (Shiffman and Jarvik, 1976). Novel interventions are needed to improve therapeutic outcome. Recently, emerging evidence has shown that transcranial direct current stimulation (tDCS) can help reduce smoking-related behaviors, such as reported craving and number of cigarettes consumed (Fregni et al., 2008; Boggio et al., 2009; Jansen et al., 2013; Fecteau et al., 2014; Meng et al., 2014). Because of non-invasiveness, ease of use and low cost, tDCS may be a potential therapeutic alternative or augmentation in future smoking cessation programs (Wing et al., 2013). However, although the clinical value of tDCS in treating addiction is advocated, the underlying neurofunctional mechanism remains ambiguous, which restricts further clinical application.

The dorsal lateral prefrontal cortex (DLPFC) is a widely used target site in tDCS studies on nicotine addiction. As the DLPFC has been associated with executive function and salience attribution (Goldstein and Volkow, 2011), one possibility is that the local function of the DLPFC may be enhanced under tDCS in order to better control impulsive, risk-taking behavior and therefore allow for optimal decisions related to cigarette consumption (Fecteau et al., 2014).

The DLPFC is also connected with lots of brain areas, especially the orbitofrontal cortex, the thalamus, dorsal caudate nucleus and the hippocampus/parahippocampal gyrus (HPG) (Miller and Cohen, 2001). Thus, an alternative hypothesis is that tDCS alters the functional connectivity between the DLPFC and other addiction-related brain regions. Several fMRI studies on healthy adults have revealed that tDCS over the DLPFC induces widespread connectivity changes (Lindenberg et al., 2013; Park et al., 2013; Weber et al., 2014), which favor a network explanation of tDCS effects instead of a pure local modulation hypothesis (Fox et al., 2014).

One important pathway underlying addiction is the coupling between prefrontal cortex and the mesolimbic system composed of the striatum, the hippocampus, etc. The mesolimbic system is a brain center of motivation, adaptive learning and memory and is deemed a source of maladaptive salience attribution to addicted cues (Hyman, 2005). Regulation of cigarette craving through cognitive strategies depends on the prefrontal-striatal pathway (Kober et al., 2010) and the interaction between the DLPFC and the OFC (Hayashi et al., 2013), a neural hub anatomically associated with ventral-striatal brain areas. Although these studies indicate the potential mechanism of craving regulation, direct evidence of tDCS modulating the prefrontal-mesolimbic system pathway in craving reduction is still lacking, not only in nicotine addiction but also in other addictive disorders.

Based on previous works, this study directly investigates the neural mechanism of tDCS effects on cigarette craving with a

combination of fMRI and tDCS. We hypothesized that stimulating the DLPFC decreases craving through modulation of local activation of the DLPFC and long-distance coupling between the DLPFC and the salience attribution system.

Materials and methods

Subjects

Subjects were recruited through advertisement from the city of Hefei in China and screened in a telephone interview, and met the following inclusion criteria: (1) The Fagerström Test for Nicotine Dependence score (FTND) ≥ 4 ; (2) consumed at least ten cigarettes per day in the past 2 years; (3) right-handed male; (4) did not receive pharmacotherapy or psychotherapy in the past 2 months; (5) never sought after nicotine addiction treatment. At the first visit, subjects were screened to exclude those who had neurological, psychiatric and other drug dependence (such as alcoholism) with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Forty male adult smokers participated in the study. Eight subjects were further excluded because of excessive head movements or dropping-out at the second fMRI session, leaving 32 subjects in the final analysis (see Table 1 for characteristics of the study sample). Informed written consent was obtained prior to study participation. Monetary compensation (400 RMB, equals 60 USD) was provided after the completion of all experimental sessions. The procedure was approved by the Institutional Review Board of Anhui Medical University in compliance with the Declaration of Helsinki.

