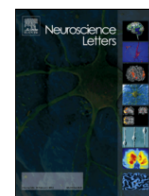




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Research article

Delayed pain decrease following M1 tDCS in spinal cord injury: A randomized controlled clinical trial

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ABSTRACT

Despite some encouraging findings for the treatment of neuropathic pain in patients with spinal cord injury (SCI), transcranial direct current stimulation (tDCS) directed to the primary motor cortex (M1) has faced some mixed results. Prior to translating this technology to clinical care, consistent results and durable effects need to be found. We, therefore, aimed to assess the direct and long-term effects of tDCS on pain following SCI.

We performed a two-phase randomized sham-controlled clinical trial where patients received 5 days of tDCS followed by a 3-month follow-up period (Phase I); then, Phase II consisted of 10 days of tDCS with an 8-week follow-up period. We assessed the level of pain with the Visual Analogue Scale (VAS). Patients' quality of life and life satisfaction were also evaluated.

33 patients were enrolled in Phase I and 9 in Phase II. We observed a treatment effect at 1-week follow-up for Phase I and at 4-week follow-up for Phase II. The overall level of pain was significantly lower for the active group, as compared to sham, in Phase II.

Our exploratory study shows that tDCS does seem to be a promising tool to manage pain in patients with SCI and repeated stimulation sessions are needed to induce long-lasting effects. Based on our protocol, it appears that adding a second treatment period could induce long-lasting effects.

Clinicaltrials.gov identification number: NCT01599767

1. Introduction

Chronic sublesional neuropathic pain in patients who suffered a spinal cord injury (SCI) is a major health problem that causes significant burden and cost to both the individual and society. Following a SCI, nearly 40% of people report neuropathic pain that is often refractory to medications [1,2]. Therefore, there is a crucial need to develop novel pain therapeutic approaches to manage pain. Chronic sublesional neuropathic pain in SCI results from a dysfunction of cortical areas associated with sensory and pain processing, which become dysfunctional after SCI due to diminished input from peripheral sensory systems [3].

Evidence suggests that the resulting chronic pain is associated with the phenomenon of central sensitization involving a large neural network that includes limbic structures, such as the anterior cingulate cortex, hippocampus and amygdala, and thalamic nuclei [4–6]. However, the precise mechanisms leading to central sensitization in SCI are not yet understood. It is known that increased spinal cord excitability leads to enhanced activity in pain-related brain structures, including the sensorimotor cortex [7]. The development of central sensitization is one of the reasons that could explain why standard treatments for chronic pain in SCI are not effective in alleviating pain since they do not target the modulation of pain-related dysfunctional brain areas. Therefore, one strategy to mitigate pain is targeting cortical area linked to pain circuitry. In this study, we propose to use a technique of cortical modu-

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lation – transcranial direct current stimulation (tDCS) – and chose the primary motor cortex (M1) as the main neural target.

tDCS is a simple method that modulates brain activity of these pain processing centers. It is based on the application of a weak direct current to the scalp, which runs between an anode and cathode electrode, inducing modulation of cortical excitability under the stimulated area [8,9]. Robust and extensive basic science research has demonstrated the effects of tDCS and many studies have confirmed that anodal stimulation increases cortical excitability while cathodal stimulation decreases it [8,10,11]. From a clinical perspective, anodal tDCS of the primary motor cortex (M1) can induce clinically significant pain relief in chronic pain syndromes [7,12–16]. In a previous study, our group has tested the effects of tDCS in SCI patients suffering from neuropathic pain, showing that 5 consecutive daily sessions of M1 tDCS significantly reduced level of pain after the end of the stimulation sessions but not when reassessed at 2-week follow-up [7]. Other studies, investigating the neural correlates of tDCS in SCI, or the combination of tDCS with adjuvant therapy, have found similar results on pain intensity reduction following the stimulation of M1 [17–20].

We chose M1 as the target given its effects as central pain modulation [21]. Several studies have shown that M1 stimulation leads to local and distant effects that result in pain reduction. For instance, stimulating M1 may counteract the lack of inhibition from M1, that could also be associated with pain reduction [22,23]. In addition, it also leads to changes in thalamic and cingulate activity [24], known to be related to pain processing.

