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Effect of transcranial direct current stimulation on cognitive functions in tobacco smokers

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a neuromodulation tool that is used widely in many medical/experimental trials. We aim to assess the effect of tDCS over the dorsolateral prefrontal cortex (DLPFC) on cognitive function and obtain safety data in tobacco smokers.

Methods: In this double-blinded experiment, 22 human subjects (male) were randomized into two groups: active (n = 12), and sham (n = 10) during three consecutive days for 20 min of continuous active versus sham stimulation each day. The cognitive functions outcome variables were the response time (attention switching task [AST]), and the percentage of correct answers (pattern recognition memory [PRM]). Safety data and visual analog scale were obtained before and after each tDCS session.

Results: After stimulation, AST showed significant improvement in mean correct latency, congruent and incongruent conditions for active group (p-value = 0.003, 0.004, and 0.005), and sham (p-value = 0.003, 0.004, and 0.003) respectively. In all 66 stimulations, mild itching was observed in 25.6% of cases and burning sensation was observed in 15.9% of cases, in both active and sham groups.

Conclusions: While we predicted that performance would only increase during real stimulation, we observed an improvement in performance regardless of whether real or sham stimulation was used. tDCS appeared to be safe, well tolerated, and adhered to the international standard of safety in local population.

1. Introduction

Neuromodulation is a rapidly growing field in the treatment of neurological and neuropsychiatric disorders and in understanding the structure-function relationship of the brain, transcranial direct current stimulation (tDCS) in particular were used in many researches as the rehabilitation after stroke, enhancing the memory in Alzheimer disease and treatment of drug-resistant major depression, especially in pregnancy as it's safe compared to the current medications (Schlaug, Renga, & Nair, 2008; Ferrucci et al., 2008, 2009; Feil & Zangen, 2010). It has been suggested that prefrontal dysfunction, particularly dysfunction of cognitive control, may be related to the loss of control over drug use, and can lead to addiction. Thus, treatment aiming to improve cognitive function for smoking addiction is clinically useful. Recently, there has been debate in the popular media over the use of transcranial direct current stimulation (tDCS), which induces polarity-dependent alterations, thereby improving attention, performance, and cognitive function (Coffman, Clark, & Parasuraman, 2014; Courtney, Ungerleider, Keil, & Haxby, 1997; Cowan et al., 2005; Curtis & D'Esposito, 2003).

However, the desire to improve function can impede our understanding of the role of placebo effects. Placebo effects are well known in the context of medical and surgical interventions (Shapiro, 1971; Turner et al., 1994). In addition to the placebo effect, it may arise in any intervention when the participant knows the desired outcome. Thus, improving cognitive abilities via tDCS is a powerful lure, raising important questions about the role of placebo effects in such studies. The question of whether cognition can be increased through stimulation has generated a lively scientific debate (Chambers, 2013; Thomson, 2010).

Considering this evidence, we hypothesize that tDCS over the dorsolateral prefrontal cortex (DLPFC) (a prefrontal area primarily involved in cognitive control) seems like an excellent method to enhance cognitive function in the nicotine addicted brain. Neuromodulation studies have shown that an increase of excitability of DLPFC modulates working memory, declarative memory, verbal memory and word

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recognition, digit span, and visual recognition memory. In addition to motor and visual learning tasks, tDCS has been effectively used in memory studies, especially working memory (Boggio et al., 2009; Coffman et al., 2014; Courtney et al., 1997; Curtis & D'Esposito, 2003; Thomson, 2010; Turner et al., 1994).

Although there have been rapid advancements towards the diverse applications of tDCS in basic and clinical neuroscience in the last decade, further progress is needed in some local agencies, where a lack of specific regulations for tDCS research has been impeding development. Thus, there has been a call by practitioners, patients, and regulatory agencies to improve the safety of the local population and provide feedback to regulate the use of tDCS. Previous studies showed speculation as to whether there is a difference in potential side effects between active and sham (placebo) groups (Kessler, Turkeltaub, Benson, & Hamilton, 2012; Nitsche et al., 2008; Poreisz, Boros, Antal, & Paulus, 2007).

In this experiment, cathodal tDCS is compared to sham (placebo) stimulation to investigate the effects of tDCS over the DLPFC on cognitive functions in smokers.

2. Methods and materials

Twenty-two nicotine-addicted smokers were recruited for this trial, all of them were male as it is hard to recruit female's smokers due to cultural reasons. The study was a double-blinded sham-controlled experimental trial, twelve participants were the active group and ten were the sham group (Fig. 1). The mean age of the participants was 24.3 ± 5.03 (SD) years, and the mean amount of cigarettes smoked was 20 ± 7.5 (SD) per day. Participants were screened for noninvasive brain stimulation contraindications (Fregni et al., 2005; Linden et al., 2003). All treatment protocols and data collection procedures were conducted according to the Declaration of Helsinki.

