Review

Invasive and non-invasive brain stimulation for treatment of neuropathic pain in patients with spinal cord injury: A review

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Context: Past evidence has shown that invasive and non-invasive brain stimulation may be effective for relieving central pain.

Objective: To perform a topical review of the literature on brain neurostimulation techniques in patients with chronic neuropathic pain due to traumatic spinal cord injury (SCI) and to assess the current evidence for their therapeutic efficacy.

Methods: A MEDLINE search was performed using following terms: “Spinal cord injury”, “Neuropathic pain”, “Brain stimulation”, “Deep brain stimulation” (DBS), “Motor cortex stimulation” (MCS), “Transcranial magnetic stimulation” (TMS), “Transcranial direct current stimulation” (tDCS), “Cranial electrotherapy stimulation” (CES).

Results: Invasive neurostimulation therapies, in particular DBS and epidural MCS, have shown promise as treatments for neuropathic and phantom limb pain. However, the long-term efficacy of DBS is low, while MCS has a relatively higher potential with lesser complications than DBS. Among the non-invasive techniques, there is accumulating evidence that repetitive TMS can produce analgesic effects in healthy subjects undergoing laboratory-induced pain and in chronic pain conditions of various etiologies, at least partially and transiently. Another very safe technique of non-invasive brain stimulation – tDCS – applied over the sensory-motor cortex has been reported to decrease pain sensation and increase pain threshold in healthy subjects. CES has also proved to be effective in managing some types of pain, including neuropathic pain in subjects with SCI.

Conclusion: A number of studies have begun to use non-invasive neuromodulatory techniques therapeutically to relieve neuropathic pain and phantom phenomena in patients with SCI. However, further studies are warranted to corroborate the early findings and confirm different targets and stimulation paradigms. The utility of these protocols in combination with pharmacological approaches should also be explored.

Keywords: Pain, Neuropathic, Deep brain stimulation, Motor cortex stimulation, Spinal cord injuries, Transcranial direct current stimulation, Transcranial magnetic stimulation

Introduction

Neuropathic pain and phantom sensations are highly disabling clinical conditions that affect a great number

of individuals following spinal cord injury (SCI) and may have a devastating impact on their quality of life. In addition to changes in motor and sensory functions, these patients report symptoms characteristic of neuropathic pain (at and/or below/above the level of injury), such as spontaneous burning, shooting, and sometimes

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excruciating pain.^{1–3} Turner *et al.*⁴ reported that 79% of 384 subjects with SCI experienced painful sensations; Rintala *et al.*⁵ found that 75% of 77 patients with SCI reported chronic pain.

Chronic pain resulting from SCI may be associated with significant dysfunction of extensive neural networks and abnormal reorganization of the central somatosensory pathways. SCI disrupts ascending and descending spinal tracts that carry information to and from the brain; the injured spinal sensory circuits are the presumable origin of aberrant nociceptive impulses that are interpreted by the brain as pain.⁶ Moreover, integrative thalamic circuits may generate and amplify these nociceptive impulses; changes in sodium channel expression within thalamic neurons are thought to play an important role in the altered processing of somatosensory information after SCI.⁷ However, the pathophysiological mechanisms involved in the development and maintenance of neuropathic pain are not fully understood.⁸

There is increasing evidence that neuropathic pain following SCI, as well as phantom limb pain and other pain syndromes (i.e. complex regional pain), is associated with substantial functional reorganization of central nervous system activity and with hyperexcitability of the somatosensory and motor cortices.

Brain stimulation can influence brain plasticity and may be thus useful for treating chronic pain. Here, we review and critically appraise the most important studies that have employed invasive and non-invasive neuromodulatory brain stimulation to reduce neuropathic and phantom pain in patients with SCI.

The use of electrical stimulation on the human brain for the treatment of chronic pain dates back to the 1950s. Neurostimulation therapy was initially an invasive procedure and required the intervention of a neurosurgeon to implant an impulse generator and electrodes. Up until the 1990s, the only approach was deep brain stimulation (DBS) of the thalamus and other brain regions through surgically implanted electrodes (for a review, see reference 1). DBS has shown promise as a treatment for neuropathic and phantom limb pain. However, its efficacy remains questionable, and the costs and risks of this neurosurgical approach are high, so the treatment should be restricted to patients with severe refractory pain.

Since the early 1990s, various forms of drug-resistant chronic neuropathic pain have been treated with a less invasive type of brain stimulation, termed epidural motor cortex stimulation (EMCS). Currently, EMCS is more frequently used than DBS because it is more easily performed and has a wider range of indication.

More recently, two non-invasive brain stimulation techniques, transcranial direct current stimulation (tDCS), and repetitive transcranial magnetic stimulation (rTMS), which also primarily target the brain cortex, were proposed as suitable methods for cortical excitability modulation. Both techniques have been clinically investigated in healthy volunteers, as well as in patients with various clinical pathologies and a variety of pain syndromes.

A comprehensive review of computerized literature databases and searches to find unpublished trials were performed to minimize publication bias.