Contrasting with these findings, other tDCS trials indicate there were no significant differences in pain reduction following active and sham stimulation [25]. In addition, nothing is known about the effects of tDCS on quality of life in people with sublesional neuropathic pain due to SCI. Finally, the clinical effects of a prolonged regimen of tDCS have not been tested. These gaps in knowledge must be addressed prior to translating this technology to clinical care.

Therefore, in this exploratory study, we aimed to assess the direct and long-term effects of tDCS on sublesional neuropathic pain following SCI. We hypothesize that active tDCS will have a greater decrease in pain level (as measured with the Visual Analogue Scale – VAS – for pain) as compared to sham tDCS. Given that we wanted to study the immediate and late effects in a 1-year study, we broke the protocol in two phases. All patients enrolled for 5 days of tDCS with a 3-month follow-up period. After this period, patients could continue to the second phase, consisting of 10 days of tDCS with an 8-week follow-up period.

Our secondary outcomes were to test the effects of tDCS on patients' quality of life and life satisfaction, as measured by the Patient Health Questionnaire (PHQ-9) and the Satisfaction with Life Scale (SWLS).

2. Methods

2.1. Study outline

Phase I: patients received 5 sessions of tDCS, once a day for 5 days. Assessments were performed at baseline, at the end of the 5 stimulation sessions, at 1-week and 3-month follow-up.

Phase II: patients received 10 sessions of tDCS, once a day during weekday for 2 weeks (same allocation group as Phase I). Assessments were performed after 5 and 10 stimulation sessions and at 2, 4 and 8-week follow-up.

Note that Phase II began at the end of the 3-month follow-up for Phase I.

2.2. Study participants

We recruited subjects, both men and women aged 18 or older with SCI (based on the American Spinal Injury Association (ASIA) Impairment Scale performed at time of enrollment) who had ongoing sublesional neuropathic pain that is moderate or severe in nature (average VAS scale score of 4 or greater at time of enrollment). Exclusion criteria were as follows: 1. active alcohol or drug dependence, as self-reported; 2. a history of bipolar disorder or psychosis, as self-reported; 3. inability to travel to the study site; 4. current use of any of the following anti-epileptic medications or dopaminergic medications known to reduce or inhibit the benefits of tDCS treatment: carbamazepine, oxcarbazepine, phenytoin, ropinirole (Requip), pramipexole (Mirapex), and cabergoline (Dostinex); 5. the following contradictions to tDCS: implanted metal plates in the head, or deep brain stimulator (spinal cord implants, including baclofen pumps, are not a contraindication as cranial currents do not reach the spinal cord); 6. pregnancy at time of enrollment; 7. current use of ventilator.

Written informed consents were obtained from all patients according to the declaration of Helsinki. The study was approved by the institutional reviewed board of Spaulding Rehabilitation Hospital, Boston. Clinicaltrials.gov registration number: NCT01599767

2.3. Assessments

We used the Visual Analog Scale (VAS) Pain scale, a simple 10-point scale (0 = “no pain”, 10 = “pain as bad as you can imagine”), to measure patients' worst pain and least pain, average level of pain and pain at present time.

The Satisfaction with Life Scale (SWLS) assessed patients' happiness with current quality of life [26,27].

The Patient Health Questionnaire (PHQ-9) evaluated patients' quality of life through mental state [28].

2.4. Transcranial direct current stimulation (tDCS)

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm²) and delivered by a battery-driven, constant current stimulator (Soterix Medical, New-York). The anodal electrode was placed over the primary motor cortex (M1), contralateral to the most painful side, and the cathodal electrode was placed over the opposite supra-orbital area. The duration of stimulation was 20 min at 2 mA with a ramp-up and ramp-down of 30 s, as previously described [7]. For the sham condition, the stimulation was applied for 30 s with the same ramp-up and down, to mimic the active condition. It has been shown that subjects usually cannot detect active from sham conditions using these parameters [29]. The device we used allows the delivery of both active and sham stimulation, and all stimulation sessions were performed by a researcher who was not involved in any of the assessments, allowing a double-blind procedure.

Both treatment groups received 5 consecutive days of tDCS (phase I) with a 3-month follow-up period. If the participant agreed to take part in the Phase II of this trial, they received an additional 10 sessions of tDCS with an 8-week follow-up.

