Review

Targeted therapies using electrical and magnetic neural stimulation for the treatment of chronic pain in spinal cord injury

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ABSTRACT

Background: Chronic neuropathic pain is one of the most common and disabling symptoms in individuals with spinal cord injury (SCI). Over two-thirds of subjects with SCI suffer from chronic pain influencing quality of life, rehabilitation, and recovery. Given the refractoriness of chronic pain to most pharmacological treatments, the majority of individuals with SCI report worsening of this condition over time. Moreover, only 4–6% of patients in this cohort report improvement. Novel treatments targeting mechanisms associated with pain-maladaptive plasticity, such as electromagnetic neural stimulation, may be desirable to improve outcomes. To date, few, small clinical trials have assessed the effects of invasive and noninvasive nervous system stimulation on pain after SCI.
Objective: We aimed to review initial efficacy, safety and potential predictors of response by assessing the effects of neural stimulation techniques to treat SCI pain.
Search strategy: A literature search was performed using the PubMed database including studies using the following targeted stimulation strategies: transcranial Direct Current Stimulation (tDCS), High Definition tDCS (HD-tDCS), repetitive Transcranial Magnetical Stimulation (rTMS), Cranial Electrotherapy Stimulation (CES), Transcutaneous Electrical Nerve Stimulation (TENS), Spinal Cord Stimulation (SCS) and Motor Cortex Stimulation (MCS), published prior to June of 2012. We included studies from 1998 to 2012.
Results: Eight clinical trials and one naturalistic observational study (nine studies in total) met the inclusion criteria. Among the clinical trials, three studies assessed the effects of tDCS, two of CES, two of rTMS and one of TENS. The naturalistic study investigated the analgesic effects of SCS. No clinical trials for epidural motor cortex stimulation (MCS) or HD-tDCS were found. Parameters of stimulation and also clinical characteristics varied significantly across studies. Three out of eight studies showed larger effects sizes (0.73, 0.88 and 1.86 respectively) for pain reduction. Classical neuropathic pain symptoms such as dysesthesia (defined as an unpleasant burning sensation in response to touch), allodynia (pain due to a non-painful stimulus), pain in paroxysms, location of SCI in thoracic and lumbar segments and pain in the lower limbs seem to be associated with a positive response to neural stimulation. No significant adverse effects were reported in these studies.
Conclusions: Chronic pain in SCI is disabling and resistant to common pharmacologic approaches. Electrical and magnetic neural stimulation techniques have been developed to offer a potential tool in the management of these patients. Although some of these techniques are associated with large standardized mean differences to reduce pain, we found an important variability in these results across studies. There is a clear need for the development of methods to decrease treatment variability and increase response to neural stimulation for pain treatment. We discuss potential methods such as neuroimaging or EEG-guided neural stimulation and the development of better surrogate markers of response such as TMS-indexed cortical plasticity.

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Introduction

The prevalence of chronic pain in subjects after a spinal cord injury (SCI) remains high. Pain affects 75–81% of SCI population with one-third reporting intense pain that have detrimental effects on their mood (Margot-Duclot et al., 2009), quality of life and progression of recovery with rehabilitation. The first studies that showed this important relationship between SCI and pain date back to the 1940's and reported painful syndromes in more than 60% of this population (Bonica, 1979; Davis and Martin, 1947; Margot-Duclot et al., 2009; Munro, 1950; Siddall and Loeser, 2001) being severe in 25–60% of them (Siddall and Loeser, 2001). Subsequent studies showed that prevalence varies between 34 and 90%, and more recent studies show prevalence rates as high as 90% during rehabilitation (Siddall and Loeser, 2001).

Most subjects with SCI report pain worsening over time, and only 4–6% report improvement. (Siddall and Loeser, 2001). One of the main reasons responsible for the establishment of chronic of pain in SCI is the refractoriness of this condition to pharmacological approaches. In fact, recent neuroimaging and neurophysiological studies that investigated the neural mechanisms underlying chronic pain in SCI have shown that this condition is mainly sustained by maladaptive plastic changes (Wagner et al., 2007). Therefore, new interventions and techniques that target these neuroplastic changes are desirable.

Electrical and magnetic neural stimulation approaches are promising tools for the treatment of chronic pain as they can induce relatively focal and targeted changes in neural plasticity. In addition, most of these techniques are associated with minor or no adverse effects. The most commonly used neuromodulatory tools in SCI chronic pain are transcranial Direct Current Stimulation (tDCS), repetitive Transcranial Magnetical Stimulation (rTMS), Cranial Electrotherapy Stimulation (CES), Transcutaneous Electrical Nerve Stimulation (TENS) and Spinal Cord Stimulation (SCS) (see Table 1).

The use of neural stimulation techniques to block or reduce chronic neuropathic pain is not new and has been used for several decades. A classic use of neuromodulation in this context was reported by Melzack and Wall (1965) and gives the scientific basis for the use of TENS in chronic neuropathic pain. Melzack and Wall proposed that the spinal cord has a gate control that either stops or allows pain from being transmitted (Blummenfeld, 2002).

Electrical and magnetic neural stimulation induces significant and long-lasting neuroplastic effects (Hallett, 2000) that involve neurochemical markers for neuroplasticity such as brain-derived neurotrophic factor (BDNF) and GluR1 subunit of AMPA receptor (Gersner et al., 2011). rTMS has been found to increase these markers in awake animals and to decrease them in anesthetized animals for 3 days after stimulation; thus, suggesting potential long term effects. Fritsch et al. (2010) showed similar results in an animal study, where tDCS was able to induce long-term potentiation (LTP). These studies support the long-lasting effects of brain stimulation techniques.

As a large portion of patients with pain due to SCI is refractory to pharmacological treatment, several neuromodulatory interventions are under investigation in an effort to target chronic pain in this population. In addition, because neuropathic pain in SCI presents the classical characteristics of mal-adaptive plasticity, it is a desirable type of neuropathic to understand the effects of targeted neural stimulation.

