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Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients

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Abstract

Cortical excitability changes induced by tDCS and revealed by TMS, are increasingly being used as an index of neuronal plasticity in the human cortex. The aim of this paper is to summarize the partially adverse effects of 567 tDCS sessions over motor and non-motor cortical areas (occipital, temporal, parietal) from the last 2 years, on work performed in our laboratories. One-hundred and two of our subjects who participated in our tDCS studies completed a questionnaire. The questionnaire contained rating scales regarding the presence and severity of headache, difficulties in concentrating, acute mood changes, visual perceptual changes and any discomforting sensation like pain, tingling, itching or burning under the electrodes, during and after tDCS. Participants were healthy subjects (75.5%), migraine patients (8.8%), post-stroke patients (5.9%) and tinnitus patients (9.8%). During tDCS a mild tingling sensation was the most common reported adverse effect (70.6%), moderate fatigue was felt by 35.3% of the subjects, whereas a light itching sensation under the stimulation electrodes occurred in 30.4% of cases. After tDCS headache (11.8%), nausea (2.9%) and insomnia (0.98%) were reported, but fairly infrequently. In addition, the incidence of the itching sensation ($p = 0.02$) and the intensity of tingling sensation ($p = 0.02$) were significantly higher during tDCS in the group of the healthy subjects, in comparison to patients; whereas the occurrence of headache was significantly higher in the patient group ($p = 0.03$) after the stimulation. Our results suggest that tDCS applied to motor and non-motor areas according to the present tDCS safety guidelines, is associated with relatively minor adverse effects in healthy humans and patients with varying neurological disorders.

Keywords: Transcranial direct current stimulation; Safety study; Motor cortex; Non-motor cortex

1. Introduction

Long-term changes in motor cortex excitability following transcranial direct current stimulation (tDCS) have recently been demonstrated non-invasively in humans [26,27,35]. During tDCS, a weak electrical current ($\leq$1 mA) is applied using two surface electrodes. Most tDCS induced changes in cortical excitability have been assessed using transcranial magnetic stimulation (TMS). These changes of motor cortex excitability have been reflected by the size of electromyography (EMG) responses to standard single-pulse probe stimuli [26,27,35]. Studies on electrode placement [26] indicate that the effect is relatively focal and stimulation of the primary motor hand area (M1) can produce long-lasting (up to 1 h) polarity-specific effects on corticospinal excitability and motor learning in humans. Animal studies suggest, that cathodal stimulation decreases the resting membrane potential and therefore hyperpolarizes neurones, whereas anodal stimulation causes depolarization [8,9,36] by increasing resting membrane potentials and spontaneous neuronal discharge rates [7,8,36]. Generally, anodal tDCS increases cortical excitability, while cathodal tDCS decreases it [26,27,32] and these changes are stable for up to 1 h after stimulation [26,27,32]. Pharmacological interventions suggest that the after-effects are mainly NMDA receptor dependent [22,31,33]. Furthermore, it was demonstrated that anodal and cathodal tDCS induce widespread modulations in regional cerebral blood flow (rCBF) in cortical and subcortical projection areas [21].

The application of tDCS is not restricted only to the motor cortex. It was found that transcranial DC polarization of the visual cortex alters the amplitude of visual evoked potentials in a polarity-dependent way [3], modifies the threshold for perception of TMS-induced phosphenes [1,2], and modulates motion perception [4,5] (for review see [6]). Cathodal polarization on the somatosensory cortex induced a prolonged decrease of tac-

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tile discrimination [37] and diminished the N20 component of somatosensory evoked potentials (SEPs) [11].

It was also observed that tDCS can change the efficacy of cognitive processes without evident side effects [39]. Weak direct currents are capable of improving implicit motor learning in human subjects [29]. Stimulation of the prefrontal cortex so far has been considered safe. It can enhance verbal fluency selectively in healthy subjects [19]. Anodal prefrontal tDCS has a facilitatory effect of probabilistic learning [20] and enhances working memory [12]. Cathodal stimulation over the left supramarginal gyrus has a detrimental effect on short-term pitch-memory performance [38].