This study was conducted at the neurophysiology laboratory in the department of Physiology, College of medicine and King Khalid University Hospital (KKUH). The IRB committee from KKUH approved the project. Informed Consent was obtained from each subject.

2.1. Brain stimulation

Participants remained seated on a comfortable chair. The StarStimNE noninvasive wireless t-DCS/EEG neurostimulator (NE Neuroelectrics®, Barcelona, Spain) was used to deliver the direct current sequentially. The StarStimNE neurostimulator included a wireless neoprene cap, based on the International 10–20 system, which was placed on the participants' heads by aligning the central CZ electrode position with the vertex (intersection of nasion-inion and inter-aural line mid-point). Small Ag/AgCl gelled electrodes, with a surface contact area of 3.14 cm^2 specific to the StarStimNE device (Pi electrodes, Neuroelectrics®), were placed over the right DLPFC at F4 (cathodal) and area F3 (return electrode). The electrodes were connected to a control box device, which was wirelessly connected to a computer and communicated with the NIC software (version 1.2, Neuroelectrics®).

During three consecutive days of cathodal stimulation, direct current was delivered from a current-control circuit at an intensity of 1.5 mA and applied for 20 min each day. For the sham stimulation, electrodes were placed in the same position and participants received a short 10 s ramp up stimulation at the beginning which gives a feeling of heat or tingling at electrode sites to convince the participant that he is having a real stimulation, and a similar 10 s ramp down stimulation at the end of the 20 min. stimulation period (Fig. 1).

2.2. Adverse effect evaluation

Each participant received a post stimulation questionnaire to evaluate the potential side effects that might be associated with the stimulation, which included tingling, itching, burning, headache, fatigue, difficulty concentrating, sudden mood change, change in visual perception, unpleasant sensation, unpleasant sensation in vision, nausea, drowsiness, whether the stimulation sensation is persistent after the end of the stimulation (right or left side of the head), and an open question for any other problem. Each one of the previously stated potential adverse events was rated from 1 to 5 (1 = very mild / 5 = very severe).

2.3. Cognitive function

Neuropsychological testing was performed using CANTAB research suite software (version 6. 0.37, Cambridge cognition) in the first day just before the stimulation, and in the last day immediately after the stimulation. The CANTAB is designed with a significant focus on neuropsychological functions, subserved by frontal lobe regions, such as frontostriatal circuitry that mediate motor, cognitive and behavioral functions within the brain (Fray, Robbins, & Sahakian, 1996). Since the CANTAB is sensitive to brain dysfunctions in frontal and temporal regions, it is highly appropriate for assessing cognitive functions, especially in studies involving passage of electrical current on the frontal and temporal regions, by means of bilateral electrodes (Falconer, Cleland, Fielding, & Reid, 2010). Considering that our study involves applying direct current stimulation to the brain, we decided to use this battery. Our entire battery for neuropsychological testing which included the Attention switching task (AST) and Pattern Recognition Memory (PRM) required 25–30 min to complete the tests. Moreover, it is believed that performance on the CANTAB is dependent on change in cortical activity, our particular tDCS montage is supposed to modulate prefrontal activity, and the CANTAB is precisely sensitive to cortical activity changes. The subject was made to sit comfortably on a stool and asked to keep pressing the response button with the index finger of his dominant hand.

2.4. Attention switching task (AST)

AST measured the participant's ability to switch attention between the direction of an arrow and its location on the screen and to ignore

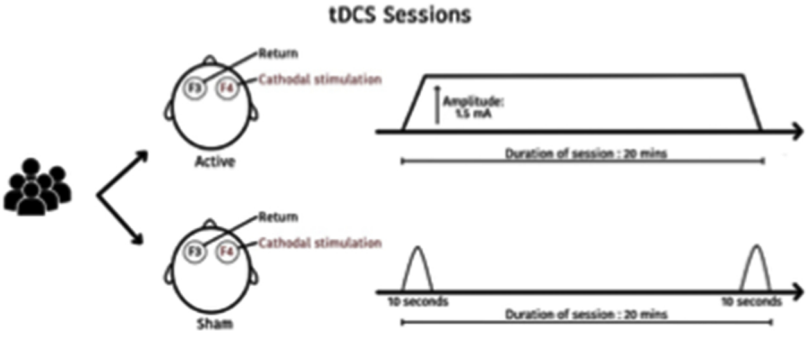

Fig. 1. Work flow of experimental design.

task-irrelevant information in the form of interfering or distracting events. This test has been designed to measure top-down cognitive control processes involving the prefrontal cortex. The test displayed an arrow, which can appear on either side of the screen (right or left) and can point either to the right or to the left. Each trial displayed a cue at the top of the screen that indicates to the participant whether they have to pressed the right or left button according to the "side on which the arrow appeared" or the "direction in which the arrow was pointing." Some trials displayed congruent stimuli (e.g. arrow on the right side of the screen pointing to the right) whereas other trials displayed incongruent stimuli, which required a higher cognitive demand (e.g. arrow on the right side of the screen pointing to the left).