In this article, we reviewed the safety and efficacy of the main techniques of electromagnetic stimulation for the treatment of chronic pain such as transcranial Direct Current Stimulation (tDCS), repetitive Transcranial Magnetical Stimulation (rTMS), Cranial Electrotherapy Stimulation (CES), Transcutaneous Electrical Nerve Stimulation (TENS), Spinal Cord Stimulation (SCS) and Motor Cortex Stimulation (MCS), and also explored potential factors that may be related to treatment response.

Targeted therapies using electromagnetic neural stimulation (Fig. 1)

TENS

During TENS, electrical current is applied over the skin with different frequency and intensity pulses. In SCI neuropathic pain, 4 electrodes are positioned paraspinally, and settings for either high frequency (80 Hz) or low frequency (2 Hz) are applied (Norrbrink, 2009). In addition to the postulated gate control mechanisms of TENS, low frequency TENS has also shown to induce a release of enkephalins and endorphins to control pain (Norrbrink, 2009). There is a third type of stimulation called burst TENS, which uses a very small frequency of 1–4 Hz with trains of 100 Hz, however, it has not been extensively studied for SCI pain. The main side effects include skin burns and irritation.

Table 1
Neuromodulatory interventions for SCI pain.

Techniques	Not invasive				Invasive	
	tDCS	rTMS	CES	TENS	SCS	MCS
Principle	Small direct current throughout the scalp that induces changes in brain excitability	Magnetic current delivered through an 8-coil wire that produces pulses inducing neuronal depolarization	Microcurrent electrical therapy to modulate cortical activity	Transcutaneous electrical stimulation with small currents	Surgical epidural placement of electrodes to apply small currents throughout the spinal cord	Motor cortex dural placement of electrodes for stimulation with small electrical current
Typical anatomical landmarks for stimulation	Electrode 1: motor cortex (M1) (C3–C4 en 10/20 EEG system) Electrode 2: contralateral supraorbital area	Motor cortex "hot spot" for activation of left FDI muscle	Ear clip electrodes	Area of intact or preserved sensibility at and directly above the level of the lesion, paraspinally	Electrodes placed percutaneously or through small laminectomy, usually between C5 and T1 for upper limb pain and between T9 and T11 for lower limb pain	Quadripolar stimulation electrode in the epidural space in light of the motor cortex contralateral to the painful area
Typical electrode size	2 electrodes, 35 cm² each	Not present	Two ear clip electrodes	4 electrodes, 40 × 60 mm	Arrays of 4, 8 or 16 electrodes for surgical electrodes or 1 × 8 or 1 × 4 for percutaneous electrodes	40 × 50 mm
Type of current delivered	Constant current at 2 mA	Magnetic field of 1–4 T rTMS: 20 trains of 10 Hz stimuli delivered for a duration of 5 s. rTMS is applied at 80% of the RMT intensity with a 55 m intertrain interval	0.1 mA	High frequency (80 Hz) Low frequency (2 Hz)	55–60 Hz with pulse widths of 210–300 μs and amplitudes between 1.5 and 6 V	0.5 to 5 V 30 to 80 Hz, the pulse width from 60 to 330 ms (mean 140)
Typical time for stimulation	20 min	20–30 min	20 min–1 h daily	30–40 min three times a day	1–2 h, three times a day	30–120 min daily
Side effects	Tingling, itching, redness	Pain at the site of stimulation, muscle twitching during treatment sessions, headache, tooth pain	Mild skin irritation, transient blurring of vision, slight dizziness, headache, giddiness, tooth pain	Skin burns or irritation	Lead migration, lead breakage, and infection	Lead migration, lead breakage, and infection

TDCS

tDCS uses a small weak current applied through two oppositely charged electrodes on the scalp to induce neuroplastic changes that can alter pain perception in patients with SCI. One electrode is placed on the scalp over the motor cortex, while the other electrode is placed over the supraorbital area, contralateral to the first electrode. Both electrodes are connected to a battery-powered device that induces a constant electrical current of 2 mA for approximately 20 min. The main reported side effects of tDCS are headache, dizziness, nausea, itchiness, as well as irritation under the area of the electrodes (Fregni et al., 2006a, 2006b). A modified type of tDCS called High Definition tDCS (HD-tDCS) that uses a different array of specialized compact electrodes in an attempt to focalize the current to specific cortical areas, is under study (Borckardt et al., 2012).

TMS

The other non-invasive brain stimulation technique, TMS, is applied through a magnetic coil that induces a transient high-intensity magnetic pulse that penetrates through the scalp, skull and meninges and causes neurons to depolarize and generate action potentials. Just like tDCS, TMS also uses the primary motor cortex as a target point of stimulation on the scalp (Wagner et al., 2007). However, it is essential to point out that induced currents by TMS and tDCS are fundamentally different; thus are associated with different underlying mechanisms. When applied repetitively, rTMS can induce effects that last outlast the stimulation session (Wagner et al., 2007). The main reported adverse effects of TMS are temporary auditory threshold shifts if no protection is used (due to the clicking sound generated by the device), mild transient headache or neck pain (Rossi et al., 2009). Although TMS-induced seizures have been reported, this instance is rare and highly dependent on stimulation parameters and clinical characteristics of subjects receiving TMS.

CES

Cranial Electrotherapy Stimulation (CES) uses a microcurrent similar to tDCS, to modulate electrical activity. One of the differences lies in the position of the electrodes, which are normally located over the ear lobules (Tan et al., 2006). The current is also smaller (100 μA) when compared to tDCS current and can have different waveforms depending on the device, which might induce variable stimulation patterns. Recently, a modeling study using different electrode montages for CES showed that the current can reach deeper brain structures according to the montage and that the magnitude of the current is preserved from cortical to subcortical areas (Datta et al., 2012), though this finding needs to be confirmed in further studies assessing subcortical changes using neurophysiological tools. Stimulation times vary from 20 min to 1 h. Side effects include mild skin irritation, transient blurring of vision, slight dizziness, headache, giddiness and tooth pain (Wagner et al., 2007).