Clinically relevant studies demonstrated beneficial effects of cathodal tDCS on the affected hemisphere in chronic stroke [18] and anodal tDCS on the unaffected hemisphere as well [13]. Anodal stimulation of the M1 compared to sham stimulation can be effective in controlling pain in patients with spinal cord lesion [15]. Recent data from a randomized, sham stimulation controlled trial evaluating the effects of cathodal stimulation of the left primary motor cortex in healthy subjects suggest that tDCS is able to decrease pain perception [10]. In addition, DC has been used for the experimental treatment of depression in humans [14,28] and in animal models of migraine and epilepsy [23,24]. Furthermore, short (3 min) anodal stimulation over the left temporoparietal area has been shown to provide a short lasting reduction of tinnitus in human patients [16].

Although tDCS recently has been a frequently used tool in cortical excitability modulations in humans, knowledge regarding safety parameters for this kind of stimulation is so far limited. Safety of brain stimulation depends on the strength of current, the size of the electrodes and the duration of the stimulation [19,26,27,30,35,39]. In an MRI study, it was found that tDCS protocols, which are known to result in cortical excitability changes persisting for an hour post-stimulation, do not induce brain edema or alterations of the blood–brain barrier or cerebral tissue [34]. The only main published safety study of DC stimulation, evaluated 103 subjects, [19] found no adverse effects on cognitive and psychomotor measures, nor EEG changes during or after 20 min of treatment. In a double-blind, sham-controlled study [17] it has been shown that comparing tDCS and sham stimulation of the motor cortex elicited minimal discomfort and difference in the duration of tingling sensations. There have not been found any differences in self-rated attention or fatigue, and the study participants or investigators could not distinguish real tDCS from sham.

In the present study, we summarized the observations of several hundred stimulations from our laboratories related to the stimulation of motor, visual, somatosensory and parietal association areas in a prospective way.

2. Methods

We analyzed data from studies investigated from 2005 to 2006 employing tDCS to any cortical regions in healthy participants or patients. The subjects were interviewed prior to experimentation regarding their state of health and gave written informed consent. All protocols confirmed to the Declaration of Helsinki, and the Ethics Committee of the University of Göttingen approved the studies. One hundred and two subjects had completed a questionnaire after the end of their participation in tDCS studies. We observed 77 healthy volunteers, (32 men), mean age 25.9 ± 4.95, and 25 patients, (14 men), mean age 46.68 ± 15.37. The patients consisted of 9 migraine patients, 10 tinnitus sufferers and 6 post-stroke patients.

The questionnaire contained rating scales for the presence and severity of headache, difficulties in concentrating, acute mood changes, visual perceptual changes, fatigue and discomforting sensations like pain, tingling, itching or burning under the electrodes during and after tDCS. The incidences of the side effects were coded in a binary system (no = 0, yes = 1) and were analysed with an independent t-test between the patients and healthy subject groups. The severities of the side effects were rated in a numerical analogue scale (NAS) from one to five, one being very mild and five being extremely strong intensity of any given side-effect, and were analysed with an independent *t*-test between the patients and healthy subject groups. The incidences and severities of the adverse effects were also analysed with the factor of time (during tDCS versus after tDCS) and with the factor of the position of the stimulation electrodes.

In our studies six cortical areas were stimulated, the left M1 (motor cortex), left S1 (primary somatosensory cortex), V1 (primary visual cortex), T3–T4 (temporal cortex), dorsolateral prefrontal cortex (DLPFC) and parietal cortex (P6–P8). The studies concerning the use of different types of paradigms are described in detail [1–6,10,20].