2.5. Statistical analysis

Differences in baseline values between the two stimulation conditions were analyzed with a Student *t*-test for continuous variables and with Chi-square tests for dichotomous variables.

All analyses were conducted according to the principle of intention-to treat using a multiple imputations model for missing data.

To determine the difference between the groups in experiencing pain (VAS – primary outcome), a multiple linear regression model was used. To control for baseline difference in level of pain between the two groups we added the baseline measure to the model. We tested other potential confounders such as age, time since injury and gender using a Pearson correlation. If the correlation between the covariate and pain improvement was significant, the covariate was added to the model. A similar model was conducted for each of our secondary outcomes (PHQ9 and SWLS).

Phase II: The same model was used for all variables. As exploratory analyses, to look at the cumulative effect of the treatment, we also compare the area under the curve (AUC) for both interventions. The AUC for each treatment group (active and sham) at each time point was determined using the trapezoidal rule, and the difference in the AUC between active and sham treatment was compared using a Student *t*-test.

Two-tailed *P* values <0.05 were considered statistically significant in all cases.

All statistical analyses were performed using STATA (StataCorp 2013. StataCorp LP, College Station, TX).

3. Results

33 patients were randomized to receive either active (*n* = 16) or sham tDCS (*n* = 17). Patients flow-chart is presented in Fig. 1.

9 patients were enrolled in the second phase of the study. In phase II, all patients completed all study visits.

Baseline comparisons between stimulation conditions showed no significant a priori differences except for gender (Chi-square: 4.90; *p* = 0.009).

None of the confounders (i.e., age, time since injury and gender) reached the significance threshold; therefore, they were not added to the model.

3.1. Phase I

Primary outcome: The linear regression models showed that the group status (active versus sham) was associated with changes in VAS scores at 1-week follow-up for average (*p* = 0.003) and least (*p* = 0.043) pain (see Fig. 2 and Table 2). Patients' individual data can be found in supplementary Table 1.

Secondary outcomes: No significant changes were found for the PHQ9 nor for the SWLS at any time points (all *p*-values > 0.05—see supplementary Table 2).

Descriptive analyses: When comparing patients suffering from severe pain (VAS average >5) with patients with lower level of pain, we observed a higher pain decrease in patients with VAS scores at baseline higher than 5 (see Table 3).

3.2. Phase II

When comparing characteristics (i.e., age, time since injury, side of stimulation, gender) and treatment allocation (active or sham) of patients enrolled in phase I with patients enrolled in Phase II, no significant differences were found (Table 1).

The linear regression models showed that the group status (active versus sham) was associated with VAS changes for VAS average at 4-week follow-up (*p* = 0.016).

No significant changes were identified for any of the other outcomes at any time points (VASs, PHQ-9 and SWLS).

When comparing the AUC between the two interventions, we observed a significant higher AUC for sham (i.e., higher VAS scores) for VAS average (*p* = 0.026) and VAS least (*p* = 0.011). None of the

other scales demonstrated a significant difference between active and sham conditions.

3.3. Safety

All study participants well tolerated tDCS sessions. The majority reported a mild-to-moderate tingling or itching sensation during both active and sham stimulations. No unexpected adverse effects were observed.

4. Discussion

In this randomized controlled clinical trial, we found that 5 sessions of tDCS can reduce the level of pain in patients with SCI. However, the effects were not noticed directly after the end of the stimulation sessions but at 1-week follow-up. For patients who continued to the second phase of this study, the overall level of pain remained significantly lower in patients who received the active treatment as compared to patients allocated to the sham intervention.

4.1. tDCS to prevent the mechanisms of chronic pain

Managing pain in patients with SCI is critical since neuropathic pain has been identified as the primary factor for poor quality of life, leading to depression, loss of employment and reduced productivity [30–32]. The analgesic effect of M1 tDCS could be related to the mechanisms of chronic pain in patients with SCI, such as central sensitization and deficient inhibitory process, as observed in previous tDCS studies focusing on pain management [33–35]. In a previous longitudinal study, the majority of SCI patients reporting chronic pain had their pain onset within six weeks post-injury and 80% of them stated that their pain started on the day of the injury [36]. There are extensive data showing that, by decreasing acute pain, the chances to develop chronic pain are reduced since the mechanisms of maladaptive plasticity are limited. In fact, hyperactivity within pain-related neural areas often precedes chronic pain; and has been recently demonstrated [37,38]. Therefore, future longitudinal trials should also evaluate the long-term effects of tDCS on acute patients suffering from neuropathic pain after a SCI, or as a prophylactic treatment. By acting in an earlier phase of the disease, tDCS could also limit the pathological reorganization of the pain matrix which leads to the occurrence of neuropathic pain.