SCS and MCS

Several techniques of invasive targeted neurostimulation have been developed and tested in SCI. These invasive techniques are based on stimulation of the spinal cord or brain structures. SCS is an invasive procedure that requires epidural placement of the electrodes either percutaneously or through laminectomy. The epidural stimulation of the spinal cord might decrease the conduction of pain in the spinothalamic tract or re-establish sensory afference, thus interrupting processing associated with pain related maladaptive plasticity (Kumar et al., 1998). The electrodes are connected to an external pulse generator that produces pulses of 50–60 Hz with pulse widths of 200–300 ms and amplitudes between 1.5 and 1.6 V. The duration for stimulation ranges from 1 to 2 h, three times a day. The main side effects are lead migration, lead breakage, infection, spinal taps, epidural punctures, seromas, hematomas and spinal cord trauma (Golovac, 2010). Although MCS has been
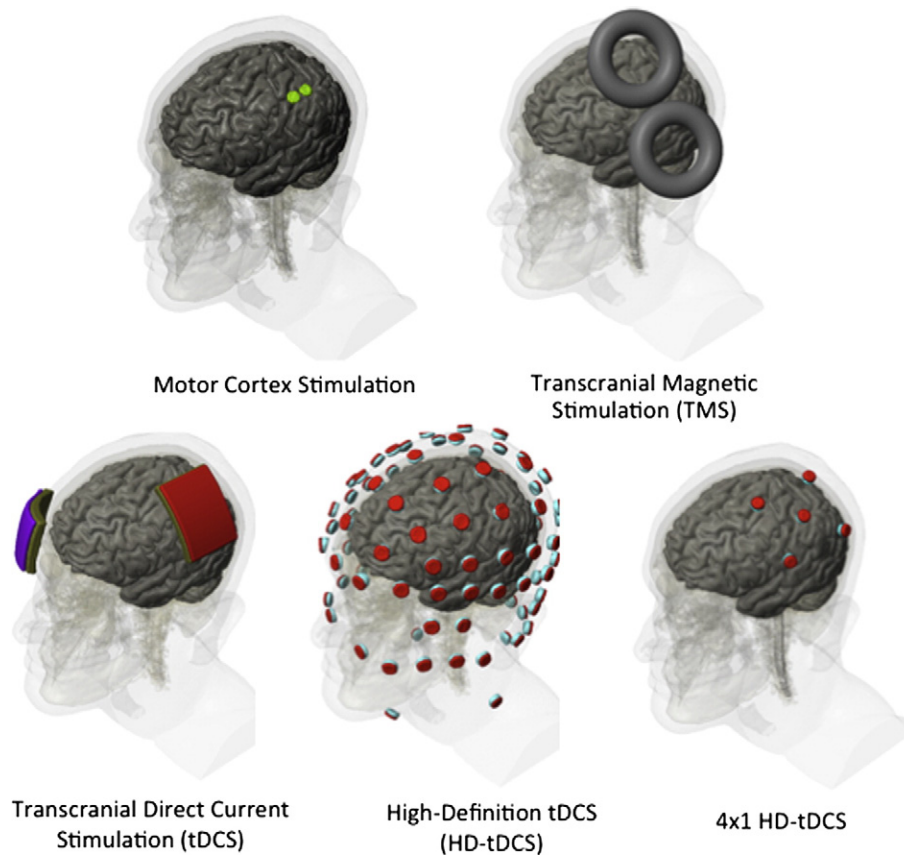
Fig. 1. Overview of selected technologies for invasive and non-invasive neuromodulation. Motor Cortex Stimulation uses electrodes positioned on the cortex. Transcranial Magnetic Stimulation used magnets to non-invasivly induce current in the brain. Transcranial Direct Current stimulation passes direct current though two electrodes on the scalp. High-Definition transcranial Direct Current Stimulation (HD-tDCS) uses arrays of scalp electrode to guide current to brain structures for example using the 4×1 HD-tDCS montage.

used for the treatment of chronic pain, we did not find trials meeting our inclusion criteria testing MCS for chronic pain in SCI.

Methods

Literature review

The first step of our systematic review was to perform a literature search utilizing the PubMed research database. In addition, we examined reference lists of the retrieved papers. We performed a literature search utilizing search terms "Spinal Cord Injury" and "pain" and "transcranial stimulation" prior to 06/06/2012. We included studies from 1998 to 2012. This initial search resulted in 4 articles. We repeated the search with the terms "Spinal Cord Injury" and "pain" and "electrotherapy" that resulted in 2 additional articles. A new search with the terms "Spinal Cord Injury" and "pain" and "transcutaneous stimulation" resulted in 2 more articles. Finally, we also used "spinal cord stimulation" and "motor cortex stimulation" as the search terms associated with "Spinal Cord Injury" and "pain" resulted in 28 articles. We found a total of 36 articles related to the use of electromagnetic neural stimulation (tDCS, HD-tDCS, rTMS, CES, TENS, SCS and MCS) as a treatment tool for chronic pain in SCI. We subsequently checked each article according to our inclusion criteria. To assess quality of the studies we used the Jadad score, which includes methodological characteristics such as randomization, blinding and a description of withdrawals and dropouts (Jadad et al., 1996).

Selection criteria

We adopted the following inclusion criteria: 1) articles written in English; 2) interventions using electromagnetic neural stimulation

techniques (tDCS, HD-tDCS, rTMS, CES, TENS, SCS and MCS) for chronic pain in SCI; 3) use of quantitative scales to measure pain (VAS, NRS); 4) studies published in a journal or indexed abstracts; 5) studies reporting pain outcomes before and after treatment; and 6) description of the SCI population. Articles were excluded if they failed to 1) include SCI subjects, 2) include pain outcomes, or 3) include tDCS, rTMS, CES, TENS, SCS and MCS as treatments. Other exclusions included 4) reviews, editorials, letters, 5) animal or pediatric populations, and 6) case reports or sample sizes ≤2 patients. Using these criteria, we included 8 clinical trials and one naturalistic study that evaluated the effects of electromagnetic neural stimulation techniques (tDCS, HD-tDCS, rTMS, CES, TENS, SCS and MCS) for chronic pain in SCI.

