The human primary somatosensory cortex is differentially involved in vibrotaction and nociception

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abbreviated title

S1 is differently involved in vibrotaction and nociception

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Abstract

The role of the primary somatosensory cortex (S1) in vibrotaction is well established. In contrast, its involvement in nociception remains debated. Here, we test whether S1 is similarly involved in the processing of non-nociceptive and nociceptive somatosensory input in humans by comparing the after-effects of high-definition transcranial direct current stimulation (HD-tDCS) of the primary sensorimotor cortex on the event-related potentials (ERPs) elicited by non-nociceptive and nociceptive somatosensory stimuli delivered to the ipsilateral and contralateral hand. Cathodal HD-tDCS significantly affected the responses to non-nociceptive somatosensory stimuli delivered to the contralateral hand: both early-latency ERPs from within S1 (N20 wave elicited by transcutaneous electrical stimulation of the median nerve) and late-latency ERPs elicited outside S1 (N120 wave elicited by short-lasting mechanical vibrations delivered to the index fingertip, thought to originate from bilateral operculo-insular and cingulate cortices). These results support the notion that S1 constitutes an obligatory relay for the cortical processing of non-nociceptive tactile input originating from the contralateral hemibody. Contrasting with this asymmetric effect of HD-tDCS on the responses to non-nociceptive somatosensory input, HD-tDCS over the sensorimotor cortex led to a bilateral and symmetric reduction of the magnitude of the N240 wave of nociceptive laser-evoked potentials elicited by stimulation of the hand dorsum. Taken together, our results demonstrate, in humans, a differential involvement of S1 in vibrotaction and nociception.

1. Introduction

The role of the primary somatosensory cortex (S1) in vibrotaction is well established (Abraira & Ginty, 2013). In contrast, its involvement in nociception remains elusive (Bushnell *et al.*, 1999). For example, lesions of S1 markedly impair many aspects of tactile perception (Penfield & Boldrey, 1937), but have little or no long-standing effect on the ability to perceive pain (Head & Holmes, 1911). Similarly, focal seizures of S1 and direct electrical stimulation of S1 in awake patients undergoing surgery for epilepsy can generate vivid touch-related paraesthesia, but do not appear to elicit pain (Penfield, 1947; Tuxhorn, 2005; Mazzola *et al.*, 2012b). Also supporting the notion that S1 is involved differentially in the processing of touch and pain is the observation, in animals, that S1 is not the main projection site of nociceptive spinothalamic input which, instead, projects predominantly to the insula, the secondary somatosensory cortex (S2) and the cingulate cortex (Dum *et al.*, 2009). Nevertheless, functional neuroimaging studies using magnetic resonance imaging (MRI) or positron emission tomography (PET) have shown that nociceptive stimuli elicit a clear haemodynamic response in the contralateral S1, at a location corresponding to the somatotopic representation of the stimulated body site (Coghill *et al.*, 1994; Bushnell *et al.*, 1999; Chen *et al.*, 2011; Chen *et al.*, 2012; Hu *et al.*, 2015). Electrophysiological studies using electroencephalography (EEG), magnetoencephalography (MEG) and intracerebral recordings have provided less consistent findings, but still suggest that nociceptive stimuli elicit responses in the contralateral S1, at latencies compatible with the earliest stages of the cortical processing of nociceptive inputs (Tarkka & Treede, 1993; Ploner *et al.*, 1999b; Kanda *et al.*, 2000; Ploner *et al.*, 2002; Valentini *et al.*, 2012).

Finally, studies have attempted to assess the differential involvement of S1 in touch and pain by characterizing the effect of repetitive transcranial magnetic stimulation (rTMS) over S1 on the perception and event-related brain potentials (ERPs) elicited by non-nociceptive and nociceptive somatosensory stimuli delivered to the ipsilateral and contralateral hemibody (Poreisz *et al.*, 2008a; Torta *et al.*, 2013). This approach is highly relevant because, unlike studies based on sluggish haemodynamic responses sampled using functional neuroimaging techniques, studies based on the direct sampling of cortical activity using ERPs have the temporal resolution required to tease out S1 responses related to the early stages of the cortical processing of ascending somatosensory input from late responses triggered by re-entrant feedback projections to S1 originating from higher-order cortical areas. Unfortunately, the results of these studies were largely inconclusive, mainly because they failed to demonstrate any clear and reproducible effect of rTMS on the excitability of S1. For instance, using various protocols of theta-burst stimulation (TBS, a special form of rTMS), Poreisz *et al.* (2008a) showed that rTMS delivered over S1 reduces the magnitude of the N240 wave of nociceptive laser-evoked brain potentials elicited by stimulation of the contralateral hand, but they did not compare directly this effect to the effect on the responses elicited by stimulation of the ipsilateral hand. Such a direct comparison was performed by Torta *et al.* (2013). In that study, they assessed the effects of TBS delivered over the primary motor cortex (M1) and S1 on the ERPs elicited by both non-nociceptive and nociceptive stimuli delivered to the two hands, but failed to disclose any specific effect of TBS on the responses elicited by stimulation of the contralateral hand. These inconstant findings could be related to the increasingly acknowledged large interindividual variability of the

effects of rTMS delivered over the sensorimotor cortex. For example, Hamada *et al.* (2013) and Huang and Mouraux (2015) recently showed that continuous TBS delivered over M1 decreases motor excitability in some individuals, whereas it increases motor excitability in a similar number of other individuals.

Here, in a first experiment we attempt to determine whether S1 is involved differentially in the processing of touch and pain using another non-invasive technique to modulate the excitability of the human sensorimotor cortex: cathodal high-definition transcranial direct current stimulation (HD-tDCS). The frequently proposed mechanism of cathodal tDCS is that neuronal populations located below the cathode become hyperpolarized, thereby reducing their excitability (Nitsche & Paulus, 2000; Nitsche *et al.*, 2008; Datta *et al.*, 2009). The cathode electrode was placed over the expected hand representation of the left or right S1, surrounded by four return anode electrodes placed on a 5-cm radius circle. Previous studies have shown that the neuromodulation induced by this 4x1 ring HD-tDCS montage is much more focal than the neuromodulation induced by the conventional tDCS configuration consisting of two large rectangular electrodes (Datta *et al.*, 2009; Edwards *et al.*, 2013; Kuo *et al.*, 2013; Villamar *et al.*, 2013b), and comparable to that of TMS delivered using a 75 mm figure-of-eight coil (Edwards *et al.*, 2013). This allowed us to compare, within-subjects, the after-effects of HD-tDCS applied for 20 minutes over S1 on the perception and ERPs elicited by non-nociceptive and nociceptive stimuli delivered to the ipsilateral and contralateral hand relative to the hemisphere onto which HD-tDCS was applied.
Transcutaneous electrical stimulation of the median nerve at the level of the wrist was used to compare the effects of HD-tDCS on the early-latency response of S1 to non-nociceptive somatosensory input originating from the contralateral and ipsilateral hands and, thereby, to confirm the specific neuromodulatory effect of HD-tDCS on S1. Within the same experimental sessions, mechanical vibrotactile stimuli and thermal nociceptive stimuli were delivered to the left and right hands to assess whether modulating the state of the sensorimotor cortex exerts a differential effect on the cortical processing of non-nociceptive and nociceptive somatosensory inputs. We hypothesized that, if S1 constitutes an obligatory relay for the cortical processing of somatic input originating from the contralateral hemibody, HD-tDCS delivered over the hand representation of the sensorimotor cortex would affect differently the ERPs elicited by stimulation of the contralateral hand vs. the ipsilateral hand.

Finally, we conducted a second experiment in another group of participants. This experiment was identical to the first experiment except for the fact that cathodal HD-tDCS was applied for only 30 seconds. Comparison of the after-effects of real HD-tDCS (HD-tDCS experiment) and sham HD-tDCS (sham experiment) allowed us to test whether the effect on the processing of non-nociceptive and nociceptive somatosensory input were due to a true neuromodulatory effect of 20 minutes of HD-tDCS or to unrelated time-dependent effects.

2. Materials and methods

2.1. Participants

Fourteen healthy right-handed volunteers were included in a first experiment assessing the effect of cathodal HD-tDCS over the sensorimotor cortex on the perception and ERPs elicited by non-nociceptive and nociceptive stimuli delivered to the ipsilateral and contralateral hand relative to the hemisphere onto which HD-tDCS was applied (HD-tDCS experiment: 12 women/2 men; 23.2 ± 1.1 years; mean ± SD; range 21-25). Fourteen other

participants took part in a second experiment in which real HD-tDCS (20 minutes of stimulation) was replaced by sham HD-tDCS (30 s of stimulation) (sham experiment: 8 women/6 men; 27.3 ± 4.7 years; range 22-35). All participants were blinded to the aims of the study. Because participants took part in one or the other experiment, all subjects were equally naïve with the procedures when coming to their first and only session. Handedness was assessed using The Flinders Handedness survey (FLANDERS; Nicholls *et al.*, 2013). Because the skin reflectance, absorption and transmittance of the infrared radiations generated by the Neodymium:Yttrium-Aluminum-Perovskite (Nd:YAP) laser used to deliver nociceptive stimuli (wavelength: 1.34 µm) are highly dependent on skin pigmentation, only participants with light skin were recruited. They were recruited among students and staff of the university. All participants were screened by a neurologist for contra-indications to tDCS (Nitsche *et al.*, 2008). None of them had any history of psychiatric or neurological disorders including epilepsy or family history of seizure. The experimental procedures were approved by the Ethics Committee (Commission d'Éthique Biomédicale Hospitalo-Facultaire) of the Université catholique de Louvain (UCL) (B403201316436) and all participants provided a written informed consent.