2.5. Pattern recognition memory (PRM)

This is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm. A sequence of visual patterns was presented in the center of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the subjects are required to choose between a pattern they have already seen and a novel pattern.

2.6. Statistical analyses

Data were presented as the mean and standard deviation (SD). The effect of tDCS on the cognitive function was analyzed via a non-parametric paired test, the Wilcoxon signed rank test, as the activity (current density) did not fulfill the criteria for normality.

Data were analyzed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). A P-value of 0.005 or less was considered statistically significant.

3. Results

Comparing the results of CANTAB test, Attention Switching Task (AST) showed a significant improvement after stimulation in mean correct latency, congruent and incongruent condition for active group (p-value = 0.003, 0.004 and 0.005), and sham (p-value = 0.003, 0.004 and 0.003) respectively. However, there was no significant effect in Pattern Recognition Memory (PRM) between pre- and post-stimulation in both groups (p = 0.477 and p = 0.677) as shown in Table 1.

There was no significant relationship between cognitive function among the groups (p-value = 0.1) for mean correct latency, (p-value = 0.288) and for congruent (p-value = 0.549) and incongruent condition in AST task (see Table 2). Participants reported a few mild, self-limited adverse events after the tDCS sessions (see Table 3). The most frequently recorded side effect was itching in the active group and sensation of stimulation on the left side of the head after taking off the cap. We could not observe any significant difference between the active and sham groups (p-value > 0.05).

4. Discussion

Two major findings and implications will be discussed in this section: (1) in contrast to the expectation that participants would perform better under tDCS stimulation, it was found that this was not the case, and that tDCS improved response time in the AST paradigm; and (2), in both conditions we observed an improvement in performance regardless of whether cathodal tDCS or sham stimulation was used. This indicates a significant placebo effect.

An interesting observation was that performance improved in both conditions regardless of whether cathodal tDCS or sham stimulation was used. This placebo effect might be due to the mere presence of the tDCS apparatus. The idea of the stimulation and the expected effects of this device might have increased cognitive performance in these cases.

Interestingly, cathodal stimulation seems to decrease performance less than sham stimulation. This effect is speculation, and needs to be explored in future research by using an active control of anodal stimulation as placebo.

An important message from this study is that it is necessary to control for placebo effects in brain stimulation, especially in other controlled clinical trials (Fregni et al., 2005; Linden et al., 2003). Additionally, only 7 of the 106 similar studies used a double blind design. Another study revealed that only 87.5% of the tDCS studies that have foundational claims on which the modern tDCS field is built, used a proper control condition (Horvath, Carter, & Forte, 2014; Horvath, Forte, & Carter, 2015). Considering brain stimulation as a hard method, it is usually neglected and thought to be redundant to use a placebo condition in brain stimulation research. Placebo effects pose problems for some intervention studies, particularly those with no clearly identified mechanism. Cognitive improvement after tDCS falls into that category, and yet the role of placebos in cognitive interventions has not yet been critically evaluated. Here, we show clear evidence of placebo effects that led to significant improvement of cognitive function for AST. There is a way to prevent placebo effects occurring from overt and suggestive recruitment, which can affect brain stimulation outcomes. The PFC and DLPFC are suggested to be engaged in cognitive functions. More specifically they are directly involved in different aspects of memory, including visual-spatial memory (Courtney et al., 1997; Cowan et al., 2005; Curtis & D'Esposito, 2003). Dysfunction of distributed cortico-subcortical, bihemispheric regions in the DLPFC network, with higher activity in the right hemisphere and lower activity in the left hemisphere, has been found central in depression pathology (Boot, Simons, Stothart, & Stutts, 2013; Cave, 2013; Chambers, 2013; Shapiro, 1971; Shipstead, Redick, & Engle, 2012). Thus modulation DLPFC cortical activity is supposed to be accompanied by cognitive improvement in smoker. Our study suggests improving effects of tDCS on attention task and not recognition memory in smoker subject by targeting right DLPFC for cathodal stimulation. This has important theoretical implications for smoker studies too, in terms of how the DLPFC contributes to smoker cognitive impairments.

