EJP
European Journal of Pain

ORIGINAL ARTICLE

The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: An evoked potentials and quantitative thermal testing study

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Funding sources
This work was supported in part by grants from the Foundation La Marató TV3 (110930 and 110932) and (grants 071930, 071931 and 070210) and grants (PI082004 and PI10/00442) from the Instituto de Salud Carlos III and grants from the Cátedra BBVA (CAT06/023).

Conflicts of interest
The authors do not have any conflicts of interest.

Accepted for publication
19 April 2012

doi:10.1002/j.1532-2149.2012.00167.x

Abstract

Background: Neuropathic pain (NP) is common in spinal cord injury (SCI) patients. One of its manifestations is a lowering of pain perception threshold in quantitative thermal testing (QTT) in dermatomes rostral to the injury level. Transcranial direct current stimulation (tDCS) combined with visual illusion (VI) improves pain in SCI patients. We studied whether pain relief with tDCS + VI intervention is accompanied by a change in contact heat- evoked potentials (CHEPs) or in QTT.
Methods: We examined 18 patients with SCI and NP before and after 2 weeks of daily tDCS + VI intervention. Twenty SCI patients without NP and 14 healthy subjects served as controls. We assessed NP intensity using a numerical rating scale (NRS) and determined heat and pain thresholds with thermal probes. CHEPs were recorded to stimuli applied at C4 level, and subjects rated their perception of evoked pain using NRS during CHEPs.
Results: Thirteen patients reported a mean decrease of 50% in the NRS for NP after tDCS + VI. Evoked pain perception was significantly higher than in the other two groups, and reduced significantly together with CHEPs amplitude after tDCS + VI with respect to baseline. Pain perception threshold was significantly lower than in the other two groups before tDCS + VI intervention, and increased significantly afterwards.
Conclusion: Two weeks of tDCS + VI induced significant changes in CHEPs, evoked pain and heat pain threshold in SCI patients with NP. These neurophysiological tests might be objective biomarkers of treatment effects for NP in patients with SCI.

1. Introduction

About 50% of subjects with spinal cord injury (SCI) suffer from neuropathic pain (NP) (Siddall et al., 2003; Soler et al., 2007). Although this represents a major burden for the subjects, the pathophysiological mechanisms mediating NP in SCI are poorly understood (Siddall et al., 2003; Yezierski, 2005; Soler et al., 2007; Wasner et al., 2008). A number of processes may be responsible for NP, possibly involving different mechanisms (Woolf et al., 1998; Woolf and Salter, 2000). Evidence exists suggesting involvement of primary somatosensory cortex (S1) reorganization, supported, e.g., by studies that reveal a correlation between S1 plasticity and pain intensity in SCI subjects (Wrigley et al., 2009). Theoretically, modulating cortical activity might result in reduction of pain. Supporting such a hypothesis, several proof-of-principle trials have reported significant improvement in the severity of NP in subjects with SCI after transcranial direct current stimulation (tDCS) or experiencing movement with virtual illusion (VI; Fregni et al.,

What's already known about this topic?
- The transcranial direct current stimulation (tDCS) with visual illusion (VI) can improve neuropathic pain in severe spinal cord injury.
- Assessment of quantitative thermal testing (QTT) and contact heat-evoked potentials (CHEPs) allow for a more objective method of evaluation of neuropathic pain pathway.

What does this study add?
- This study shows effect of treatment (tDCS with VI) in neuropathic pain in SCI and on the neurophysiological examination. It shows relation between changes in pain perception and evoked pain perception.

2006; Moseley, 2007). In a recent study, we found that tDCS combined with VI led to greater and more sustained analgesic effect than any one intervention separately or sham control (Soler et al., 2010).

Assessment of pain thresholds with quantitative thermal testing (QTT) reflects the function of C- and Aδ fibres (Verdugo and Ochoa, 1992; Cohen et al., 1996; Arendt-Nielsen and Chen, 2001; Truini et al., 2007; Casanova-Molla et al., 2011). The study of contact heat-evoked potentials (CHEPs) allows for a more objective method of evaluation of small fibre function. Nociceptive evoked potentials have been used for the study of various pain syndromes (Truini et al., 2007; Casanova-Molla et al., 2011; Kumru et al., 2011). Evoked pain produced by thermal stimuli is a common characteristic of central pain syndrome (CPS; Vestergaard et al., 1995; Finnerup et al., 2003; Kumru et al., 2011). CPS is most commonly expressed with hyperalgesia below and at the level of the spinal lesion and only rarely in spinal segments above the lesion in animals (Masri et al., 2009) and in humans (Cohen et al., 1996; Kumru et al., 2011). The hypothesis of the study was that the abnormally enhanced CHEPs amplitude and threshold changes in QTT ratings at dermatomes rostral to the injury level could normalize in those subjects who report improvement with the combined tDCS and VI intervention. We also investigated whether these measures correlate with the subjective rating of alleviation of NP.

2. Subjects and methods

We studied 18 SCI subjects with NP (SCI-NP). To compare CHEPs and QTT of those subjects with NP at baseline and to study whether clinical improvement in NP with effective treatment can induce changes in CHEPs and QTT, 20 subjects with SCI without NP (SCI-noNP) and 14 healthy subjects served as a control groups. The inclusion criteria for SCI subjects with NP were (1) age above 18 years; (2) cervical or thoracic complete or incomplete SCI (classified according to the American Spinal Injury Association 'ASIA' Impairment Scale; Marino et al., 2003); (3) preserved sensory perception at C4 level (most rostral lesion level at C5, according to ASIA; Marino et al., 2003); (4) NP of more than 3 months duration, with pain intensity higher than 4 on a numerical rating scale (NRS); and (5) stable medication for at least 3 weeks immediately prior to testing. Inclusion criteria for SCI subjects without NP were the same except that they experienced no pain (including spasm- and movement-related pain) at or below the neurological level of the lesion since time of injury. Healthy control subjects were required to be free of any chronic or acute pain conditions, to have had normal medical and neurological history and examinations, and to be taking no medication.