The MEDLINE, accessed by Pubmed (1966–July 2012) and EMBASE (1980–July 2012) electronic databases were searched using the medical subject headings “Spinal cord injury”, “Neuropathic pain”, “invasive Brain stimulation”, “non-invasive Brain stimulation” as well as following free terms, combined in multiple search strategies with Boolean operators in order to find relevant articles: “deep brain stimulation”, “motor cortex stimulation”, “transcranial magnetic stimulation”, “transcranial direct current stimulation”, “cranial electrotherapy stimulation”, “phantom”, “motor cortex excitability”, “intracortical inhibition”, “cortical plasticity”.

Two review authors (Y.H. and S.L.) screened the titles and abstracts of the initially identified studies to determine whether they satisfied the selection criteria. Any disagreement was resolved through consensus. Full-text articles were retrieved for the selected titles, and reference lists of the retrieved articles were searched for additional publications. In case of missing or incomplete data, principal investigators of included trials were contacted and additional information requested. No language restrictions were applied.

The two reviewers independently assessed the methodological quality of each study and risk of bias, focusing on blinding and other potential sources of bias. The search strategy described above yielded 77 results. Only articles reporting data on studies using brain neurostimulation techniques in patients with chronic neuropathic pain due to SCI were considered eligible for inclusion; therefore, 22 papers were provisionally selected. We excluded three studies after reading the full published papers; thus, 19 studies contributed to this review: the earliest was published in 1985 and the most recent in 2011.

Invasive brain stimulation

Deep brain stimulation

DBS is a surgical treatment involving the implantation of a battery-operated medical device called a

neurostimulator – similar to a heart pacemaker – that sends electrical signals to specific parts of the brain.^{9,10} DBS in selected brain regions has provided remarkable therapeutic benefits for otherwise treatment-resistant movement and affective disorders such as Parkinson's disease, tremor, dystonia, obsessive or compulsive disorders, and chronic pain.¹¹

It has been hypothesized that DBS generates a depolarizing blockade that mimics the effects observed following lesioning of the same structures, but the exact underlying mechanisms remain unclear. DBS directly alters brain activity in a controlled manner and, unlike lesioning techniques, it is adjustable and reversible. The first attempt at employing therapeutic electrical stimulation of the human brain was carried out by J.L. Pool in 1954.¹² In the following years, electrical stimulation of the septal area and supraoptic nuclei was used to treat pain;^{13,14} patients suffering from deafferentation pain in the 1960s were treated with electrical thalamic stimulation.¹⁵ The earlier studies that led to the development of DBS as employed in the current clinical practice took place in the early 1970s. In the following decades, electrical stimulation of the thalamus, internal capsule, and periaqueductal gray matter or periventricular gray matter (PVG) became commonly used procedures to treat chronic refractory pain.^{16–35} Within the last decade, the number of patients with chronic pain treated with DBS, as well as the number of the published studies, have progressively decreased, mainly because of the lack of solid scientific evidence of DBS safety and efficacy and the development of less invasive alternatives to manage nociceptive pain. Although DBS produced impressive results in a subset of patients, the results were highly variable, and appropriate patient selection seems to be very important.

In an operating room setting, microelectrode recordings and macrostimulation are used to map the targets. Extracellular recordings are made to assess the activity of individual neurons and their receptive fields, defined as the body site(s) where tactile stimulation or movement evoked changes in electrical firing patterns. Microstimulation is used to define projection fields, which are characterized as the body location where the patients perceived a microelectrode stimulus-induced sensation, and is typically performed with 1–100 μ A, 300 Hz, and a 200- μ s pulse width. A stereotactic head frame is applied under local anesthesia. Magnetic resonance imaging (MRI) is performed, and axial T2-weighted images or three-dimensional (3D) inversion recovery axial images are transferred to a neuro-navigation station. Once the surgical site is mapped,

a DBS electrode is implanted into the target. Macrostimulation is usually conducted through the DBS to ensure that there are no adverse effects. The four electrode contacts are systematically explored through monopolar and bipolar stimulation.

Epidural motor cortex stimulation

Namba and Nishimoto³⁴ first reported deafferentation pain relief after cerebral cortex stimulation in 1988.³⁴ Treatment for central neuropathic pain with electrical stimulation of the primary motor cortex (M1) began in the 1990s; Tsubokawa *et al.*³⁵ published his early results regarding the treatment of pharmacologically intractable central pain by EMCS in 1991. Since then, many studies have elaborated on the optimal indications, surgical technique, degree of pain relief, and mechanism of effectiveness. Since the first reports by Tsubokawa *et al.*^{35–37} showing the analgesic effects of M1 stimulation (electrically and chronically), ECMS has been applied worldwide to relieve medically refractory neuropathic pain. This technique is generally proposed to patients with post-stroke or post-traumatic neuropathic pain or trigeminal deafferentation pain.^{38–42} However, the pathophysiological mechanisms underlying analgesic effect of EMCS are still incompletely understood, and this hinders the technique's further development. Thus, EMCS should be considered as a last resort therapy for patients in whom attempts at treating pain with various drugs have failed. In the early descriptions of the procedure, the operation was performed while the patient was under local anesthesia. However, general anesthesia may be used because of the accuracy of target planning achieved with intraoperative 3D image-guided neuronavigation. Before the surgical procedure, the contralateral central sulcus, sylvian fissure, and inferior and superior frontal sulci are usually identified using MRI (1-mm cuts), although computerized tomograms may also be employed. Stimulation is generally performed at a frequency range of 25–55 Hz, pulse width of 90 ms, and amplitude of 1.5–4 V. Bipolar stimulation is used with the negative pole overlying the motor cortex and the positive pole over the sensory cortex. Continuing review of treatment results, especially by prospective study, will provide additional information regarding the optimal indications and techniques and their long-term effectiveness.