2.2. Experimental design

HD-tDCS experiment. Subjects were comfortably seated on a reclining chair during the entire experiment, consisting of two successive EEG recording sessions, immediately before and immediately after applying cathodal HD-tDCS over the left or right sensorimotor cortex (Fig. 4.1). The side of stimulation was counterbalanced across participants. The second recording always began within 5 minutes and ended within 25 minutes of the end of HD-tDCS. Each EEG recording consisted of four blocks whose order was counterbalanced across subjects. In two separate blocks, transcutaneous electrical nerve stimuli were delivered to the left or right median nerve to characterize the early-latency N20 wave, i.e. the first cortical response to non-nociceptive somatosensory input ascending through lemniscal pathways. A total of 500 stimuli were delivered to each hand, using a constant 0.25 s inter-stimulus interval (ISI). In a third block, non-nociceptive vibrotactile stimuli were applied to the left and right index fingertip to elicit ERPs related to the selective activation of tactile mechanoreceptors. In a fourth block, nociceptive laser stimuli were applied to the left and right hand dorsum to elicit ERPs related to the selective activation of heat-sensitive Aδ-fiber nociceptors. In these blocks, the stimuli were delivered randomly to the left or right hand using a random 5-7 s ISI. A total of 25 stimuli were delivered to each hand.

After each stimulus, participants were asked to verbally report the intensity of perception using a numerical rating scale (NRS) ranging from 0 (no sensation) to 10 (most intense sensation), 5 marking the border between non-painful and painful domains of sensation.

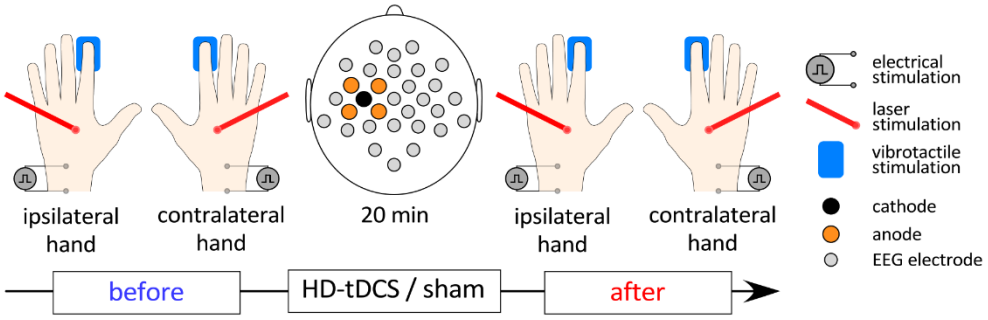


Figure 4.1. In two separate groups, we assessed the effects of 20 minutes of HD-tDCS vs. sham HD-tDCS over the sensorimotor cortex on the perception and ERPs elicited by non-nociceptive and nociceptive stimuli delivered to the ipsilateral and contralateral hands. The two experiments consisted of two EEG recording sessions, immediately before and immediately after 20 minutes of real HD-tDCS (HD-tDCS experiment) or sham HD-tDCS (sham experiment) of the left or right sensorimotor cortex. During each EEG session, ERPs elicited by non-nociceptive and nociceptive stimuli delivered to the ipsilateral and contralateral hands were recorded. Non-nociceptive stimuli were transcutaneous electrical stimuli delivered to the median nerve at the level of the wrist, and vibrotactile stimuli delivered to the index fingertip. Nociceptive heat stimuli were laser pulses delivered to the hand dorsum. The second recording session always began within 5 minutes after the end of HD-tDCS or sham stimulation, and was completed within 25 minutes.

Sham experiment. The sham experiment was identical to the HD-tDCS experiment except for the fact that participants received sham cathodal HD-tDCS instead of real HD-tDCS over the left or right sensorimotor cortex (Fig. 4.1). Such as in the HD-tDCS experiment, the stimulation procedure lasted 20 minutes. However, the duration of actual current stimulation lasted less than two minutes.

2.3. Cathodal HD-tDCS

Cathodal HD-tDCS was delivered for 20 minutes using a 4 × 1 ring montage of five Ag-AgCl sintered ring electrodes (B10 Easycap GmbH, Germany), inserted in a ring electrode adapter to increase the area of contact between the electrode, gel and skin (electrode-gel contact area: 100 mm^2; gel-skin contact area : > 1.5 cm^2; Minhas *et al.*, 2010). The 4 × 1 ring montage consisted of one cathode electrode placed over the International 10-20 position C3 or C4, surrounded by four return anode electrodes placed on a circle of approximately 5 cm radius around the cathode (FC5, FC1, CP1, CP5 or FC6, FC2, CP2, CP6). Edwards et al. demonstrated using electric field modelling and by comparing the effects on motor excitability of HD-tDCS delivered at adjacent positions relative to M1, that the focal aspect of HD-tDCS delivered using this 4 × 1 montage is comparable to that of TMS delivered using a 75 mm figure-of-eight coil (Edwards *et al.*, 2013). Impedances between the cathode electrode and each anode electrode were kept below 5 kΩ. The stimulation was generated using a constant current electrical stimulator (Eldith, NeuroConn GmbH, Germany). In the HD-tDCS experiment, the current was ramped up from 0 to 1 mA during the first 40 s of stimulation, and was then maintained constant during 20 minutes. At the end of these 20 minutes, the current was ramped down in 40 s. In the sham experiment, the stimulation protocol also lasted 20 minutes. However, the actual duration of the stimulation was set to 30 s. Such as in previous studies (Minhas *et al.*, 2010; Borckardt *et al.*, 2012), both real HD-tDCS and sham HD-tDCS elicited a moderate tingling and itching sensation at the site of stimulation. Because this sensation faded within a couple

of minutes even when HD-tDCS was maintained for 20 minutes, the sensations generated by real HD-tDCS and sham HD-tDCS were highly similar and, most probably, indistinguishable.

2.4. Non-nociceptive and nociceptive somatosensory stimuli

Non-nociceptive transcutaneous electrical stimulation of the median nerve was used to assess in a reliable fashion the early-latency S1 response elicited by non-nociceptive somatosensory input ascending through the lemniscal pathway (i.e., the N20 wave). The stimuli consisted of non-painful constant-current square-wave (0.5 ms) electrical pulses generated using a DS7 stimulator (Digitimer Ltd, Letchworth, UK) and delivered using a pair of 24 mm diameter adhesive electrodes (Covidien Kendall Disposable Surface EMG/ECG/EKG, Mansfield, USA) separated by a 2 cm inter-electrode distance, placed over the median nerve at the level of the wrist. The cathode electrode was positioned proximal relative to the anode electrode. The intensity of stimulation (7.1 ± 1.8 mA) was set such as to elicit a consistent and visible twitch of the thumb. The same intensity of stimulation was used before and after HD-tDCS, and the adhesive electrodes were not displaced.

Non-nociceptive vibrotactile stimuli were short-lasting (50 ms) mechanical vibrations (300 Hz) delivered on the index fingertip using a vibrotactile transducer (length: 2.8 cm; width: 1.2 cm; Haptuators; Tactile Labs, Montreal, Canada). The index fingertip was chosen because of the important density of Pacinian mechanoreceptors in that skin area (Abraira & Ginty, 2013). During vibrotactile stimulation, white noise was played through headphones to avoid any auditory response to the sound produced by the transducers.

Nociceptive heat stimuli were short-lasting (5 ms) pulses of radiant heat delivered on the hand dorsum using an Nd:YAP laser (wavelength, 1.34 µm ; ElEn Group, Firenze, Italy). The hand dorsum was chosen to avoid issues related to the conduction of heat within the thicker skin of the fingertip. Beam diameter at target site was set to 5 mm. The energy of the stimulus (2.0 ± 0.2 J) was adjusted individually such as to elicit a clear pinprick sensation detected with a reaction time shorter than 650 ms, i.e. a reaction time compatible with the conduction velocity of Aδ-fibers (Plaghki *et al.*, 1994; Towell *et al.*, 1996; Mouraux *et al.*, 2003). The same energy was used before and after HD-tDCS. The target of the laser stimulus was slightly displaced after each trial such as to avoid nociceptor habituation and/or sensitization.