Data extraction

The data was extracted by 2 authors (FF and IMD) using a structured form. The following variables were extracted: 1) mean pain scores at baseline, post-intervention and follow-up (if available) and standard deviation (when available) of pain scales for the active and control groups; 2) demographic, clinical, and treatment characteristics (e.g., number of subjects in the control and treatment groups, age, gender, baseline characteristics, nature of injury (complete vs. incomplete), etiology (traumatic vs. non-traumatic), level of injury (cervical vs. below cervical), classification of pain (neuropathic including at level and below level pain vs. others including musculoskeletal and visceral pain), timing of pain (continuous, paroxysmal), site of pain and duration of SCI); 3) intervention protocol type; 4) stimulation parameters for each neuromodulation technique (type of stimulation, number of electrodes (if applicable), frequency, intensity, principle of the technique, anatomical landmarks for

stimulation, type of current, timing of stimulation and side effects); 5) concomitant treatments (therapy and medications); and 6) number of responders in each group (if available). When a study did not report the standard deviation for pain outcomes, we deduced them from other parameters or made a note as to their availability.

Quantitative analysis and statistical analysis

In addition to the descriptive report of results, we also performed initial exploratory studies given the limited data. We utilized Cohen's d to estimate the standardized mean difference (also known as effect size) for each study, which was calculated by comparing pre- and post-treatment mean changes between the treatment groups divided by the pooled standard deviation between measurements. We classified the studies according to the outcome in three categories: *highly responsive*, *responsive* and *non-responsive*. The studies were classified as non-responsive if there was no significant change ($p > 0.05$) between pain scores at baseline and after the treatment or if the Cohen's d is below 0.5. Studies were classified as responsive if there was a significant change of the pain scores between baseline and after treatment but the Cohen's d (if reported or possible to calculate) was below 0.5 or, when the standardized mean difference was unavailable, if the proportion of responders was less than 35%. If the change on pain scores was significant and the standardized mean difference equal or higher than 0.5 or the proportion of responders higher or equal than 35%, then the study was classified as highly responsive (see Table 2).

Results

Study characteristics

Eight clinical trials and one observational study (nine studies in total) met our inclusion criteria. The techniques used in these trials were tDCS (three studies), CES (two studies), rTMS (two studies), TENS (one study) and there was one naturalistic study testing SCS (see Table 1). We did not find clinical trials either for HD-tDCS or motor cortex stimulation (MCS).

In terms of demographic and stimulation characteristics, there was an important heterogeneity in the population investigated in these studies. Male was the predominant gender in all studies and age varied between 24 and 74 years old. Most of the subjects included in the studies had complete SCI injury of traumatic etiology, located below cervical level (Fregni et al., 2006a, 2006b; Kang et al., 2009; Kumru et al., 2013; Norrbrink, 2009; Soler et al., 2010; Tan et al., 2006, 2011). The duration of the injury varied between 6 months (Tan et al., 2011) and 20 years (Kang et al., 2009). Most of the studies that reported the onset of stimulation started the intervention between 6 months and 3.7 years after SCI (Fregni et al., 2006a, 2006b; Tan et al., 2011). Parameters of stimulation across studies also varied significantly, for instance, duration of stimulation varied from 30–120 min administered daily (Fregni et al., 2006a, 2006b; Kang et al., 2009; Kumru et al., 2013; Soler et al., 2010; Tan et al., 2006, 2011) to 30–40 min sessions three times a day (Kumar et al., 1998; Norrbrink, 2009).

Clinical trial characteristics

We assessed the design of these trials. Six were randomized parallel clinical trials (Defrin et al., 2007; Fregni et al., 2006a, 2006b; Soler et al., 2010; Tan et al., 2006, 2011). Two studies were crossover trials (Kang et al., 2009; Norrbrink, 2009) and two studies were non-controlled, open-label trials (Kumar et al., 1998; Kumru et al., 2013). As to assess quality of these studies we used the Jadad scale. Five studies had an overall satisfactory quality with Jadad scores of 3 (Defrin et al., 2007; Tan et al., 2006) and 5 (Fregni et al., 2006a, 2006b; Soler et al., 2010;

Tan et al., 2011) whereas four studies (Kang et al., 2009; Kumar et al., 1998; Kumru et al., 2013; Norrbrink, 2009) had low Jadad scores showing a potential increase for bias.

Most of the outcomes used in these studies were clinical outcomes. The Visual Analogue Scale (VAS), Numbered Rating Scale (NRS), Brief Pain Inventories (BPI), McGill pain questionnaire (MPQ) and Multidimentional Pain Inventory (MPI) were used for pain; the Beck Depression Inventory was used to assess depression; and the VAS was used to assess anxiety. Only one study conducted quantitative sensory testing combined with evoked potentials (Kumru et al., 2013).

Combination therapy and confounders

Different approaches were tested using these neuromodulation tools. One of them was to combine neuromodulation techniques with behavioral interventions. Two studies used tDCS combined with visual illusion (VI) (Kumru et al., 2013; Soler et al., 2010). Soler et al. (2010) showed that after the last day of stimulation pain scores were reduced by 29.7% in the tDCS + VI group when compared to the VI group alone ($p = 0.008$) and the sham stimulation group alone ($p = 0.004$). A significant effect (pain reduction by approximately 30% in the tDCS + VI group) remained at the last visit and the three follow-up evaluations. In the follow-up study from the same group (Kumru et al., 2013), 72.3% of the subjects with SCI and neuropathic pain who received tDCS combined with VI treatment also reported a large mean reduction of 50% in the pain scores ($p < 0.05$). Although this follow-up study had no placebo control, the main goal was to assess neurophysiological changes (on evoked potentials and quantitative thermal testing) associated with the combined intervention. The authors found a significant decrease of contact heat-evoked potential N2/P2 amplitude as compared with baseline. Furthermore, this reduction was significantly larger in subjects who had larger pain reduction.

