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The fade-in – Short stimulation – Fade out approach to sham tDCS – Reliable at 1 mA for naïve and experienced subjects, but not investigators

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ABSTRACT

Objective: Slowly ramping down initial current intensity after a minimal interval of stimulation is the de facto standard for sham stimulation in transcranial electrical stimulation research. The aim of this study is to further investigate the effectiveness of this method of blinding.
Methods: We have investigated the time course of the cutaneous perception during 10 min of anodal, cathodal, and sham transcranial direct current stimulation, probing the perceived strength and site of the perceived sensation. We have also utilized post-stimulation assessment and measurements of sleepiness prior to and after the intervention. Previous exposure to tDCS has also been taken into account: the experiment has been repeated in naïve and experienced subject groups, and a group consisting of investigators who use tDCS as a research tool.
Results: Although we have observed a general reduction in the perceived strength of the stimulation with time, we have not found the complete disappearance of the cutaneous perception during either the verum or the sham conditions. Experienced subjects were more likely to be able to differentiate between trials with stimulation and non-stimulation trials and to correctly identify sham and verum stimulation conditions.
Conclusion: When taking only naïve and experienced subjects into account, there was no significant difference between the strength of the perceived stimulation in the verum and sham conditions. The fade-in – short stimulation – fade-out sham stimulation can be indistinguishable from verum stimulation, but not because it mimics the disappearance of the cutaneous sensations associated with the verum stimulation, but because these sensations persist also in the sham stimulation. The significance of this finding with potential confounding factors and limitations are discussed.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive method that induces changes in cortical excitability outlasting the duration of the stimulation in a spatially restricted and reversible manner [1]. Among the most widely reported phenomena associated with the application of stimulation are the itching and tingling sensations under the electrodes [2]. Few reports of headache and burning sensations also exist [3]. It is widely assumed in the literature that the cutaneous perception associated is restricted to the initial few seconds of the stimulation [4–6].

The standard method of administering the sham intervention is therefore the *fade in*, *short stimulation*, *fade out* approach, in which the stimulation intensity is slowly ramped down after a few seconds of actual stimulation, mimicking the initial sensations associated with the stimulation. It has been shown by Gandiga et al. [6] that this method is reliable method of sham stimulation and is suitable for double-blind experiments. This approach is now a generally accepted procedure for blinding purposes, but its underlying assumption, that in the case of verum stimulation the sensations are only perceived during the initial phase of the stimulation, has not been quantitatively examined so far. Thus, it can be speculated that blinding, using this method, is achieved not by the mimicking of the complete disappearance of the sensations after the initial phase of the stimulation, but by inducing a subjective sensation that can still be perceived after the intensity has been ramped down, and this subjective sensation is not easily distinguishable from the perceptions associated with the verum stimulation in quality and quantity.

That this speculation might have merit, is hinted at by Dundas et al. [4], who have found that their subjects perceived the sensations even 1 min after the beginning of the stimulation. As this

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study only assessed perception at one time point (1 min after the stimulation onset), did not control for sham and had not reported whether or not an initial ramping up of the stimulation intensity had been performed, further investigation is deemed necessary.

Whether the subject perceives sensations associated with the sham and/or verum stimulation only initially or throughout the duration of the experiment, may have important consequences, as they can elevate arousal, focus, or divert attention (depending on task difficulty, see: Yerkes and Dodson [7]; Diamond et al. [8]), thus, potentially compromising the validity of the acquired results.

In previous blinding-related studies we have explored the cutaneous perception characteristics of tES. We have probed the cutaneous perception thresholds of tDCS using short stimulation durations in the current intensity range of 200–2000 μA [9], and have probed the blinding potentials of rectangular and circle-shaped electrode configurations [10]. In this present study we aim to investigate the characteristics of the cutaneous perception during the entire course of the stimulation.

Methods

Subjects

Thirty-six healthy volunteers, students and employees of the University of Göttingen, participated in the study (17 male; age 25.80 ± 4.28). Participants reported no previous history of neurological or psychological disorders, drug or alcohol abuse, and had no metal implants. None of the subjects were taking any chronic or acute medication at the time of the study. All subjects gave written informed consent before participating. The study was conducted with the approval of the ethics committee of the University of Göttingen and in accordance with the guidelines of the Declaration of Helsinki.