Pain was considered to be neuropathic if it involved an area of sensory abnormality consistent with the expected consequences of the spinal cord lesion. At injury level, NP was defined as sensation of burning, stabbing or electrical quality, located in the dermatomes at or just above the level of injury. Below-level NP was defined as burning, stabbing or shooting pain located diffusely at least two dermatomes below the SCI level (Siddall et al., 2003). Pain was considered only if onset occurred after the SCI and had no primary relation to spasms or other movement. Subjects with severe pain of other origin, e.g., musculoskeletal pain, were excluded.

Exclusion criteria were head trauma and other chronic medical conditions or which tDCS is relatively contraindicated, such as pregnancy or epilepsy (Rossi et al., 2009). We also excluded subjects with moderate or severe depression (Beck Depression Inventory with more than 14 points), which could have an effect on performance of the VI task (Soler et al., 2010). The study was reviewed and approved by our institution's review board, and all subjects or their representatives gave written informed consent.

2.1 Clinical evaluation of NP

All subjects underwent an interview to assess clinical and phenomenological characteristics of the pain: localization, descriptive characteristics and intensity. To evaluate average pain intensity perception over the previous 24 h, NRS (ranging from 0 = no pain to

10 = unbearable pain; NRS ongoing pain) was used. Subjects were asked to rate pain indicating the number that best described their average pain over the previous 24 h from 0 (no pain) to 10 (unbearable pain). Ongoing pain score (overall pain intensity perception) was registered before intervention (baseline) and at day 14 (last day) of intervention. We noted the descriptors that subjects used for their NP (Bouhassira et al., 2004). All clinical evaluations and measurements of NP were performed by the same researcher (D.S.). All tDCS + VI interventions were carried out by a clinical psychologist.

2.2 CHEPs

Thermal stimuli were delivered using Pathway (Medoc, Ramat Yishai, Israel), equipped with a fast-heating/fast-cooling probe of 5.7 cm^2 surface area. Stimuli were delivered at the fastest available ramp rate of 70 °C/s from a baseline temperature of 32 °C. Cut-off temperature was 51 °C. We set the peak temperature to deliver a stimulus experienced as pricking pain (thermodePS). A total of 10 stimuli were applied with an interstimulus time interval of 30 s and at a slightly different spot within a squared area of about 5 × 5 cm, in order to reduce receptor fatigue or sensitization by overheating of the skin.

CHEPs were recorded through pairs of 9 mm Ag/AgCl surface disc electrodes filled with conductive adhesive gel. The active electrode was placed on Cz and referenced to linked ears (A1-A2), where pain-related evoked potentials are maximal, with a ground placed on the right arm. Analysis time was 1 s. Amplifier bandpass frequency filter was 0.1 Hz to 50 Hz. Gain was 50 μV/division. Impedance was kept less than 5 kOhm. CHEPs were recorded using routine electrodiagnostic equipment (Medelec Synergy, Oxford Instruments; Surrey, England). Data were collected with a sampling rate of 1000 Hz using the BrainAmp system (Brain Products GmbH, Munich, Germany) and analysed off-line. For each SCI subject with NP, we recorded CHEPs stimulating at the C4 ASIA sensory point on the contralateral side to application of anodal tDCS (Soler et al., 2010), and in SCI subjects without NP and healthy subjects on the dominant hand side.

2.3 Evoked heat pain perception

For each patient, we recorded the NRS for their subjective evoked pain perception using the NRS (ranging from 0 = no pain to 10 = unbearable pain; NRS evoked pain) following each of the 10 evoked potential recordings (see above).

2.4 QTT: warm and heat pain threshold

Subjects were examined in the seated position in a quiet room. Stimuli were applied at two levels (above and at lesion level) on both sides of the body (total of four ASIA sensory points; Marino et al., 2003). For the site above lesion, we selected a sensory area dependent on C4 around the acromioclavicular joint because all our SCI subjects had lesions caudal to C4 (Kumru et al., 2011), and we found other sites above level to be unsuitable (C2 has a small innervation zone that does not allow for convenient thermode placement, and some subjects had scars after surgical intervention in C3 innervated areas). We did not consider the face because of brainstem innervation. The level of the lesion varied among individuals, so that the sensory points evaluated at the level of lesion varied between C4-T12.

Warm perception and heat pain perception threshold were measured with a Medoc Thermal Sensory Analyser (Pathway; Medoc, Ramat Yishai, Israel) equipped with a 5.7 cm^2 probe, using the method of limits. Subjects were required to stop the progressive stimulus intensity increase by pressing a button as soon as they perceived the specific thermal modality being tested (four stimuli for warm sensation and four stimuli for heat pain). In those subjects with cervical lesions who were unable to use their hands, the button was placed under the wrist (one SCI-NP patient and one SCI subject without NP). The stimuli started at an adaptation temperature of 32 °C and increased at a rate of 1 °C/s. Cut-off temperature was 51 °C. Thresholds of warm and heat pain perception were taken as the average of four successive readings in each session.

2.5 Experimental procedure

All patients underwent the following tests: (1) clinical evaluation of NP; (2) psychophysical study of warm and heat pain threshold; (3) recording CHEPs to thermal stimulation,; and (4) evoked pain perception measured by NRS after each recording of CHEPs. Patients with NP then submitted to the tDSC + VI intervention for 2 weeks (10 sessions). All patients underwent a second clinical, psychophysical and neurophysiological re-evaluation after the last session of tDSC + VI. Subjects without NP and healthy subjects were evaluated only once.

