Modulating the pain network—neurostimulation for central poststroke pain

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Abstract | Central poststroke pain (CPSP) is one of the most under-recognized consequences of stroke, occurring in up to 10% of patients, and is also one of the most difficult to treat. The condition characteristically develops after selective lesions to the spinothalamic system, most often to the ventral posterior thalamus. Here, we suggest that CPSP is best characterized as a disorder of brain network reorganization, and that this characterization offers insight into the inadequacy of most current pharmacological treatments. Accordingly, we review the progress in identification of nonpharmacological treatments, which could ultimately lead to mechanism-based therapeutics. Of the invasive neurostimulation treatments available, electrical motor cortex stimulation seems to be superior to deep brain stimulation of the thalamus or brainstem, but enthusiasm for clinical use of the procedure is limited by its invasiveness. The current preference is for noninvasive transcranial magnetic stimulation, which, though effective, requires repeated application, causing logistical difficulties. Although CPSP is often severe and remains difficult to treat, future characterization of the precise underlying neurophysiological mechanisms, together with technological innovation, should allow new treatments to evolve.

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Introduction

"Le syndrome thalamique" was first described in 1906, on the basis of clinical and pathological case studies of patients who presented with pain that was accompanied by cerebrovascular lesions in the posterolateral region of the thalamus and the posterior limb of the internal capsule.[1] This presentation is now known as central poststroke pain (CPSP),[2,3] and comprises chronic neuropathic pain caused by cerebrovascular lesions of the central somatosensory nervous system, as defined by the International Association for the Study of Pain.[4] In clinical practice, however, CPSP can be difficult to distinguish from other pain conditions that present after stroke, such as hemiplegic shoulder pain, painful spasticity, tension headache, and other types of musculoskeletal pain.[3] CPSP is, therefore, still an underappreciated sequela of stroke that impairs quality of life, disrupts rehabilitation, interferes with sleep and affects mood, occasionally leading to suicide. Furthermore, the difficulty of diagnosing CPSP means that many patients do not receive adequate treatment.

Treatment of CPSP remains challenging, and evidence-based treatment options are scarce. Comprehensive approaches that include medication, patient education, cognitive behavioural therapy and/or other nonpharmacological treatments are required.[3,5] Treatment of CPSP frequently begins with medication, but the condition is typically pharmacoresistant, and inadequate pain relief is often accompanied by adverse effects. For this reason, nonpharmacological approaches, such as neurostimulation therapies, have been developed.

In this Review, we consider CPSP as a brain network reorganization disorder and assess the implications of this model for treatment of the condition, focusing on nonpharmacological treatments and the progress in their development. We first review the clinical features of CPSP and discuss how they inform current ideas about the condition, and we suggest that a progressive mechanism leads to pathogenetic network reorganization. After briefly considering the efficacy of pharmacological treatments, we review the evidence supporting the use of technological treatments to target specific network nodes and induce pain relief. We focus on four such approaches: deep brain stimulation (DBS), electrical motor cortex stimulation (EMCS), repetitive transcranial magnetic stimulation (rTMS), and spinal cord stimulation (SCS). We argue that advances in our understanding of the pathogenesis of CPSP, combined with technological innovation, offer hope for successful mechanism-based approaches to what remains a difficult clinical problem.

Characteristics of CPSP

Epidemiology

The reported prevalence of CPSP among patients with stroke ranges from 1% to 12%.[6–16] The condition can result from any lesion of the somatosensory pathway—but particularly those of the spinothalamocortical sensory pathway (including the thalamus, lenticulocapsular region, cerebral cortex, pons, and medulla)[17–19]—after ischaemic or haemorrhagic stroke.[6,13,15,20,21]

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Key points

- Central poststroke pain (CPSP) is an under-recognized and severe complication of stroke, and remains extremely difficult to treat by conventional pharmacological means
- Pathophysiologically, CPSP might be best understood as a network reorganization disorder that leads to a maladaptive central state in which selective disruption of spinothalamic sensory pathways is a key feature
- The network reorganization hypothesis offers insight into nonpharmacological treatments for CPSP—such as neurostimulation—that target specific network nodes
- Of the invasive neuromodulatory strategies, electrical motor cortex stimulation is the most efficient, but the benefits must be carefully balanced against the risks of invasive treatments
- Noninvasive repetitive transcranial magnetic stimulation of the motor cortex is currently the preferred treatment approach, but must be applied repeatedly to maintain its effect
- A greater understanding of the pathophysiology of CPSP, together with technological innovation, could lead to safer, more-practical and more-efficient treatments