4.2. Delayed tDCS effects on pain reduction

The low number of sessions (i.e., 5) may have prevented larger tDCS effects in the present study. However, we did find significant *delayed* tDCS-related effects, which confirms our hypothesis that M1 tDCS effects on pain reduction are driven by changes in cortical plasticity, and not only related to direct and short-lasting increase in cortical excitability. Long-lasting changes in plasticity, as observed in this study, have been seen before in other conditions using tDCS [7,46,47]. Even considering the delayed effects of tDCS observed in this study, it is important to stress that repeated exposure to tDCS is needed to induce lasting plastic changes promoting synaptic strengthening of the structures targeted, especially in a chronic population. It is conceivable that these patients have important plastic changes in pain-related neural networks. Hence, this might explain why we only observed a delayed effect after the end of stimulation. Delayed tDCS-response has been observed in previous studies assessing the effect of tDCS on pain and MEP in patients with migraine and elderly people, respectively [48,49]. tDCS mechanisms are related to its influence on sodium and calcium channels opening and NMDA receptors excitability [50], while long-lasting effects are analogous to activity-dependent synaptic plasticity,

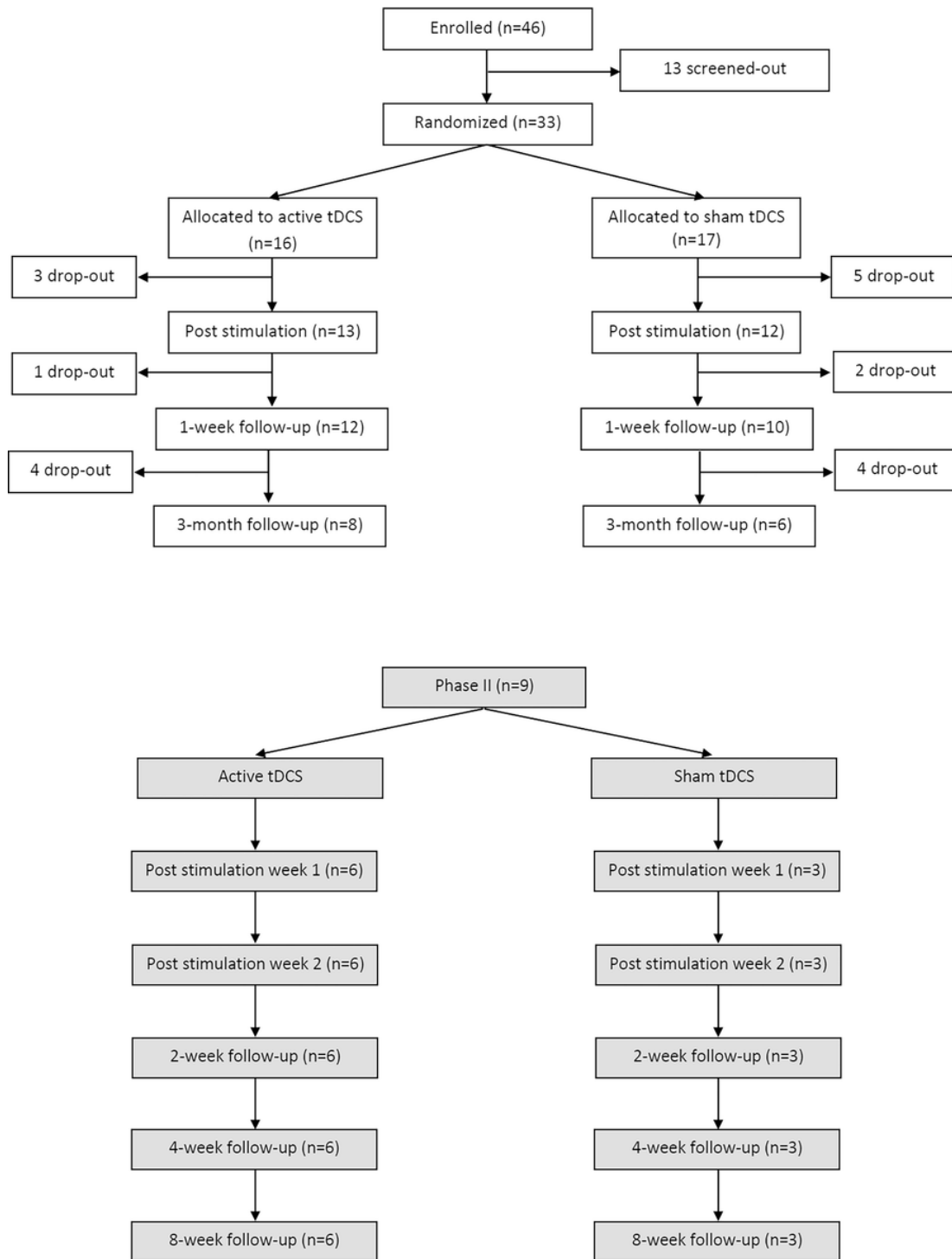


Fig. 1. Flow chart of participant enrollment, randomization and follow-up (based on the CONSORT Flow Diagram: <http://www.consort-statement.org/consort-statement/flow-diagram/>).