Neurophysiological and psychophysical evaluations were carried out by an independent examiner (H.K.), who was unaware of the results of the clinical evaluation. The subjects studied were blinded to the aim of

the study. All evaluations were carried out in the morning with subjects lying in a relaxed supine position in a warm and dimly lit room.

2.6 tDCS + VI intervention

2.6.1 tDCS

Direct current was delivered with a battery-driven constant current stimulator (NeuroConn-GmbH, Ilmenau, Germany) by saline-soaked surface sponge electrodes (35 cm^2). SCI subjects received anodal stimulation over the primary motor cortex (M1). For stimulation, the anode was placed over C3 or C4 (EEG 10/20 system) and the cathode over the contralateral supraorbital area. For subjects with asymmetric pain, stimulation was applied to the contralateral M1 to the NP side, and for subjects with symmetric pain, the dominant hemisphere was stimulated. A constant current of 2 mA intensity (subthreshold intensity) was applied for 20 min (Fregni et al., 2006; Soler et al., 2010). The choice of stimulation sites and stimulation parameters was based on previous studies showing effective improvement of NP in SCI subjects (Fregni et al., 2006; Soler et al., 2010).

2.6.2 VI

While receiving tDCS, subjects were seated either in a wheelchair or a normal chair (depending on their level of impairment) placed 2.5 m in front of a screen. After 5 min of tDCS, a video was played on a portable computer in front of the patient. The video showed the legs of a man or a woman, matching the gender of the patient, walking on a treadmill. The video was continuously played for the remaining 15 min of the tDCS session. In order to induce the experience of realistic gait perception, a vertical mirror (150 cm × 52 cm) was placed in front of the subjects on top of the screen, so that the mirror reflection of the upper part of the patient's own body and the walking legs displayed on the screen were aligned in the most realistic position possible (Moseley, 2007; Soler et al., 2010). The sound of walking shoes synchronized to the walking rhythm of the legs was also played via loudspeakers to enhance the realism of gait perception for the patient.

2.7 Data and statistical analysis

For QTT, we determined the mean threshold values for warm and heat pain perception. QTT data were separated into those from the contralateral side to stimulated hemisphere (CSH) and those from the ipsilateral side to the stimulated hemisphere (ISH). To allow for comparison, in SCI subjects without NP and healthy subjects, data were gathered separately for the dominant hand side (= CSH) and the non-dominant hand side (= ISH).

For CHEPs, we averaged off-line 10 individual recordings for each body side per study subject. We measured the mean latency of relevant peaks (N2 and P2) as the time difference between the stimulus and each of the peaks, and the mean amplitude between the N2 and P2 peaks (N2/P2 amplitude). We calculated the mean and the SD of all variables.

In order to assess changes in ongoing pain and in evoked pain perception, the values obtained after the last tDCS + VI session were expressed as percentage of those at baseline (pre-tDCS + VI). The ≤15% value is considered the confidence interval for the placebo effect of tDCS + VI intervention according to Soler et al. (2010).

To estimate possible habituation in the amplitude of CHEPs and evoked heat pain perception, the habituation rate was calculated as the percentage of the amplitude of the evoked potentials and the score for evoked heat pain perception to the last stimulus with respect to the first stimulus for each subject.

We used one-factor analysis of variance and χ^2 tests for comparison of demographic and clinical data between groups of subjects and healthy controls. Since the distribution of the data was not normal according to the Kolmogorov–Smirnov test, Kruskal–Wallis *H*-test was used for multiple repeated measures comparisons, and Mann–Whitney *t* was used for post hoc comparisons. For paired comparison, Wilcoxon signed rank test was used to compare data from pre- and post-tDCS + VI sessions in subjects with NP. Correlation analyses were carried out using the Pearson's test for comparison of amplitude of CHEPs and demographical, clinical and psychophysical characteristics. Statistical analyses were performed with the SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Significance level was set as $p < 0.05$ with Bonferroni correction for multiple comparisons.

3. Results

Clinical and demographic characteristics of all subjects are given in Tables 1 and 2. No statistically significant differences appeared between groups regarding subjects' age and gender distribution. Mean age was 49.4 ± 12.4 years for SCI-NP subjects; 45.5 ± 11.6 years for SCI-noNP subjects and 45.6 ± 11.7 years for healthy controls. Time lapse since SCI was similar between subjects with and without NP (100 ± 120.3

Table 1 Clinical and demographical characteristics of SCI subjects with and without neuropathic pain.

Age (years)	Sex	Aetiology	Sensory level	ASIA	Months since SCI	Pain location	Description of pain	Ongoing pain	
								Pre	Post
SCI subjects with neuropathic pain									
44	F	non-T	C5	D	48	Arms (at)	Burning, allodynia	8	2
68	F	T	C5	D	12	Leg (below)	Burning, tightness	8	4
40	M	T	C6	B	8	Arms (at-below)	Burning	8	6
30	M	T	C6	C	84	Abdomen (below)	Burning, electrical currents	6	3
50	M	T	C7	D	36	Leg (below)	Burning, tightness, allodynia	6	2
35	M	T	C6	A	36	Arms (at-below)	Burning, tightness	8	4
28	M	T	C7	B	84	Leg (below)	Burning, allodynia	7	6
42	M	non-T	Th11	D	480	Legs (below)	Dysesthesia, paraxysms	8	8
55	M	non-T	Th6	D	96	Legs (below)	Tightness, paraxysms	9	6
40	M	non-T	Th11	B	8	Legs, feet (below)	Paraxysm	8	2
69	F	T	Th10	A	8	Legs (below)	Tightness	8	4
64	M	T	Th12	D	216	Leg (below)	Burning, tightness	8	6
61	M	non-T	Th3	D	216	Abdomen (below)	Burning, tightness	7	3
46	M	non-T	Th6	A	60	Abdomen, leg (at-below)	Tightness	8	5
61	M	non-T	Th3	D	72	Abdomen (below)	Tightness, allodynia	8	8
57	F	non-T	Th9	D	240	Genital area (below)	Burning, tightness, paraxysms	7	6
53	F	non-T	Th2	D	84	Legs, feet (below)	Burning, tightness, allodynia	8	8
47	F	Non-T	Th12	D	12	Genital area, leg (below)	Tightness	10	5
SCI subjects without neuropathic pain									
35	F	T	C6	D	6				
60	M	T	C5	A	8				
49	M	T	C6	B	60				
32	M	T	C7	B	156				
57	M	T	C6	D	12				
62	F	T	C7	D	6				
57	F	non-T	C6	D	4				
57	M	T	Th11	D	260				
34	M	T	Th10	D	84				
63	M	T	Th3	D	180				
48	F	non-T	Th 7	C	8				
44	M	T	Th 6	B	276				
46	M	non-T	Th 6	D	216				
37	F	T	Th 12	B	228				
42	M	T	Th 3	A	228				
39	M	T	Th7	D	30				
25	M	T	Th8	A	90				
44	M	T	Th11	A	144				
27	F	T	Th3	B	96				
52	F	T	Th6	A	216				