Because medications are an important confounder for the effects of neural stimulation on neuroplasticity, we reviewed whether electromagnetic stimulation was given together with drugs. Two studies explored this combination (Fregni et al., 2006a, 2006b; Soler et al., 2010) however, the medications varied from antidepressants such as amitryptiline to antiepileptics (gabapentin, pregabalin), neuroleptics, benzodiazepines (clonazepam) and opioids (fentanyl, ketamine, oxycodone, tramadol), making difficult to understand whether combination with drugs have an increased, decreased or no effect.

Efficacy and adverse effects

In terms of efficacy and according to our criteria, four studies were classified as highly responsive (Fregni et al., 2006a, 2006b; Kumru et al., 2013; Soler et al., 2010; Tan et al., 2011), one as responsive (Defrin et al., 2007) and four as non-responsive (Kang et al., 2009; Kumar et al., 1998; Norrbrink, 2009; Tan et al., 2006). We then assessed in an exploratory manner factors related to response to neuromodulation. Studies in the highly responsive group (Fregni et al., 2006a, 2006b; Kumru et al., 2013; Soler et al., 2010; Tan et al., 2011) were heterogeneous in terms of the nature of the injury (complete vs. incomplete), the etiology (traumatic vs. non-traumatic), age, gender, time since SCI or duration of pain; thus suggesting that these factors are less likely to play an important role. Interestingly, it appears that presence of dysesthesia, paroxysmal pain (Fregni et al., 2006a, 2006b; Soler et al., 2010), location of SCI in thoracic and lumbar segments and pain in the lower limbs were associated with a positive response to neuromodulation. In particular, injuries in thoracic and lumbar were significantly associated with better outcomes compared to cervical regions and pain in lower limbs was also significantly associated with better outcomes compared to pain in upper limbs (Fregni et al., 2006a, 2006b). Similarly, the responsive study (Defrin et al., 2007) also demonstrated that subjects with incomplete injuries or neuropathic pain with paroxysms responded better to neuromodulation.

Table 2
Studies on non-invasive brain stimulation for chronic pain in SCI.

Studies	Type of study	Sample size	Intervention	Nature of injury		Etiology of SCI	
				Complete	Incomplete	Traumatic	No trauma
Very responsive							
Fregni et al. (2006a, 2006b) A Sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury	Randomized, double-blinded, placebo-controlled, single-center, phase II parallel-group	17	tDCS for 5 days (Sham vs. Active)	11 (8 Active)	6 (3 Active)	17	None
Tan et al. (2011) Efficacy of cranial electrotherapy stimulation for neuropathic pain following spinal cord injury: a multi-site randomized controlled trial with a secondary 6-month open-label phase	Multi-site, double-blind, sham-controlled study with a blinded phase for 21 days	105	CES for 21 days (Sham vs. Active)	19/105 Active 23/105 Sham	24/105 Active 28/105 Sham Unknown 11/105	N/R	N/R
Soler et al. (2010) Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury	Placebo-controlled, double blind, parallel group design (factorial design)	39	tDCS + VI	tDCS + VI: 8/10 tDCS: 8/10 VI: 7/9 Placebo: 8/10	tDCS + VI: 2/10 tDCS: 2/10 VI:2/9 Placebo:2/10	tDCS + VI: 7/10 tDCS: 8/10 VI: 6/9 Placebo:8/10	tDCS + VI: 3/10 tDCS: 2/10 VI: 3/9 Placebo: 2/10
Kumru et al. (2013) The effects of transcranial direct current stimulation with visual illusion in neuropathic pain (NP) due to spinal cord injury: An evoked potentials and quantitative thermal testing study	Uncontrolled, unblinded clinical trial	52 (18 with SCI + NP, 20 with SCI w/o NP, 14 healthy)	tDCS + VI for 2 weeks only in SCI + NP	SCI + NP: 3/18 SCI not NP: 4/20	SCI + NP: 15/18 SCI not NP: 16/20	SCI + NP: 8/18 SCI not NP: 17/20	SCI + NP: 10/18 SCI not NP: 3/20
Responsive							
Defrin et al. (2007) The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury	Double-blind randomized controlled trial	11	rTMS for 10 days (Active vs. Sham)	N/R	N/R	11/11	0
Non-responsive							
Kang et al. (2009) Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury	Randomized, double-blinded, crossover	11	rTMS for 5 days (Active vs. Sham)	3	8	N/R	N/R
Kumar et al. (1998) Epidural spinal cord stimulation for treatment of chronic pain— some predictors of success. A 15-year experience	Naturalistic study	10	Epidural SCS	N/R but found no response	N/R but found fairly good response	N/R	N/R but found good response
Norrbrink (2009) Transcutaneous electrical nerve stimulation	Crossover, unblinded, Clinical trial	24	HF-TENS vs LF-TENS for two weeks	N/R	N/R	16	8
Tan et al. (2006) Using cranial electrotherapy stimulation to treat pain associated with spinal cord injury	Double-blind, Sham controlled study with a blinded phase for 21 days	38	CES for 21 days (Sham vs. Active)	N/R	N/R	Sham 90% (18/20) Active 83%(15/18)	Sham 10% (2/10) Active 17% (3/18)
N/R: not reported	tDCS: transcranial Direct Current Stimulation				VI: Visual Illusion		

Overall, the effects were heterogeneous. The four studies showing relatively large and significant pain improvements after stimulation (Fregni et al., 2006a, 2006b; Kumru et al., 2013; Soler et al., 2010; Tan et al., 2011) used the following interventions: tDCS alone, tDCS + VI and CES. These studies tested interventions targeting different levels of the nervous system such as the primary motor cortex (tDCS) and the hypothalamic region (CES). On the other hand, studies showing less or no effect used rTMS, CES, TENS and SCS and aimed at different or sometimes at the same targets of nervous system such as brain motor cortex (rTMS), hypothalamus (CES), peripheral nerves (TENS) and the dorsal horn (SCS).