2.5. EEG recording

The EEG was recorded at a sampling rate of 4000 Hz using an average reference (32-channel ASA-LAB EEG system; Advanced Neuro Technologies, The Netherlands), with 32 actively shielded Ag-AgCl electrodes mounted in an elastic electrode cap and arranged according to the International 10-20 system (Easycap 32, EASYCAP GmbH, Germany). During the entire EEG recording, participants were instructed to keep their gaze fixed on a black cross displayed in front of them and to sit as still as possible. Eye movements were recorded using two adhesive surface electrodes placed at the upper-right and lower-left sides of the left eye. Impedances were kept below 5 kΩ for all leads. The continuous EEG recordings were processed offline using Letswave6 (https://www.letswave.org).

2.6. ERP waveforms

Non-nociceptive ERPs elicited by transcutaneous electrical stimulation of the median nerve. Within the continuous EEG recordings, the electrical stimulation artefact was suppressed using a linear interpolation of the signals recorded from -1 to +7 ms relative to stimulation onset. The recordings were then high-pass filtered using a 0.3 Hz Butterworth zero phase filter and segmented into 0.2 s epochs ranging from -0.05 to +0.15 s. Artefacts due to eye blinks or eye movements were removed using a validated method based on an independent-component analysis (FastICA algorithm; Hyvarinen & Oja, 2000). After applying a baseline correction (subtraction of the average amplitude of the signal within the reference interval 7-11 ms), the signals were re-referenced to Fz. Epochs containing signals exceeding ±75 μV were rejected to reduce the contribution of artefacts such as head movements, eye blinks or muscular activity. Finally, average waveforms were computed for each participant, session and stimulation side. Within these waveforms, the N20 wave was identified as the most negative deflection occurring 17-23 ms after stimulus presentation (Fig. 4.2), at the parietal electrode contralateral to the stimulated hand (left hand : P4; right hand : P3; Cruccu *et al.*, 2008).

Non-nociceptive vibrotactile ERPs and nociceptive laser ERPs. After applying a 0.3-40 Hz Butterworth zero phase band pass filter, the continuous recordings were segmented into 3 s epochs ranging from -0.5 to +2.5 s relative to stimulus onset. Artefacts due to eye blinks or eye movements were removed using the FastICA algorithm (Hyvarinen & Oja, 2000). After baseline correction (reference interval -0.5 to 0 s), epochs containing signals exceeding ±75 μV were rejected before computing separate average waveforms for each participant, session, stimulation type and stimulation side. Within the non-nociceptive vibrotactile ERP waveforms, two distinct peaks (N120 and P250) were identified at electrode Cz, referenced to M1M2 (Miltner *et al.*, 1989; Garcia-Larrea *et al.*, 1995; Kenntner-Mabiala *et al.*, 2008). The N120 was defined as the most negative deflection peaking 90-160 ms after stimulus onset. The P250 was defined as the most positive deflection following the N120 (Fig. 4.2). Within the nociceptive laser ERP waveforms, three distinct peaks were identified (N160, N240 and P350) (Bromm & Treede, 1984; Treede *et al.*, 1988; Cruccu *et al.*, 2008; Hu *et al.*, 2010). At electrode Cz referenced to M1M2, the N240 was identified as the most negative deflection peaking 140-260 ms after stimulus presentation, and the P350 as the most positive deflection following the N240 (Fig. 4.2). The N160 was defined as the most negative deflection peaking 140-220 ms at the central electrode C3 or C4 contralateral electrode to the stimulated hand, and referenced to Fz (Bromm & Treede, 1984; Treede *et al.*, 1988).

2.7. High-frequency oscillations (HFOs)

Previous studies have shown that, in addition to the N20 waveform, transcutaneous electrical stimulation of the median nerve also elicits an early-latency burst of high-frequency oscillations (HFOs: 400-900 Hz) (Ozaki & Hashimoto, 2011). These HFOs are commonly separated in an early component thought to be generated by thalamocortical and pyramidal neurons, and a late component reflecting inhibitory interneuronal S1 activity (Ozaki & Hashimoto, 2011; Restuccia *et al.*, 2011). Such HFOs have not been reported using mechanical stimulation of skin receptors, probably because identifying this high frequency activity requires a very phasic stimulus repeated a large number of times (Katayama *et al.*, 2010). To evaluate the effects of HD-tDCS on the magnitude of the HFOs elicited by stimulation of the ipsilateral and contralateral median nerve, the continuous EEG recordings were band-pass filtered using a 400-1000 Hz bandpass Butterworth zero phase filter after

suppression of the electrical stimulation artefact (-1 to 7 ms), and segmented into 0.2 s epochs ranging from -0.05 to +0.15 s relative to stimulus onset. A baseline correction (reference interval 7 to 11 ms) was performed and the signals were averaged across trials after re-referencing to Fz. A Hilbert transform was then used to obtain an estimate of the envelope of HFOs (Restuccia *et al.*, 2011). Such as in previous studies (Restuccia *et al.*, 2007; Katayama *et al.*, 2010), the early and late subcomponents of HFOs were defined relative to the latency of the N20 wave. The early subcomponent extended between -5 and 0 ms relative to the N20 peak, and the late subcomponent extended between 0 and +8 ms (Fig. 4.3A). The magnitudes of these two subcomponents were estimated by averaging the result of the Hilbert transform within these two intervals. Averaged across participants and conditions, the amplitude of HFOs were maximal at the central-parietal electrodes contralateral to the stimulated hand (left hand : CP6; right hand : CP5) (Fig. 4.3B). These electrodes were thus chosen to estimate the magnitude of early and late HFOs across participants and conditions.

2.8. Statistical analyses

A mixed-model ANOVA with the between-subject factor 'group' (real HD-tDCS vs. sham HD-tDCS) and the within-subject factors 'time' (before vs. after HD-DCS) and 'side' (somatosensory stimuli delivered to the ipsilateral vs. contralateral hand relative to the sensorimotor cortex onto which the neuromodulation was applied) was used to test directly the differential effects of real vs. sham HD-tDCS on the perception and ERPs elicited by nociceptive and non-nociceptive stimuli delivered to the ipsilateral and contralateral hands. Indeed, a significant three-way interaction between the factors 'group', 'time' and 'side' would demonstrate a differential effect of HD-tDCS vs. sham stimulation on the responses to stimuli delivered to the ipsilateral vs. contralateral hand; whereas a two-way 'time' $\times$ 'group' interaction would indicate a bilateral effect of HD-tDCS vs. sham stimulation, and a two-way 'time' $\times$ 'side' interaction would indicate an asymmetric effect on the responses to stimuli delivered to the ipsilateral vs. contralateral hands present both after real and sham HD-tDCS. Finally, a main effect of 'time' would indicate a bilateral change in the responses.

In a second step, the effects of real HD-tDCS and sham HD-tDCS were assessed within each experiment separately using a repeated-measures ANOVAs with the within-subject factors 'time' (before vs. after HD-tDCS) and 'side' (somatosensory stimuli delivered to the ipsilateral vs. contralateral hand relative to the hemisphere onto which the neuromodulation was applied). A Greenhouse-Geisser correction was used when necessary. When a significant interaction was found, post-hoc pairwise comparison or paired t-tests were performed. Significance threshold was set at $p < .05$.

3. Results

3.1. Intensity of perception

The intensity of the percept elicited by non-nociceptive tactile stimuli were largely unchanged (Figure 4.4). Accordingly, the mixed-model ANOVA showed no main effect of 'time' ($F_{(1,26)} = .013$; $p = .908$), and no interaction between the factor 'time' and the factors 'group' or 'side' (Table 4.1).

	'time × side × group'		'time × group'		'time × side'		'time'	
	F value	**p**	**F value**	**p**	**F value**	**p**	**F value**	**p**
			Non-nociceptive stimulation					
Intensity of perception	0.151	0.701	0.48	0.495	**5.32**	**0.029***	0.013	0.908
N20 amplitude	2.07	0.163	0.03	0.858	**8.42**	**0.007***	0.00	0.989
N20 latency	**6.93**	**0.014***	1.98	0.181	0.37	0.549	0.68	0.417
N120 amplitude	**7.35**	**0.012***	0.65	0.429	0.08	0.785	3.11	0.09
P250 amplitude	0.57	0.457	0.01	0.921	0.36	0.556	**4.76**	**0.038***
HFOs late subcomponent	0.92	0.347	**7.03**	**0.013***	3.29	0.081	1.36	0.254
			Nociceptive stimulation					
Intensity of perception	0.14	0.716	1.71	0.203	0.203	2.97	**11.4**	**0.002***
N160 amplitude	0.08	0.787	1.27	0.269	0.40	0.531	**8.33**	**0.008***
N240 amplitude	0.47	0.501	**6.06**	**0.021***	0.36	0.556	**12.78**	**0.001***
N240 latency	0.03	0.874	2.12	0.157	**4.61**	**0.041***	0.24	0.625
P350 amplitude	3.46	0.074	0.28	0.602	2.26	0.145	**21.91**	**0.000***

Table 4.1. Mixed-model ANOVAs with between-factor 'group' (HD-tDCS experiment vs. sham experiment) and within-subject factors 'time' (before vs. after HD-tDCS) and 'side' (stimulation of ipsilateral vs. contralateral hand) A 3-way 'time × side × group' interaction indicates a differential effect of HD-tDCS vs. sham stimulation on the responses to stimuli delivered to the ipsilateral vs. contralateral hand. A 2-way 'time × group' interaction indicates a bilateral effect of HD-tDCS vs. sham stimulation on the responses to stimuli delivered to both hands, whereas a 2-way 'time × side' interaction indicates an asymmetric effect on the responses to stimuli delivered to the ipsilateral vs. contralateral hand both after real HD-tDCS and after sham HD-tDCS. Finally, a main effect of 'time' indicates a bilateral change in the responses in both experiments. Significant values are in bold. *p < 0.050.