M, male; F, female. Aetiology: T, trauma; non-T, no traumatic origin; Neurological level (C, cervical; Th, thoracic); ASIA classification, American Spinal Injury Association Impairment Scale (grade A, B, C, D); NRS, numerical rating scale (0–10).

months vs. 115 ± 98.3 months, respectively; $p = 0.2$). There were no differences between subjects with and without NP in the lesion level and ASIA grade (Table 2).

3.1 Data in subjects with NP, no NP and control subjects

At baseline, our subjects with SCI and NP reported a mean pain intensity (NRS) of 7.8 ± 0.9.

3.1.1 CHEPs

No statistically significant differences occurred in the N2 latency between subjects with NP (317.6 ± 65.0 ms), subjects without NP (290.8 ± 72.9 ms) and healthy subjects (324.4 ± 95.2 ms; Kruskal–Wallis *H*; $p = 0.37$). Results were similar for the P2 latency (pre-tDCS + VI 391.7 ± 91.1 ms; in subjects without NP 363.8 ± 80.6 ms, in healthy controls 404.8 ± 105)

Table 2 Clinical and demographical characteristics of SCI subjects with and without neuropathic pain and healthy subjects.

Subjects	Age (years) Mean (SD)	Sex F/M	Neurological lesion level C/Th	ASIA A/B/C/D	Time since SCI (months) Mean (SD)
SCI with NP	49.4 (12.4)	6/12	7/11	3/3/1/11	100.0 (120.3)
SCI without NP	45.5 (11.6)	7/13	7/13	4/5/1/10	115.4 (98.2)
healthy subjects	45.6 (11.7)	5/9	–	–	–
p	0.49	0.78	0.72	0.38	0.41

ASIA, American Spinal Injury Association Impairment Scale (grade A, B, C, D); C/Th, cervical/thoracic level; F/M, female/male; NP, neuropathic pain; SCI, spinal cord injury; SD, standard deviation.

(Kruskal–Wallis *H*; $p = 0.1$). Also, no statistically significant differences were found for the N2/P2 amplitude between SCI subjects with NP and either SCI subjects without NP or healthy subjects (Kruskal–Wallis *H*; $p = 0.37$; Table 3A).

3.1.2 Evoked heat pain perception

Evoked heat pain was significantly higher in SCI subjects with NP at baseline in comparison to SCI subjects without NP or healthy subjects (Mann–Whitney *U*: $p < 0.03$ for each comparison; Table 3A).

Habituation rate in evoked pain perception was significantly lower in subjects with NP at baseline in comparison to that of the subjects without NP and healthy subjects (Mann–Whitney *U*; $p = 0.015$ and $p = 0.003$, respectively; Table 3).

3.1.3 Warm and heat pain perception thresholds

Warm perception threshold was significantly higher at lesion level in patients with NP and in those without NP in comparison to healthy subjects (Mann–Whitney *U*; $p < 0.001$; except for the left side of SCI subjects without NP which was $p = 0.16$). However, no differences were observed among the three groups above lesion level (Kruskal–Wallis *H*: $p > 0.2$; Table 4A).

Heat pain perception threshold was significantly lower in subjects with NP in comparison to SCI subjects without NP and healthy subjects at and above SCI level (Mann–Whitney *U*: $p < 0.05$ for each comparison).

3.2 Effect of the tDCS + VI intervention in SCI subjects with NP

None of the subjects who underwent the tDCS + VI intervention reported any side effects. In patients with SCI and NP, mean pain intensity after the intervention was 4.9 ± 2.0 (indicating a mean improvement of 37.4 ± 24.8%). Five subjects in this group (27.7%) were considered not to improve with tDCS + VI intervention. They reported a <15% change in NRS, with a

Table 3 Numerical rating scale for ongoing and evoked heat pain perception, habituation rate of evoked pain perception and amplitude of contact heat-evoked potentials N2-P2, (A) in SCI subjects with NP at baseline condition (pre-tDCS + VI), in SCI subjects without NP and healthy subjects; (B) in SCI subjects with NP at pre- and post-tDCS + VI intervention.