Study design and procedure

The study used a single blind sham controlled within-subject design (see Figure 1 for an illustration of the study procedures). The order of real and sham stimulation for each participant was generated by a homemade script using MATLAB before data collecting. Orders were produced at balanced permutations with equal number of real-sham order and sham-real order with block size of 10. In the first visit, subjects were screened for psychiatric condition and smoking history. At the second and third visits, all subjects attended a real tDCS session and a comparable sham session separated by 1 week, the order of which was counterbalanced between subjects. In each session, subjects received either real or sham stimulation for 30 min in the MRI scanner using a MRI compatible tDCS equipment (see details in “tDCS protocol” section), during which they also completed a go/no-go task and a monetary incentive delay task (data of these two tasks will be presented elsewhere). Then, subjects were scanned during a resting state, a cue-reactivity task and an emotion task. In addition, an anatomical scan was performed. The craving level prior to, and after, the cue-reactivity task was collected using a computerized visual analogue scale. Furthermore, participants completed two Positive and Negative Affective Scales in each session; one at the beginning of scanning and one at the end of scanning.

tDCS protocol

Direct current was applied by a battery-driven and MRI compatible stimulator (DC-Stimulator Plus, neuroConn GmbH). The anode electrodes (size $5 \times 7 \text{ cm}^2$) and the cathode electrodes (size $10 \times 10 \text{ cm}^2$) were inserted into saline-soaked synthetic sponges. A symmetrical bilateral tDCS protocol was used with the anode over the F3 and the cathode over the F4 according to

Table 1. Descriptive statistics of the smoker sample ($n = 32$)

	Mean	SD	Min	Max
Age (years)	26.68	6.28	21	49
Number of Cigarettes per day	14.41	4.36	10	30
Years of Smoking (years)	8.11	7.02	3	32
FTND	5.03	1.4	4	9

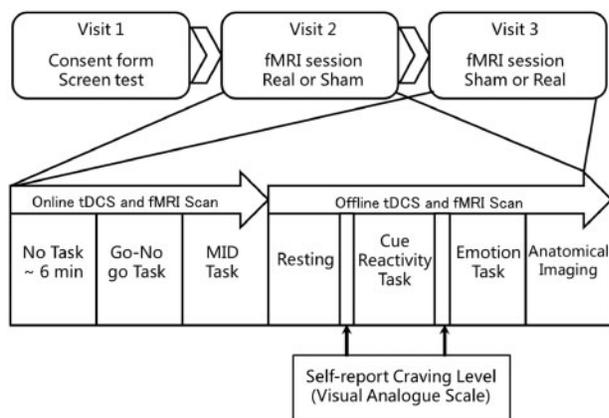


Fig. 1. Overview of the study procedure. The go/no-go task and MID task (Monetary Incentive Delay task) belonged to another study on the online effect of tDCS.

the 10–20 EEG system. Proper localization of the F3 and the F4 was aided by an elastic Quick EEG cap (Neuroscan Inc., USA). The stimulation started and ended in a ramp-like fashion over 30 s. Direct and constant current of 1 mA was delivered for 30 min in the real tDCS session. The sham tDCS only consisted of 30 s of ramp-up and 30 s of ramp-down to let subjects feel the itching sensation analogous to the real stimulation.

Tasks

Cue-reactivity task. The cue-reactivity task, adopted from a previous study (Luijten et al., 2011), was designed to measure neural responses to smoking cues. In each trial, a picture with either a smoking-related stimuli or a neutral stimuli was presented for 900 ms following a fixation cross (jittered from 1100 to 5100 ms). Two to five semi-randomly distributed lines were displayed within each picture. Participants were instructed to count the number of lines and to press the corresponding button as fast as possible. The picture content was not related to the number of lines. The task was composed of 150 trials.