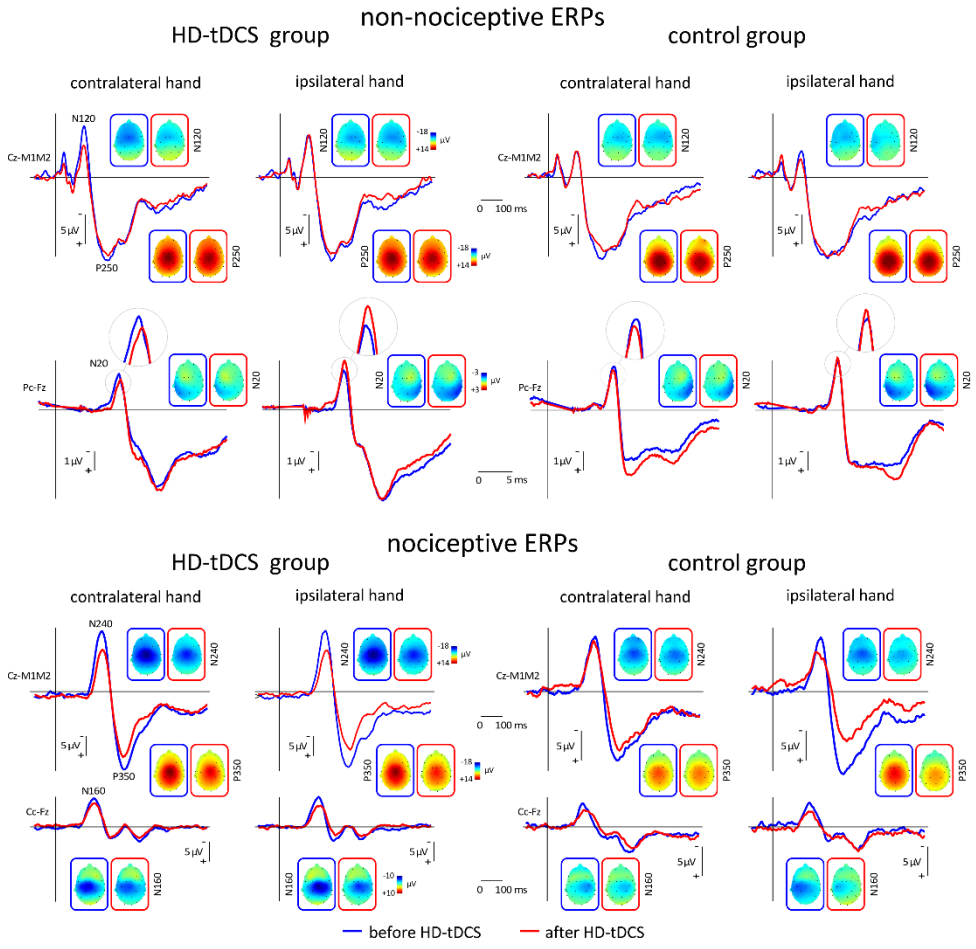


Figure 4.2. Non-nociceptive and nociceptive somatosensory ERPs recorded before and after real HD-tDCS (HD-tDCS experiment, left part) and sham HD-tDCS (sham experiment, right part) of sensorimotor cortex (group-level average waveforms). The N120 and P250 waves (vibrotactile stimulation) and the N240 and P350 waves (laser stimulation) of the ipsilateral and contralateral hand are shown at Cz vs. M1M2. The N20 waves (transcutaneous electrical stimulation of the median nerve) are shown at the contralateral parietal electrode (Pc : P3 or P4) vs. Fz. The N160 wave (laser stimulation) is shown at the contralateral central electrode (Cc : C3 or C4) vs. Fz. Scalp topographies of the ERPs components recorded before (blue frames) and after (red frames) HD-tDCS or sham

stimulation. Note the marked reduction of the N120 wave elicited by tactile stimulation of the contralateral hand after HD-tDCS, the amplitude reduction and the latency decrease of the N20 wave elicited by electrical stimulation of the contralateral median nerve, and the absence of such changes in the sham experiment. Also note the symmetric reduction of the N240 wave in the HD-tDCS experiment, and the lack of such a reduction in the sham experiment.

	HD-tDCS experiment			
	main effect of 'time'		interaction 'time' x 'side'	
Non-nociceptive stimulation	F value	p	F value	p
Intensity of perception	0.40	0.536	2.14	0.167
N20 amplitude	0.01	0.907	9.27	**0.009***
N20 latency	2.09	0.172	9.24	**0.009***
N120 amplitude	4.05	0.065	11.03	**0.006***
P250 amplitude	2.02	0.179	0.62	0.445
HFOs late subcomponent	6.45	**0.025***	3.82	0.072
Nociceptive stimulation				
Intensity of perception	9.4	**0.009***	0.89	0.362
N160 amplitude	4.88	**0.046***	0.05	0.833
N240 amplitude	13.20	**0.003***	0.60	0.453
N240 latency	1.59	0.229	2.53	0.136
P350 amplitude	10.82	**0.006***	0.08	0.777

Table 4.2. Repeated-measures ANOVAs for HD-tDCS experiment with factors 'time' and 'side'. Values are results of repeated-measures ANOVAs for the HD-tDCS experiment with factors 'time' (before vs. after HD-tDCS) and 'side' (stimulation of ipsilateral vs. contralateral hand). Significant values are in bold. *p < 0.050.

	sham experiment			
	main effect of 'time'		interaction 'time' x 'side'	
Non-nociceptive stimulation	F value	p	F value	p
Intensity of perception	0.14	0.714	3.19	0.098
N20 amplitude	0.02	0.894	1.09	0.315
N20 latency	0.18	0.679	1.43	0.253
N120 amplitude	0.39	0.545	0.74	0.406
P250 amplitude	2.81	0.118	0.02	0.880
HFOs late subcomponent	1.27	0.280	0.37	0.555
Nociceptive stimulation				
Intensity of perception	2.57	0.133	2.24	0.158
N160 amplitude	4.42	0.056	0.70	0.418
N240 amplitude	1.00	0.336	0.01	0.941
N240 latency	0.57	0.462	2.09	0.172
P350 amplitude	11.56	**0.005***	4.55	0.052

Table 4.3. Repeated-measures ANOVAs for sham experiment with factors 'time' and 'side'. Values are results of repeated-measures ANOVAs for the sham experiment with factors 'time' (before vs. after sham HD-tDCS) and 'side' (stimulation of ipsilateral vs. contralateral hand). Significant values are in bold. *p < 0.050.

In contrast, the intensity of the percept elicited by nociceptive laser stimuli was reduced both after real HD-tDCS and after sham HD-tDCS. This reduction was symmetric at both hands and, on average, more pronounced in the group that received real HD-tDCS (average reduction at both hands: -15 to -20%) as compared to the group that received sham HD-tDCS (average reduction at both hands: -1 to -11%). The mixed-model ANOVA confirmed a main effect of 'time' ($F_{(1,26)} = 11.4$; $p = .002$), but showed no significant interaction between the factor 'time' and the factors 'group' or 'side' (Table 4.1). The within-subject ANOVAs conducted separately for each experiment showed a significant main effect of 'time' in the HD-tDCS experiment ($F_{(1,13)} = 9.4$; $p = .009$), but not in the sham experiment ($F_{(1,13)} = 2.57$; $p = .133$) (Tables 4.2 and 4.3, Figure 4.4).