namely long-term potentiation (LTP) and long-term depression (LTP or LTD) [51–53]. Structural, functional and connectivity alterations at the cortical level have been described in patients with SCI, especially in the somatosensory cortex, consequently to the injury itself, as well as a result of the lack of sensory and motor inputs [54–56]; these changes being related to neuropathic pain [57]. Therefore, it is possible that patients with SCI sustain a decline in plasticity mechanisms as compared to those observed in healthy subjects, and therefore, tDCS related neuroplastic mechanisms may occur in a delayed manner.

Two studies on tDCS in patients with SCI are worth mentioning to discuss. One of them investigated the effect of 5 sessions of tDCS on pain level in a small sample of patients with SCI (n = 10); no difference between active and sham tDCS was observed [25]. The authors explained that lack of effects is likely due to refractoriness of pain and duration of disease since most of the patients enrolled had injury durations of 10 or more years. In addition, the limited number of sessions and small sample size, may not have been sufficient to observe significant effects at follow-up. The second study, on low back pain, even

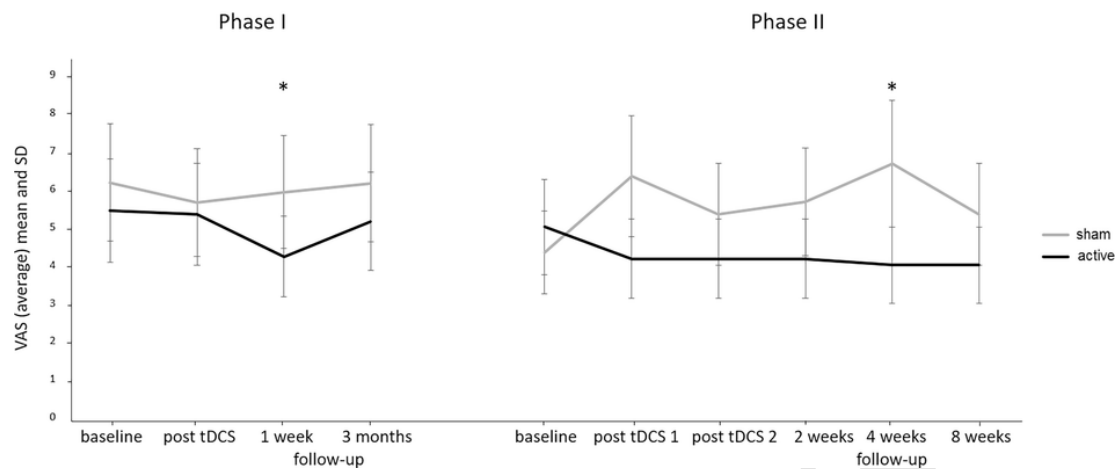


Fig. 2. Change in visual numerical scale for pain for sham (grey lines) and active tDCS (black lines) measured at baseline, immediately after 5 days of tDCS, at 1 week and 3-month follow-up for phase I and at baseline, after 5 and 10 sessions of tDCS and at 2, 4 and 8-week follow-up. Bars represent the standard deviation. *represent the significant difference between the active and sham groups.