Image acquisition

All images were collected on a Philips Achieva 3.0 Tesla scanner (Philips Medical Systems, Best, The Netherlands) with an eight-channel coil. Functional BOLD images in each task and resting scans were acquired using the T2-weighted echo planar imaging sequence (32 axial slices, slice thickness = 4 mm, TR = 2 s, TE = 30 ms, FA = 90°, Matrix = 64 × 64, FOV = 240 × 240). Individual high-resolution structural images were also obtained.

fMRI image processing

Task-based fMRI. Images were processed using AFNI (Cox, 1996). The functional 3D volume images were corrected for slice acquisition time differences and were registered to the last volume and spatially normalized to the Talairach space. Then the images were spatially smoothed (full width at half maximum = 6 mm) and each voxel time series was temporally normalized by scaling each run by its mean so that all runs had a mean signal of 100. In the first level GLM, head movements in the six directions were entered as covariates. The contrast

between smoking pictures and neutral pictures (smoking-neutral) in the cue-reactivity task was the interest. A 2×2 ANOVA model was used to investigate the within subjects effects of tDCS (real vs sham) and cue type (smoking vs neutral) in the second level group analysis. The smoking-neutral contrast was used to define the main nodes of cue reactivity system. To correct for multiple comparisons, a cluster-wise threshold was determined using the Monte Carlo simulation implemented within the 3dClustSim of the AFNI (version: AFNI_16.2.06 released on July 25 2016). The results revealed that a voxel-wise threshold of $P < 0.005$ combined with a minimum volume of 1203 mm³ is needed to get a family-wise error corrected $P < 0.05$.

To explore whether the connectivity between prefrontal cortex and the cue reactivity system was modulated by tDCS, we performed the psychophysiological interaction (PPI) analysis. To avoid double dipping, the seed of IDLPFC was defined using a 5-mm-radius sphere with center at the corresponding cortex coordinate of F3 (Talairach space: -33.6, 27.2, 39.2) (Keeser et al., 2011) but not from the result of our cue-reactivity task (see Supplementary Figure S1 for an illustration). The time course of IDLPFC was extracted by averaging voxel seed region, with linear trends removed (3dDetrend) and deconvolved to get neural activity (3dTfitter). The PPI model included a psychological regressor comparing smoking vs neutral cue (coded as 1 and -1, respectively) convolved with a hemodynamic response function, a physiological regressor (the mean time course from IDLPFC) and the interaction between the two. Head motions in the six directions were also controlled as covariates. Whole brain PPI analysis was performed for each condition for each subject. Then the PPI value was extracted from the main nodes of the cue reactivity system (defined using significant clusters of smoking-neutral contrast) and averaged to represent the connectivity modulated by cue type between IDLPFC and a specific node. Whether the PPI value in each node of cue reactivity system was altered by tDCS was tested using pairwise *t* test for each node of the cue reactivity system.

Resting-state fMRI. Preprocessing of resting images was similar to task-based fMRI except for the addition of a 3dDespike step before time correction. In addition, signals originating from head motion, white matter and CSF were regressed out. Finally, the data were band-pass filtered (0.01–0.08 Hz). Then a seed-based connectivity analysis using IDLPFC (same as the PPI analysis) was performed. The correlation coefficients were fisher-transformed. Average correlation coefficients within the main nodes of cue-reactivity system (same as the PPI analysis) were computed to represent the connectivity between IDLPFC and a certain node. The definition of seed regions and regions of interest were the same as in the former PPI analysis of the cue-reactivity task. Then, a pairwise *t*-test employed to test whether the seed-based resting-state functional connectivity in each node of the cue reactivity system was altered by tDCS.