2.1. DC polarization

All studies have been conducted with a battery-driven stimulator (Schneider Electronic, Gleichen, Germany, or Eldith, Electro-Diagnostic & Therapeutic Systems GmbH, Ilmenau, Germany). The bipolar tDCS was applied to the scalp with 35 cm^2 sponge electrodes dampened with tap water. Current strength was 1 mA in all stimulations. This produced current densities of 28.57 $\mu A/cm^2$ at the skin surface of the scalp.

Most of the subjects received three types of stimulation (anodal, cathodal and sham) at least once. In these studies in which we aimed to examine cortical excitability, using TMS or evaluating evoked potentials the participants received all three types of stimulation, whilst in psychophysical studies in which we examined learning function, our subjects received just one type of tDCS. Twenty of our participants took part in more than one study in which different cortical regions were stimulated. The volunteers were blinded concerning the type of tDCS administered. The duration of the stimulations was between 9 and 15 min depending on experimental paradigm. The current was always ramped up or down over the first and last 8–10 s of stimulation. For sham (placebo) treatment, the electrodes were placed in the same locations and the current was delivered for 10–30 s, so that subjects experienced the sensations initially associated with the onset of DC (mild local tingling) without inducing any real effects. Preliminary studies suggested that subjects habituate rapidly to the skin sensation.

2.2. Electrodes positions

During the motor cortex stimulation electrodes were positioned over the left M1 [optimal M1 representation of the right abductor digiti minimi muscle (ADM) or the right first dorsal interosseus muscle (FDI) as revealed by TMS] and right frontopolar cortex (above the eyebrow).

In case of somatosensory stimulation, the active electrode was placed 6 cm lateral and 2.5 cm posterior to Cz (according to the 10–20 EEG electrode placement system) on the left side. During left DLPFC stimulation, the active electrode was over F3 and the reference above the right orbit. In the case of visual stimulation, the active electrode was placed over Oz and the reference over Cz. By parietal cortex stimulation, active electrode was positioned at P6–P8 and reference at Cz. During the stimulation of the auditory cortex they were placed over T3 and T4 (Table 1). The electrodes were fixed with elastic, self-adhesive, bandage material.

3. Results

We analysed the data from 567 tDCS sessions on 102 participants. Table 2 summarizes the number of tDCS sessions within different groups of participants and the numbers of sub-

Table 1
Positions of the tDCS electrodes in the different studies

	Active electrode	Reference electrode
Motor cortex (M1)	Representation of the right ADM or FDI as revealed by TMS	Right frontopolar cortex (above the eyebrow)
Somatosensory cortex (S1)	6 cm lateral and 2.5 cm posterior to Cz	Right frontopolar cortex (above the eyebrow)
Dorsolateral prefrontal cortex (DLPFC)	F3	Right frontopolar cortex (above the eyebrow)
Visual cortex (V1)	Oz	Cz
Temporal cortex	T3	T4
Parietal cortex	P6–P8	Cz

jects from studies with tDCS stimulations on different cortical areas.

3.1. Adverse effect of tDCS

None of the subjects requested the stimulation be terminated, or needed any medical intervention during or after the end of tDCS. Tables 3a and 3b summarize the adverse effects in the 567 tDCS sessions on healthy participants and patients from our laboratory. A mild tingling sensation was the most common adverse effect; reported by 70.6% of the subjects (mean intensity of NAS ± S.D. = 1.74 ± 0.84) during and 7.8% (1.22 ± 0.67) after the stimulation. Moderate fatigue was the second most frequent adverse effect, as felt by 35.3% of the participants (2.17 ± 1.11) during tDCS and 22.6% (1.83 ± 0.98) after tDCS, whereas a light itching sensation under the electrodes occurred in 30.4% (1.6 ± 0.72) through the stimulation and in 14.9% (1.6 ± 0.99) after the stimulation. 21.6% of our volunteers felt a slight burning (1.59 ± 0.91) and 15.7% of them a mild pain sensation (1.41 ± 0.71) under the electrodes during the stimulation. Visual sensation, associated with switching on and off the stimulation, occurred in 10.8% of the cases. 17.7% of the volunteers found the stimulation procedure mildly unpleasant (1.24 ± 0.44) and only 16.7% of our subjects claimed to feel a difference between the type of stimulations (anodal, cathodal or sham). Only 10.8% reported difficulties in concentrating (1.73 ± 1.10) under tDCS and only four of them (3.9% of all) after stimulation (2.25 ± 1.26). Headache occurred in 4.9% of cases during (1.4 ± 0.89) and 11.8% (1.92 ± 1.44) after stimulation. 4.9% of all subjects felt nervous or overexcited (1.0 ± 0) during the stimulation but none after the termination of tDCS. Only three healthy participants (2.9% of all) experienced nausea after the stimulation within a maximum duration of 2 h (mean = 1.5 ± 0.71 h) and only one migraine patient reported acute sleeping disturbances for 2 days post tDCS. None of the participants had any changes in visual perception or was hyperactive either during or after stimulation.