Table 1

Clinical and Demographic Characteristics . SD = standard deviation; tDCS = transcranial direct current stimulation; VAS = visual analogue scale. + side of stimulation was based on the most painful area. *p-value comparing difference between patients' demographic characteristic enrolled in Phase I and in phase II.

	Active tDCS	Sham tDCS	P values (active/sham)	Group	P values* (PhI/PhII)
Phase I (n = 33)					
Number of subjects	16	17		33	
Age (years, mean ± SD)	51.38 (±14.89)	51.00 (±10.11)	0.932	51.18 (±12.45)	
Gender (Number of males – %)	15 (94%)	9 (53%)	0.009	24 (73%)	
Side of stimulation+ (left hemisphere – %)	15 (94%)	15 (88%)	0.582	30 (91%)	
Time since injury (years, mean ± SD)	5.81 (±6.27)	4.56 (±3.54)	0.481	5.17 (±5.01)	
Level of pain at baseline (VAS, mean ± SD)	5.44 (±1.90)	6.06 (±2.01)	0.369	5.76 (±1.95)	
Phase II (n = 9)					
Number of subjects	6	3		9	0.333
Age (years, mean ± SD)	49.47 (±16.01)	47.67 (±3.54)	0.835	49.00 (±14.38)	0.653
Gender (Number of males)	6 (100%)	1 (33.33%)	0.023	7 (78%)	0.760
Side of stimulation+ (left hemisphere)	5 (83.33%)	3 (100%)	0.453	8 (89%)	0.855
Time since injury (years, mean ± SD)	7.67 (±9.50)	3.67 (±1.41)	0.370	6.33 (±8.14)	0.589
Level of pain at baseline (VAS, mean ± SD)	5 (±2.25)	4.33 (±1.53)	0.628	4.78 (± 2.05)	0.194

Table 2

Visual Analogue Scale (VAS) at all time points for active and sham tDCS, mean, standard deviation (SD), change from baseline (i.e, delta) and p-values of the treatment effect. Bold number represent a significant p-value (p < 0.05).

	Active		Sham		P value
	Mean (SE)	Delta – Mean (SE)	Mean (SE)	Delta – Mean (SE)	
VAS average					
Baseline	5.33 (0.49)	/	6.05 (0.49)	/	0.369
After stimulation	5.39 (0.61)	0.05 (0.30)	5.50 (0.40)	–0.56 (0.32)	0.323
1-week follow-up	4.22 (0.59)	–1.11 (0.56)	5.79 (0.45)	–0.26 (0.63)	0.003
3-month follow-up	5.22 (0.54)	–0.11 (0.85)	6.22 (0.51)	0.16 (0.68)	0.353
VAS present					
Baseline	5.20 (0.70)	/	6.00 (0.46)	/	0.396
After stimulation	4.98 (0.76)	–0.22 (0.35)	5.44 (0.59)	–0.56 (0.30)	0.701
1-week follow-up	3.74 (0.69)	–1.46 (0.71)	5.31 (0.43)	–0.69 (0.52)	0.274
3-month follow-up	5.30 (0.61)	0.10 (1.10)	5.21 (0.47)	–0.79 (0.70)	0.491
VAS least					
Baseline	2.93 (0.64)	/	4.41 (0.57)	/	0.115
After stimulation	3.78 (0.66)	0.84 (0.43)	3.75 (0.42)	–0.67 (0.50)	0.068
1-week follow-up	3.06 (0.62)	0.13 (0.66)	5.05 (0.57)	0.64 (0.76)	0.043
3-month follow-up	2.88 (0.44)	–0.06 (0.85)	3.31 (0.52)	–1.10 (0.79)	0.819
VAS worst					
Baseline	7.33 (0.61)	/	7.35 (0.44)	/	0.976
After stimulation	5.92 (0.61)	–1.41 (0.57)	6.89 (0.67)	–0.48 (0.64)	0.534
1-week follow-up	5.91 (0.66)	–1.42 (0.64)	7.27 (0.47)	–0.08 (0.64)	0.239
3-month follow-up	7.37 (0.42)	0.03 (0.11)	7.36 (0.40)	–0.08 (0.64)	0.313

Table 3

Visual Analogue Scale (VAS average) at all time points (Phase I) for active tDCS, mean, standard deviation (SD), change from baseline (i.e., delta) for patients divided by their level of pain (i.e., VAS average > or ≤5 at baseline).