Results

fMRI results

Cue-reactivity task. A 2×2 ANOVA model with tDCS (real vs sham) and cue type (smoking vs neutral) as two within-subject factors was performed (see Table 2 for detailed results). The smoking-neutral contrast was mainly manifested in the

Table 2. The whole-brain analysis of the cue-reactivity task

	Peak coordinates (Talairach space)			Maximum F	Volume size (mm ³)
	X	Y	Z		
Smoking-neutral contrast					
rPHG/rFG	26	-36	-9	26.51	4594
lMTG	-41	-74	26	19.74	3766
lMFG	-11	44	19	25.10	3734
rMTG	39	-76	11	17.02	2094
lPHG	-29	-31	-11	25.09	2031
PCC	1	-36	31	24.98	1719
Real-sham contrast					
-					
tDCS × cue interaction					
lSFG	-6	31	46	22.41	1313
lMPFC	-29	19	44	43.97	1218

Note: l, left; r, right; MFG, medial prefrontal cortex; PHG, para-hippocampal gyrus; FG, right fusiform gyrus; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; SFG, superior frontal gyrus; MFG, middle frontal gyrus. The left, the posterior and the inferior directions are negative.

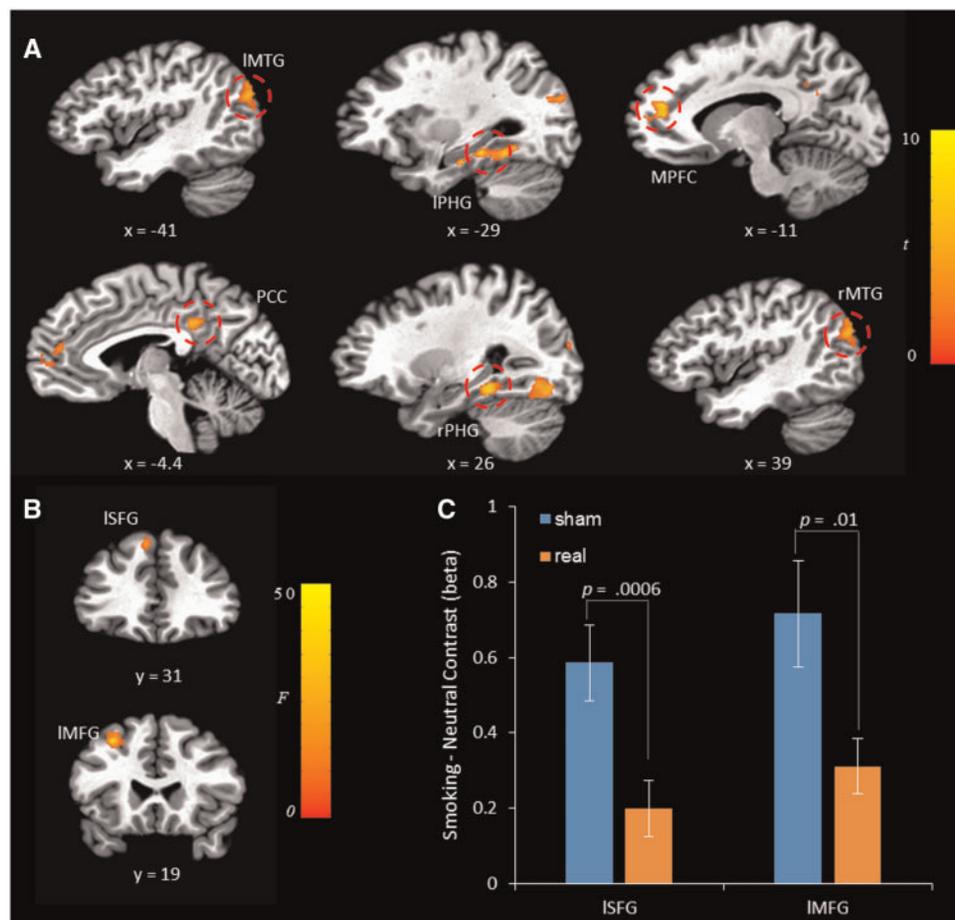


Fig. 2. (A) The smoking-neutral contrast map in the cue-reactivity task. l: left; r: right; MPFC, medial prefrontal cortex; PHG, para-hippocampal gyrus; FG: right fusiform gyrus; MTG: middle temporal gyrus; PCC, posterior cingulate cortex; SFG: superior frontal gyrus; MFG: middle frontal gyrus. The left, the posterior, and the inferior directions are negative. The contrast map was thresholded with cluster-wise P values < 0.05 . (B) tDCS \times cue type interaction. (C) A detailed illustration of the tDCS \times cue interaction in the left SFG and the left MFG.