A

Subjects	Intervention	Ongoing pain	Evoked pain perception	Habituation in evoked pain perception (%)	Amplitude N2-P2 (μV)
SCI with NP	pre-tDCS + VI	7.8 (0.9)	4.5 (2.3)	113.9 (87.8)	43.3 (21.3)
SCI without NP			2.7 (1.2)#	51.9 (52.4)#	39.3 (24.7)
Healthy subjects		–	2.3 (1.1)#	48.5 (43.6)#	36.8 (22.6)

B

Subjects	Intervention	Ongoing pain	Evoked pain perception	Habituation in evoked pain perception (%)	Amplitude N2-P2 (μV)
SCI with NP	pre-tDCS + VI	7.8 (0.9)	4.5 (2.3)	113.9 (87.8)	43.3 (21.3)
	post-tDCS + VI	4.9 (2.0)*	2.8 (1.8)*	56.9 (33.7)*	29.6 (14.5)*

amp, amplitude; NP, neuropathic pain; NRS, numerical rating scale; SCI, spinal cord injury; tDCS, transcranial direct current stimulation; VI, visual illusion.
#$p < 0.05$ (Mann–Whitney *U*) between SCI subjects with NP pre-tDCS + VI intervention versus SCI subjects without NP and versus healthy subjects.
*$p < 0.05$ (Wilcoxon *t*) between pre- and post-tDCS + VI intervention in SCI subjects with NP.

Table 4 Warm and heat pain thresholds at four different ASIA sensory points (A) in SCI subjects with NP at baseline condition, in SCI subjects without NP and healthy subjects; (B) in SCI subjects with NP at pre- and post-tDCS + VI intervention.

A

Subjects	QTT		CSH-above SCI	ISH-above SCI	CSH-at SCI	ISH-at SCI
SCI with NP	Warm threshold	Pre	35.5 (1.6)	35.8 (1.3)	36.3 (2.9)**	36.2 (2.2)***
SCI without NP	Warm threshold		35.5 (0.6)	35.2 (0.4)	35.5 (1.5)**	35.2 (1.3)
Healthy subjects	Warm threshold		35.3 (1.7)	35.4 (1.2)	34.0 (0.6)**	34.6 (0.8)***
SCI with NP	Pain threshold	Pre	40.9 (2.6)	40.2 (2.6)	40.0 (2.8)	39.5 (3.5)
SCI without NP	Pain threshold		43.1 (2.2)*	43.3 (1.0)*	42.5 (1.0)*	42.2 (1.0)*
Healthy subjects	Pain threshold		42.6 (1.1)*	43.1 (0.7)*	43.2 (1.6)*	42.9 (1.1)*

B

Subjects	QTT		CSH-above SCI	ISH-above SCI	CSH-at SCI	ISH-at SCI
SCI with NP	Warm threshold	Pre	35.5 (1.6)	35.8 (1.3)	36.3 (2.9)	36.2 (2.2)
	Warm threshold	Post	35.2 (1.1)	34.9 (1)	36.7 (3.0)	36.6 (2.7)
SCI with NP	Pain threshold	Pre	40.9 (2.6)#	40.2 (2.6)#	40.0 (2.8)#	39.5 (3.5)#
	Pain threshold	Post	42.6 (1.8)	42.0 (2.0)	42.8 (2.4)	42.3 (2.5)

CSH, contralateral side to stimulated hemisphere (to the anodal stimulation) or contralateral to dominant hand side in SCI subjects without NP and healthy subjects; ISH, ipsilateral side to stimulated hemisphere (or to the anodal stimulation) or ipsilateral side to dominant hand side in SCI subjects without NP and healthy subjects; NP, neuropathic pain; SCI, spinal cord injury.

*$p < 0.05$ (Mann–Whitney *U*) between SCI subjects with NP pre-tDCS + VI intervention and SCI subjects without NP, and versus healthy subjects.

**$p < 0.05$ (Mann–Whitney *U*) between healthy subjects versus SCI subjects with NP pre-tDCS + VI intervention and versus SCI subjects without NP

***$p < 0.05$ (Mann–Whitney *U*) between SCI subjects with NP pre-tDCS + VI intervention versus healthy subjects.

#$p < 0.05$ (Wilcoxon *t*) between pre- and post-tDCS + VI intervention in the group SCI with NP.

mean of 5.7 ± 7.8%. The 13 remaining subjects reported a percentage NRS change >15%, with a mean of 49.6 ± 16.5%.

3.2.1 CHEPs

Fig. 1 shows representative CHEP recordings at baseline and after the last day of tDSC + VI intervention for a patient with SCI + NP (C6 lesion level; ASIA-A). In SCI subjects with NP, no significant change was observed between pre- and post-intervention N2 latency (317.6 ± 65.0 ms vs. 324.6 ± 64.5 ms; Wilcoxon *t*; $p = 0.1$) or P2 latency (391.7 ± 91.1 ms vs. 401.4 ± 73.9 ms; Wilcoxon *t*; $p = 0.1$).

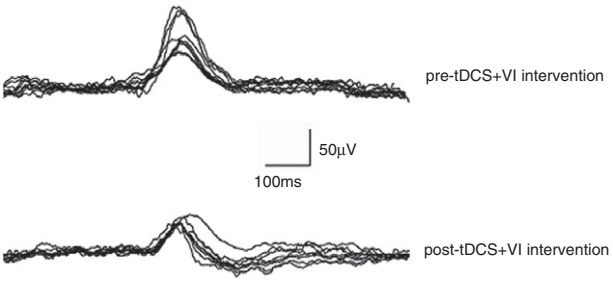

Figure 1 Representative recordings of CHEPs obtained at baseline (pre-) and after (post-) the intervention condition in a patient with SCI + NP (C6 level; ASIA-A). This patient reported 50% improvement in NP. The 10 traces recorded at each time are superimposed.

However, there was a significant effect of the tDCS + VI intervention on N2/P2 amplitude, which diminished in SCI subjects with NP with respect to baseline (Wilcoxon *t*; $p = 0.02$; Table 3B). Amplitude reduction was significantly more marked in patients who reported improvement of >15% in the NRS after tDCS + VI intervention (N2/P2 amplitude of 41.3 ± 20.3 μV at baseline, and 24.7 ± 12.7 μV post-intervention; Wilcoxon *t*; $p < 0.001$) in comparison to those who reported no changes (changes in the NRS < 15%; N2/P2 amplitude of 47.8 ± 28.0 μV at baseline and 42.3 ± 11.6 μV; Wilcoxon *t*; $p = 0.8$).