As in our previous investigation [9], we have given special attention to the participants' prior knowledge of and exposure to tES stimulation. We have created three experimental groups:

Group 1. Naïve subjects (n = 12; 6 male; mean age = 24.66 ± 2.34). Newly recruited participants with no previous experience with tES methods.

Group 2. Experienced subjects (n = 12; 6 male; mean age = 26.16 ± 4.60). Participants who took part in at least one study involving tES prior to this current experiment.

Group 3. Investigators (n = 12; 5 male; mean age = 26.58 ± 5.43). Investigators at the Department of Clinical Neurophysiology, University of Göttingen, who took part, and also, have conducted experiments involving tES methods.

Transcranial direct current stimulation

Stimulation was delivered by a battery-driven constant current stimulator (neuroConn GmbH, Ilmenau, Germany). The current was transferred by a pair of standard carbon rubber electrodes (Physiomed Elektromedizin AG, Schnaittach, Germany) placed in viscose sponge wrappers soaked in isotonic sodium chloride solution. One electrode was placed over the left supraorbital area; the other electrode, to which polarity refers to, was placed contralaterally, over the C3, the approximate location of the M1. The electrodes were fixed to the head with elastic rubber bands. The stimulator was triggered by a personal computer via parallel port connection.

No special skin surface preparation was performed before the experiment. The rubber bands have been fixed firmly so that the electrodes were not able to move, but no extraneous pressure was applied. Approximately 15 ml of NaCl solution was applied to wet the sponge.

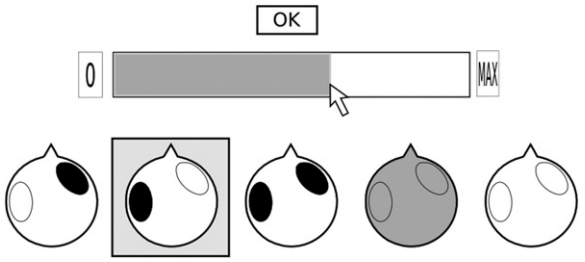

Fig. 1. The computerized form used for entering the perceived stimulation strength and the site of the cutaneous perception.

Experimental design and data acquisition

The experiment was conducted according to a sham controlled, double blind, repeated measures design. Each subject participated in three sessions (anodal, cathodal and sham tDCS), in a randomized and counterbalanced order. Two consecutive sessions were separated by an interval of at least four days.

As the standard procedure in our lab requires, a written information sheet and consent form was handed to the participants. It is important to note that this sheet informs the participants that during the stimulation they might perceive a slight itching sensation under the electrodes, and that in rare cases a light and transient headache or skin irritation may occur.

During the experiment participants were seated in front of a computer display and were given a mouse. At the beginning of each session, the investigator and the subject reviewed the experimental workflow. The subject started the stimulation by pressing the space bar. The trial lasted for approximately 10 min, during which real or sham (placebo) stimulation is applied continuously (the nature of the sham stimulation is not disclosed at this point). The task of the subject is, when prompted, to report the perceived strength and site of the cutaneous sensation associated with the stimulation. The subject enters these parameters using a computerized form (Fig. 1), where a horizontal slider and two additional buttons (*no sensation*; *extreme discomfort*) represents the perceived strength, and five buttons represent the site of the sensation. The subject finalizes the form by pressing the OK button, after which the form disappears.

The choices for sites of perception were based on the findings of our previous experiments investigating cutaneous perceptions associated with tES methods, where subjects reported having perceived the sensation either form the orbital electrode, the M1 electrode, from both electrodes, or from the whole scalp surface [9,10].

After reviewing the objectives the investigator fixed the electrodes and tested the devices to ensure normal functioning of the setup. A second investigator in a separate room then programmed the stimulator to give anodal, cathodal, or sham stimulation, according to a randomized, balanced schedule. The first investigator took a position outside the visual field of the participant for the rest of the session, connected the stimulator to the computer, and instructed the subject to start the experiment. During the course of the study the first investigator had no access to the session/stimulation condition schedule, and the second investigator did not come into contact with the subjects during the experimental sessions.

The parameters for the verum and sham stimulation are as follows.