This technical procedure was elaborated based on empirical experience,^{35,36} but because the mechanisms underlying the effects of EMCS are still not fully documented,^{43–46} all attempts to improve the technique's efficacy depend on iterative empirical trials, in particular stimulation parameters adjustments. The M1 is

commonly localized with the somatosensory-evoked potential (SEP) phase-reversal technique. Concomitant with SEPs, optimized image-guided surgery is performed by MRI neuronavigation. One or two quadripolar electrodes are implanted over the motor cortex representation of the painful area. The suprasylvian region of the convexity is stimulated if the pain is located in the face and/or upper limb (the electrode is placed immediately anterior and parallel to the central sulcus), and the paramedian region is stimulated if the pain is located in the lower limb (parasagittal anteroposterior electrode). The electrodes are usually implanted extra-durally, but they can also be placed sub-durally in the interhemispheric fissure over the medial part of the precentral gyrus to treat lower limb pain.

Therapeutic applications

The clinical and demographic features of patients treated with invasive brain stimulation techniques are shown in Table 1. In a prospective study, Kumar *et al.*³³ followed 68 patients with chronic pain syndromes who underwent DBS implantation within specific sensory thalamic nuclei, the PVG, or the internal capsule to evaluate the long-term outcomes and thus clarify patient selection criteria for this surgical treatment. The patients were referred from a multidisciplinary pain clinic after conservative treatment failed: 43 of them had failed back syndrome, 6 had peripheral neuropathy or radiculopathy, 5 experienced thalamic pain, 4 suffered from trigeminal neuropathy, 3 had traumatic spinal cord lesions, 2 had causalgic pain, 1 experienced phantom limb pain, and 1 had carcinoma pain. Follow-up periods ranged from 6 months to 15 years, with an average follow-up period of 78 months. After initial screening, 53 of 68 patients chose device internalization, and 42 of the 53 continue to report adequate pain control. Effective relief of pain, as evaluated with a modified visual analog scale (VAS), was therefore achieved in 62% of patients. Subjects with failed back syndrome, trigeminal neuropathy, and peripheral neuropathy seem to respond positively to DBS, whereas those with thalamic pain, postherpetic neuralgia, and SCI fared poorly.

Spooner *et al.*⁵² reported an interesting case in which a patient with complete C4 SCI who suffered from drug-refractory neuropathic pain underwent high-frequency DBS of the cingulum. Standard stereotactic techniques were used for implantation in the right PVG and bilateral cingulum. After a 1-week blinded stimulation trial, the authors elected to implant a permanent pulse generator. Stimulation of the cingulum resulted in pain relief similar to that achieved with stereotactic lesion

of the cingulate gyrus and superior to that achieved with PVG stimulation or medication alone, as assessed using a VAS and pain medication usage. The authors concluded that cingulum stimulation could benefit patients with severe neuropathic pain that is refractory to other treatments. The major advantage of DBS over cingulotomy is represented by its reversibility and the possibility to adjust stimulation parameters to reach optimal efficacy.

Prévaire *et al.* analyzed the efficacies of DBS and EMCS within the framework of neuropathic pain management in patients with SCI and elaborated some recommendations.⁵³ Using the methodology proposed by the French Society of Physical Medicine and Rehabilitation (SOFMER),⁵⁴ they performed a systematic review of the existing literature. The authors reviewed five case series and found that just 36 out of 334 patients benefitted from implanted DBS.^{28,33,47,50,51} It should be noted that the nature or characteristics of the neuropathic pain in these patients was not described. In four studies with a total of 266 implantations, 80 major adverse events were reported that required 63 new surgical procedures. The most frequent complications were infections ($n = 31$), scalp erosion ($n = 11$), intracranial hemorrhages ($n = 7$), and seizures ($n = 3$). These led to 17 definite surgical removals of the stimulation devices. Although the frequency of stimulation device dysfunction was high in the 1980s, it decreased over the following decades.

The authors also reviewed seven patients with SCI who benefited from EMCS, who were described in two published series^{42,49} and one unique case report.⁴⁸ These seven patients with SCI were part of an initial group of 52 patients; just four of them reported long-term improvements. The inclusion criterion was chronic neuropathic pain refractory to conventional treatments.

Interestingly, only one study reported several adverse events, i.e. infection requiring removal of the implanted device ($n = 1$), headaches ($n = 3$), and spinal hematoma ($n = 1$). All had a spontaneous positive evolution, and a dehiscence of the stimulator's pocket requiring another surgical intervention.⁴² Rasche *et al.*⁵¹ reported an infection occurring in the implanted area that required a unilateral removal of the device at 6 months.