3.2.2 Evoked heat pain perception

After the last tDCS + VI sessions, evoked heat pain perception in patients with NP was significantly reduced with respect to baseline (Wilcoxon *t*; $p = 0.006$), reaching a mean value, which was no different from those of SCI subjects without NP and healthy subjects Kruskal–Wallis *H*: $p = 0.079$; Table 3A–B). Evoked heat pain reduction was significantly more marked in patients who reported improvement in NP (5.1 ± 2.1 vs. 2.4 ± 1.7 (Wilcoxon *t*; $p < 0.0001$). The five SCI subjects with NP who did not report a significant change in NRS

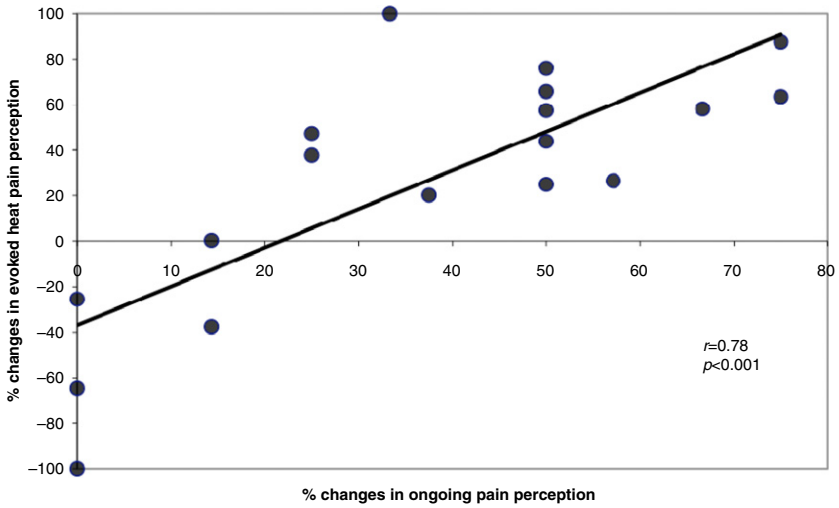

Figure 2 Relation between percentage of changes in the ongoing pain and evoked heat pain perception as measured by NRS (numerical rating scale) after tDCS + VI intervention in comparison to baseline in SCI subjects with neuropathic pain.

(<15%) reported similar evoked heat pain perception at baseline and after tDCS + VI (3.5 ± 1.7 vs. 3.9 ± 1.8, respectively; Wilcoxon *t*; $p = 0.59$).

Habituation rate in evoked pain perception increased significantly after tDCS + VI (Wilcoxon *t*: $p = 0.01$) in comparison to baseline, becoming similar to that of the subjects without NP and healthy subjects (Kruskal–Wallis *H*; $p = 0.6$; Table 3). When data from subjects with NP with and without improvement were analysed separately, we found a significant change in habituation rate between pre- and post-tDCS + VI in subjects with improvement (pre 95.5 ± 43.9%, post 45.7 ± 34.3%; Wilcoxon *t*; $p = 0.008$), but not in subjects without improvement (pre 137.0 ± 152.7% and post 92.0 ± 25.1%; Wilcoxon *t* $p = 0.6$).

Percentage improvement in ongoing pain post-tDCS + VI correlated significantly with the percentage change of evoked heat pain perception ($r = 0.78$; $p < 0.001$; Fig. 2). In contrast, percentage change in CHEPs amplitude did not correlate either with the percentage changes in ongoing pain nor with those of evoked heat pain perception ($p > 0.07$ for each correlation).

3.2.3 Warm and heat pain perception thresholds

Warm perception threshold in SCI subjects with NP at or above the SCI level did not change after tDCS + VI intervention in comparison to baseline (Wilcoxon *t*; $p > 0.3$; Table 4B).

After the last day of tDCS + VI session, the heat pain perception threshold increased significantly at all ASIA sensory points tested in comparison to baseline (Wilcoxon *t*: $p < 0.05$ for each comparison; Table 4). In subjects who did not report subjective improvement in NP following tDCS + VI intervention ($n = 5$), the heat pain perception threshold did not change in comparison to baseline (Wilcoxon *t*; $p > 0.4$ for each comparison; Fig. 3).

4. Discussion

In this study, we found significant changes in heat pain perception threshold and evoked heat pain perception in dermatomes rostral to the injury level in SCI subjects with NP in comparison to subjects without NP and healthy subjects, which has been recently reported in SCI subjects with NP (Kumru et al., 2011).

Additional findings included the following: (1) significant reduction of CHEPs amplitude and evoked heat pain perception after tDCS + VI intervention in comparison to baseline; (2) reduced habituation rate in the evoked heat pain score to repeated pain stimulation before treatment, which however normalized (increased significantly) after tDCS + VI intervention; (3) significant correlation between percentage changes in ongoing pain and in evoked heat pain perception after tDCS + VI intervention; and (4) normalization of heat pain perception threshold in dermatomes rostral to the injury level after tDCS + VI intervention. In contrast, warm perception threshold did not change after intervention in SCI subjects with NP.