3.2. Differences between the groups of patients and healthy subjects

The incidence of the itching sensation during tDCS, occurred in 12% of patients and 36.4% of healthy participants (see

Table 2
The number of the tDCS sessions in different groups and the number of the subjects from all of the studies including different cortical areas

	Total number of tDCS sessions	Number of participants	Mean number of tDCS sessions	Number of participants in studies with					
				Motor cortex (M1) stimulation	Visual cortex stimulation	Left DLPFC stimulation	Temporal cortex stimulation	Somato-sensory cortex stimulation	Parietal cortex stimulation
Migraineurs	50	9	5.55 ± 5.32	5	5	0	0	0	0
Post stoke patients	33	6	5.50 ± 2.07	0	6	0	0	0	0
Tinnitus sufferers	36	10	3.60 ± 1.27	0	0	0	10	0	0
Patients total	119	25	4.76 ± 3.44	5	11	0	10	0	0
Healthy participants	448	77	5.91 ± 5.61	47	35	15	2	7	2
All subjects	567	102	5.61 ± 5.17	52	46	15	12	7	2

Table 3a
Adverse effects of tDCS during stimulation in different groups of participants

Participants	Tingling			Itching sensation			Burning sensation			Pain			Headache			Fatigue			Difficulties in concentrating		
	N	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity
Migraine patients	6	66.7	1.67 ± 0.82	1	11.1	2.0 ± 0	2	22.2	2.0±1.41	1	11.1	2.0 ± 0	1	11.1	1.0 ± 0	4	44.4	2.5 ± 1.29	0	0	0
Post-stroke patients	2	33.3	1.0 ± 0	1	16.7	1.0 ± 0	0	0	0	1	16.7	1.0 ± 0	1	16.7	3.0 ± 0	2	33.3	2.5 ± 2.12	1	16.7	4.0 ± 0
Tinnitus sufferers	8	80	1.13 ± 0.35	1	10	1.0 ± 0	3	30	1.0 ± 0	0	0	0	0	0	0	3	30	1.33 ± 0.58	1	10	1.0 ± 0
Patients total	16	64	1.31 ± 0.60	3	12	1.33 ± 0.58	5	20	1.4 ± 0.89	2	8	1.5 ± 0.70	2	8	2.0 ± 1.41	9	36	2.11 ± 1.27	2	8	2.5 ± 2.12
Healthy subjects	56	72.7	1.86 ± 0.86	28	36.4	1.63 ± 0.74	17	22.7	1.65 ± 0.93	14	18.2	1.4 ± 0.74	3	3.9	1.0 ± 0	27	35.1	2.19 ± 1.08	9	11.7	1.56 ± 0.88
Participants total	72	70.6	1.74 ± 0.84	31	30.4	1.6 ± 0.72	22	21.6	1.59 ± 0.91	16	15.7	1.41 ± 0.71	5	4.9	1.4 ± 0.89	36	35.3	2.17 ± 1.11	11	10.8	1.73 ± 1.10

