



Effects of transcranial direct current stimulation of the primary sensory cortex on somatosensory perception

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Background

Transcranial direct current stimulation (tDCS) is able to modify cortical excitability and activity in humans.

Objective

The aim of the present study was to analyze the effects of tDCS of the primary sensory cortex (SI) on thermal and mechanical perception, assessed by quantitative sensory testing (QST).

Methods

The comprehensive QST protocol encompassing thermal and mechanical detection and pain thresholds as devised by the German Research Network on Neuropathic Pain (DFNS) was applied to skin areas innervated by the radial and median nerve of 12 healthy subjects, who were examined before and after each tDCS stimulation type. Anodal, cathodal, and sham tDCS was applied at a 1 mA current intensity with the active electrode placed over the left primary sensory cortex (SI) and the reference electrode above the right orbit for 15 minutes.

Results

After cathodal tDCS cold detection threshold (CDT) significantly increased in the contralateral ($P < .01$) and ipsilateral hand ($P < .05$) as compared to baseline condition and sham stimulation, after cathodal stimulation significantly increased warm detection threshold (WDT) was observed in the contralateral hand when compared with the baseline condition ($P < .05$) but not with sham stimulation. Thermal pain as well as mechanical detection and pain thresholds remained unaltered.

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Conclusions

Cathodal tDCS of the primary sensory cortex significantly reduced the sensitivity to A δ -fiber-mediated cold sensation, C-fiber-mediated warm sensation was reduced only compared with baseline, whereas A β -fiber-mediated somatosensory inputs were less affected. Our results correspond with our previous observations of primary motor cortex tDCS effects on QST parameters.

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Transcranial direct current stimulation applied to the human cortex has been shown to modify cortical excitability. Anodal stimulation is known to increase cortical excitability, whereas cathodal stimulation decreases it. The length of tDCS after-effects depends on the duration of stimulation.¹⁻³ Promising results of pilot studies showing evidence for its efficiency and the convenience of a portable equipment lead to an enhanced use of tDCS.⁴

Matsunaga et al.⁵ demonstrated that 1 mA anodal tDCS over the motor cortex results in long-lasting facilitation of somatosensory evoked potential (SEP) amplitudes evoked by stimulation of the contralateral, but not ipsilateral median nerve. Cathodal stimulation had no effect on SEPs from either arm. For the somatosensory cortex a sustained reduction of the N20 source component of the SEP was shown after anodal tDCS. Based on those results, tDCS was proposed to primarily have local effects, because the N20 source amplitude is known to be generated in the depth of area 3b of the primary sensory cortex.^{6,7}

These findings correspond with the study of Rogalewski et al.⁸: They were the first to show that tDCS of the somatosensory cortex modulates the excitability of the somatosensory system. Cathodal stimulation applied to this area induced a prolonged decrease of tactile discrimination, while anodal and sham stimulation had no effect.

A recent study of our group assessed the effects of tDCS of the primary motor cortex on thermal and mechanical perception by quantitative sensory testing (QST). An increase of cold detection threshold (CDT) and mechanical detection threshold (MDT) after cathodal stimulation at the contralateral hand as compared with the baseline condition was observed.⁹ Further investigation showed that tDCS has an antinociceptive effect when applied to the somatosensory cortex: it diminishes experimentally induced acute pain perception.¹⁰ In addition, tDCS ameliorates pain perception in patients with central pain^{11,12}

The aim of the current study conducted was to assess the effect of tDCS over the sensory cortex (SI) on QST parameters. The applied QST protocol of the German Research Network on Neuropathic Pain (DFNS) is a battery of reliable and valid tests¹³ for nearly all aspects of somatosensation.^{9,14-16}

Bachmann et al.⁹ showed that tDCS of the motor cortex is able to modulate distinct aspects of somatosensation. It is tempting to speculate that a direct stimulation of the

somatosensory cortex has even a greater effect on those parameters, because SI receives the bulk of thalamocortical projection from the sensory input fields.

Materials and methods

Subjects

Twelve healthy subjects (five female, seven male, mean age 30.0 years; range: 22-42 years of age) were included in the experiment, each showed normal nerve conduction velocities and normal somatosensory evoked potentials of both median nerves. There were no abnormalities in the neurologic examination and global laboratory chemistry parameters. Any relevant previous or concomitant psychiatric or neurologic diseases or any condition associated with acute or chronic pain or somatosensory abnormalities were excluded. All subjects were able to understand the instructions of the QST protocol. In addition, none of the subjects received regular or acute medication, except for those females taking oral contraception. All subjects gave their written informed consent. The study was performed in accordance with the declaration of Helsinki and approved by the ethics committee of the Georg August University, Goettingen, Germany.