left/right middle temporal gyrus (MTG), the left/right HPG, medial prefrontal cortex (MPFC), and posterior cingulate cortex (PCC). Although no significant effect of tDCS was found, a significant tDCS \times cue type interaction was revealed in the left

superior frontal gyrus (SFG) and the left middle frontal gyrus (MFG) (Figure 2). As illustrated in Figure 2C, the smoking-neutral contrast was reduced in the real stimulation condition compared with sham stimulation condition in both the left SFG

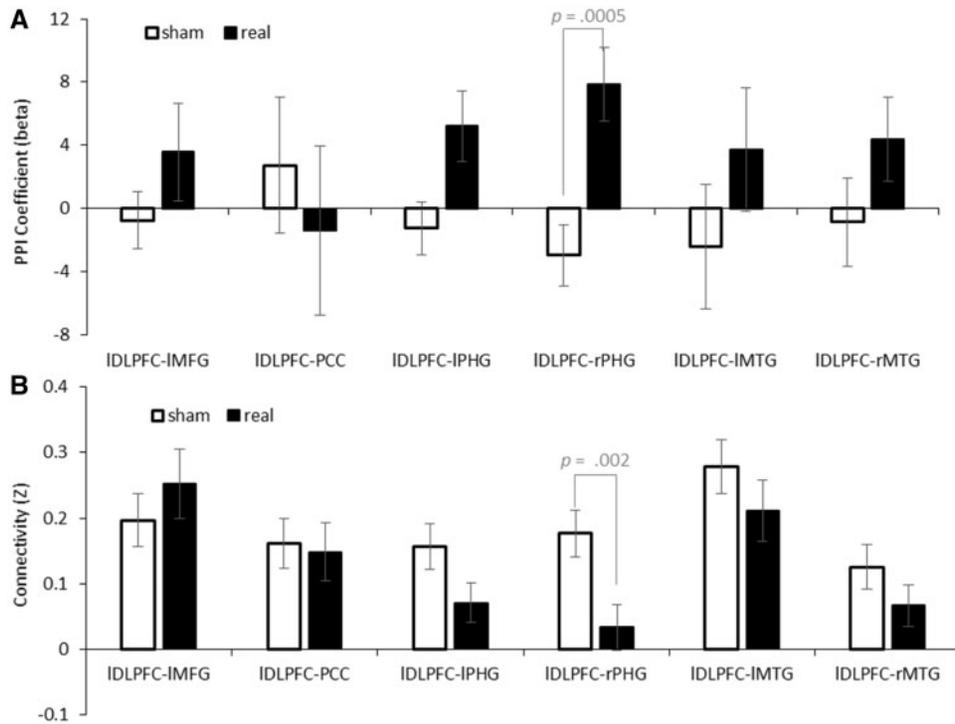


Fig. 3. (A) The tDCS effect on PPI between IDLDFC and cue-related brain regions. (B) The tDCS effect on resting state functional connectivity between IDLDFC and cue-related brain regions.