Participants	Nervousness			Changes in visual perception			Unpleasant sensation			Visual sensation, associated with the start/end of the stimulation		Difference between stimulations		Others			
	N	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	*N*	%	*N*		*N*	
Migraine patients	1	11.1	1.0 ± 0	0	0	0	2	22.2	1.0 ± 0	3	33.3	4	44.4	–		–	
Post-stroke patients	0	0	0	0	0	0	1	16.7	1.0 ± 0	1	16.7	1	16.7			–	
Tinnitus sufferers	0	0	0	0	0	0	0	0	0	0	0	1	10	1	Drowsiness	–	
Patients total	1	4	1.0 ± 0	0	0	0	3	12	1.0 ± 0	4	16	6	24	1	Drowsiness	–	
Healthy subjects	4	5.2	1.0 ± 0	0	0	0	15	19.5	1.29 ± 0.47	7	9.1	11	14.3	1	Drowsiness	1	Nausea
Participants total	5	4.9	1.0 ± 0	0	0	0	18	17.7	1.24 ± 0.44	11	10.8	17	16.7	2	Drowsiness	1	Nausea

Table 3b
Adverse effects of tDCS after stimulation in different groups of participants effects after tDCS sessions

Participants	Tingling			Itching sensation			Burning sensation			Pain			Headache			Fatigue			Difficulties in concentrating		
	N	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean intensity
Migraine patients	2	22.2	1.5 ± 0.71	1	11.1	3.0 ± 0	0	0	0	1	11.1	1.0 ± 0	5	55.6	1.6 ± 1.34	1	11.1	2.0 ± 0	0	0	0
Post-stroke patients	1	16.7	1.0 ± 0	1	16.7	1.0 ± 0	0	0	0	0	0	0	0	0	0	2	33.3	2.5 ± 2.12	1	16.7	4.0 ± 0
Tinnitus sufferers	0	0	0	1	10	1.0 ± 0	0	0	0	1	10	1.0 ± 0	1	10	1.0 ± 0	1	10	2.0 ± 0	1	10	1.0 ± 0
Patients total	3	12	1.33 ± 0.58	3	12	1.67 ± 1.15	0	0	0	2	8	1.0 ± 0	6	24	1.5 ± 1.22	4	16	2.25 ± 1.26	2	8	2.5 ± 2.12
Healthy subjects	5	6.5	1.17 ± 0.75	12	15.8	1.58 ± 1.00	3	4.0	1.33 ± 0.58	1	1.3	3.0 ± 0	6	7.8	2.33 ± 1.63	19	24.7	1.74 ± 0.93	2	2.6	2.0 ± 0
Participants total	8	7.8	1.22 ± 0.67	15	14.9	1.6 ± 0.99	3	3.0	1.33 ± 0.58	3	3.0	1.67 ± 1.15	12	11.8	1.92 ± 1.44	23	22.6	1.83 ± 0.98	4	3.9	2.25 ± 1.26

Participants	Nervousness			Changes in visual perception			Nausea			Acute sleeping disturbance			Others	
	N	%	Mean intensity	*N*	%	Mean intensity	*N*	%	Mean duration[a]	*N*	%	Mean duration[b]	*N*	%
Migraine patients	0	0	0	0	0	0	0	0	0	1	11.1	2.0 ± 0	–	
Post-stroke patients	0	0	0	0	0	0	0	0	0	0	0	0	–	
Tinnitus sufferers	0	0	0	0	0	0	0	0	0	0	0	0	–	
Patients total	0	0	0	0	0	0	0	0	0	1	4	2.0 ± 0	–	
Healthy subjects	0	0	0	0	0	0	3	3.9	1.5 ± 0.71	0	0	0	–	
Participants total	0	0	0	0	0	0	3	2.9	1.5 ± 0.71	1	0.98	2.0 ± 0	–	

[a] Duration in h.
[b] Duration in days.