The level of scientific evidence of these studies on DBS and EMCS is low (level 4). Using the rating system proposed by the SOFMER,⁵⁴ the grading of recommendations A, B, and C was determined: A, established scientific evidence level (level 1 of evidence); B, scientific presumption (level 2 of evidence); C, low level of evidence (level 3 and 4 of evidence).

Table 1 Clinical and demographic features of the patients treated with invasive brain stimulation techniques

Authors	Intervention	n	Age (years)	Gender	SCI lesion	Etiology	Pain evolution	Follow-up (m)	Pain evaluation	Long-term success (n)
Young <i>et al.</i> ²⁸	DBS (VPL ± PVG ± PAG)	6	?	?	?	?	?	20.0	BS short-term improvement	1
Levy <i>et al.</i> ⁴⁷	DBS (VPL ± PVG/PAG)	11	?	?	?	?	6	80.0	BS short-term improvement; drugs consumption	0
Kumar <i>et al.</i> ³³	DBS (VPL)	3	?	?	?	After excision Lumb. neurofibr (1) Gunshot wounds (2)	?	78.0	BS short-term improvement; VAS; MPQ; DAL improv.	0
Nguyen <i>et al.</i> ⁴²	EMCS	3	?	?	Thoracic	Traumatic	?	27.3	VAS; DAL improv.	2
Tani <i>et al.</i> ⁴⁸	EMCS	1	42	F	Incomplete cervical	Traumatic	13	6.0	Interview	1
Nuti <i>et al.</i> ⁴⁹	EMCS	3	45.3 ± 5.9	1F/2M	Incomplete cervical/lumbar	Herniated disc	5.25	49.0	VAS, drugs consumption	1
Hamani <i>et al.</i> ⁵⁰	DBS (VPL ± PVG/PAG)	4	43.3 ± 9.4	4M	?	?	13	60.0	VAS	1
Rasche <i>et al.</i> ⁵¹	DBS (VPL ± PVG/PAG)	12	55.2 ± 9.2	3F/9M	Unclear	Heterogeneous	?	6.0	VAS, PDI, SF-36	
Spooner <i>et al.</i> ⁵²	DBS (Cingulum)	1	40	M	Complete cervical	Traumatic	12	4.0	VAS	1

n, number of patients; SCI, spinal cord injury; y, years; m, months; DBS, deep brain stimulation; VLP, ventroposterolateral nucleus of the thalamus; PVG/PAG, periventricular/periaqueductal gray matter; EMCS, epidural motor cortex stimulation; F, female; M, male; VAS, visual analogue scale; MPQ, McGill Pain Questionnaire; PDI, Pain disability index; SF-36, 36-item Short Form Health Survey; DAL, daily life activities; BS, binary scale.

DBS is more effective against nociceptive pain than deafferentation pain. For central pain in SCI patients, the long-term efficacy of DBS is quite low (16%, 3 of 19 patients). Therefore, for neuropathic pain in SCI patients, there is no scientific argument in favor of DBS. With a long-term success rate above 50% (57%, 4 of 7 patients), EMCS seems more promising and is associated with fewer complications than DBS.

In conclusion, the level of evidence is not sufficient to validate the use of DBS, although there is a low level of evidence for EMCS. Further comparative clinical studies with larger cohorts or controlled versus placebo are needed to confirm and validate these results.

Non-invasive brain stimulation

Neuromodulatory techniques

The two major techniques of non-invasive brain stimulation, rTMS and tDCS, may modulate cortical excitability to induce lasting effects.^{55,56} Both have been proven to have potential therapeutic efficacy in various neurological and psychiatric disorders.

rTMS delivers single TMS pulses in trains with a constant frequency and intensity for a given time. It has been shown to influence cortical excitability and neuronal metabolic activity.⁵⁷

tDCS is another safe and non-invasive procedure that can be clinically applied to modulate cortical excitability by delivering direct low-intensity electrical currents (below the perceptual threshold, 1–2 mA) over the scalp using two large saline-soaked sponge electrodes placed in the region of interest. The resulting constant electrical field penetrates the skull, induces intracerebral current flow, and modulates neuronal excitability.⁵⁸

rTMS can be applied as continuous trains of low-frequency (1 Hz) or bursts of higher frequency (≥ 5 Hz),⁵⁹ while tDCS can be applied as anodal or cathodal stimulation.⁶⁰ In general, low-frequency rTMS and cathodal tDCS are thought to reduce activity, and high-frequency rTMS and anodal tDCS are considered to enhance excitability in the targeted cortical region. The physiologic impact of both neuromodulatory techniques involves synaptic plasticity, specifically long-term potentiation and depression. A link between the after-effects induced by rTMS and the induction of synaptic plasticity was recently identified.⁶¹