4.1 The effect of treatment

The tDCS combined with VI intervention caused significant improvement in 13 subjects (72.2% of SCI subjects) with a mean reduction of almost 50% in

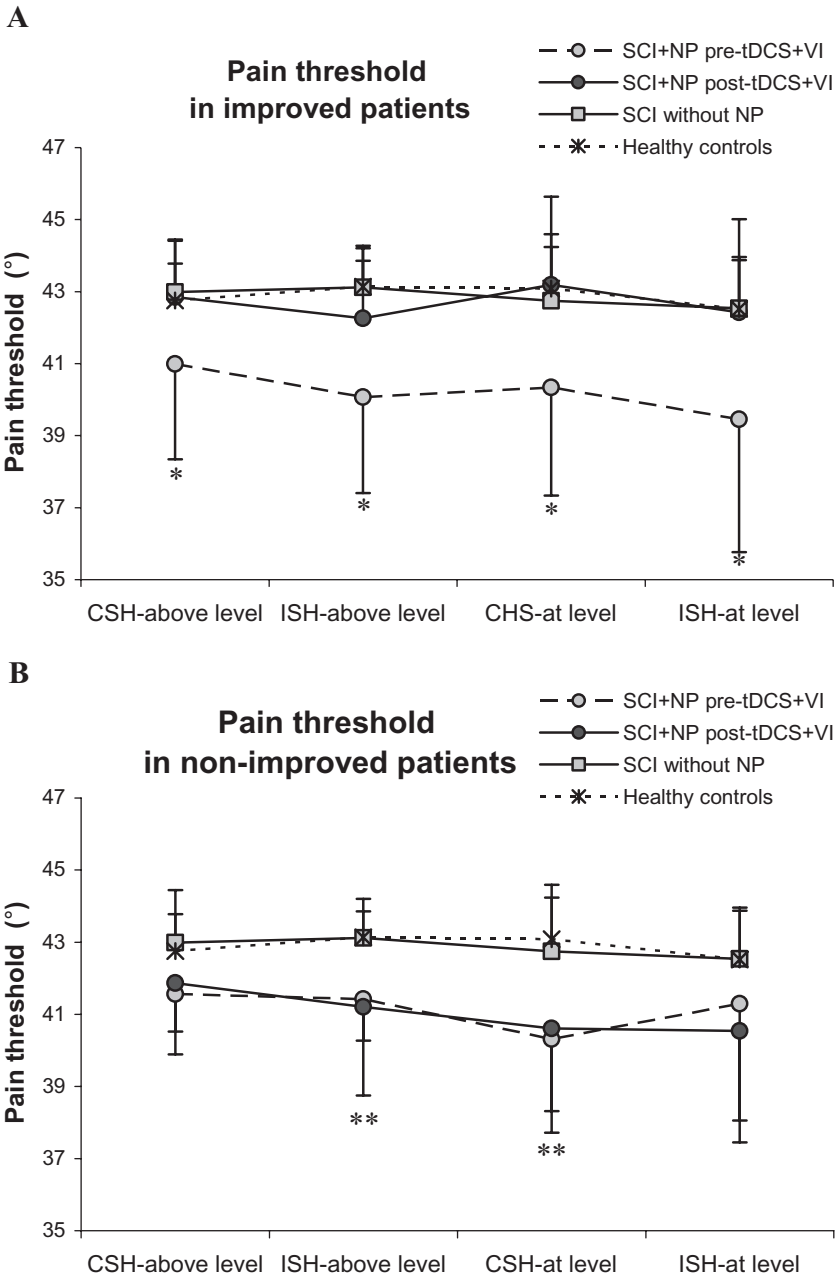

Figure 3 Mean and standard deviation of heat pain perception threshold in SCI subjects with neuropathic pain who improved (A) and in those who did not improve (B), pre- and post-treatment with tDCS combined with visual illusion, in comparison with SCI subjects without pain and with healthy subjects. SCI: spinal cord injury; NP: neuropathic pain; CSH: contralateral side to stimulated hemisphere (to the anode); ISH: ipsilateral side to stimulated hemisphere (to the anode). tDCS: transcranial direct current stimulation; VI: visual illusion. *$p \leq 0.05$ (Mann–Whitney *U*, for each comparison): heat pain perception threshold in SCI + NP pre-tDCS + VI in comparison to other groups. **$p \leq 0.05$ (Mann–Whitney *U*, for each comparison): heat pain perception threshold in SCI + NP pre- and post-tDCS + VI in comparison to SCI without NP and healthy controls.

overall pain intensity. These results confirm our prior findings (Soler et al., 2010). The degree of improvement in the present study is higher than that in the study published by Soler et al. (2010). This discrepancy may be due to differences in inclusion criteria between the two studies and the fact that the present intervention was not a sham-controlled, randomized clinical trial. Subjects with incomplete motor SCI as well as SCI subjects with subacute NP were included in this study. Anodal tDCS is associated with an increase of cortical excitability, which lasts beyond the stimulation period (Nitsche and Paulus, 2001). It has been suggested that tDCS induces changes in neuronal membrane potential due to shifts in extracellular ion concentration (Nitsche et al., 2003). Indeed, analgesic properties of tDCS or VI intervention alone have been described in painful conditions, such as in SCI with NP (Fregni et al., 2006; Moseley, 2007), or multiple sclerosis with NP (Mori et al., 2010). On the other hand, visual illusion of walking has been shown to have induced a significant reduction of NP in subjects with cauda equina injury (Moseley, 2007), and VI com-

bined with tDCS in severe SCI above Th12 lesion level (Soler et al., 2010). As previously hypothesized (Soler et al., 2010), tDCS and VI could have synergistic effects.