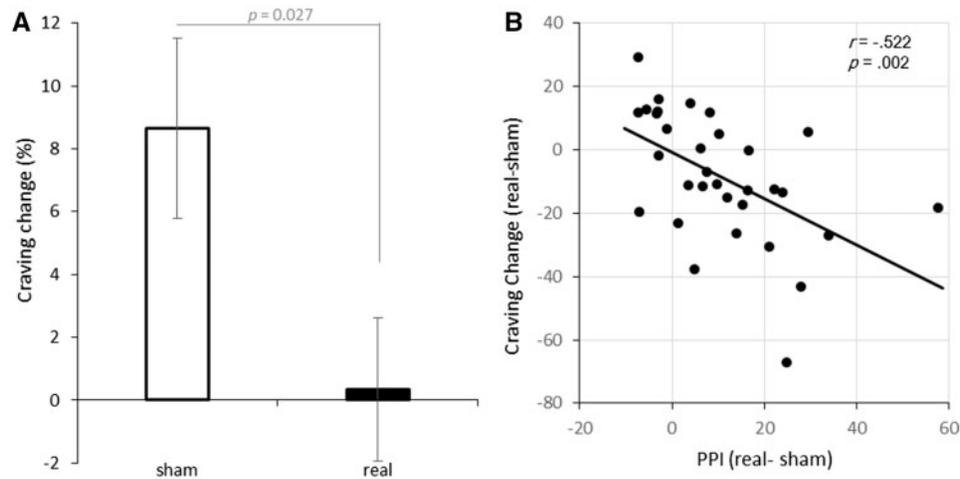


Fig. 4. (A) Craving change (%) across cue-reactivity task in sham and real stimulation. The length of the error bar represents the standard error of the mean. (B) The changes of PPI between IDLDFC and rPHG across the two sessions (real-sham) correlated with the craving changes across the two sessions (real-sham).

($t = 3.812$, $df = 31$, $P = 0.0006$, Cohen's $d = 0.674$) and the left MFG ($t = 2.721$, $df = 31$, $P = 0.011$, Cohen's $d = 0.481$).

PPI analysis. Whole brain PPI analysis (from IDLDFC) was performed for each tDCS condition for each subject. Then, we tested whether the PPIs were modulated by tDCS using the pairwise t -test for each node of the cue reactivity system. Results showed that the PPI between IDLDFC and rPHG was modulated by tDCS stimulation ($t = 3.859$, $df = 31$, $P = 0.0005$, Cohen's $d = 0.682$). None of other PPI were significant (all P s > 0.1). See Figure 3A for detail information. Besides, individual analysis suggested that the PPI between the IDLDFC and the rPHG was

negatively correlated with craving change in the two tDCS sessions ($r = -0.522$, $P = 0.002$, Figure 4B).

Resting state fMRI. We also tested whether the seed-based resting-state functional connectivity between the IDLDFC and the rPHG was altered by tDCS. The definition of seed regions and regions of interest were the same as in the former PPI analysis of the cue-reactivity task. A pairwise t -test revealed that the resting-state functional connectivity between the IDLDFC and the rPHG was increased by real stimulation as compared with sham stimulation ($t = 3.332$, $df = 31$, $P = 0.002$, Cohen's $d = 0.589$). None of connectivity in other cue-reactivity ROIs was significant (all P s > 0.2). See Figure 4B for detail information.

Emotion task. A 2×2 ANOVA model with tDCS (real vs sham) and valence (negative vs neutral) as within-subject factors was performed. No significant main effect or interaction effect of tDCS was found in the task (see Supplementary Figure S2 and Table S1 for further information).

Behavior results

Response times (RTs) and accuracies in cue-reactivity task. Separate $2(\text{tDCS condition}) \times 2(\text{cue type})$ repeated measures Analysis of Variance (ANOVA) was performed on RTs and accuracy. No significant effect was found in any analysis (all $P > 0.2$).

Craving self-reports. Subjects reported a generally higher craving level after the cue-reactivity task ($t = 2.369$, $df = 63$, $P = 0.021$, Cohen's $d = 0.296$). Despite this, the craving change across the cue-reactivity task was lower during real stimulation than during sham stimulation ($t = -2.319$, $df = 31$, $P = 0.027$, Cohen's $d = 0.410$). See Figure 2 for an illustration. For analysis on absolute craving level, please refer to Supplementary Figure S3.

Positive and negative affective scale. No significant effect of tDCS was found on either change in positive affect or change in negative affect (all $P > 0.2$). See supplementary Material (Supplementary Figure S4) for further information.