Verum stimulation

In the case of the verum (anodal and cathodal) stimulation trials, the stimulation intensity was ramped up from 0 to 1 mA in 20 s. The

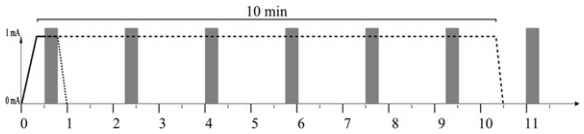

Fig. 2. The time course of the sham and verum stimulation. Both conditions begun with a 20 s fade-in phase; in the case of sham stimulation the current was ramped down in 10 s after 30 s of stimulation, in the verum case the stimulation lasted for 10 min, after which it was ramped down in 10 s. During the course of the session the participant was propmted to report the cutaneous perception (grey bars).

current intensity then remained constant for another 10 min (600 s), after which it was ramped down in 10 s.

Sham stimulation

In the case of sham stimulation the initial ramp-up phase was also 20 s, after which 30 s of stimulation followed with 1 mA intensity. The current then was ramped down during the following 10 s. The polarity of the sham stimulation was randomized and counterbalanced across groups and conditions.

The participants were prompted to input the cutaneous perception parameters consecutively every 1.75 min; seven times during the verum stimulation interval, starting from 30 s after the beginning of the trial, and once after the verum stimulation had ceased, at 11 min (see Fig. 2).

The double blind procedure, the use of a computer interface to report the sensations, and locating the investigator outside the visual field of the participant during the course of the trial were all conscious measures taken in order to avoid any observer-expectancy biases and verbal or non-verbal cues potentially capable of influencing the subjects' responses.

Before and after the stimulation we have assessed the wakefulness of the subjects using the Stanford Sleepiness Scale (SSS). Furthermore, in a post-stimulation questionnaire we have asked the subjects to describe the perceived sensations during the experiment in their own words. We have also asked them whether the sensations during the stimulation were painful at any time, and if the answer was yes, they had to report the painfulness on an analog scale, ranging from "not painful at all" to "intolerably painful". Then, we have asked them whether they have felt itching, light flashes or headache during, and/or after the stimulation. Finally, we have asked them if, in their opinion, they have received real, or placebo stimulation, and to rate their confidence in this decision on an analog scale ranging from "not sure at all" to "I am certain".

Data acquisition and analysis

To assess the effects and interactions of stimulation type, experience and the factor of time on the perceived stimulation strength, we have used a repeated measures analysis of variance (rmANOVA). For each subject in every condition, the ratios of reports identifying the different sites of perception have been calculated. These values have been analyzed using rmANOVA. Greenhouse-Geisser corrections have been applied, where the assumption of sphericity has been violated. Bonferroni-corrected post-hoc analyses have been used. The subjects' groupwise assessments of stimulation conditions were analyzed using Cochrane's Q test.

For each participant, hit and false alarm rates were derived from the responses given during active (at the first trial time-point in the sham condition, when the stimulation was still present, and during all but the last trials in the active conditions) and non-stimulation (all but the first trial in the sham condition, and the last trials in the active conditions) trials. From these values, the d' sensitivity index was calculated for each subject, and a One-Way ANOVA was used to assess group level differences.

For the analysis of the SSS, the differences in the scores before and after the stimulation have been calculated for each participant in every stimulation condition. These values have been analyzed using a Friedman ANOVA.

All statistical comparisons have been conducted with a significance level of 5% ($P < 0.05$).

Results

All of the subjects completed all three experimental sessions, tolerated the tDCS procedure and reported no side-effects (other than those discussed below) during or after the experimental sessions.

Qualitative assessment of the sensations associated with the stimulation

After the stimulation we asked the subjects to fill in both an open-ended questionnaire and a checklist of some of the commonly reported sensations (itching, pain, light flashes, headache) associated with tDCS. The reports of the sensations from both sources have been combined, and are presented in Table 1. The most prominent sensation was itching, reported in 85.1% of the cases. Pain was reported in 24% of the sessions. The strength of the pain sensation has also been assessed; see Fig. 3. Burning was reported in 11.1% of the sessions, while tingling was reported in 16.6% and headache in 9.2% of the sessions. Prickling was reported in 2.7% of the sessions. None of subjects reported seeing light flashes during the stimulation.