Table 4
The first column contains the results of independent *t*-test of the analysis during vs. after tDCS sessions

		During tDCS vs. after tDCS	Motor vs. visual cortex stimulation	Motor vs. temporal cortex stimulation	Visual vs. temporal cortex stimulation
Tingling	Incidence	$p < 0.005^{*}$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Itching sensation	Incidence	$p < 0.05^{*}$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Burning sensation	Incidence	$p < 0.005^{*}$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Pain	Incidence	$p < 0.005^{*}$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Headache	Incidence	n.s.	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Fatigue	Incidence	$p < 0.05^{*}$	$p < 0.05^{**}$	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Difficulties in concentrating	Incidence	n.s.	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Nervousness	Incidence	$p < 0.05^{*}$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Difference between stimulations	Incidence	–	$p < 0.05^{**}$	n.s.	n.s.
Visual sensation, associated with the start/end of the stimulation	Incidence	–	n.s.	n.s.	n.s.

The columns 2–4 contain the results of t-test compared the side effects depending on the tDCS electrodes.
* Significantly higher during stimulation.
** Significantly higher in case of motor cortex stimulation but only during tDCS sessions.

Table 3a), and was significant ($p = 0.02$; $t = -2.34$). The intensity (NAS 1–5) of tingling sensation during tDCS has also found to be significantly less ($p = 0.02$; $t = -2.36$) in the patient group (1.31 ± 0.60 to 1.86 ± 0.86). Headache occurred after stimulation with a significantly higher incidence ($p = 0.029$; $t = 2.22$) in patients (24%) than in healthy subjects (7.8%) (Table 3b). There was no significant difference ($p = 0.344$; $t = -0.952$) between the two groups concerning the mean number of stimulation sessions (4.76 ± 3.44 by patients and 5.91 ± 5.61 by healthy subjects). In addition, none of the other examined parameters showed any significant difference.

3.3. Comparisons between the side effects during and after tDCS

An independent *t*-test showed a significantly higher incidence of some of the side effects (pain, tingling, itching and burning under the electrodes, self-related fatigue and nervousness) during tDCS compared to the data from after tDCS. However, concerning the intensities (NAS 1–5) of the observed side effects there was no significant difference between the two time points (see Table 4).

3.4. Differences in the adverse effects between the stimulated cortical regions

We identified 33 participants who received tDCS only over the motor cortex. Thirty-one subjects had only visual cortex stimulation and 11 only temporal cortex stimulation. In the case of the other stimulated areas, the number of participants in each group was too low to include them in the analysis. An independent *t*-test showed significantly higher incidence of the side effects in only two cases. The incidence of fatigue was significantly higher ($p < 0.05$, $t = 2.46$) during tDCS in the case of motor cortex stimulation when compared to visual stimulation. Additionally, the subjects felt a difference between the type of the tDCS (anodal, cathodal or sham) when the motor cortex was stimulated, compared to visual cortex stimulation in significantly more cases ($p < 0.05$, $t = 2.26$) (see Table 4). There was no significant difference in the side effects between the different stimulation sites after tDCS.

4. Discussion

Our results, from the analysis of 567 tDCS sessions on more than hundred participants suggest, that tDCS applied to motor and non-motor areas according to the present tDCS safety guidelines [19,30,39], is associated with relatively minor adverse effects. Although the most frequent side effect was the tingling sensation (70.6%), only 17.7% of the volunteers found the stimulation procedure mildly unpleasant. In accordance with further published observations, we found similar side effects such as slight tingling (72.7% of healthy subjects) or transient mild burning (22.7% of healthy participants) in approximately similar ratios as found in the Gandiga and Hummel study [17]. They observed tingling in 73.7% and burning sensation in 15.8% of cases in aged matched groups of healthy volunteers ($n = 9$, mean age $= 26.6 \pm 1.77$, whereas $n = 77$, mean age $= 25.9 \pm 4.95$ in our study). In addition, older subjects and patients experienced a different incidence of these side effects (tingling 46.4%, mild burning 33.9%) which reflected our findings (64% and 20%). With regards to patients, the data are not directly comparable because in the study of Gandiga et al. only stroke patients were evaluated and received tDCS only over the motor cortex.