QST

A standardized QST battery, developed by the German Research Network on Neuropathic Pain (DFNS) and consisting of seven tests measuring 13 parameters of somatosensation, was performed on skin areas innervated by the radial and median nerve of both hands:^{14,15}

- Thermal detection threshold for cold and warm perception and paradoxical heat sensations,
- thermal pain thresholds for cold and hot stimuli,
- mechanical detection thresholds (MDTs) for touch and vibration,
- mechanical pain sensitivity including thresholds for pinprick and blunt pressure, a stimulus-response-function for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli.¹⁴

All tests for thermal perception were performed using a Thermal Sensory Analyzer TSA 2001-II (MEDOC, Ramat Yishai, Israel).^{17,18} Mechanical detection threshold (MDT) was assessed with a standardized set of modified von Frey hairs (Optihair2-Set, Marstock Nervtest, Germany).^{19,20}

Mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), and wind-up ratio (WUR), as the perceptual correlate of temporal pain summation, were measured with a set of custom-made pinprick stimulators.^{21,22} Dynamic mechanical allodynia (DMA) was determined using a set of light tactile stimulators alternately with the pinprick stimuli applied in balanced order. Vibration detection threshold (VDT) was tested with a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale) as a disappearance threshold. The pressure pain threshold (PPT) was assessed by using a series of increasing ramps induced by a pressure gauge device (FDN, Wagner Instruments, Greenwich, CT) exerting a pressure up to 20 kg/cm² or similarly 200 N/cm² or 2000 kPa over muscle tissue of the thenar eminence.²³

tDCS of the somatosensory cortex

The tDCS was performed using a portable stimulator (DC-Stimulator, Eldith, Germany). Cathodal, anodal, or sham stimulation were applied in randomized order. One electrode was placed over the left primary somatosensory cortex, whereas the other electrode was placed above the right orbit. The electrode stimulating the primary somatosensory cortex was placed 2 cm posterior of the position C3 according to the 10-20 EEG system,²⁴ thus, definitely not above the hand motor cortical representation. The polarity of tDCS refers to the electrode over the primary sensory cortex. For sham condition, the placement of the electrodes was identical. During anodal and cathodal stimulation, a current intensity of 1 mA was applied for 15 minutes via a pair of surface water soaked sponge electrodes.¹ For sham stimulation, current flow increased gradually over 5 seconds reaching 1 mA and imitated the initial itching skin sensation of anodal or cathodal tDCS and then stopped after 10 seconds. This period of time is too short to induce lasting effects on brain excitability.¹ For the sham condition, the electrodes remained in place for 15 minutes to mimic the duration of anodal and cathodal stimulation. Subjects were blinded to the respective stimulation condition.

Low-intensity tDCS is capable of inducing long-lasting after-effects. Nitsche and Paulus² demonstrated that motor cortex stimulation from 9 to 13 minutes resulted in excitability alterations that lasted up to 90 minutes after the end of stimulation monitored by MEP amplitudes.

Experimental procedures

The experiments took place in a quiet and air-conditioned environment to minimize distractions. The subjects were seated on an upright chair and all the measurements were performed between 1 and 5 PM. Each experimental session

was operated by the same trained female examiner (L.G.). At the beginning, QST was performed at the radial part of the ipsilateral hand, afterward at the contralateral hand. Subsequently, cathodal, anodal, or sham stimulation was applied in three experimental sessions. After tDCS, QST was conducted at first at the contralateral hand, then at the ipsilateral hand. Each QST procedure took approximately 28 minutes, each session that applied QST to both sides before and after tDCS lasted about 2 hours 15 minutes. An interval of 1 week was required between each of the three experimental sessions to avoid interferences of long-lasting after-effects of tDCS.

Statistics

All statistical calculations were performed using “Excel” (Microsoft Corporation, Redmond, WA) and “Statistica” (StatSoft Inc, Tulsa, OK) software. Cold pain threshold, heat pain threshold, paradoxical heat sensations during TSL procedure, and VDT were normally distributed as analyzed with the Kolmogorov-Smirnov test. All other QST parameters were normally distributed in log-space and were transformed logarithmically before statistical analysis.¹⁴ QST raw data were z-transformed using the expression: Z-score = $(\text{Mean}_{\text{post tDCS}} - \text{Mean}_{\text{baseline}}) / \text{SD}_{\text{baseline}}$. Differences of Z-score QST data for each perceptual modality before and after anodal, cathodal, or sham stimulation, right (contralateral) and left (ipsilateral to stimulation) hand dorsum were compared using a three-way analysis of variance (ANOVA) with the factors “time” (comparing QST data before and after the different types of tDCS), “type of stimulation” (anodal, cathodal, or sham), and “body side” (right hand = contralateral to tDCS; left hand = ipsilateral). Whenever the performed ANOVA revealed significant effects, LSD post hoc-tests were conducted. All Z-score data are shown as means \pm SEM.