	Baseline	Post active tDCS		1-week follow-up		3-month follow-up	
	Mean (SD)	Mean (SD)	Delta mean (SD)	Mean (SD)	Delta mean (SD)	Mean (SD)	Delta mean (SD)
VAS ≤ 5	3.88 (1.25)	4.13 (1.96)	0.25 (0.71)	3.29 (1.32)	-0.58 (0.07)	5.57 (2.26)	1.69 (1.01)
VAS > 5	7.00 (0.76)	6.54 (1.98)	-0.47 (1.23)	5.28 (2.81)	-1.72 (2.05)	4.72 (1.86)	-2.28 (1.11)

though the sample size was large ($n = 135$), did not show significant differences between sham and active tDCS [58]. However, low back pain is not a neuropathic pain and therefore the results cannot be directly translated to our findings. In addition, it is worth mentioning that study did not include follow-ups to assess the long-lasting effects of tDCS, since, directly after the end of the stimulation sessions, a new intervention was applied. Therefore, the possible long-term effects of tDCS were not directly investigated in that large randomized clinical trial.

Regarding the outcome measures, the data variability of pain scores might have decreased the power for the analysis during the stimulation period. In addition, it is well known that the VAS and other quality of life scales (e.g., SWLS and PHQ-9) can be affected by patients' expectations and therefore, may be a reason why a treatment effect was only observed a 1-week follow-up. Indeed, patients' expectations, or the placebo effect, may have had an important component in the present findings since both groups, active and sham, improved after the first treatment session. However, the active group only demonstrated tDCS-related improvements at follow-up. It is, therefore, essential to define new clinical measures requiring more objective reports of pain from patients, such as task-related outcomes to disentangle the treatment effect from the placebo effect.

4.3. Long-lasting effects of tDCS

In the second phase of the present trial (Phase II: 10 tDCS sessions 3 months subsequently Phase I), we did not observe any significant treatment effect at any time point, except for the VAS average at 4-week follow-up, which is in line with the results we observed in Phase I. The lack of significant results can also be explained by the small sample size since only 9 patients enrolled in Phase II, 6 in the active group and 3 in the sham group. Therefore, we looked at the AUC to evaluate the cumulative effect of tDCS during these 2 weeks of stimulation with an 8-week follow-up period. For both VAS average and VAS least we found that the active group had significant lower AUC as compared to the sham group, suggesting overall lower VAS scores. When looking at the results, the active group demonstrated a consistency in lower VAS scores, while the sham group presented higher variability in level of pain. This observation highlights the long-term effects of tDCS in maintaining low level of pain as compared to the sham intervention. As abovementioned, several studies have highlighted the need for repeating the number of tDCS sessions (10–20) to induce long-lasting and clinically relevant effects. In the present study, even with a limited sample size, we demonstrated that adding a second phase of 10 stimulations sessions can help maintaining the benefits induced by tDCS.

4.4. Adherence to extended tDCS protocol

It has been shown that a minimum of 10–20 sessions of tDCS need to be performed in order to induce relevant clinical improvements [39–42]. However, in clinical trials involving patients with severe disabilities, such as SCI as in the present study, we experienced a high rate of drop-out which limits the power of clinical results. Conducting