Cochrane's Q test did not show any difference between subject groups and stimulation conditions regarding *itching* (all groups: $Q = 1.555$; df $= 2$; $P < 0.459$; naïve group: $Q = 2$; df $= 2.000$; $P < 0.367$; experienced group: $Q = 2.666$, df $= 2$, $P < 0.263$; investigator group: $Q = 2.800$; df $= 2$; $P < 0.246$). Also, no such differences could be observed in the case of *pain* (all groups: $Q = 0.347$; df $= 2$; $P < 0.840$; naive group: $Q = 3.714$, df $= 2$; $P < 0.156$; experienced group: $Q = 0.222$; df $= 2$; $P < 0.894$; investigator group: $Q = 0.142$; df $= 2$; $P < 0.564$). No significant differences were observable regarding *headache* (all groups: $Q = 5.600$; df $= 2$; $P < 0.060$; naive group: $Q = 2.666$; df $= 2$; $P < 0.263$; experienced group: $Q = 3.500$; df $= 2$; $P < 0.173$; investigator group: $Q = 0.666$; df $= 2$; $P < 0.716$). Also, there was no difference regarding *burning sensation* (all groups: $Q = 4.800$; df $= 2$; $P < 0.090$; naive group: $Q = 2.000$; df $= 2$; $P < 0.367$; experienced group: $Q = 2.000$; df $= 2$; $P < 0.367$; investigator group: $Q = 2.666$; df $= 2$; $P < 0.263$).

Differences in perceived discomfort between stimulation conditions

The rmANOVA revealed a main effect of stimulation condition ($F [(2, 66] = 7.739$; $P = 0.001$). Bonferroni post-hoc tests revealed that the perceived strength of stimulation in the sham condition was significantly lower than it was in both verum stimulation conditions (anodal: $P = 0.002$; cathodal: $P = 0.006$), and that was no significant difference between the anodal and cathodal stimulation conditions in that regard ($P = 1.000$).

Group level differences

The repeated measures ANOVA has shown no main effect of subject group ($F [2, 33] = 0.254$; $P = 0.776$). The rmANOVA revealed an interaction between group and stimulation type ($F [4, 66] = 2.501$, $P = 0.050$). A Bonferroni-corrected post-hoc analysis

Table 1
Reports of perceived phenomena associated with the stimulation. The table also shows the number and percentage of the subjects correctly identifying the given stimulation session as real or placebo ("identified"), and the number and percentage of subjects who identified all of the stimulation sessions correctly ("all correct").

		Itching		Tingling		Burning		Pain		Headache		Prickling		SSS difference	Identified		All correct	
		n	%	n	%	n	%	n	%	n	%	n	%	Mean ± SD	n	%	n	%
Naive $n = 12$	Anodal	10	83.33	0	0.00	0	0.00	2	16.67	0	0.00	0	0.00	0.33 ± 0.89	11	91.67		
	Cathodal	11	91.67	0	0.00	1	8.33	3	25.00	0	0.00	1	8.33	0.00 ± 0.43	10	83.33	1	8.33
	Sham	11	91.67	0	0.00	0	0.00	3	25.00	1	8.33	0	0.00	−0.42 ± 0.79	2	16.67		
Experienced $n = 12$	Anodal	11	91.67	1	8.33	0	0.00	1	8.33	0	0.00	0	0.00	−0.58 ± 0.89	10	83.33		
	Cathodal	9	75.00	2	16.67	1	8.33	4	33.33	1	8.33	0	0.00	−0.58 ± 2.07	9	75.00	2	16.67
	Sham	9	75.00	1	8.33	0	0.00	3	25.00	1	8.33	0	0.00	−0.17 ± 1.85	2	16.67		
Investigator $n = 12$	Anodal	10	83.33	4	33.33	4	33.33	5	41.67	2	16.67	1	8.33	0.08 ± 0.79	11	91.67		
	Cathodal	12	100.00	4	33.33	4	33.33	4	33.33	3	25.00	1	8.33	−0.18 ± 0.40	11	91.67	8	66.67
	Sham	9	75.00	6	50.00	2	16.67	1	8.33	2	16.67	0	0.00	−0.08 ± 0.51	10	83.33		

has shown significant differences between the sham and verum stimulation conditions (anodal: $P = 0.002$; cathodal: $P = 0.004$) in the investigator group, with perceived stimulation strength in sham condition being markedly lower. No such differences have been observed in the naïve or the experienced group (all comparisons: $P = 1.000$).