Results

All QST data were assessed from 12 healthy subjects on the contralateral and ipsilateral body side immediately before and after tDCS. Cathodal tDCS resulted in a significantly decreased sensitivity to A δ -fiber input, namely, to nonpainful CDT of the contralateral hand, as compared with the baseline and sham tDCS conditions. Moreover, the ipsilateral CDT was increased after cathodal stimulation of the left primary sensory cortex compared with the corresponding baseline condition and to sham stimulation. After cathodal stimulation, the contralateral WDT was increased when compared with baseline, but not in comparison with sham stimulation. Sham and anodal stimulation had no significant effect on any of the assessed QST parameters, neither on the contralateral nor on the ipsilateral body side. Neither paradoxical heat sensations nor DMA were detected in any of the subjects before and after stimulation (Figure 1, Table 1).

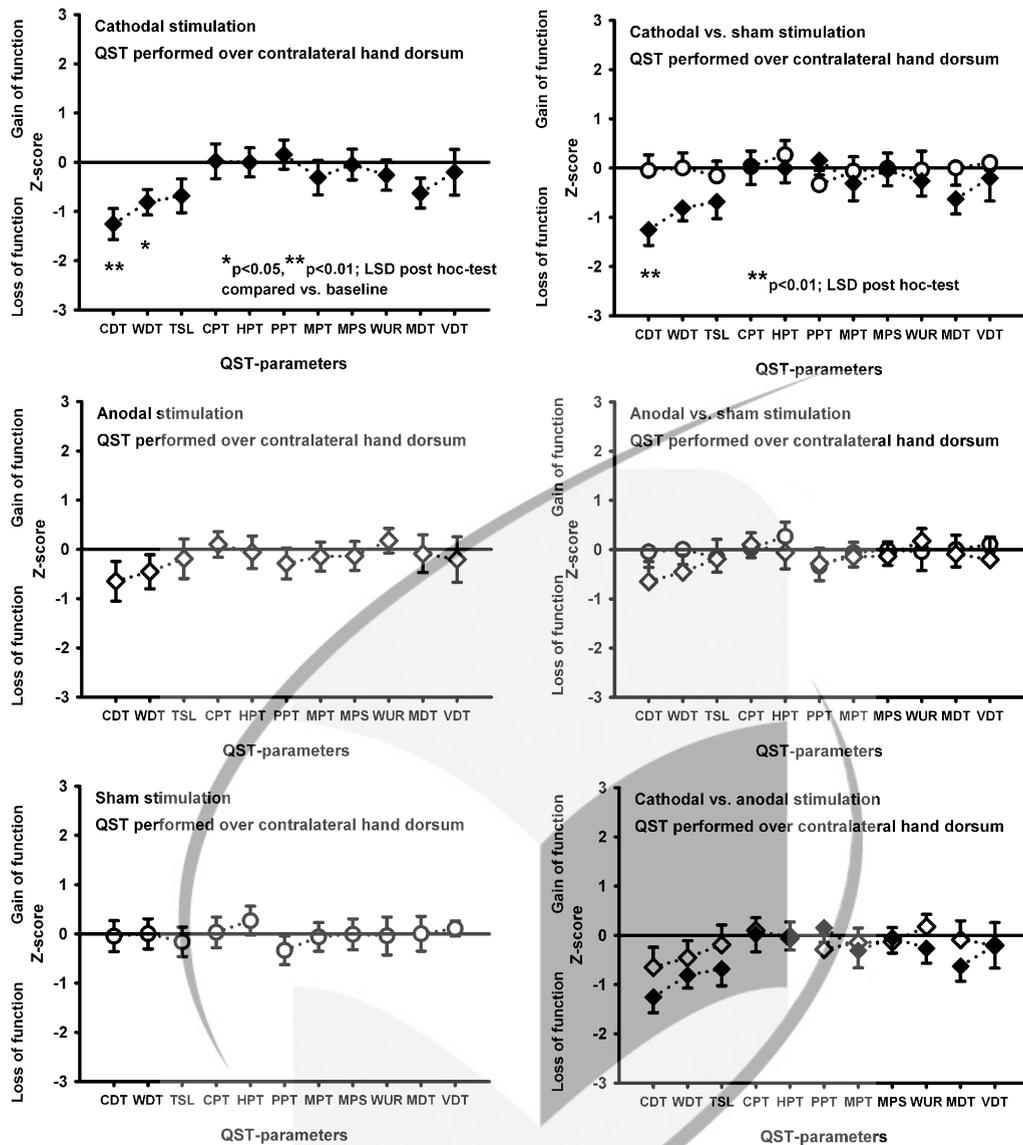


Figure 1 This figure shows QST data as z-transformed values according to the expression: $Z = (\text{Mean}_{\text{post tDCS}} - \text{Mean}_{\text{baseline}}) / \text{SD}_{\text{baseline}}$. Positive z-scores point to a gain of sensory function after tDCS, whereas negative z-scores indicate a loss of sensory function compared with the baseline condition. The z-score sensory profiles in the left column display the effects of cathodal, anodal, and sham stimulation on somatosensory perception as compared with their referring baseline data (baseline = control condition). Cathodal tDCS significantly decreased sensitivity for nonpainful cold (CDT; A δ -fiber mediated; contralateral $P < .01$, ipsilateral $P < .05$) as compared with the baseline condition. Cathodal tDCS decreased contralateral sensitivity to warm (WDT) compared with the baseline condition ($P < .05$), but not in comparison with sham stimulation. The right column compares the different types of stimulation. Cathodal tDCS induces a significantly decreased sensitivity to CDT as compared with sham stimulation. Results after sham stimulation did not differ for any of the tested QST parameters over contralateral hand dorsum. Stars denote the level of significance as depicted from LSD post hoc-test (* $P < .05$, ** $P < .01$).

Sensory profiles of z-transformed QST data

Figure 1 shows the complete sensory profile of the 12 healthy subjects after cathodal, anodal, and sham stimulation of the primary sensory cortex as compared with the baseline condition. Z-score profiles present data from the contralateral hand dorsum (right hand). Cathodal tDCS showed significant effects with a contralaterally reduced sensitivity to innocuous cold compared with the baseline