Both neuromodulatory techniques have been employed to treat patients with neuropathic pain.^{62–74} Recent guidelines on the use of rTMS⁷⁵ and three meta-analyses on the role of rTMS in the treatment of neuropathic pain^{11,76,77} indicate that rTMS delivered to M1 produces significant analgesic effects in 45–60% of patients. Fewer tDCS studies have been published

in the context of neuropathic pain treatment, and the level of evidence is currently lower than that for rTMS. A recent meta-analysis of published tDCS studies demonstrated significant heterogeneity and did not identify a significant difference between active and sham stimulation.⁷⁸

Cranial electrotherapy stimulation (CES) represents a non-traditional, non-invasive brain stimulation technique, and involves the application of a small amount of current, usually less than 1 mA, through the head via ear clip electrodes. Its analgesic action has been demonstrated in various anti-nociception models.^{79,80} The mechanism of action of CES in humans is not fully understood, but it has been shown to “normalize” neurotransmitter homeostasis⁸¹ and increase beta-endorphins in patients with chronic back pain.⁸² CES has been found to be effective in controlling central pain,⁸³ but a recent meta-analysis of four studies that enrolled 133 patients with neuropathic pain failed to show statistically significant difference between active and sham stimulation.⁷⁸

Repetitive transcranial magnetic stimulation

Lefaucheur *et al.*⁶² applied high-frequency rTMS over the M1 in 60 patients with drug-resistant neurogenic pain, including 12 patients with SCI. Overall, rTMS was found to significantly but transiently reduce chronic pain. However, these effects were significantly influenced by pain origin and site. The most favorable conditions were trigeminal nerve lesions, thalamic stroke, and brachial plexus lesion; results were worse in patients with spinal cord and brainstem lesions.

In a subsequent study, Defrin *et al.*⁶⁵ evaluated the analgesic effect of rTMS over the M1 on chronic central pain in 11 patients with thoracic SCI that resulted in paraplegia. Both real or sham 10 daily motor rTMS treatments induced similar significant reductions in VAS scores immediately after each of the 10 treatment sessions and in VAS and McGill Pain Questionnaire (MPQ) scores after completion of all the sessions. However, only real rTMS led to a significant increase in heat-pain threshold at the end of the treatment series. Another important finding was that the reduction in MPQ scores in the patients who received real rTMS continued during the follow-up period, ranging from 2 to 6 weeks after the end of the treatment sessions. The level of depression as assessed by the Beck Depression Inventory was reduced in both groups without significant differences but only continued to improve at follow-up in the real rTMS group. Therefore, while the pain relief induced by a single rTMS treatment is probably related to a placebo

effect, the authors demonstrated that patients with SCI may benefit from a series of rTMS treatments.

In a blinded and randomized crossover study, Kang *et al.*⁷¹ applied rTMS (1,000 stimuli/day for 5 consecutive days) over the M1 hand area in 11 patients with complete or incomplete SCI and chronic neuropathic pain at multiple sites (including the lower limbs, trunk, and pelvis). Real and sham rTMS sessions were performed, separated by 12 weeks. One week after the end of the rTMS application, the outcome measures, that is numeric rating scale (NRS) for average, worst pain and the interference items of the Brief Pain Inventory (BPI) did not differ significantly between real and sham rTMS. Conversely, the effect of time on the NRS score for worst pain showed a significant reduction with real stimulation but not with sham stimulation. These results suggest that, even if the therapeutic efficacy of rTMS was not demonstrated when applied to the M1 hand area in patients with chronic neuropathic pain at multiple sites, more intensive rTMS protocols should be assessed.

Lefaucheur *et al.*⁸⁴ also assessed the value of rTMS targeted over the cortical representation of the painful area to predict the efficacy of EMCS to treat neuropathic pain. In 59 patients who were treated with EMCS for more than 1 year (in 12 of them pain etiology was related to SCI) active and sham 10-Hz rTMS sessions were performed as preoperative tests.

A VAS was used to rate the analgesic effects of tTMS; pain scores were significantly reduced by EMCS and active rTMS, but sham rTMS was ineffective. The most salient finding of this study was that 26 of the 33 patients (79%) who responded to active rTMS and all the 21 patients (100%) who responded to active-sham stimulation also responded to EMCS.

The effects of rTMS or EMCS were not related to the side, origin, or duration of pain or by the presence of motor or sensory deficits in the painful area. Poorer results were observed in patients with lower limb pain for rTMS and in older patients for EMCS. This study confirms that neuropathic pain can be significantly reduced by motor cortex rTMS or EMCS. Moreover, the analgesic efficacy of rTMS is predictive of that of EMCS, and a single session of rTMS can be used as a preoperative assessment tool. Therefore, a positive outcome of EMCS can be predicted by a real response to rTMS, and rTMS tests can be used to confirm the indication of EMCS therapy, but single sessions of sham-controlled preoperative rTMS tests have no value to exclude patients. New rTMS protocols are required to improve the usefulness of preoperative rTMS in EMCS practice.