Discussion

Neuroimaging studies have identified the DLPFC as one of the most important areas involved in the cue-associated anticipation and planning of drug use (Goldstein and Volkow, 2011). Although previous studies on cigarette craving assumed that local function of the prefrontal cortex might be affected when applying tDCS to it (Fregni et al., 2008; Boggio et al., 2009), direct support of this assumption is rare. We demonstrated that reactivity of the left SFG and the left MFG to smoking cues in the cue-reactivity task is modulated by tDCS; specifically, smoking cues elicited stronger activation than the neutral cues in the sham condition, while this pattern was reduced by real stimulation.

We identified several key cue reactivity brain regions including the MPFC, the left and right PHG, the left and right MTG and the PCC, which have also been reported in the literature of smoking-cue reactivity (Engelmann et al., 2012; Yalachkov et al., 2012; Jasinska et al., 2014). We found the coupling between the IDLPFC and the rPHG was relevant for smokers' craving change and those couplings were altered both in the resting-state functional connectivity and the task-based functional connectivity after stimulation. Moreover, the IDLPFC-rPHG coupling correlated with smokers' craving change as revealed by PPI analysis. Our results imply that tDCS over the DLPFC may change craving through the connection with other deep-brain neural circuits, which is consistent with the network explanation of non-invasive brain stimulation (Fox et al., 2014).

The PHG is associated with processing and representation of contextual associations, a core feature common to episodic memory (Aminoff et al., 2013). We found that the PHG was activated during the implicit cue-reactivity task, which is consistent with the viewpoint that strong desire, such as craving, reflects involuntary retrieval and processing of drug usage experience (Franken, 2003; Kavanagh et al., 2005). The tDCS effect on IDLPFC-rPHG coupling correlated with the tDCS effect on craving change individually, which indicates that tDCS may enhance the ability of the DLPFC in regulating retrieval of addiction memory. A noteworthy finding is that the IDLPFC-PHG

coupling was altered even during the resting state after stimulation, which implies that tDCS may induce both intrinsic changes and task-specific effects on the IDLPFC network.

One alternative mechanism of tDCS effects on craving may be due to the amelioration of negative emotions induced by applying electrical stimulation over the DLPFC (Lang et al., 1997). This possibility is supported by a recent study, in which a tDCS effect on negative emotion instead of craving was detected (Xu et al., 2013). However, our results do not support this hypothesis: On the one hand, negative emotions across real and sham stimulation were comparable; on the other hand, brain activation related to negative valence pictures was insensitive to the modulation of tDCS (Supplementary Table S1). Moreover, the IDLPFC-rPHG coupling, as revealed by a similar PPI analysis on an emotion task, was not affected by electrical stimulation (Supplementary Figure S5). However, as the emotion task always followed the cue-reactivity task, the null effect in the emotion task may originate from the weak effect failing to modulate brain activation after about 20 min (the scanning time for resting and cue-reactivity task). Despite this possibility, the current evidence, at least, does not favor the hypothesis that negative emotions are altered by tDCS.

We only recruited male chronic smokers in the study because of the asymmetry of number of male smokers and number of female smokers. According to a recent survey, two-thirds of men smoked in contrast with <1% smoking rate in females who were born after 1960s in China (Chen et al., 2015). Despite of this, it is interesting to focus the tiny population of Chinese female smokers in the future studies.

In summary, our results provide direct evidence that local smoking cue-elicited activation of the left DLPFC was altered by tDCS. Furthermore, we demonstrate that the coupling between the DLPFC and the PHG correlated with craving changes. The tDCS effect on the DLPFC-PHG coupling is even manifested in the resting state after stimulation. These findings imply that tDCS may help smokers to regulate involuntary memory retrieval and support the clinical application of tDCS in nicotine addiction.

Supplementary data

Supplementary data are available at SCAN online.

Acknowledgements

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Conflict of interest. None declared.

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