One important question in the neuromodulation field is whether analgesic effects induced by neuromodulation tools are long-lasting. Only four studies investigated the effects of neuromodulation after the end of treatment sessions; assessing the effects of up to 4.5 weeks (Defrin et al., 2007; Fregni et al., 2006a, 2006b; Kang et al., 2009; Soler et al., 2010). They show that the effect was significant for a study with tDCS and visual illusion (Cohen's d = 0.61) after 12 weeks (Soler et al., 2010) while Kang et al. (2009) using TMS and Fregni et al. (2006a, 2006b) using tDCS did not find any significant difference between baseline and follow-up at 3 weeks (Cohen's d = 0.091) and 16 days (p = 0.1) respectively.

One encouraging finding was the lack of moderate and severe adverse effects in these studies. Five studies (Defrin et al., 2007; Kang et al., 2009; Kumar et al., 1998; Kumru et al., 2013; Tan et al., 2006) did not report adverse effects or reported as absent. Four studies (Fregni et al., 2006a, 2006b; Norrbrink, 2009; Soler et al., 2010; Tan et al., 2011) reported the following minor adverse effects: mild headache, itchiness, tiredness, tingling sensation, small electric feeling, drowsiness, sleepiness, dizziness and muscle spasms. None of the studies

Level of injury		Age	Sex	Type of pain	Presence of paroxysms	Location of pain
Cervical	Below					
9/17, 5 in Active	8/17, 6 in Active	36.6	M 82%, F 18%	Burning (76.5%), stabbing (58.9%), tingling (35.3%)	17.6%	Lower limbs (64.7%), back pain (29.4%), pain in the upper limb (17.6%)
Active: 19/105 Sham: 17/105	Active 27/105 Sham 39/105	Active: 52+/−10.5 Sham: 52.5+/−11.7	Active: M 38% Sham: M 52%	100% neuropathic	N/R	N/R
tDCS + VI:4/10 tDCS: 1/10 VI: 1/9 Placebo:4/10	tDCS + VI:6/10 tDCS: 9/10 VI: 8/9 Placebo: 6/10	43.5	tDCS + VI: M 80%, F 20% tDCS: M 90%, F 10%	100% neuropathic	22/39	Lower limbs 35/39, abdomen 14/39, upper limbs 4/39, genital 2/39, thoracic 4/39
SCI + NP: 7/18 SCI not NP: 7/20	SCI + NP: 11/18 SCI not NP: 13/20	SCI + NP: 49.4+/−12.4 SCI not NP: 45.5+/−11.6	SCI + NP: M 67%, F 33% SCI not NP: M 50%, F 50%	50% neuropathic	N/R	Arms: 3/18 Legs: 10/18 Abdomen: 4/18 Genital area: 2/18
0	11/11	52	Active: M 66% Sham: M 60%	N/R	N/R	Lower limbs 100%
5/11,	6/11,	54.8 +/−13	M 55%; F 45%	Neuropathic (pricking, tingling, hot burning, stabbing, shooting)	N/R	Lower limbs (100%), trunk (27%), pelvis (36%)
N/R	N/R but found fairly good response	N/R	N/R	N/R	N/R	N/R
13	11	47.2+/−11.2	M80% F: 20%	100% neuropathic	N/R	N/R
Sham 20% (4/20) Active 22% (4/18)	Sham 80% (16/20) Active 77% (14/18)	Sham 42–82 Active 38–74	100% M	Sham: Neuropathic 55%, musculskeletal 45% Active: neuropathic 67%, musculoskeletal 33%	N/R	N/R

(continued on next page)

reported any serious adverse effects defined by FDA as death, life threatening, hospitalizations, disability, permanent damage or congenital anomalies.

Table 2 summarizes the results and design of each individual study considered in this review. We found trials testing three techniques of non-invasive brain stimulation: rTMS, tDCS and CES. Results were mixed though trials testing the use of tDCS were consistently positive.

Discussion

Eight clinical trials and one naturalistic observational study met the inclusion criteria. Among the clinical trials, three studies assessed the effects with tDCS; two with CES; two with rTMS and one with TENS. The naturalistic study assessed the effects of SCS. We did not find trials for epidural motor cortex stimulation (MCS). Parameters of stimulation and also clinical characteristics varied significantly across studies. Three out of eight studies showed large effects sizes (0.73, 0.88 and 1.86 respectively) for pain reduction. The presence of characteristics of neuropathic pain such as dysesthesia, paroxysmal pain, location of SCI in thoracic and lumbar segments and pain in lower limbs seem to be associated with a positive response to neuromodulation. No significant adverse effects were reported in these studies. Based on our fields we discuss 5 important issues on development of targeted neurostimulation therapies for chronic pain in SCI.

1st—should testing of targeted neurostimulation for SCI pain continue?