condition (Figure 1, left column, $P < .05$; ANOVA, LSD post hoc-test).

Analysis comparing the effects of the different types of tDCS on QST parameters revealed a significant increase of CDT ($P < .01$) when cathodal tDCS was compared with sham stimulation (Figure 1, right column). Cathodal stimulation resulted in increased WDT ($P < .05$) when compared with baseline values but not with sham stimulation (Figure 1). Sham and anodal stimulation did not show

Table 1 ANOVA comparing the effects of cathodal, anodal, and sham tDCS over ipsi- and contralateral hand

ANOVA factor	1. tDCS stimulation type (cath vs anod vs sham)		2. Time (post-tDCS vs baseline)		3. Body side (contra vs ipsi)		Interaction 1 by 2		Interaction 1 by 3		Interaction 2 by 3		Interaction 1 by 2 by 3	
	F value	P value	F value	P value	F value	P value	F value	P value	F value	P value	F value	P value	F value	P value
QST parameter														
CDT	1.65	n.s.	7.86	.0058	1.68	n.s.	4.43	.0138	0.04	n.s.	0.02	n.s.	0.22	n.s.
WDT	3.16	.0456	3.37	.07	1.92	n.s.	2.76	n.s.	0.46	n.s.	0.09	n.s.	0.09	n.s.
TSL	0.36	n.s.	2.08	n.s.	0.65	n.s.	1.63	n.s.	0.11	n.s.	0.00	n.s.	0.15	n.s.
CPT	0.08	n.s.	0.08	n.s.	0.01	n.s.	1.01	n.s.	0.08	n.s.	0.00	n.s.	0.17	n.s.
HPT	0.58	n.s.	0.2	n.s.	0.05	n.s.	0.66	n.s.	0.75	n.s.	0.02	n.s.	0.05	n.s.
MDT	1.07	n.s.	0.1	n.s.	2.68	n.s.	0.41	n.s.	0.25	n.s.	0.14	n.s.	0.37	n.s.
MPT	0.12	n.s.	0.59	n.s.	0.19	n.s.	0.01	n.s.	0.05	n.s.	0.00	n.s.	0.25	n.s.
MPS	0.01	n.s.	0.01	n.s.	0.16	n.s.	0.12	n.s.	0.02	n.s.	0.30	n.s.	0.00	n.s.
WUR	0.28	n.s.	0.00	n.s.	0.49	n.s.	0.35	n.s.	0.41	n.s.	0.15	n.s.	0.01	n.s.
VDT	0.07	n.s.	0.00	n.s.	0.35	n.s.	0.68	n.s.	0.42	n.s.	0.35	n.s.	0.15	n.s.
PPT	1.55	n.s.	0.03	n.s.	4.73	.031	0.04	n.s.	0.12	n.s.	0.00	n.s.	0.12	n.s.

This table presents the effects of tDCS before and after different tDCS stimulation types (cathodal, anodal, sham). All subjects were stimulated over left sensory cortex. QST was performed over right hand (contralateral to stimulation) and left hand (ipsilateral) before and after tDCS. A three-way ANOVA was performed with comparison of the type of stimulation (factor 1), baseline vs. poststimulation (factor 2) and contralateral vs. ipsilateral hand (factor 3). There was no occurrence of paradoxical heat sensations (PHS) and dynamic mechanic allodynia (DMA) before and after tDCS for any type of stimulation in any of the healthy subjects. P values were shown for values <.10, in all other cases "n.s." for not significant was noted. Whenever a significant effect of tDCS was observed, LSD post hoc-tests were calculated.

any significant effects compared with the referring baseline values. No significant differences were observed when anodal stimulation was compared with sham stimulation.