Only 16.7% of our subjects felt a difference between the type of stimulations (anodal, cathodal or sham) and it was signifi-

cantly higher in cases of motor cortex stimulation in comparison with visual tDCS. This difference might depend on the placement of the stimulation electrodes: in the case of motor cortex stimulation, the reference electrode was over the right orbit and the sensibility of the skin is higher over the orbit, than over the hairy skin at Cz.

A comparison of the adverse effects of the different types of DC stimulations could not be done in this study, because the volunteers filled out the questionnaire only once after the end of their participation in the tDCS studies and were blinded as so the type of tDCS administered. Preliminary studies suggest, if the current is turned up for several seconds the beginning and at the end of sham stimulation the subjects were not able to differentiate sham from real stimulation [15,17,19,39]. According to our experience, many subjects do not feel anything even after real stimulation and many of them report tingling during sham stimulation.

The significantly higher incidence of itching, tingling, burning and pain under the electrodes during stimulation than after it suggests, that these sensations are associated with the onset of tDCS. (Please note that in case of sham tDCS the current was turned on for several seconds.) The severity of the itching sensation and the intensity of the tingling were significantly lower in the patient group, and this may be related to the higher age and trust in a new therapeutic method. The significant difference in the occurrence of headache after stimulation seems to be related to the type of disorder our patient group. Five of the 9 migraineurs (55.6%) reported mild headache after tDCS, in comparison to 1 of the 10 tinnitus sufferers (10%) and 6 of 77 healthy volunteers (7.8%). In addition, we found a relatively high incidence of fatigue (35.3% during and 22.6% after the end of the tDCS) that was not significantly different between groups, but it was significantly higher during the stimulation compared to the data post tDCS. This fatigue sensation may be related to the prolonged and sometimes uninteresting task implemented our studies. Furthermore, a significant difference in fatigue sensation between motor cortex stimulation and visual cortex tDCS was also observed. During visual cortex stimulation the participants had to do some visual or cognitive tasks but not in the studies where the motor cortex was stimulated.

The visual sensation, which associated with switching on and off the stimulation, occurred only in several percent of all stimulation cases. This phenomenon might be related to retinal stimulation, but has also occurred during visual cortex stimulation when the stimulation electrodes were relatively far away from the retina. The sufficiently long fade in and fade out of the current (at the beginning and at the end of the stimulation) reduced the incidence of this side effect.

We have not experienced any serious complications, such as seizure or instance of psychotic symptoms, in connection with the application of tDCS. The incidence of remarkable adverse effects such as headache was much less (11.8% of our subjects) after tDCS, than what was observed in the repetitive transcranial magnetic stimulation (rTMS) safety study by Pascual-Leone et al. [25] (23%), after several hundred rTMS sessions on clinically depressed patients and healthy volunteers. Although tDCS and rTMS are capable of inducing long-lasting modification of excitability of cortical neurons, the mechanism of their effects are different. TMS induces short electrical currents in the brain, which in turn most likely elicit spikes in dendrites or axons, whilst tDCS is a technique that modifies the membrane potentials of cortical neurons. The applicability of tDCS is not restricted to the motor cortex, as it has been shown to be also effective in visual, prefrontal, somatosensory and temporal cortices. However, the extension of tDCS concerning different paradigms and higher intensities of stimulation and longer stimulation durations in healthy subjects and different groups of patients needs additional safety studies to explore the limits of safe stimulation.

Conflict of interest statement

This work has not been published and it is not intended to be published anywhere, except in *Brain Research Bulletin*. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The corresponding author states that all of authors had full access to all the data in the study and had final responsibility for the decision to submit it for publication. The authors have no financial or personal conflicts of interest.

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