Although we only found a small number of studies testing this approach for the treatment of chronic pain in SCI and they used different techniques which resulted in varied outcomes; the lack of significant

Table 2 (continued)

Studies	Duration of SCI	Mean VAS at baseline	Mean VAS after intervention	Reduction in pain scores	Responders	Effect size
Very responsive						
Fregni et al. (2006a, 2006b) A Sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury	3.7 years (mean)	Active: 6.2	Active: 2.6	58% (p = 0.0001)	7/8 (88%) responders	Not enough data for calculation
Tan et al. (2011) Efficacy of cranial electrotherapy stimulation for neuropathic pain following spinal cord injury: a multi-site randomized controlled trial with a secondary 6-month open-label phase	6 months	Active 5.6	Active 2.2	60% (p = 0.001)	N/R	0.73
Soler et al. (2010) Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury	N/R but found no correlation	tDCS + VI: 7.5 +/−1.2 tDCS: 6.3 +/−2 VI: 7.2 +/−1.6 Placebo: 7.1 +/−1.5	tDCS + VI: 5.2 +/−1.2 tDCS: 5.3 +/−2.6 VI: 6.4 +/−1.6 Placebo: 6.6 +/−1.9	tDCS + VI: 30% (p < 0.005) tDCS: 15% (p < 0.005) VI: 10% (p < 0.005) Placebo: 5% (p < 0.005)	30% of patients in the tDCS + VI.30% of patients in the tDCS	0.88
Kumru et al. (2013) The effects of transcranial direct current stimulation with visual illusion in neuropathic pain (NP) due to spinal cord injury: An evoked potentials and quantitative thermal testing study	SCI + NP: 8.3 SCI not NP: 9.6	SCI + NP: 7.8 +/−0.9	SCI + NP: 4.9 +/−2.8	50% (p < 0.05)	72.3% in the SCI + NP group	1.86
Responsive						
Defrin et al. (2007)The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury	N/R	N/R	N/R	30% reduction in intensity of pain in Active (p < 0.05)	30% in Active	Not enough data for calculation
Non-responsive						
Kang et al. (2009) Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury	15−231 months	Active 6.45 +/−2.25 Placebo 6.18 +/−1.83	Active 5.82 +/−1.47 Placebo 5.09 +/−1.87	No significant change (p > 0.05)	N/R	0.43
Kumar et al. (1998) Epidural spinal cord stimulation for treatment of chronic pain— some predictors of success. A 15-year experience	N/R	N/R	N/R	No significant change (p > 0.05)	N/R	Not enough data for calculation
Norrbrink (2009) Transcutaneous electrical nerve stimulation	N/R	HF: 4 LF: 4	HF: 3.8 LF: 3.9	No significant change (p > 0.05)	29% in HF TENS	Not enough data for calculation
Tan et al. (2006) Using cranial electrotherapy stimulation to treat pain associated with spinal cord injury	N/R	Active 6.46 +/−1.95 Placebo 6.08 +/−2.42	Active 5.73 +/−2.56 Placebo 6.00 +/−2.41	No significant change (p > 0.05)	N/R	0.1

N/R: not reported

adverse effects, the adequate quality of studies (given Jadad scores) and the initial efficacy results of some strategies encourage further research in this area. Many questions remain to be answered in this field, such as the optimal parameters of stimulation, determining the best responders for this treatment and whether results could be replicated in larger clinical trials. Finally, results of targeted neurostimulation, especially non-invasive devices, support further exploration of this technique.

2nd—development of novel interventions aiming to reduce or block maladaptive plasticity in chronic pain

The field of neuromodulation for the treatment of pain has rapidly developed in the last few years. One of the main reasons is the better understanding of the mechanisms of chronic neuropathic pain and the underlying mechanisms of neuromodulation techniques. Neuropathic pain in SCI is reported as severe or very intense in approximately 32–58% of this population (Siddall et al., 2003). The sustaining and refractory nature of this pain is associated with functional and anatomical neuroplastic changes in the neural circuitry of chronic pain; sharing similar mechanisms with learned behaviors such as motor learning. In this context, chronic neuropathic pain has been referred to as maladaptive plasticity.

The techniques of noninvasive brain stimulation target different structures and it is still unclear what is the best target to modulate plasticity in the neuromatrix of pain. While rTMS and tDCS target the primary motor cortex, CES might have an effect on brainstem structures due to cortical–subcortical connections (Datta et al., 2012) while TENS directly stimulates peripheral nerves locally. The trial included in this review testing TENS did not find any statistically significant differences between the group in high frequency TENS vs. low frequency TENS (Norrbrink, 2009). In this study, the authors suggest that lack of effects is due to methodological issues such as lack of a control group, use of different outcome measures and stimulation

parameters compared with published studies. Indeed although TENS is an interesting alternative for chronic neuropathic pain, its effects are mainly based on bottom-up neural modulation. Given the effects of neuropathic pain on central neural circuits; techniques of central modulation may be more effective.

The effects of M1 stimulation, on the other hand, are based on secondary modulation of critical pain modulating areas such as thalamic nuclei (Fregni et al., 2006a, 2006b). Although CES is also a technique targeting cortical neural structures, its effects are shown to modulate deeper areas involved in the emotional component of pain such as the hippocampus and some nuclei of brainstem (Datta et al., 2012; Tan et al., 2011) probably through a secondary modulation from the cortex in a similar fashion as tDCS. In fact, a recent modeling study has shown that CES current can reach subcortical areas with peak electrical fields similar to those in cortical regions (Datta et al., 2012). One important issue is that although rTMS and tDCS target similar structures they have different mechanisms of action; rTMS induces supra-threshold pulsed stimulation (Brunelin et al., 2007), while tDCS uses weak electrical currents to increase the excitability of pain modulating areas in the brain (Fregni et al., 2006a, 2006b). Only few studies measured long lasting effects (Defrin et al., 2007; Fregni et al., 2006a, 2006b; Kang et al., 2009; Soler et al., 2010). One of these studies suggest that there could be significant differences in pain scores at 12 weeks follow-up (Soler et al., 2010), while the other studies did not find any significant difference (Fregni et al., 2006a, 2006b; Kang et al., 2009).