Significant effects on QST parameters after different types of stimulation were demonstrated across the ipsilateral and contralateral body side

The three-way ANOVA performed for CDT showed a significant main effect of factor 2. The "time" ($F = 7.86, P = .0058$) and also of the two-way interaction of factor "time" by factor "tDCS stimulation type" ($F = 4.43, P = .0138$) (Table 1). This finding indicates an increased CDT contra- and ipsilaterally after cathodal stimulation as compared with the baseline condition. Cathodal tDCS induced a significant decrease in cold sensitivity in the contralateral hand as the mean values went down from -1.2°C to -2.1°C (difference from baseline; 32°C), corresponding to about 75% loss of sensitivity to Aδ-fiber input (LSD $P < .01$ contralateral, $P < .05$ ipsilateral) (Figure 2). The three-way ANOVA performed for WDT showed a significant main effect of the factor "tDCS stimulation type" ($F = 3.16, P = .0456$) and a significant decrease in the contralateral warm sensitivity (LSD $P < .05$) compared with baseline.

The three-way ANOVA conducted for PPT did not show any significant effects for the ANOVA factors "time" and "tDCS stimulation type" but for the factor "body side" ($F = 4.73, P = .031$). However, none of the two-way interactions, nor the three-way interaction showed any significances. In addition, the performed post hoc-tests did not exhibit any significant effects. The ANOVAs performed for thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), MDT, MPT, mechanical pain sensitivity (MPS), WUR, and VDT did not reveal any significant effects for "time," "tDCS stimulation type," or "body side." In addition, none of the respective interactions were significant (Table 1).

Discussion

This study demonstrates that tDCS of the primary sensory cortex modulates distinct parameters of somatosensation. Cathodal stimulation induced a decrease of Aδ-fiber-mediated sensitivity, namely, cold detection at innocuous intensities of cold stimulation. CDT was significantly increased in the contralateral hand after cathodal stimulation, when compared with the baseline and with sham stimulation. WDT was increased after cathodal stimulation only when compared with baseline, but not when compared with the sham condition. After sham stimulation, no threshold alterations could be observed. Diminishment of cold temperature perception indicates a suppression of Aδ-fiber thermal sensory pathways following cathodal

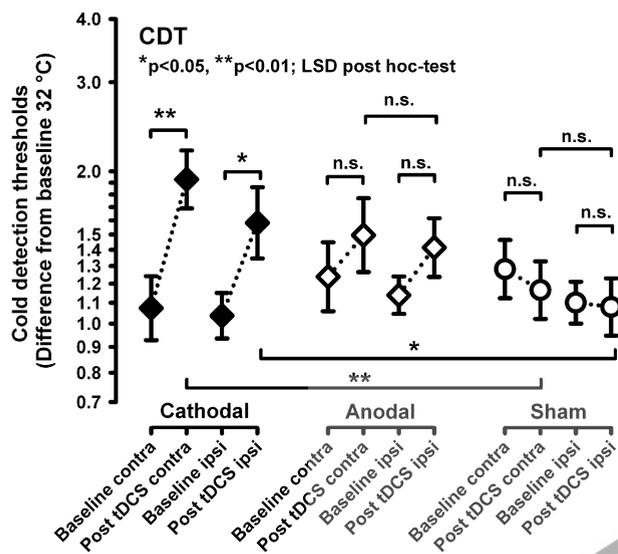


Figure 2 In this figure cold detection thresholds (CDT) are shown as differences from the baseline temperature 32°C. Baseline thresholds contralateral and ipsilateral to the tDCS electrode over the left primary sensory cortex are presented next to the referring threshold after cathodal tDCS (filled diamonds), anodal tDCS (open diamonds), or sham stimulation (open circles). CDT after cathodal tDCS was increased over the contralateral hand dorsum by about 75% when compared with the referring baseline value (** $P < .01$). CDT was also increased over the ipsilateral hand (* $P < .05$). All data are presented as mean \pm SEM. Stars denote the level of significance as depicted from ANOVA, LSD post hoc-test.

stimulation of the primary sensory cortex. The effects of cathodal and anodal tDCS did not differ significantly from each other. This may be due to the presence of virtual cathodes at the edges of the electrodes during anodal tDCS.²⁵ Another explanation for this observation might be that the effect of tDCS depends on the orientation of cortical neurons, which is not uniform. This will cause hyperpolarizing effects of anodal stimulation in some neurons,²⁶ probably resulting in a similar trend of effects of anodal tDCS as compared with cathodal tDCS.