Transcranial direct current stimulation

Fregni *et al.*⁶⁴ first studied the effects of the tDCS on pain control in patients with central pain due to traumatic SCI. Patients were randomized to receive sham or active motor tDCS (2 mA, 20 minutes for 5 consecutive days). The pain was rated by a blinded evaluator using the VAS for pain, Clinician Global Impression and Patient Global Assessment. The patients underwent a neuropsychological battery, and depression and anxiety changes were also evaluated. There was significant pain improvement after active anodal tDCS of the motor cortex but not after sham stimulation. Depression or anxiety changes did not influence these results. Furthermore, cognitive performance was not significantly changed throughout the trial in either treatment group. The findings of this study suggest that tDCS can effectively ameliorate pain in patients with SCI. The authors hypothesized that a secondary modulation of thalamic nuclei activity may play a critical role.

In a more recent study, Soler *et al.*⁷⁴ investigated the analgesic effect of tDCS of the motor cortex and techniques of visual illusion applied in isolation or in combination. In a sham-controlled, double-blind, parallel group design, 39 patients with neuropathic pain following SCI were randomized into four groups receiving tDCS with a walking visual illusion or a control illusion and sham stimulation with visual or control illusion. The authors found that the combination of tDCS and visual illusion significantly reduced neuropathic pain intensity more than any single intervention. Patients receiving tDCS and visual illusion reported a significant improvement regarding all pain subtypes, patients receiving tDCS alone improved only in continuous and paroxysmal pain, and those receiving tDCS with visual illusion only showed improvement in continuous pain and dysesthesias.

Cranial electrotherapy stimulation

In a pilot study, Tan *et al.*⁸⁵ examined the effects of daily 1-hour treatment for 21 days on pain intensity and interference with activities in 38 male patients with SCI who were randomized to receive active CES ($n = 18$) or sham CES ($n = 20$). The active CES group reported significantly decreased daily pain intensity and pain interference compared with the sham CES group. These results suggest that CES can effectively relieve chronic pain in patients with SCI. A study by Capel *et al.*⁸⁶ found that mixed-type pain intensity was significantly decreased in 15 participants with SCI who received active 2-hour CES treatment twice a day on 4 consecutive days compared to 15 participants who received sham CES for the same amount of time.

A multi-site double-blind study assessed the effects of active and sham CES ($n = 45$ and 55 , respectively, randomly assigned) in adults with SCI and chronic neuropathic pain at or below the level of injury.⁸⁷ The active group reported a significantly greater decrease in pain during daily treatments than the sham group. During the 21-day trial, the active group showed larger pre- to post-treatment decreases in the pain interference subscale of the BPI than the sham group. Daily treatment CES provided relatively small but statistically significant improvements in both, the pain intensity and interference subscales of the BPI, and no serious side-effects were reported. Notably, individual responses to CES varied widely, ranging from no pain relief to a great deal of relief.

The most important findings regarding rTMS, tDCS, and CES in patients with SCI who have neuropathic pain are listed in Table 2.

Phantom limb pain and brain stimulation

Phantom pain sensations are defined as perceptions that are related to a limb or organ that is not physically part of the body, and the majority of these sensations are painful. Even if limb loss is due to amputation or congenital limb deficiency,⁸⁹ phantom limb sensations can also occur in many other pathological conditions following peripheral or central nervous system damage. Phantom sensations and non-painful sensory phenomena are commonly observed after SCI, and many patients with SCI report sensory disturbances that are similar to phantom limb sensations that are experienced following an amputation.^{90–92} Siddal *et al.*⁹³ observed that patients who do not report neuropathic pain might complain of non-painful phantom sensations below the level of the lesion.

Katayama *et al.*⁹⁴ compared the effects of spinal cord stimulation (SCS), DBS of the thalamic nucleus ventralis caudalis (VC), and EMCS in 19 patients with phantom limb pain. All of the patients initially underwent SCS and were then considered for the treatment with DBS and/or EMCS if SCS was unsuccessful. Long-term satisfactory pain control was achieved in 6 of 19 (32%) by SCS, 6 of 10 (60%) by DBS, and 1 (20%) of 5 by EMCS. SCS and thalamic DBS sometimes dramatically reduced pain, leading to a long pain-free interval and infrequent stimulation use. The effects of both DBS of the VC and EMCS were examined in four patients. One patient reported better pain relief by MCS than DBS, whereas two reported the opposite results. Therefore, there is no evidence at present for an advantage of EMCS over SCS and thalamic DBS in controlling phantom limb pain.

Discussion and future direction

This narrative review summarizes the findings from the most important published studies of brain stimulation in patients with neuropathic pain following SCI, describes the current understanding of the neurophysiological mechanisms by which brain stimulation may produce an analgesic effect, and discusses the clinical applicability of these findings and future research directions.

Despite the availability of multiple pharmacological approaches, a considerable proportion of patients with SCI cannot efficiently manage their chronic neuropathic pain with conventional pharmacological treatments. In fact, neuropathic pain originating from SCI is often refractory to the usual medical treatment with anticonvulsants or antidepressants. This has led to increased interest in adjunct therapies in the hope of improving pain management.