3rd—finding the best responders as to optimize future clinical trials

One important issue is whether the response to stimulation varies within people with SCI. The relationship of pain with other variables such as level of injury, etiology, completeness of SCI and psychosocial issues has not been extensively studied. Some studies (Margot-Duclot et al., 2009; Siddall et al., 1999) have suggested that variables such as advanced age at the time of injury (pain is rare for SCI in childhood), bullet injury as a cause of trauma (more severe pain and negative impact in quality of life) (Richards et al., 1990), onset of pain early in the weeks following the injury and initial nature (influencing the intensity level of pain and the severity of pain after five years) and onset intensity that predicts continuity of pain and associated symptoms (fatigue, infection, spasticity, constipation, urine retention, joint mobilization, mood changes) are negative prognostic factors. One study has established variables such as injury related factors, level of injury (Siddall et al., 1999), complete or incomplete injury (Siddall et al., 1999), previous SCI surgery and gender as non-valid predictors for developing chronic pain (Margot-Duclot et al., 2009). Because this review included studies with different methodologies and heterogeneous samples, it is difficult to make any substantial conclusions on best predictors of response; but it appears that characteristics associated with neuropathic pain such as dysesthesia (defined as an unpleasant burning sensation in response to touch), paroxysmal pain, location of SCI in thoracic and lumbar segments and pain in lower limbs (suggesting sublesional pain) are associated with positive response to brain stimulation.

Some insights on best responders also may be given from studies using neuromodulatory techniques in other conditions such as major depression. Factors related with a positive response to rTMS in subjects with depression include absence of anxiety disorders, high number of prior treatment failures (Lisanby et al., 2009), high level of sleep disturbances, low level of treatment resistance, short duration of a depressive episode (Brakemeier et al., 2007), psychosis, younger age and previous response to rTMS therapy (Brunelin et al., 2007). Negative predictors include treatment refractoriness and older age (Fregni et al., 2006a, 2006b). Some researchers have used neurophysiological measurements to predict the response to brain stimulation. In a study performed by Arns M et al. they used EEG

and Evoked Related Potentials (ERP) in 90 subjects with depression treated with rTMS and psychotherapy to identify predictors of non-response. In this study increased fronto-central theta EEG power, slower anterior individual alpha peak frequency, and larger P300 amplitude were seen in non-responders (Arns et al., 2012). Researchers have also included measurements such as cerebral blood flow to predict response to neuromodulation in subjects with depression. One trial (Kito et al., 2012) used the ratio of cerebral blood flow in the dorsolateral prefrontal cortex to the ventromedial prefrontal cortex showing that treatment response was positively correlated with a lower ratio, which could be used as a predictor to response.

4th—using neurophysiological markers to find good responders and optimize parameters of stimulation

The development of the field of brain stimulation has been based on off- and on-line monitoring of neurophysiological activity during stimulation as to optimize parameters of stimulation. Although this strategy is useful, there are still several challenges for such feedback system. One of them is to find the neural signature of chronic pain. Although recent studies have shown promising results in this area such as with fMRI (Antal et al., 2012; Pereira et al., 2013; Polania et al., 2012), EEG (Antal et al., 2012; Faria et al., 2012; Kimiskidis et al., 2013) and TMS (Cengiz et al., 2013; Datta et al., 2012; Kuo et al., in press), none of the studies we included used neurophysiological or cerebral blood flow measurements in SCI subjects to investigate combined closed loop systems with electromagnetic stimulation. One marker that has been extensively investigated in chronic pain is motor cortex excitability as indexed by TMS. Recent studies show defective intracortical inhibition in chronic pain (Zaghi et al., 2011). Future studies should include these tools to analyze its role as predictors and also to optimize parameters of stimulation in SCI pain.

5th—exploring combined approaches with targeted electromagnetic neural stimulation

Two studies investigated the use of concomitant drugs with neuromodulatory interventions. Assessing this issue is important as many medications are related to changes in cortical excitability. Ziemann (2004) reported that drugs such as carbamazepine (Schulze-Bonhage et al., 1996; Ziemann et al., 1996a, 1996b), phenytoin (Chen et al., 1997; Mavroudakis et al., 1994) and lamotrigine (Boroojerdi et al., 2001; Tergau et al., 2003; Ziemann et al., 1996a, 1996b) increase the motor threshold in TMS. Others such as lorazepam and thiopental (Ziemann et al., 1996a, 1996b, 1997) decrease motor evoked potentials (MEP). On the other hand, sertraline (Ilic et al., 2002), haloperidol (Ziemann et al., 1997) and ketamine (Di Lazzaro et al., 2003) increase MEPs. At the same time lorazepam, ethanol (Ziemann et al., 1995) and L-DOPA (Ziemann et al., 1997) increase the cortical silent period. Benzodiazepines (Ziemann et al., 1996a, 1996b) and dopaminergic drugs such as cabergoline and bromocriptine (Ziemann et al., 1997) increase short intracortical inhibition (SICI) and decrease intracortical facilitation. Benzodiazepines also decrease short intracortical facilitation. In fact, a recent study has shown that combination of tDCS with antidepressants has a synergistic beneficial effect on mood. In addition, in this study it was also shown that benzodiazepines might decrease the effects of tDCS on mood (Brunoni et al., in press; Bueno et al., 2011).

Limitations

Our study was limited due to the small number of studies included in the analysis; however, adequate quality of most trials provides evidence to support larger clinical trials to assess the effectiveness of targeted neural stimulation methods for the treatment of pain in SCI. An additional limitation involves the use of only one database (PubMed) in the

selection of the studies that were included. In addition, it is possible that negative studies have not been published, because data was limited we were not able to test for heterogeneity or publication bias in this study. Thus our results need to be interpreted in view of this limitation.

Conclusion

Electromagnetic neural stimulation techniques have been developed to offer a potential tool in the management of these patients. Although some of these techniques are associated with large standardized mean differences to reduce pain, we found an important variability in these results across studies. In addition, future studies are needed to investigate optimal parameters of stimulation, as well as predictive factors of response to neuromodulatory techniques using electrical stimulation and also other types of pain in SCI. The relative safety of targeted neural stimulation techniques associated with long-lasting effects makes these techniques attractive therapeutic tools for chronic pain in SCI.

Authors' financial disclosure

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Conflicts of interest

The authors declare no conflict of interest related to this work.

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