Influence of tDCS on different thermal modalities

In the current investigation cathodal tDCS of the somatosensory cortex decreased the sensitivity to innocuous cold, whereas the sensitivity to innocuous warm stimuli was decreased only compared with baseline values. Cold perception is known to be more sensitive for nerve block by compression compared with other thermal qualities (thermal discrimination, warm thermal perception, heat and cold pain perception thresholds).²⁷ The sensation of warmth is transmitted via unmyelinated C-fibers, whereas nonpainful cold is conducted by small myelinated A δ fibers.^{28,29} Our findings are in line with several other

studies: Oliviero and colleagues³⁰ reported an increased threshold for cold perception immediately after repetitive TMS (rTMS) of the left sensorimotor cortex but not for warm perception. The increase of warm threshold observed in the same study was not significant, corresponding with our current study. In another study, after low- and high-frequency rTMS of the motor cortex a significant increase of CDTs in healthy adults was observed. Although both low- and high-frequency stimulation lead to a significant reduction of the temperature at which cold sensation was detected, only high-frequency rTMS significantly reduced cold pain perception.³¹ Similar to the results of the latter study, the impact of tDCS differs between the modulation of innocuous thermal thresholds on the one hand, and painful heat and cold sensitivity on the other. Although we detected an increase of CDT, no modifications of painful thermal sensitivity (CDT, HPT) were observed. The discernable alterations of different somatosensory modalities by tDCS and rTMS might be caused by distinct techniques of stimulation: although tDCS and low-frequency (1 Hz) rTMS modulate the CDT, only high-frequency (20 Hz) rTMS seems to be able to affect the CPT as well.³¹

Activity alterations induced in separate cortical and subcortical areas by each respective stimulation type might also contribute to an explanation for the above-named phenomenon. Many areas of the brain are involved in processing painful stimulation, including the somatosensory and motor cortices, anterior cingulate cortex (ACC), thalamus, hypothalamus, prefrontal and parietal cortices, and insular cortex.^{32,33} Of these structures, the thalamus is the main relay structure for passing sensory input to the cortex and, thus, the thalamus plays a major role in pain modulation.³¹ Previous studies showed that tDCS of the motor cortex induces activity alterations in many cortical and subcortical areas, including the mediodorsal thalamus,³⁴ whereas application of rTMS to the motor cortex is proposed to induce excitability changes in ventroposterolateral (VPL) and ventroposteromedial (VPM) thalamic nuclei.³¹

In a positron emission tomography study, Craig and colleagues³⁵ showed that innocuous cold stimuli primarily activated the contralateral insular cortex, whereas painful thermal stimuli activated the contralateral ACC, contralateral MI and SI, bilateral secondary sensory (SII: secondary sensory cortex), and midinsular cortex, contralateral ventroposterior (VP) thalamus, medial ipsilateral thalamus, and the vermis and paravermis of the cerebellum.³⁶⁻³⁸ These findings encourage the concept of different pathways for innocuous and painful thermal perception and might explain why tDCS did not affect all of the tested thermal qualities. The tDCS of the primary sensory cortex may exert its effects on the cold signaling pathway via the insular cortex, as neuroanatomical studies in rhesus monkeys demonstrated that the insula has extensive connections with the primary and secondary sensory cortex SI and SII.³⁹

In addition, a recent investigation of our group observed a significantly increased CDT after cathodal tDCS of the primary motor cortex, whereas it increased MPTs but did not affect thermal pain thresholds.⁹ Previous studies indicated that the effect of tDCS on experimentally induced pain in healthy volunteers may be limited, as tDCS over MI generated a mild antinociceptive effect on experimentally induced heat pain with laser-evoked potentials (LEPs).^{10,40} In phase II trials the efficiency of tDCS in patients with central pain and fibromyalgia was demonstrated.^{11,12} However, the mechanisms of experimentally induced acute pain in healthy volunteers and chronic pain sufferers are at least partially different, which may explain the efficiency of tDCS to reduce pain as demonstrated in phase II trials in patients with central pain and fibromyalgia.^{11,12} After cathodal stimulation of MI, not only the sensitivity to innocuous cold (CDT) was significantly decreased, but also the MDT was significantly increased.⁹ In the current study, however, no significant alterations of MDT after cathodal stimulation of SI could be observed. The results of our studies seem to suggest that tDCS of the primary motor cortex (MI) may have a more pronounced effect on somatosensory perception than transcranial stimulation of the primary sensory cortex (SI). However, the distinct outcome may be explained by interindividual variability, as some of the included subjects were different.⁹ In this pilot study, a relatively limited number of subjects was included. Consequently, we did not correct the ANOVA calculations for multiple comparisons. These factors enhance the risk for type I and type II errors. Therefore, larger consecutive studies should be performed to substantiate our results.