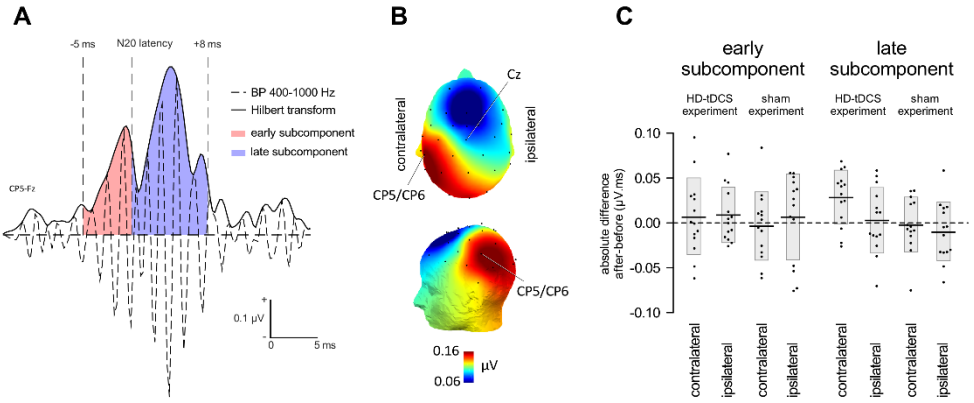


Figure 4.3. A. High frequency oscillations (HFOs) elicited by non-nociceptive electrical stimulation of the median nerve can be separated into an early component (red: -5 to 0 ms relative to the latency of the N20 wave) and a late component (blue: 0 to +8 ms relative to the latency of the N20 wave). The dashed line represents the EEG signal band-pass filtered using a 400-1000 Hz Butterworth zero phase filter, the solid line represents its Hilbert transform (average waveform from one recording performed in one subject while stimulating the right hand; contralateral central-parietal electrode CP5 vs. Fz). An estimate of the magnitude of early and late HFOs components was computed by calculating the area under the curve of the Hilbert transform, from -5 to 0 ms (early subcomponent) and from 0 to +8 ms (late subcomponent). **B.** Scalp topography of the maximum peak amplitude of HFOs averaged across all participants and all conditions. The amplitude of HFOs was maximal at the contralateral central-parietal electrode (CP5 or CP6 vs. Fz). **C.** Magnitudes of the early and late components of HFOs in the HD-tDCS experiment and the sham experiment. The scatter plots represent for each subject the change in amplitude of the responses elicited by stimulation of the contralateral and ipsilateral hands, after vs. before treatment. The box plots show the group-level average ± SD. Note, in the HD-tDCS experiment as compared to the sham experiment, the increase in magnitude of late-latency HFOs most evident when stimulating the contralateral hand.

3.2. Early-latency ERPs elicited by electrical stimulation of the median nerve

Transcutaneous electrical stimulation of the median nerve elicited a consistent N20 wave in each participant and condition (Fig. 4.2). As compared to the N20 wave elicited by stimulation of the hand ipsilateral to the sensorimotor cortex onto which HD-tDCS was applied, the magnitude of the N20 wave elicited by stimulation of the contralateral hand was, on average, reduced both after real HD-tDCS and after sham HD-tDCS. This asymmetric reduction in amplitude was more pronounced after real HD-tDCS as compared to sham HD-tDCS.

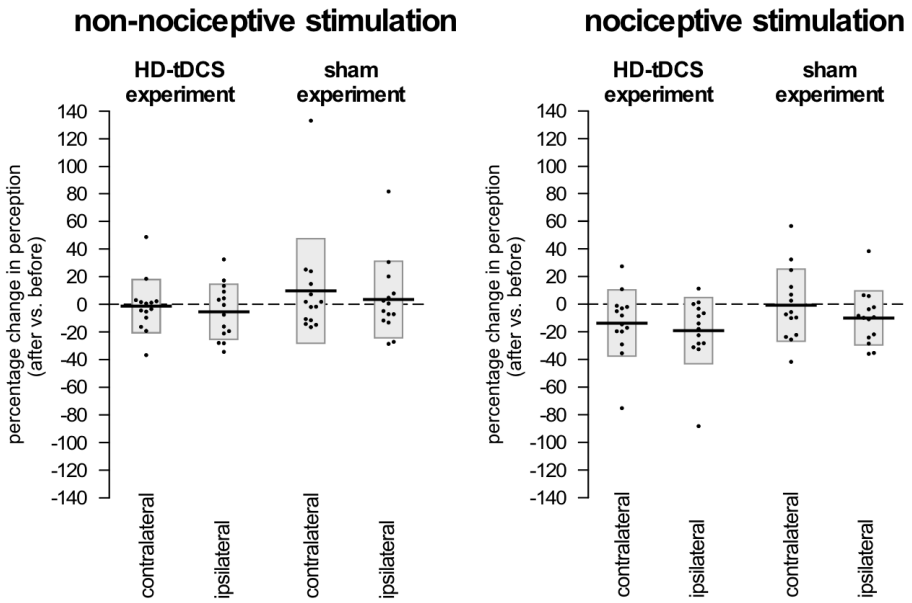


Figure 4.4. Effect of real HD-tDCS (HD-tDCS experiment) and sham HD-tDCS (sham experiment) on the intensity of the perception elicited by non-nociceptive vibrotactile and nociceptive laser stimuli delivered to the contralateral and ipsilateral hand. The scatter plots represent for each subject the average percentage change in percept before vs. after HD-tDCS or sham stimulation. The box plots show the group-level average ± SD. Note, the bilateral reduction of the perception elicited by nociceptive laser stimulation, which is most pronounced after real HD-tDCS.

This observation was confirmed by the mixed-model ANOVA, which showed a significant interaction between the factors 'time' and 'side' ($F_{(1,26)}$ = 8.42; p = .007), but no significant interaction between these two factors and the between-subject factor 'group' ($F_{(1,26)}$ = 2.07; p = .163; Table 4.1). In the HD-tDCS experiment, the within-subject ANOVA showed a significant 'time' × 'side' interaction ($F_{(1,13)}$=9.27; p= .009; Table 4.2), and post-hoc comparisons confirmed that, after real HD-tDCS, the magnitude of the N20 wave elicited by stimulation of the contralateral hand was significantly reduced (-0.31 ± 0.48 μV; t = 2.436; p = .030), whereas the magnitude of the N20 wave elicited by stimulation of the ipsilateral hand tended to increase (+0.28 ± 0.69 μV), but this increase was not significant (t = 1.52; p = .152). In the sham experiment, the 'time' × 'side' interaction was not significant ($F_{(1,13)}$ = 1.09; p = .315).

HD-tDCS exerted a significant effect on the latency of the N20 wave. On average, the latency of the N20 wave elicited by stimulation of the contralateral hand was significantly increased after real HD-tDCS but not after sham HD-tDCS (Figure 4.2). The mixed-model ANOVA showed a significant three-way interaction between the factors 'group', 'time' and 'side' ($F_{(1,26)}$ = 6.93; p = .014; Table 4.1). In the HD-tDCS experiment, the within-subject ANOVA showed a significant 'time' × 'side' interaction ($F_{(1,13)}$ = 9.24; p = .009), and the post-hoc comparisons confirmed that, after HD-tDCS, the latency of the N20 elicited by stimulation of the contralateral hand was significantly increased (+0.3 ± 0.4 ms; t = 2.51; p = .026), whereas the latency of the N20 elicited by stimulation of the ipsilateral hand was unchanged (+0.0 ± 0.4 ms; t = .000; p = 1.0). In the sham experiment, the within-subject ANOVA showed no significant 'time' × 'side' interaction ($F_{(1,13)}$ = 1.43; p = .253; Table 4.3).

3.3. HFOs elicited by electrical stimulation of the median nerve

In all conditions of both experiments, transcutaneous electrical stimulation of the median nerve elicited a significant burst of HFOs, centered around the latency of the N20 wave.

On average, the magnitude of the early subcomponent of HFOs was not changed after real HD-tDCS and after sham HD-tDCS (Fig. 4.3C). The mixed-model ANOVA showed no main effect of 'time' and no interaction between the factor 'time' and the factors 'group' or 'side'.

In contrast, the magnitude of the late subcomponent of HFOs was, on average, increased after HD-tDCS but not after sham HD-tDCS. This was confirmed by the results of the mixed-model ANOVA, which showed a significant interaction between the factors 'time' and 'group' ($F_{(1,26)} = 7.03$; $p = .013$; Table 4.1). In the HD-tDCS group, although the increase in HFOs magnitude was, on average, more pronounced for stimuli delivered to the contralateral hand as compared to the ipsilateral hand, the within-subject ANOVA showed a main effect of 'time' ($F_{(1,13)} = 6.45$; $p = .025$), but no significant 'time' × 'side' interaction ($F_{(1,13)} = 3.82$; $p = .072$; Table 4.2). In the sham group, the within-subject ANOVA showed no significant changes in HFOs magnitude (Table 4.3).

3.4. ERPs elicited by non-nociceptive vibrotactile stimulation of the hand dorsum

Non-nociceptive vibrotactile stimuli delivered to the index fingertip elicited a consistent negative-positive potential (N120, P250) maximal at the scalp vertex in each participant and condition (Fig. 4.2).