EMCS and DBS were the first invasive brain stimulation techniques available and commonly used for the symptomatic control of central neuropathic pain in patients with SCI. The level of scientific evidence of the published studies is low for both techniques (level 4), and there is no scientific argument in favor of DBS. Future prospective studies are needed to identify and more carefully determine the indications for DBS, as well as the ideal surgical candidates, the best surgical target, and optimal surgical techniques. Important questions such as the clinical features that respond best to DBS or the long-term benefits from this treatment remain unanswered. The relatively low efficacy of DBS for the treatment of neuropathic pain stresses the need for further investigation and the exploration of new surgical targets. Past evidence has shown that invasive and non-invasive stimulation of the motor cortex can relieve central pain. EMCS is thought to revert neuropathic pain phenomena through activation of the limbic and descending pain inhibitory systems, similar to that reported in experimental animals.⁹⁵ Implanted MCS seems to have an interesting potential with greater long-term efficacy, but larger comparative and controlled versus placebo clinical studies are required to confirm and validate previously published results. Moreover, further investigation of the mechanisms involved in this effect may improve the clinical treatment of persistent pain.

The field of non-invasive brain stimulation for the treatment of pain is expanding rapidly, and several techniques, such as rTMS, tDCS, and CES, have been clinically investigated in patients with various central pain syndromes.

The exact mechanisms responsible for the analgesic effects of anodal tDCS and rTMS over the motor

Table 2 Major findings of the rTMS, tDCS, and CES studies

Authors	Intervention	N	Age (years)	Gender	SCI lesion	Level	Etiology	Parameters	Brain target	Nr. session	Pain evaluation	Type of pain	Time since of SCI	Time of injury
Lefaucheur <i>et al.</i> ⁶²	rTMS	12	?	?	?	?	Syringomyelia, post-traumatic ischemia	20 trains 10 Hz 10 s, 80% M	Hand M1	1	VAS	Chronic neurogenic	?	?
Defrin <i>et al.</i> ⁶⁵	rTMS	11	54 ± 6	4F/7M	2 complete/9 incomplete	Thoracic	?	500 pulses, 5 Hz, 10 s 115% M	Vertex	10	VAS, MPQ	Chronic central	> 12 mo	>2 mo
Kang <i>et al.</i> ⁷¹	rTMS	11	54.8 ± 13.7	5F/6M	6 complete/5 incomplete	5 cervical/6 thoracic	?	20 trains, 10 Hz, 5 s, 85% MT	Hand M1	5	NRS, BPI	Neuropathic	60.5 ± 17 mo	60.5 mo
Lefaucheur <i>et al.</i> ⁸⁸	rTMS	12	?	?	?	?	?	20 trains, 10 Hz, 10 s, 90 % MT	Cortical representation of painful area	1	VAS	Neuropathic	?	?
Fregni <i>et al.</i> ⁶⁴	tDCS	17	35.7 ± 13.3	3F/14M	11 complete/6 incomplete	9 cervical/8 thoracic or lumbar	Traumatic	Anodal/sham 2 mA, 20 m	M1	5	VAS, CGI, PGA	Chronic neuropathic	3.7 ± 1.8 ¹ 3.4 ± 1.6 ²	3.7 (1.8) active 3.4 (1.5) sham
Soler <i>et al.</i> ^{3,74}	tDCS	39	44.1 ± 11.6	9F/30M	31 complete/8 incomplete	10 cervical/29 thoracic	?	Anodal/sham 2 mA, 20 m	M1	10	NRS,BPI	Chronic neuropathic	> 12 mo	>6 mo
Capel <i>et al.</i> ⁸⁶	CES	30	?	?	?	9 cervical/16 thoracic; 5 lumbar	?	Active/sham 12 µA, 53	Ear clip electrodes	8	SF-MPQ, PPI, PRI, VAS	?		?
Tan <i>et al.</i> ⁸⁵	CES	38	56 ± 8.3 ¹ 66 ± 10.9 ²	38M	?	?	33 traumatic/5 nontraumatic	Active/sham 100 µA, 1 h	Ear clip electrodes	21	BPI	Neuropathic/musculoskeletal.	20.1 ± 13.3 ¹ 19.7 ± 16.0 ²	20.1 (10.3) active
Tan <i>et al.</i> ⁸⁷	CES	115	52.1 ± 10.5 ¹ 52.5 ± 11.7 ²	15F/90M	42 complete/62 incomplete/11?	37 cervical/66 thoracic/2?	?	active/sham 100 µA, 1 h	Ear clip electrodes	21	BPI, Pain Subsc. SF-36, PQAS, PBCS	Neuropathic/musculoskeletal.	14.6 ± 9.5 ¹ 15.8 ± 12.1 ²	14.6 (9.5) active

N, number of patients; SCI, spinal cord injury; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; CES, cranial electrotherapy stimulation; 1, active stimulation; 2, sham stimulation; F, female; M, male; Hz, Herz; MT, motor threshold; mA, milliampere; µV, microampere; s, seconds; ms, milliseconds; h, hours; m, minutes; y, years; mo, months; M1, primary motor cortex; VAS, visual analogue scale; MPQ, McGill Pain Questionnaire; SF-MPQ, Short Form McGill Pain Questionnaire; NRS, Numeric Rating Scale; BPI, Brief Pain Inventory; CGI, Clinician Global Impression; PGA, Patient Global Assessment; PPI, Present Pain Index; PRI, Pain Rating Index; SF-36, 36-item Short Form Health Survey; PQAS, Pain Quality Assessment Scale; PBCS, Pain Beliefs and Coping Strategies.

cortex on several painful conditions are still unknown. These techniques up-regulate M1 excitability, which can modulate pain perception through changes in activity at local cortical sites and in pain-modulating areas, such as the thalamic and subthalamic nuclei. Indeed, it has been demonstrated that both rTMS and tDCS influence the neuronal activity of these nuclei.^{96,97}

Non-invasive brain stimulation techniques seem to represent an interesting option; after a rigorous patient selection, they may have therapeutic utility, and the preliminary data are promising. However, the investigation of non-invasive brain stimulation for therapeutic effects is in the initial stages.