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Table 1
Comparison between pre and post stimulation in active and sham groups.

	Pre (mean)	Post (mean)	P-value
Active			
AST Mean correct latency	590.97 (107.70)	525.77 (110.29)	0.003*
AST Mean correct latency (congruent)	564.31 (100.1)	501.49 (109.43)	0.004*
AST Mean correct latency (incongruent)	619.77 (119.9)	551.45 (115.29)	0.005*
PRM Percent correct	88.78 (7.49)	90.27 (6.36)	0.477
Sham			
AST Mean correct latency	611.63 (161.08)	504.91 (127.88)	0.003*
AST Mean correct latency (congruent)	586.73 (157.04)	478.8 (115.61)	0.004*
AST Mean correct latency (incongruent)	632.06 (174.86)	532.65 (143.00)	0.003*
PRM Percent correct	77.92 (28.40)	80.30 (27.58)	0.677

Table 2
Comparison between active group and sham group in the mean difference of cognitive function.

	Active (n = 13)	Sham (n = 11)	p-value*
AST Mean correct latency (millisecond)	11.14 (7.46)	16.65 (8.22)	0.100
AST Mean correct latency (congruent) (millisecond)	11.36 (8.11)	17.18 (9.74)	0.125
AST Mean correct latency (incongruent) (millisecond)	10.86 (8.95)	14.85 (8.96)	0.288
PRM Percent correct (%)	−0.20 (6.70)	−2.07 (8.34)	0.549

* All values NS > 0.05.

Table 3
Number of the occurrence of the side effects between active and sham groups.

	Total (n = 66)	Condition		*p*-value
		Active (n = 33)	Sham (n = 33)	
Tingling*	13	4	9	0.057
Itching*	21	14	7	0.208
Burning*	13	8	5	0.599
Headache*	12	5	7	0.320
Fatigue**	7	3	4	0.695
Difficulty in concentration**	9	5	4	1.000
Sudden mode change**	10	4	6	0.335
Change in visual perception**	8	2	6	0.079
Unpleasant sensation**	5	4	1	0.372
Unpleasant sensation in vision**	11	9	2	1.000
Nausea**	4	2	2	1.000
Drowsiness**	6	3	3	1.000
Feeling the stimulation R**	10	8	2	0.105
Feeling the stimulation L*	17	11	6	0.360

* Pearson Chi-Square test.
** Fisher's Exact Test.

information that may provide the goals of the research and omit mention of any anticipated outcomes to the participants (Boot, Blakely, & Simons, 2011; Ryan, Lynch, Vansteenkiste, & Deci, 2010; Torgerson, Klaber-Moffett, & Russell, 1996). The purpose of such a design would be to minimize any confounding effects (e.g., placebo or expectation).

This view is in line with some from the medical domain, who argue that researchers can make use of participant expectation to better test treatment effects in randomized controlled trials (Boot et al., 2011). This view is also in line with some from the psychotherapy domain who argue that motivation is important for treatment effectiveness (Open Science Collaboration, 2015).

It will be important in future work to investigate the relationship between expectation and processes of learning after stimulation. Our data does not allow us to understand the field as a whole; instead, it allows us to understand existing limitations of current research, which require further exploration.

The possible reasons for the contradicting findings of this study might be due to a relatively small sample size, which also lacked variation in age. This was a limitation in the study. Due to the small effects of tDCS, a large sample is required to detect a significant effect. Moreover, there might be an unchangeable limit of PRM that cannot be exceeded in any way. The fact that the capacity can be decreased does not necessarily mean that it can also be increased. Another issue that needs to be considered is the fact that the task required constant fast reactions from participants, and attention processes might not depend on the inhibition of the DLPFC.

5. Conclusion

Our findings have important implications for tDCS research. Previous cognitive- improvement results may have been inadvertently influenced by placebo effects arising from recruitment or design. For the field of neuromodulation to advance, it is important that future studies report recruitment information to determine the relation between observed effects of training and of expectancy.

Authors' contributions

FA carried out subject's assessment, AA, FA, MA and AA, TA participated indata collection and writing and analyzing the data, SB participated in the design of the study and performed the statistical analysis. SF, SSS participated in the writing of the study and performed the statistical analysis. All authors read and approved the final manuscript".

Finical disclosure

All authors have nothing to declare for finical disclosure.

Ethical statement

All participants fulfill the required ethical procedure.

Declarations

Ethics approval and consent to participate: ("King Khalid university Hospital")
Consent to publish: ("Not applicable").

Availability of data and materials

Available on request.

Competing interests

No conflict declared.

Funding

Nothing declared.

Conflict of interest

All authors declare non-conflict of interest.

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