Sensitivity index

Groupwise comparison of the d' values using a One-Way ANOVA revealed a significant main effect (F [2, 33] = 7.067; $P = 0.002$). Bonferroni-corrected post-hoc comparisons have shown that the difference between the investigator group (mean = 2.168 ± 0.968) and the naïve (mean = 0.749 ± 1.153; $P = 0.013$) and the experienced (mean = 0.572 ± 0.1.278; $P = 0.004$) groups was significant, but no significant difference could be observed between the naive and the experienced groups ($P = 1.00$).

Subjects' assessments of stimulation type

Taken the whole sample into consideration, Cochrane's Q yielded a significant difference in the subjects' assessment of stimulation type ($Q = 8.10$; df = 2; $P < 0.017$). Group-level analysis of the responses did not find any differences regarding the naïve ($Q = 0.50$; df = 2; $P < 0.77$) or the experienced ($Q = 0.33$; df = 2; $P < 0.84$) group. In the investigator group, however, we have found that the "placebo" answers in the sham condition significantly outweighed those in the in the verum conditions ($Q = 16.20$; df = 2; $P < 0.000$).

Investigating how sure participants were in their assessment of the type of stimulation, rmANOVA did not show a significant main effect of group (F [2, 33] = 1.243; $P = 0.301$), type of the received stimulation (F [2, 66] = 0.342; $P = 0.711$), or an interaction of group and stimulation type (F [4, 66] = 0.241; $P = 0.913$). Table 1 shows the number of subjects in each group and stimulation condition who have identified the stimulation session correctly as real or placebo stimulation.

Time-course of the reported perception of stimulation strength

The rmANOVA, corrected for sphericity (Mauchly's test: χ^2 [22] = 136.48; $P = 0.000$), using a Greenhouse-Geisser correction ($\varepsilon = 0.37$), revealed a significant main effect of time (F [2.24, 74.04] = 38.063; $P = 0.000$), and the Bonferroni-corrected post-hoc analysis revealed consecutive drops in perceived strength in the first three trials (4 min, $P < 0.007$); the change in perceived strength in the remaining trials was not shown to be significant ($P > 0.9$).

The time course of the reported strength of the stimulation in the different stimulation conditions has been found to be significantly different. An rmANOVA, corrected for sphericity (Mauchly's test: χ^2 [77] = 184.06; $P = 0.000$) using the Greenhouse-Geisser correction ($\varepsilon = 0.53$) found a significant interaction between stimulation type and time (F [8.71, 287.61] = 1984; $P = 0.042$). A post-hoc Bonferroni test was used to explore the differences in and between the stimulation conditions. No significant differences have been observed between the stimulation conditions during the first time-point (all comparisons: $P = 1.000$). In the case of sham stimulation condition, the reported strength of the stimulation dropped significantly in the subsequent trials (from the 2.25th minute, all comparisons: $P = 0.000$). In the case of the anodal condition, the drop in the perceived stimulation strength reached significance form the third (4 min, all comparisons: $P = 0.000$), and in the cathodal condition, the fourth time-point (5.75 min, all comparisons: $P = 0.000$). The time course of the perception of stimulation strength in all conditions and groups is shown in Fig. 4.

As investigators have shown to be more capable of discriminating between sham and active trials, and as investigators are generally not assumed to form a significant part of an experimental sample, we have also performed a second rmANOVA on a dataset containing only the responses of naïve and experienced subjects. This analysis yielded only a significant main effect of time (Greenhouse-Geisser [$\varepsilon = 0.36$] corrected, F [2.162, 47.582] = 15.021; $P = 0.000$), with post-hoc Bonferroni analysis showing a significant decline in perceived strength from the third trial (4 min), when

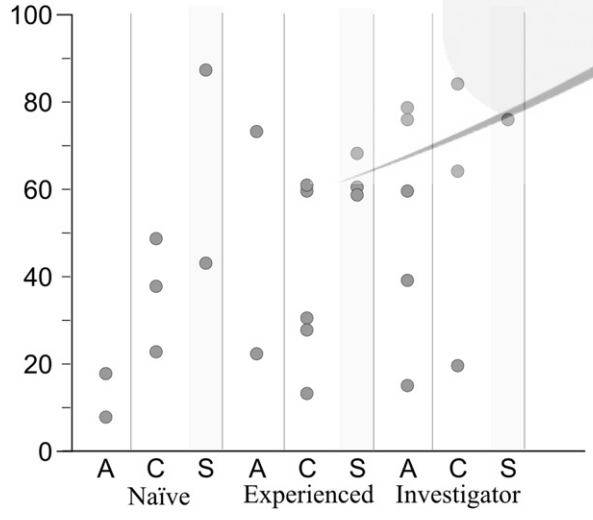

Fig. 3. Strength of perceived pain. The figure shows individual data for all subject groups and stimulation conditions (A: anodal, B: cathodal, S: sham).