After real HD-tDCS, the magnitude of the N120 wave was, on average, reduced after stimulation of the hand contralateral to the sensorimotor cortex onto which HD-tDCS was applied, but not after stimulation of the ipsilateral hand. After sham HD-tDCS, the magnitude of the N120 wave was virtually unchanged. This differential effect of real HD-tDCS on the magnitude of the N120 waves elicited by vibrotactile stimulation of the contralateral and ipsilateral hands was confirmed by the results of the mixed-model ANOVA which revealed a significant three-way interaction between the factors 'group', 'time' and 'side' ($F_{(1,26)} = 7.35$; $p = .012$). In the HD-tDCS group, the within-subject ANOVA showed a significant 'time' × 'side' interaction ($F_{(1,13)} = 11.03$; $p = .006$), and post-hoc comparison showed that the magnitude of the N120 elicited by stimulation of the contralateral hand was significantly reduced after HD-tDCS (-3.1 ± 3.3 μV; $t = 3.46$; $p = .004$), whereas the magnitude of the N120 elicited by stimulation of the ipsilateral hand was not (-0.1 ± 3.5 μV; $t = .113$; $p = .912$). In the sham group, the within-subject ANOVA showed no significant changes in N120 magnitude (Table 4.3).

Contrasting with the selective effect of real HD-tDCS on the magnitude of the N120 elicited by stimulation of the contralateral hand, the magnitude of the later P250 was, on average, slightly reduced at both hands, both after real HD-tDCS and sham HD-tDCS. This was corroborated by the results of the mixed-model ANOVA, which showed a main effect of 'time' ($F_{(1,26)} = 4.76$; $p = .038$), and no interaction between the factor 'time' and the factors 'group' or 'side' (Table 4.1; Fig. 4.5).

The latency of the N120 and P250 were not significantly affected after real or sham HD-tDCS (Fig. 4.5).

3.5. ERPs elicited by nociceptive laser stimulation

Nociceptive laser stimuli delivered to the hand dorsum elicited a consistent negative-positive complex maximal at the scalp vertex (N240-P350) in each participant and each condition. This complex was preceded by an earlier N160 wave, maximal at central-temporal regions contralateral to the stimulated hand (Fig. 4.2).

After real HD-tDCS, the magnitude of the N240 was, on average, markedly reduced both for stimuli delivered to the ipsilateral hand and for stimuli delivered to the contralateral hand. In contrast, the magnitude of the N240 was virtually unchanged after sham HD-tDCS (Fig. 4.2; Table 4.4). This symmetric reduction of the N240 in the HD-tDCS group was confirmed by the results of the mixed-model ANOVA, showing a significant interaction between the factors 'group' and 'time' ($F_{(1,26)} = 6.06$; $p = .021$). The within-subject ANOVAs confirmed a main effect of 'time' in the HD-tDCS experiment ($F_{(1,13)} = 13.2$; $p = .003$), and the lack of effect of 'time' in the sham experiment ($F_{(1,13)} = 1.0$; $p = .336$).

Contrasting with this specific but symmetric effect of HD-tDCS on the magnitude of the N240 wave, the magnitudes of the N160 and P350 waves were, on average, reduced both after real HD-tDCS and after sham HD-tDCS, in a symmetric fashion. The mixed-model ANOVAs revealed a main effect of 'time' (N160: $F_{(1,26)} = 8.33$; $p = .008$; P350: $F_{(1,26)} = 21.9$; $p < .001$) and no interaction between the factor 'time' and the factors 'group' or 'side' (Table 4.1).

The mixed-model ANOVA showed a marginal interaction between the factors 'time' and 'side' on the latency of the N240 wave ($F_{(1,26)} = 4.61$; $p = .041$). However, the within-subject ANOVAs showed no significant differences in N240 latencies, both in the HD-tDCS experiment and in the sham experiment (respectively Table 4.2 and 4.3). There was no significant effect of real or sham HD-tDCS on the latencies of the N160 and P350 (Fig. 4.5).

		HD-tDCS experiment				sham experiment			
		contralateral hand		ipsilateral hand		contralateral hand		ipsilateral hand	
		before	after	before	after	before	after	before	after
		Non-nociceptive stimulation							
N20	amplitude (µV)	-2.47±1.76	-2.15±1.52	-2.30±1.42	-2.58±1.12	-2.14±0.95	-2.06±1.13	-2.36±0.92	-2.48±1.26
	latency (ms)	19.3±1.5	19.6±1.3	19.5±1.3	19.5±1.0	19.2±0.5	19.1±0.6	19.1±0.7	19.2±0.7
N120	amplitude (µV)	-9.92±4.94	-6.85±4.51	-8.70±5.12	-8.60±3.62	-6.17±4.48	-6.08±4.64	-5.98±3.89	-4.90±5.35
	latency (ms)	130±7	131±9	130±11	135±9	124±15	126±12	125±14	127±14
P250	amplitude (µV)	16.7±6.56	15.2±5.23	16.2±5.55	15.5±5.14	17.1±5.78	15.9±5.68	17.5±5.26	16.3±5.26
	latency (ms)	233±44	248±45	247±43	247±40	258±56	265±49	244±47	276±43
HFOs	early component (µV.ms)	0.130±0.064	0.137±0.062	0.100±0.040	0.109±0.039	0.121±0.045	0.117±0.047	0.118±0.049	0.124±0.023
	late component (µV.ms)	0.106±0.055	0.135±0.068	0.115±0.064	0.118±0.044	0.092±0.027	0.090±0.021	0.109±0.032	0.099±0.033
Intensity of perception (NRS)		2.8±1.7	2.6±1.6	2.8±1.6	2.6±1.5	2.6±1.1	2.8±1.3	2.8±1.3	2.8±1.2
		Nociceptive stimulation							
N160	amplitude (µV)	-9.29±6.27	-6.73±4.42	-9.46±8.83	-6.67±5.42	-5.96±4.34	-5.07±3.47	-6.68±5.75	-5.23±5.78
	latency (ms)	175±20	178±16	176±20	182±21	179±28	188±25	182±29	184±25
N240	amplitude (µV)	-19.7±12.7	-14.0±10.1	-20.6±15.6	-13.3±10.3	-13.2±10.3	-12.0±9.67	-12.5±8.60	-11.3±9.81
	latency (ms)	219±21	219±19	208±24	222±26	224±21	215±28	223±21	226±27
P350	amplitude (µV)	21.7±11.02	16.0±11.92	21.3±11.66	15.9±14.00	15.6±9.67	13.0±7.04	17.8±8.65	11.6±6.99
	latency (ms)	326±31	326±34	325±33	339±41	344±44	352±53	341±43	337±48
Intensity of perception (NRS)		4.4±1.8	3.9±2.1	4.5±1.7	3.8±2.2	3.8±1.3	3.7±1.4	3.9±1.1	3.6±1.3

Table 4.4. ERP magnitude, ERP latency, HFO amplitude, and intensity of perception before and after real or sham HD-tDCS following stimulation of ipsilateral or contralateral hand. Values are group-level average (±SD) ERP magnitude, ERP latency, HFO amplitude, and intensity of perception [numerical rating scale (NRS) extending between 0 and 10] obtained before and after real or sham HD-tDCS following stimulation of ipsilateral or contralateral hand.