Furthermore, the spatial pattern of the induced functional interaction may be more complex than previously thought. Regional effects of tDCS may critically depend on the placement of the electrodes over the scalp and on inhomogeneities of electrical conductivity of the skull, cerebrospinal fluid, and brain tissue.³⁴ In line with this notion, Lefaucheur and colleagues⁴¹ demonstrated that rTMS was more effective in pain relief when the stimulation was applied to an area adjacent to the cortical representation of the painful zone rather than to the motor (or sensory) cortical area corresponding to the painful zone itself. Even though cathodal tDCS was applied contralaterally to the corresponding cortical representation, ipsilateral thresholds for CDTs were also increased after cathodal tDCS when compared with pre-tDCS and with sham stimulation. Therefore, tDCS may have secondary effects on processing in the sensory cortex which may have induced different excitability alterations in sensory cortical areas distant from the electrode,³⁴ for example, insular cortex involved in processing of innocuous cold perception. In line with this notion, rTMS of the primary somatosensory cortex (SI) resulted in an activation of the sensorimotor cortex contralateral to the stimulated index finger and of the anterior insula of both hemispheres.⁴²

Insignificant effects of tDCS on mechanical modalities

A δ -fiber function is assessed by different tests of the QST protocol: CDT and MPT.¹⁵ Because of our observation of an increased CDT after cathodal tDCS, the lack of significant effects on MPT may be surprising. However, C-fiber nociceptors make a small contribution to pinprick pain,⁴³ whereas innocuous cold perception is purely A δ -fiber-mediated. Similarly, after high-frequency rTMS of sensorimotor cortex Oliviero et al.³⁰ observed much more pronounced effects on cold perception thresholds as compared with warm perception and ascribed this finding to the different population of fibers involved.

In addition, we did not observe any significant threshold alterations for mechanical QST parameters MDT, MPS, WUR, VDT, and PPT. In our previous study,⁹ the stimulation electrode was placed over MI (C3) similar to Rogalewski et al.,⁸ who also placed the stimulation electrode over the primary motor cortex. This may explain our previous observation⁹ of increased MDTs after tDCS over MI in accordance with decreased tactile sensation reported by Rogalewski et al.,⁸ who did not examine any thermal or pain parameters. In the current study, however, the stimulation electrode was placed above the primary sensory cortex (SI, C3'), which resulted in different tDCS effects on QST parameters.

Conclusion

In summary, the results of this study suggest that an A δ -fiber-mediated somatosensory modality, specifically the sensitivity to nonpainful cold, can be reduced by cathodal tDCS applied over the primary sensory cortex. Furthermore, cathodal tDCS reduced sensitivity to warm detection only in comparison with the baseline, whereas sham and anodal stimulation showed less pronounced effects. This suggests a suppression of suprathermal somatosensory pathways for painful cold stimuli induced by cathodal tDCS and, to a lesser extent, for nonpainful warm stimuli.

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References

1. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527:633-639.
2. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 2001;57:1899-1901.