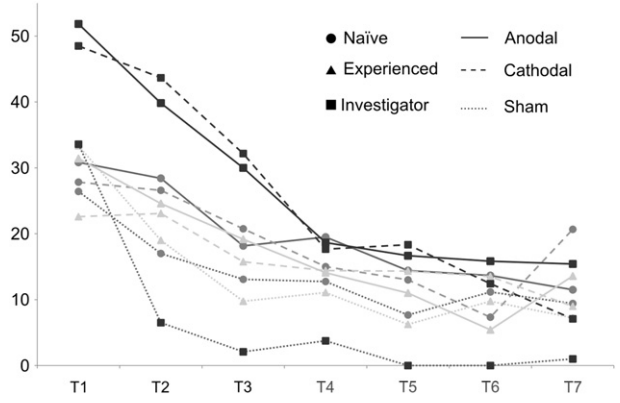

Fig. 4. The time course of the perceived stimulation strength for all subject groups and stimulation conditions.

compared to the first trial (all comparisons: $P = 0.000$). No main effects of stimulation type (Greenhouse-Geisser [$\varepsilon = 0.931$] corrected, F (1.862, 40.984) = 1.241; $P = 0.297$) or subject group (F [1, 22] = 0.084; $P = 0.773$) were observed, furthermore, no interactions between stimulation type and subject group (F [2, 44] = 0.108; $P = 0.897$), subject group and time (F [6, 13] = 0.166; $P = 0.985$), stimulation type and time (Greenhouse-Geisser [$\varepsilon = 0.513$] corrected, F [6.164, 135.616] = 0.943; $P = 0.467$), or stimulation type, time, and subject group (Greenhouse-Geisser [$\varepsilon = 0.513$] corrected, F [6.164, 135.616] = 0.967; $P = 0.451$), have been observed.

Reported sites of cutaneous perception

Analyzing the ratios of the sites of perception, the rmANOVA has shown a main effect of stimulation site (Greenhouse-Geisser [$\varepsilon = 0.734$] corrected, F [2.202, 72.684] = 13.561; $P = 0.000$) and an interaction between the stimulation condition and the stimulation site (Greenhouse-Geisser [$\varepsilon = 0.595$] corrected, F [3.573, 117.916] = 2.321; $P = 0.002$). Bonferroni-corrected post-hoc test have shown that the orbit was significantly more frequently identified as the site of stimulation than the other locations ($P < 0.03$), the M1 and both electrodes was more frequently reported than the whole scalp ($P = 0.003$ and $P = 0.006$, respectively), and that there was no difference in the rate of M1 and both electrodes responses ($P = 1.000$).

Sleepiness scale

Friedman's ANOVA did not reveal any significant differences between the changes in SSS scores before and after the stimulation between the stimulation conditions in any subject group (χ^2 [2] = 2.065; $P = 0.356$).

Discussion

In this study we have assessed the cutaneous perception characteristics of verum and sham tDCS stimulation during a 10 min interval.

Regarding the site of the perceived stimulation, our results have shown that the orbit is the most frequently identified location. This finding is in agreement with our previous data [9], and with those of Dundas et al. [4] and may be related to greater skin sensibility of the forehead compared to the piliferous skin under the M1 electrode.

In our study, itching was the most often reported sensation associated with the stimulation. We have however found no significant differences in the case of the rate of responses regarding itching, pain, and headache.

Our results indicate that in the case of naive and experienced subjects, sham stimulation is indistinguishable from verum stimulation regarding both perception of stimulation strength and assessment of stimulation type. In the case of investigators, however, sham stimulation significantly more often identified as "placebo", and it also differed in perceived stimulation strength.

In the light of these results, we can still consider this method of blinding efficient, but not because the sham fade-out phase mimics the presumed disappearance of the sensations in the verum stimulation conditions, instead, the cutaneous sensations associated with the sham stimulation persist after the ramp-down phase.