The findings on tDCS in patients with chronic pain are especially promising and justify its use of tDCS to treat pain in selected patient populations. TDCS presumably has some advantages over rTMS; it may exert longer-lasting modulatory effects on cortical function and has been shown to be very safe if utilized within the current protocols. In addition, the current tDCS devices are easy to apply, relatively inexpensive, and portable, which allows patients to receive this therapy in their homes. The clinical potential of this technique is enhanced by the possibility to perform a reliable sham-stimulation condition. Another non-invasive technique that delivers a microcurrent to the brain via ear clip electrodes is represented by CES, which is also very easy to use and can be performed by the patient.

On the other hand, several questions still need to be addressed before firm conclusions about the non-invasive brain stimulation therapy are made. Most interventions have been of short duration and conducted in small groups of patients; therefore, the power to establish evidence for therapeutic efficacy was not always adequate. At present, especially rTMS can only induce acute beneficial effects. Prolonged pain relief can be obtained by repeating rTMS sessions every day for several weeks. Interestingly, Lefaucheur *et al.*⁸⁸ demonstrated that the analgesic effects of “conventional” 10 Hz-TMS delivered to M1 can be enhanced by priming with theta burst stimulation (TBS), a novel rTMS paradigm that produces greater changes in cortical excitability than “conventional” protocols.⁹⁸ Similarly, consecutive tDCS sessions over the M1 may be suitable to treat chronic neuropathic pain in SCI subjects as it can modulate neural activities in stimulated and interconnected regions. Other stimulation parameters, such as TBS and the combination of tDCS and rTMS, need to be further explored. In future long-term studies, multiple rTMS or tDCS sessions may also interact, and metaplasticity effects may affect the ultimate functional outcome. Because therapeutic

effect duration is an important issue to be considered, maintenance therapy regimens, as well as the development of portable stimulators, should be investigated. Overall, future trials must be carried out to determine optimum stimulation parameters. Animal studies revealed that the effects of neuromodulation are dependent on stimulation parameters, and the strongest stimulation parameter (i.e. higher intensity) is not necessarily associated with the largest beneficial effect.⁹⁹

Stimulating the human cortex using tDCS or TMS temporarily reduces clinical and experimental pain; however, it is unclear which cortical targets are the most effective, and the mechanisms of central pain relief remain poorly understood. M1 has been a popular target for managing neuropathic pain, but it is unclear whether M1 is the only effective cortical target; to date, no studies have thoroughly investigated the effects of stimulation of other cortical targets (i.e. prefrontal or parietal areas, primary or secondary somatosensory cortex, supplementary motor area) on neuropathic pain in subjects with SCI. The stimulation of prefrontal regions has been demonstrated to be effective in the treatment of depression, and there is a close relationship between depression and chronic pain, suggesting that potential value of this target should be better evaluated.

Other apparently minor topics have been scarcely addressed, and the long-term risks have not been sufficiently considered. Given the difficulties of a reliable sham TMS intervention, some of the TMS studies lacked reliable blinding of subjects, and the technicians or experimenters applying the TMD/tDCS were not blinded in several studies. The major limitations of clinical research on non-invasive techniques are the insufficient understanding of its mechanisms of action, the lack of adequate safety data, and some disparities with regard to stimulation parameters, which have limited the generalizability of the studies' findings.

Furthermore, the rationale for treating neuropathic pain originating from the spinal cord with brain stimulation techniques is not completely convincing. It seems paradoxical that while TMS studies of several pain syndromes show cortical hyperexcitability, most therapeutic attempts are based on techniques that enhance cortical excitability, such as high-frequency TMS or anodal tDCS. An appropriate examination of cortical excitability and reactivity should be performed before and after therapeutic interventions.

Conclusion

New studies assessing other parameters of stimulation to achieve long-lasting effects and investigations that

compare the effects of drugs with those of non-invasive brain stimulation are needed to increase our understanding and knowledge of the clinical implications for the use of these new neuromodulatory methods. The beneficial effects of neuromodulatory techniques and analgesic drugs may be synergistic. In some cases, neurostimulation therapy could be considered as an add-on treatment in combination with drugs, rehabilitation techniques, and psychotherapy.

Although further research and confirmatory studies are still critically necessary to draw definitive conclusions about the clinical role of neurostimulation, non-invasive neuromodulation techniques hold promise as new therapeutic options for SCI patients with chronic neuropathic pain.

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