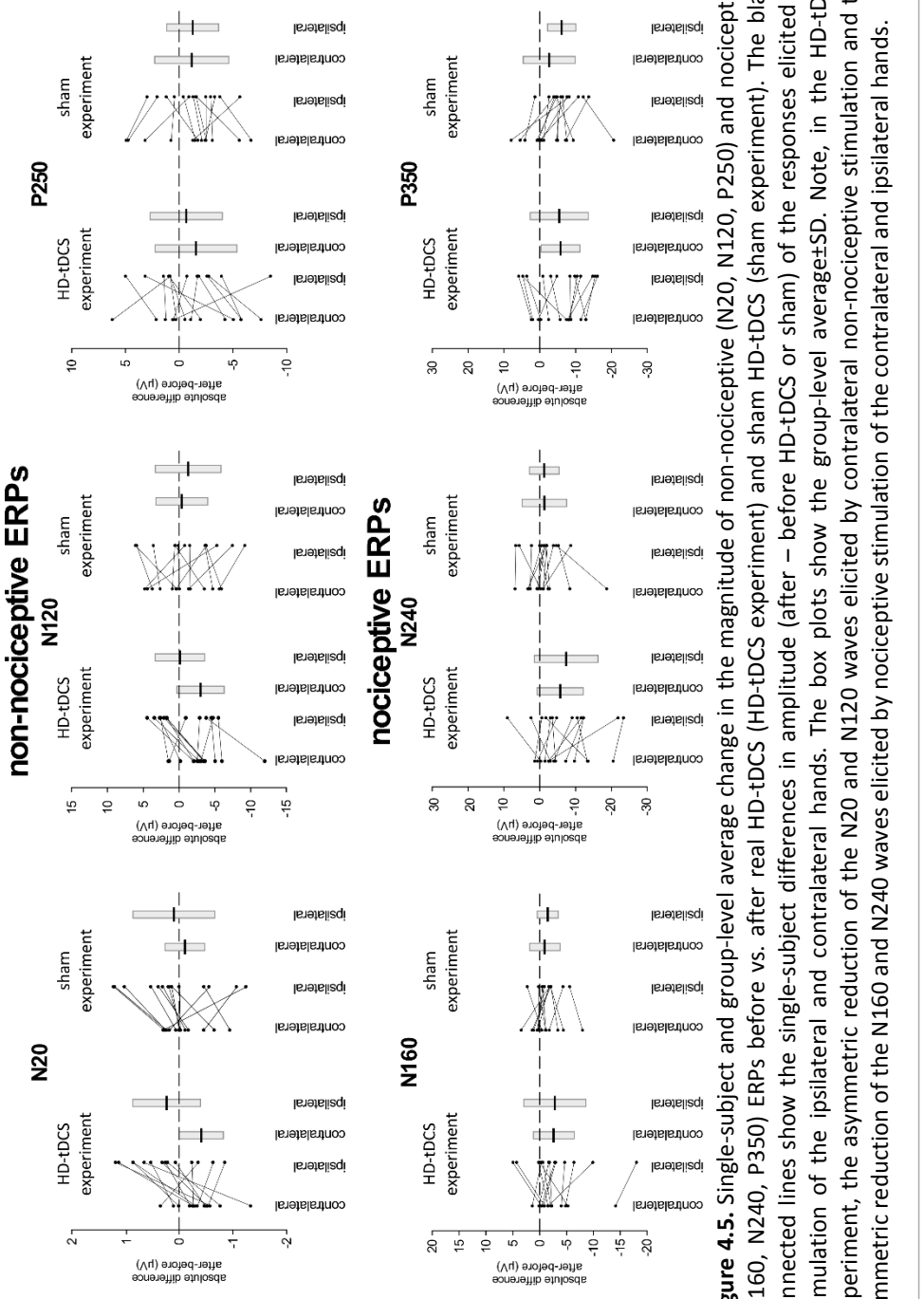


Figure 4.5. Single-subject and group-level average change in the magnitude of non-nociceptive (N20, N120, P250) and nociceptive (N160, N240, P350) ERPs before vs. after real HD-tDCS (HD-tDCS experiment) and sham HD-tDCS (sham experiment). The black connected lines show the single-subject differences in amplitude (after – before HD-tDCS or sham) of the responses elicited by stimulation of the ipsilateral and contralateral hands. The box plots show the group-level average±SD. Note, in the HD-tDCS experiment, the asymmetric reduction of the N20 and N120 waves elicited by contralateral non-nociceptive stimulation and the symmetric reduction of the N160 and N240 waves elicited by nociceptive stimulation of the contralateral and ipsilateral hands.

4. Discussion

Our results show that cathodal HD-tDCS applied over the hand area of the primary sensorimotor cortex exerts a different effect on the cortical processing of non-nociceptive and nociceptive somatosensory input in humans. Specifically, cathodal HD-tDCS significantly affected the responses to non-nociceptive stimuli delivered to the hand contralateral to the sensorimotor cortex onto which HD-tDCS was applied, as demonstrated by the reduced magnitude and increased latency of the N20 wave elicited by electrical stimulation of the contralateral median nerve, and the reduced magnitude of the later-latency N120 wave elicited by vibrotactile stimulation of the contralateral hand dorsum. In contrast, cathodal HD-tDCS of the sensorimotor cortex induced a symmetric effect on the responses to nociceptive stimuli. Rather than reducing the responses elicited by stimulation of the

contralateral hand, HD-tDCS led to a symmetric reduction of the N240 wave which was, at least in part, due to a true neuromodulatory effect of HD-tDCS as it was not observed after sham HD-tDCS.

4.1. HD-tDCS of the sensorimotor cortex decreases the responsiveness of S1

After cathodal HD-tDCS, the magnitude of the N20 wave elicited by stimuli delivered to the contralateral hand was significantly reduced as compared to the N20 wave elicited by stimuli delivered to the ipsilateral hand. This finding is consistent with the results of a previous study showing that cathodal tDCS over the sensorimotor cortex results in a reduction of magnitude of the N20 wave (Dieckhöfer *et al.*, 2006). Considering that the N20 wave originates from Brodmann area 3b of S1 and that it constitutes the earliest measurable cortical response to non-nociceptive somatosensory input (Hari *et al.*, 1984; Wood *et al.*, 1985; Allison *et al.*, 1989a; Hari & Forss, 1999; Valeriani *et al.*, 2000; Valeriani *et al.*, 2004), our finding demonstrates that cathodal HD-tDCS delivered over the sensorimotor cortex significantly reduces the responsiveness of S1 to thalamocortical input ascending within the lemniscal pathways.

Further supporting the fact that HD-tDCS exerted an inhibitory effect on S1 was the finding that the latency of the N20 wave elicited by stimulation of the contralateral hand was significantly increased after cathodal HD-tDCS. Because it seems unlikely that HD-tDCS exerts an effect on the time required for somatosensory afferent volleys to reach the cortex, a possible explanation for the increased latency of the N20 peak is that, due to the reduced responsiveness of S1 neurons, generation of the postsynaptic cortical activity leading to the N20 wave required accumulating more afferent input over time. This postsynaptic interpretation is also supported by our finding that HD-tDCS did not modulate early-latency HFOs thought to predominantly reflect synchronized action potentials ascending the thalamocortical projections to S1 (Hashimoto *et al.*, 1996; Curio *et al.*, 1997; Ozaki & Hashimoto, 2011; Restuccia *et al.*, 2011).

Cathodal HD-tDCS tended to exert an opposite, excitatory effect on the responsiveness of the contralateral S1. Indeed, whereas the magnitude of the N20 wave elicited by stimulation of the contralateral hand was significantly decreased after HD-tDCS, the magnitude of the N20 wave elicited by stimulation of the ipsilateral hand tended to increase (Fig. 4.2). Because the four return anode electrodes were located immediately adjacent to the cathode electrode, this opposite effect of HD-tDCS on the responsiveness of the contralateral S1 cannot be explained by an anodal stimulation of the contralateral hemisphere. One possibility could be that it resulted from inter-hemispheric inhibitory interactions between the left and right sensorimotor cortices (Mochizuki *et al.*, 2007; Ragert *et al.*, 2011; Brodie *et al.*, 2014): applying cathodal HD-tDCS on the sensorimotor cortex could lead to a reduced inter-hemispheric inhibitory drive towards the contralateral homotopic sensorimotor cortex.

Finally, cathodal HD-tDCS led to a significant increase of the late-latency HFOs immediately following the N20 wave, and this enhancement was more pronounced for the responses elicited by stimulation of the contralateral median nerve (Fig. 4.3C). Although this constitutes further evidence that HD-tDCS modulated the state of S1, further studies are needed to understand why HD-tDCS reduced the magnitude of the N20 wave but tended to increase the magnitude of late-latency HFOs. Nevertheless, the genuineness of our results is supported by several previous studies showing that various experimental manipulations can lead to dissociated effects on the

N20 wave and HFOs (Gobbele *et al.*, 2003; Ogawa *et al.*, 2004; Katayama *et al.*, 2010). Although it is generally assumed that cathodal tDCS decreases cortical responsiveness because it hyperpolarizes the stimulated neurons (Nitsche & Paulus, 2000; Nitsche *et al.*, 2008; Datta *et al.*, 2009), Rahman *et al.* (2013) recently suggested that, during tDCS, different cellular elements can become hyperpolarized or depolarized in any given brain region. Such variable effects could be an explanation for the differential effect of HD-tDCS on the magnitude of the N20 wave and that of late-latency HFOs.

4.2. S1 is an obligatory relay for the higher-order cortical processing of tactile input

Cathodal HD-tDCS delivered over the sensorimotor cortex did not only reduce the early-latency responses to tactile stimuli originating from within S1. Indeed, cathodal HD-tDCS also affected later brain responses to vibrotactile stimulation of the contralateral hand, specifically, the N120 wave which is thought to predominantly reflect later stages of cortical processing within the left and right operculo-insular cortex and the cingulate cortex (Allison *et al.*, 1989b; Allison *et al.*, 1992; Kunde & Treede, 1993; Garcia-Larrea *et al.*, 1995; Mouraux *et al.*, 2013; Hu *et al.*, 2015). Because there was no reduction of the N120 wave elicited by vibrotactile stimuli delivered to the ipsilateral hand, and no reduction of the N120 wave after sham HD-tDCS in the sham experiment, this finding suggests that late responses to tactile stimuli originating from outside S1 are dependent on the state of S1. In other words, this finding provides support for a serial processing of tactile input from the thalamus to S1 and from S1 to other brain areas such as the operculo-insular cortex and the cingulate cortex. This interpretation is also supported by the observation of Pons *et al.* (1992), showing that the responses in S2 to tactile stimuli delivered to the hand of Rhesus monkeys are reduced after lesions of the S1 hand area. However, we cannot exclude that the modulation of the N120 wave observed after HD-tDCS resulted from a neuromodulatory effect of HD-tDCS on other brain regions located close to S1, such as S2 or M1 (see following Section 4.3).