The fact that the sensations associated with both verum and sham stimulation can be perceived throughout the experiment may have methodological implications. As first described by Yerkes and Dodson [7] in mice, for every task there exists an optimal level of arousal, above and beyond which performance is going to decline. This optimal level of arousal changes with the type of task in question; it is lower in tasks that burden attention and cognitive resources, while it is higher in tasks that are less demanding.

Possible correlates of the interaction between arousal/stress levels and task performance in the prefrontal areas are extensively discussed in a review article by Diamond and colleagues [8], who propose that if the task performance relies on the PFC, a higher level of arousal is more likely to have a detrimental effect on performance, while a task less reliant on PFC-mediated cognitive processes benefit from increased arousal. Our initial results measuring wakefulness using the SSS did not show a difference between any of the stimulation conditions in any of the groups. This result is consistent with the findings reported by Gandiga and colleagues [6], who found that ratings of attention have not shown to be significantly altered by stimulation. It is conceivable that these kinds of self-reported questionnaires are not sensitive enough to show changes in attention and arousal *during* stimulation. Further behavioral studies, such as measurements of vigilance using varying levels of difficulty may tell more about the influence of the stimulation-related procedural discomfort on task performance.

Limitations

In an experiment by van Laarhoven et al. [11] it has been shown that verbal suggestions can enhance the nocebo effect regarding itching and pain: when participants are told that most people experience itching or pain when exposed to a procedure, they are more likely to report an itching/pain sensation when exposed to the stimulus in question, compared to the participants who have been given the information that only a minority of the subjects experience itching/pain. Our consent form/information sheet informed the subjects that they might experience an itching sensation under the electrode; an information that may elevate their expectations, and thereby the actual number of the reports in both the verum and the sham stimulation conditions, regarding itching. It has to be noted that it is required that the participants must be informed about the circumstances and the potential adverse effects of the intervention, thus the potential expectation effects should also be present in the all studies using tDCS.

Similarly to experiments investigating the effects of electrical stimulation on the motor system, our subjects during this experiment were idle during the stimulation. In other experiments, such as many of those assessing the influence of stimulation on aspects of cognition, the stimulation is applied during task performance. In that setting, it can be argued that the execution of a task may help the habituation to the sensations associated with the stimulation by diverting attention.

Also, during our experiment the participants have been instructed to pay attention to and report the sensations and this might have hindered habituation to the associated sensations, elevating the level of the perceived sensations.

Another factor confounding our results may be the acquiescence bias, that is, the participants' tendency to confirm with the questions asked or to indicate a positive connotation. We cannot rule out the possibility that the acquiescence bias can elevate the reported level of procedural discomfort, both in the verum and in the sham stimulation condition.

Conclusion

We have found that investigator participants could more easily distinguish between verum and sham trials; this finding has to be taken into account when investigators are used in e.g. pilot studies.

Our investigation supports the use of the fade-in – short stimulation – fade-out approach to sham stimulation. It should be noted, however, that the reported strength of the perception decreased significantly with time, contrary to the observations reported previously, as most naïve and experienced subjects did not perceive the disappearance of the sensations after the initial phase of the verum stimulation procedure, and the sensations associated with the stimulation also persisted in the sham stimulation condition.

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Conflicts of interest

The authors declare no conflicts of interest.

References

[1] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1:206–23.
[2] Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 2007;72(4–6):208–14.
[3] Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychoph 2011.
[4] Dundas JE, Thickbroom GW, Mastaglia FL. Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes. Clin Neurophysiol 2007;118(5):1166–70.
[5] Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. Supplements to Clin Neurophysiol 2003;56:255.
[6] Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117(4):845–50.
[7] Yerkes R, Dodson J. The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol 1908;18:459–82.
[8] Diamond DM, Campbell AM, Park CR, Halonen J, Zoladz PR. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson law. Neural Plast 2007.
[9] Ambrus GG, Paulus W, Antal A. Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. Clin Neurophysiol 2010; 121(11):1908–14.
[10] Ambrus GG, Antal A, Paulus W. Comparing cutaneous perception induced by electrical stimulation using rectangular and round shaped electrodes. Clin Neurophysiol 2011;122(4):803–7.
[11] van Laarhoven AIM, Vogelaar ML, Wilder-Smith OH, van Riel PLCM, van de Kerkhof P, Kraaimaat FW, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain 2011.