clinical trials requesting daily visits in a research facility with people with mobility problems represents a challenge and may influence subjects' poor adherence. We investigated the issue of poor adherence in this specific SCI trial, showing that people with higher levels of pain are more motivated to travel to the research facility for multiple tDCS sessions [43]. As patients with more severe level of pain had higher pain reduction following tDCS, it may be possible that treatment efficacy could have impacted adherence too. This is particularly true for patients with pain symptoms for which compliance is a burden [44]. Strategies to improve patients' compliance are needed to obtain more accurate data that could be translated to clinical practice. Indeed, even though we used a multiple imputation model, it may not exactly reflect the results that would have been obtained with a fully adherent population. In addition, patients who did not complete the entire protocol, may not have benefited from the effects of tDCS on pain reduction. Therefore, it is essential to develop strategies to improve patients' adherence to, (i) collect exact data and (ii) determine the exact proportion of patients responding to tDCS, as well as the amount of pain relief tDCS can induce. One solution that has been tested in patients with Parkinson Disease is the use of a home-based device with close supervision by researchers and clinicians [45]. In this study, the compliance was as high as 100% (for a total of 40 sessions) and no adverse events occurred, showing that remotely supervised tDCS could be a valuable option to reduce the number of drop-outs, in addition to represent a step forward in the clinical translation of tDCS.

4.5. Patients with higher pain levels seem to respond better to tDCS

Even though the analyses performed were descriptive, it seems that tDCS induces stronger pain reduction in patients with higher pain level. Indeed, when looking at the results for patients with VAS scores above 5, pain reduction was higher as compared to patients with lower level of pain (see Table 3). It is well known that tDCS works better when it targets a behavior or a function that has some room to improve. For instance, tDCS can enhance hand motor function when applied over the non-dominant hemisphere but not when the dominant motor cortex is stimulated [63], this is what is called the *ceiling effect*. For patients with lower pain level, it is possible that the sensorimotor cortex does not show pathophysiological modification or is less alerted when compared to patients with higher pain intensity. Indeed, several neuroimaging studies have demonstrated the correlation between pain intensity and degree of abnormal activity and connectivity within areas of the pain matrix in various chronic pain syndromes [60,64,65]. Future research to identify biomarkers and predictors of tDCS response could help to identify who and why some patients could benefit from this treatment, as well as to develop a patient-tailored stimulation protocol.

4.6. How to improve the effects of tDCS?

The combination of tDCS with pharmacological agents could also be a way to increase pain-related effects of tDCS, in term of dose response and timing. For instance, it has been shown that pain reduction

induced by pregabalin intake was related to a decrease in connectivity between the default mode network (DMN) and the insular cortex [59], which is hyperactivated in patients with chronic pain [60,61]. In another neuroimaging study (i.e., functional MRI) evaluating the effects of M1 tDCS in patients with fibromyalgia, the authors demonstrated that tDCS induced a significant reduction in functional connectivity between the thalamus and the supplementary motor area, the medial prefrontal cortex and the cerebellum [62]. It can be hypothesized that combining two treatments acting on the reduction of hyperactivity in pain-related cortical and subcortical regions could lead to higher and longer pain decrease.

4.7. Limitations

There are several limitations of this study that need to be considered when interpreting the results. Firstly, these findings must be considered preliminary since we performed exploratory analyses, as a consequence of the limited size of the population enrolled in this study. In addition, the descriptive analyses showed that patients with higher level of pain seems to respond better to tDCS. However, due to the small sample size, we could not perform further sub-group analyses. The high degree of variability within the groups (e.g., for gender or initial level of pain) is another limitation that need to be considered and that may have influenced the results. Future large sample size controlled clinical trials, should be performed to validate our findings, and provide more details regarding the subpopulation of patients that may benefit the most of tDCS. Finally, another important limitation, is the high rate of drop-out, which could have biased our findings for Phase I, even though we used a multiple imputation model to replace missing data.

5. Conclusion

In conclusion, tDCS seems to be a promising tool to manage pain in patients with SCI and repeated stimulation sessions are needed to induce long-lasting effects. In fact, it is clear that parameters of stimulation may not be optimal yet. Based on our protocol, it appears that adding a second treatment period could help maintain the effects of tDCS. Therefore, future trials evaluating the impact of tDCS on pain management should investigate the effect of intermittent tDCS sessions (e.g., 5 daily (or more) tDCS sessions, once a month for 6 months) to better characterize the number of sessions needed to induce sustainable effects. Finding ways to limit the number of drop-outs is another challenge we need to tackle particularly if we want to investigate tDCS long-term effects. Finally, patients with higher level of pain tend to respond better to tDCS as compared to patients with lower pain intensity.

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Conflict of interest

The authors are responsible for the content and writing of this article. The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neulet.2017.08.024>.

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