4.3. Bilateral effect of HD-tDCS on nociceptive processing vs. response habituation

Both the nociceptive ERPs elicited by stimulation of the contralateral hand and the nociceptive ERPs elicited by stimulation of the ipsilateral hand were reduced after cathodal HD-tDCS of the left or right sensorimotor cortex. To examine whether this symmetric reduction of amplitude was due to a neuromodulatory effect of HD-tDCS or to unrelated time-dependent effects such as response habituation (Greffrath *et al.*, 2007) or decreased vigilance (Miltner *et al.*, 1989; Garcia-Larrea *et al.*, 1997; Legrain *et al.*, 2002), we conducted a second experiment in which participants received sham HD-tDCS over the left or right sensorimotor cortex. The reduction of the N240 was present only after real HD-tDCS, indicating that this effect was not merely the consequence of habituation or decreased vigilance. In contrast, the magnitude of the earlier N160 wave and the later P350 wave were similarly reduced after real HD-tDCS and after sham HD-tDCS, suggesting that they could, at least in part, be due to habituation or decreased vigilance.

It seems unlikely that the bilateral effect of HD-tDCS on the N240 waves of nociceptive ERPs could be explained by a change in the responsiveness of S1 to ascending nociceptive input, as such a change would be expected to preferentially affect the responses to nociceptive input originating from the contralateral hemibody. Considering

the size of the electric field generated by the HD-tDCS montage, it is likely that the effects of HD-tDCS were not restricted to S1, but also extended to nearby areas such as M1 and S2. Furthermore, HD-tDCS can be expected to not only affect the targeted area, but also remote areas having strong connections with the targeted area (Rahman *et al.*, 2013). The bilateral effect of HD-tDCS on the N240 wave of nociceptive ERPs could thus be due, at least in part, to an indirect modulation of other brain areas (Tamura *et al.*, 2004b; Lefaucheur *et al.*, 2006; Antal & Paulus, 2010; Mylius *et al.*, 2012a). One possibility could be that the bilateral reduction of the N240 resulted from an effect of HD-tDCS on S2 or the highly-connected insular and cingulate cortices, as these areas are thought to be the main sources of the N240, and are known to respond to nociceptive stimuli delivered to both the ipsilateral and contralateral hemibody (Tarkka & Treede, 1993; Kakigi *et al.*, 1995; Valeriani *et al.*, 1996; Chen *et al.*, 1998; Kanda *et al.*, 2000; Valeriani *et al.*, 2000; Frot & Mauguiere, 2003; Garcia-Larrea *et al.*, 2003; Vogel *et al.*, 2003).

Garcia-Larrea et al. showed using PET that direct electrical epidural stimulation of M1 (a procedure sometimes used for the treatment of intractable chronic pain) induces a significant increase in cerebral blood flow in the ipsilateral thalamus, the anterior cingulate and orbitofrontal cortex, the insula and the upper brainstem (Garcia-Larrea *et al.*, 1999). This has led some authors to propose that the rTMS or tDCS delivered over the sensorimotor cortex may activate descending inhibitory control mechanisms acting on the spinal transmission of ascending nociceptive inputs (Garcia-Larrea & Peyron, 2007). This hypothesis, which is also supported by the results of Onesti *et al.* (2013) showing that rTMS delivered over the lower limb representation of M1 in patients suffering from diabetic neuropathic pain leads to a reduction of the spinal nociceptive withdrawal reflex (RIII), could also explain our finding that cathodal HD-tDCS leads to a symmetric reduction of the N240 waves of laser-evoked potentials.

In addition to reducing the magnitude of the N240 of both hands, HD-tDCS also appeared to reduce the intensity of the percept elicited by laser stimulation of both hands, and this decrease was, on average, more pronounced after real HD-tDCS as compared to sham HD-tDCS. This symmetric effect on pain perception contrasts with the results of some previous studies suggesting that tDCS exerts a stronger effect on the responses elicited by nociceptive stimulation of the contralateral hand (Antal *et al.*, 2008; Csifcsak *et al.*, 2009a). However, these studies did not compare directly the responses elicited by stimulation of the ipsilateral and contralateral hands. Furthermore, several previous studies have shown that rTMS or tDCS delivered over the sensorimotor cortex induces a bilateral reduction of pain perception in healthy volunteers (Poreisz *et al.*, 2008b; Terney *et al.*, 2008; Nahmias *et al.*, 2009).

4.4. S1 is differentially involved in processing non-nociceptive and nociceptive inputs

Regardless of the mechanism explaining the bilateral and symmetric reduction of nociceptive ERPs after HD-tDCS delivered over the sensorimotor cortex, our finding that cathodal HD-tDCS exerts a clearly lateralized effect on the responses to tactile input originating from the contralateral hand, but does not exert any lateralized effect on the responses to nociceptive input, indicates that S1 is not similarly involved in the processing of non-nociceptive and nociceptive inputs. Considering that the early-latency N160 wave of nociceptive ERPs is thought

to reflect, at least in part, activity originating from the contralateral S1, one may wonder why HD-tDCS did not induce a lateralized reduction of the N160, similar to the lateralized reduction of the N20 and N120 elicited by non-nociceptive stimulation. This lack of a lateralized effect suggests that HD-tDCS over the sensorimotor cortex does not similarly affect the ability of S1 to respond to nociceptive and non-nociceptive somatosensory inputs. It has been suggested that area 3b of S1 constitutes the primary target of vibrotactile input, whereas nociceptive input predominantly elicits responses in areas 1 and 2 (Bushnell *et al.*, 1999; Valeriani *et al.*, 2004; Whitsel *et al.*, 2009; Vierck *et al.*, 2013). Differences in the orientation of the cortical surface of the different sub-regions of S1, being more radial or tangential to the scalp surface, could lead to differential effects of HD-tDCS. Modelling studies have shown that, even directly under the stimulating electrode, tDCS predominantly produces currents that are tangential to the scalp surface, and studies on the effects of direct current stimulation of cortical slices have suggested that the after-effects of tDCS mainly result from changes in the synaptic efficacy of pyramidal neurons whose somatodendritic axis is parallel to the current flow (Rahman *et al.*, 2013).

4.5. Study limitations

A first limitation of our study is the lack of behavioural evidence that HD-tDCS over the sensorimotor cortex modulated the perception of vibrotactile stimuli delivered to the contralateral hand. However, this was also the case in previous studies assessing the effect of cathodal tDCS or TBS over S1 (Grundmann *et al.*, 2011; Torta *et al.*, 2013), and could be related to the fact that subjective reports of the intensity of perception elicited by brief variations of constant amplitude are not a sensitive mean to assess tactile discrimination performance (Tame & Holmes, 2016). Future studies should examine whether changes in vibrotaction induced by HD-tDCS over S1 can be identified using more sensitive tasks to assess intensity, frequency or spatial discrimination abilities (Rogalewski *et al.*, 2004; Morley *et al.*, 2007).

A second limitation of our study is that the mixed-model ANOVA conducted to compare directly the effects of real HD-tDCS vs. sham HD-tDCS on the magnitude of the N20 wave elicited by electrical stimulation of the median nerve revealed a significant interaction between the factors ‘time’ (before vs. after HD-tDCS) and ‘side’ (somatosensory stimuli delivered to the ipsilateral vs. contralateral hand), but no interaction with the factor group (real vs. sham HD-tDCS). This suggests that, even though the lateralized reduction in N20 magnitude was clearly more pronounced after real HD-tDCS, a lateralized reduction might also have been present after sham HD-tDCS. This raises the question as to whether HD-tDCS delivered during 110 seconds (40 s ramp-up from 0 to 1 mA, 30 s plateau at 1 mA, 40 s ramp-down from 1 to 0 mA), which is commonly used as a sham condition (Nitsche *et al.*, 2008; Tanaka *et al.*, 2009), might actually exert a slight neuromodulatory effect.

Finally, because nociceptive laser stimuli were delivered to the hand dorsum and non-nociceptive vibrotactile were delivered to the index fingertip, one should consider whether slight differences in the somatotopic representation of the hand dorsum and index fingertip could have explained the differential effects of HD-tDCS on nociceptive and vibrotactile ERPs. Source analysis studies using MEG (Omori *et al.*, 2013) and high-resolution functional MRI studies (Nelson & Chen, 2008) indicate that the distance between the S1 response to nociceptive stimuli delivered to the hand dorsum and vibrotactile stimuli delivered to the index fingertip is below 1 cm, i.e.

well below the focus of the HD-tDCS montage used in the present study, which is thought to generate an electric field having a grossly approximate radius of 5 cm. More importantly, considering interindividual variations in anatomy and the fact that the position of the electrodes was defined based on standard scalp locations, slight differences in the location of the cortical patches processing hand dorsum vs. fingertip input cannot be expected to result in a differential effect of HD-tDCS that was consistent across individuals.

5. Conclusion

We show that cathodal HD-tDCS delivered over the hand area of the sensorimotor cortex clearly affects the responses to tactile input originating from the contralateral hand in a lateralized fashion, whereas it affects the responses to nociceptive input in a symmetric fashion. Taken together, these results demonstrate, in humans, a differential involvement of S1 in vibrotaction and nociception.

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