3. Nitsche MA, Liebetanz D, Antal A, et al. Modulation of cortical excitability by weak direct current stimulation-technical, safety and functional aspects. *Suppl Clin Neurophysiol* 2003;56:255-276.
4. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimulation* 2008;1:206-223.
5. Matsunaga K, Nitsche MA, Tsuji S, Rothwell JC. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clin Neurophysiol* 2004;115:456-460.
6. Wood C, Spencer DD, Allison T, McCarthy G, Williamson PD, Goff WR. Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. *J Neurosurg* 1988;68:99-111.
7. Allison T, McCarthy G, Wood CC, Darcey TM, Spencer DD, Williamson PD. Human cortical potentials evoked by stimulation of the median nerve: I, cytoarchitectonic areas generating short-latency activity. *J Neurophysiol* 1989;62:694-710.
8. Rogalewski A, Breitenstein C, Nitsche MA, Paulus W, Knecht S. Transcranial direct current stimulation disrupts tactile perception. *Eur J Neurosci* 2004;20:313-316.
9. Bachmann CG, Muschinsky S, Nitsche MA, et al. Transcranial direct current stimulation of the motor cortex induces distinct changes in thermal and mechanical sensory percepts. *Clin Neurophysiol* 2010;121:2083-2089.
10. Antal A, Brepohl N, Poreisz C, et al. Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clin J Pain* 2008;24:56-63.
11. Fregni F, Gimenes R, Valle AC, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis Rheum* 2006;54:3988-3998.
12. Fregni F, Boggio PS, Lima MC, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 2006;122:197-209.
13. Geber C, Klein T, Rolke R. Test/retest- and interobserver-reliability in quantitative sensory testing according to the protocol of the German network on neuropathic pain (DFNS). *Eur J Pain* 2007;11:87.
14. Rolke R, Magerl W, Campbell KA. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain* 2006;10:77-88.
15. Rolke R, Baron R, Maier C. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006;123:231-243.
16. Bachmann CG, Rolke R, Scheidt U, et al. Thermal hypesthesia differentiates secondary RLS due to small fiber neuropathy from primary RLS. *Brain* 2010;133:762-770.
17. Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry* 1976;39:1071-1075.
18. Yarnitsky D, Sprecher E, Zaslansky R, Hemli JA. Heat pain thresholds: normative data and repeatability. *Pain* 1995;60:329-332.
19. Fruhstorfer H, Gross W, Selbmann O. Von Frey hairs: new materials for a new design. *Eur J Pain* 2001;5:341-342.
20. Von Frey M. Untersuchung über die Sinnesfunktionen der menschlichen Haut. In: *Erste Abhandlung: Druckempfindung und Schmerz. Abhandlungen der mathematisch-physischen Klasse der Königlich-Sächsischen Gesellschaft der Wissenschaften* 1896;23. Translated in: Handwerker HO, Brune K, eds. *Classical German Contributions to Pain Research*, Gesellschaft zum Studium des Schmerzes. Heidelberg; 1987. p. 69-131.
21. Magerl W, Wilk SH, Treede RD. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain* 1998;74:257-268.
22. Baumgärtner U, Magerl W, Klein T, Hopf HC, Treede RD. Neurogenic hyperalgesia versus painful hypoalgesia: two distinct mechanisms of neuropathic pain. *Pain* 2002;96:141-151.
23. Kosek E, Ekholm J, Hansson P. Pressure pain thresholds in different tissues in one body region: the influence of skin sensitivity in pressure algometry. *Scand J Rehabil Med* 1999;31:89-93.
24. Jasper HH. The ten-twenty electrode system of the international federation. *Electroencephalogr Clin Neurophysiol* 1958;10:371-375.
25. Roth BJ. Mechanisms for electrical stimulation of excitable tissue. *Crit Rev Biomed Eng* 1994;22:253-305.
26. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. *J Neurophysiol* 1965;28:166-185.
27. Ziegler D, Mayer P, Gries FA. Evaluation of thermal, pain, and vibration sensation thresholds in newly diagnosed type 1 diabetic patients. *J Neurol Neurosurg Psychiatr* 1988;51:1420-1424.
28. Fowler CJ, Sitzoglou K, Ali Z, Halonen P. The conduction velocities of peripheral nerve fibres conveying sensations of warming and cooling. *J Neurol Neurosurg Psychiatry* 1988;51:1164-1170.
29. Hendry SH, Hsiao SS, Bushnell MC. Somatic sensation. In: Zigmund MJ, Bloom FE, Landis SC, Roberts JL, Squire LR, editors. *Fundamental neuroscience*. San Diego: Academic Press; 1999. p. 761-789.
30. Oliviero A, Esteban MR, de la Cruz FS, Cabredo LF, Di Lazzaro V. Short-lasting impairment of temperature perception by high frequency rTMS of the sensorimotor cortex. *Clin Neurophysiol* 2005;116:1072-1076.
31. Summers J, Johnson S, Pridmore S, Gajinder O. Changes to cold detection and pain thresholds following low and high frequency transcranial magnetic stimulation of the motor cortex. *Neurosci Lett* 2004;369:197-200.
32. Almeida TF, Roizenblatt S, Tufik S. Afferent pain pathways: a neuro-anatomical review. *Brain Res* 2004;1000:40-56.
33. Tracey I, Becerra L, Chang I, et al. Noxious hot and cold stimulation produce common patterns of brain activation in humans: a functional magnetic resonance imaging study. *Neurosci Lett* 2000;228:159-162.
34. Lang N, Siebner HR, Ward NS, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur J Neurosci* 2005;22:495-504.
35. Craig AD, Chen K, Bandy D, Reimann EM. Thermosensory activation of insular cortex. *Nat Neurosci* 2000;3:184-190.
36. Davis KD, Lozano RM, Manduch M, et al. Thalamic relay site for cold perception in humans. *J Neurophysiol* 1999;81:1970-1973.
37. Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain: a review and meta-analysis. *Neurophysiol Clin* 2000;30:263-288.
38. Casey KL, Morrow TJ, Lorenz J, Minoshima S. Temporal and spatial dynamics of human forebrain activity during heat pain: analysis by positron emission tomography. *J Neurophysiol* 2001;85:951-959.
39. Mesulam MM, Mufson EJ. Insula of the old world monkey, III: efferent cortical output and comments on function. *J Comp Neurol* 1982;212:38-52.
40. Csifcsak G, Antal A, Hillers F, et al. Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. *Pain Med* 2009;10:122-132.
41. Lefaucher JP, Hatem S, Nineb A, et al. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. *Neurology* 2006;67:1998-2004.
42. Pleger B, Ruff CC, Blankenburg F, et al. Neural coding of tactile decisions in the human prefrontal cortex. *J Neurosci* 2006;26:12596-12601.
43. Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. *Brain* 2001;124:1754-1764.