4.2 CHEPs amplitude

In our SCI subjects with NP, tDCS + VI induced significant reduction in CHEPs amplitude as well as in both ongoing pain and evoked heat pain perception with respect to baseline. These effects may be explained through sustained excitation of the motor cortex under motor imagery possibly causing inhibition of pain perception via neural connections between the motor cortex and the nociceptive systems. The anterior cingulate cortex (ACC) is one potential site for the effect to take place since the N2-P2 components are generated mainly in the ACC (Bromm and Chen, 1995; Lenz et al., 1998; Inui et al., 2003). Anatomic studies have shown dense neural connections between M1 and ACC (Dum and Strick, 1991; Morecraft and Van Hoesen, 1992). However, the primary somatosensory cortex and the thalamus cannot be excluded as regions responsible for this effect via projections from M1. During invasive electrical stimulation of the motor cortex, the regional cerebral blood flow increases in the ipsilateral thalamus, cingulate gyrus, orbitofrontal cortex and brainstem but does not change in M1 or S1 (Garcia-Larrea et al., 1999). Therefore, secondary activation of the cingulate/orbitofrontal cortex by M1 stimulation could influence the affective/emotional component of chronic pain and subsequently lead to descending inhibition of pain impulses by activation of the brainstem (Garcia-Larrea et al., 1999). A decrease in laser-evoked potentials amplitude has been reported in previous studies as an effect of medical treatment (Schestatsky et al., 2007), non-invasive repetitive magnetic brain stimulation with a theta burst paradigm (Csifcsak et al., 2009a), or cathodal tDCS on motor cortex (Csifcsak et al., 2009b).

4.3 Warm perception threshold

Higher warm detection thresholds appeared at lesion level in SCI, as has been previously reported in SCI subjects both with and without NP, at lesion level but not above (Kumru et al., 2011). Therefore, warm threshold abnormalities might possibly be found in dermatomes clinically defined as normal in some subjects with complete or incomplete SCI (Kumru et al., 2011). Our intervention (tDCS + VI) did not induce changes in warm perception threshold.

4.4 Heat pain thresholds, evoked heat pain perception and habituation

Our results also showed a significantly lower heat pain threshold in SCI-NP at and above the level of injury at baseline with respect to the same subjects post-tDCS + VI, and also to subjects without NP and to healthy subjects. A previous study of SCI subjects reported that pain threshold for noxious electrical stimuli, delivered above the level of injury, decreased in subjects with NP when compared to healthy adults and to SCI subjects without NP (Cohen et al., 1996). Using QTT, decreased heat pain threshold and increased evoked pain perception in the dermatomes rostral to the injury level in SCI subjects with neuropathic pain have also been reported recently (Kumru et al., 2011).

The mechanisms responsible for NP in SCI may include interrupted sensory pathways, interference with inhibitory pathways and modulation of cell assemblies engaged in sensory inhibition (Woolf et al., 1998; Yezierski, 2005; Wrigley et al., 2009). Interruption of ascending spinal pathways disrupts thalamic function, resulting in loss of inhibitory effects of the afferent impulses. The massive deafferentation following SCI could lead to neuronal disinhibition and/or hyperexcitability and finally to hyperalgesia and pain from maladaptive plastic changes throughout the neural axis in animals and in humans (Siddall et al., 2003; Masri et al., 2009; Masri and Keller, 2011). Chronic NP may induce secondary changes in the central nervous system, such as an increased response to painful stimuli (hyperalgesia; Cohen et al., 1996; Woolf and Salter, 2000; Kumru et al., 2011). Chronic pain conditions may also activate endogenous pain suppression systems as expressed for example in the diffuse noxious inhibitory control (DNIC; Dickenson et al., 1980), through which distant noxious inputs activate a spinal–supraspinal–spinal feedback loop, which subsequently inhibits pain (Roby-Brami et al., 1987). It is possible that the DNIC system does not function properly in SCI subjects suffering NP (Kumru et al., 2011), whereas central sensitization in turn could be the cause of the changes in heat pain threshold and evoked pain perception from dermatomes rostral to the injury level in SCI subjects. The significant correlation between percentage changes in ongoing pain and in evoked pain with effective treatment (e.g. tDCS + VI intervention) and reduction in CHEPs amplitude may also indicate generalized sensitization in SCI subjects after NP, which might be reversible with adequate treatment and/or intervention.

At pretreatment testing, our SCI subjects with NP showed significantly less habituation to repeated ther-

moalgesic stimuli than the other groups of subjects. Such a decrease in habituation may be due to hyperexcitability of the brain areas generating the response or hypoexcitability of the central systems that regulate habituation (Becerra et al., 1999; Kumru et al., 2011). In any case, our results show tDCS + VI to be an effective treatment to reverse the abnormality in habituation to repeated stimulation, an effect that likely contributed to the decrease in pain ratings.

5. Conclusion

The findings of our study indicate that NP in SCI subjects is associated with altered processing of somatosensory pathways in dermatomes rostral to the injury level, which has recently been demonstrated (Kumru et al., 2011). In SCI subjects who reported clinical improvement in NP, CHEPs, evoked pain and heat pain perception changed significantly and normalized, but not in those subjects who reported no improvement. Although the pathophysiology of ongoing NP is different from that of evoked pain, we consider that our results may contribute to the understanding of the mechanisms underlying NP relief and the potential therapeutic use of effective treatment and/or intervention. However, our study has some important limitations: (1) we did not run a control condition for tDCS + VI intervention group; (2) our study was not blinded for patients; (3) our intervention always included both tDCS and VI so that we are unable to discriminate between the effects on pain of each separately. The use of CHEPs and QTT could be helpful in the clinical practice for objective measurement of results of clinical changes with treatment.

Acknowledgements

The authors express their gratitude to Ellen Quirbach, Hochzirl, Austria, for providing editorial help with the manuscript.

Author contributions

H. Kumru, D. Soler, J. Vidal, A. Pascual-Leone, J. Tormos and J. Valls-Sole conceived and designed the experiments. H. Kumru, D. Soler, J. Vidal performed the circuitry of the study and analysis. H. Kumru and D. Soler analysed the data and together with A. Pascual-Leone, X. Navarro and J. Valls-Sole wrote the manuscript. All authors discussed the results and commented on the manuscript. J.M. Tormos and J. Vidal provided financial support.

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