The prevalence of CPSP is high among patients with lateral medullary infarction (Wallenberg syndrome; 25%)[22] or a lesion in the ventroposterior nucleus of the thalamus (18%).[23] The ventroposterior nucleus is a key sensory relay point at which the spinothalamic tract is known to terminate,[24] and is considered critical to the development of CPSP.[2,25–27] Two volumetric MRI studies suggest that the posterior and inferior regions of the ventroposterior nucleus are associated with the development of CPSP.[28,29] The posterior ventral medial nucleus (VMpo) is also a proposed relay point for thermosensory and nociceptive fibres, and sends projections to the dorsal posterior insular cortex.[30] However, involvement of this nucleus in CPSP is still under debate.

Other lesions of the sensory pathways can cause CPSP. For example, one study presented a series of 20 patients who developed CPSP after lenticulocapsular haemorrhage that involved the posterior limb of the internal capsule, indicating involvement of the ascending thalamocortical sensory tracts.[31]

Importantly, CPSP has also been observed in association with cortical lesions. For example, patients with lesions in the posterior insula and inner parietal operculum (secondary somatosensory cortex) have presented with pure thermoalgesic sensory loss.[32] By contrast, lesions of the postcentral gyrus (primary somatosensory cortex) have been related to dominant impairment of position sense but not of thermoalgesic sensation, and have not been related to CPSP.[33] Furthermore, whether cortical and thalamic lesions cause CPSP through a common pathogenetic mechanism is difficult to ascertain.

Clinical characteristics

CPSP can emerge at any time from immediately after stroke to several years later, but typically manifests several months after the initial event.[6,15] The clinical symptoms are similar to those of other types of central and peripheral neuropathic pain, and are often lifelong.[3] Pain is felt in the area that is affected by sensory abnormalities, which corresponds topographically to the brain region affected by stroke;[19] this observation is an important criterion for diagnosis of CPSP.[3,34] The affected area can range from half of the body to restricted regions, often distal parts of the limbs.[2] Lateral medullary lesions can cause pain in the ipsilateral face and contralateral body or limbs.[22] Hemibody pain has frequently been reported in patients with thalamic lesions,[3,25] whereas leg pain is most prominent in those with lenticulocapsular lesions.[31]

Most patients with CPSP experience continuous pain—often described as burning, aching, pricking, freezing, squeezing and/or throbbing—and tingling and/or numbness; some patients experience spontaneous, intermittent pain that they describe as lacerating or shooting.[6,13,20,22,31] These symptoms often fluctuate with factors such as temperature, psychological stress, fatigue and body movement.[31,35] Allodynia has been reported in 45–56% of patients with CPSP,[6,13,15] and other frequently reported sensory abnormalities are dysaesthesia, hyperalgesia, and paraesthesia.[2,17,20,25] Almost all patients present with thermoceptive and/or nociceptive sensory abnormalities, and approximately 50% present with somatic sensory abnormalities that affect sensations such as touch and vibration.[6,17–19,35]

Mechanisms

Physiological pain

The mechanisms that produce pain as a result of central brain lesions are poorly understood, largely because our understanding of the basic central mechanisms of physiological pain is incomplete. This problem stems from two key facts. First, multiple ascending pathways transmit nociceptive (and thermoceptive) sensory information to the brain. Second, no single 'pain cortex' exists; instead, multiple cortical regions are involved in pain perception, with each presumably involved in distinct aspects of pain processing, as well as in multiple cognitive processes. A classic psychological characterization of the multiple dimensions of pain (sensory, emotional and cognitive) originally yielded a parallel processing neural model,[36] which proposed that the different dimensions were processed in largely independent cortical streams.[37] However, this model has given way to a network model of pain, in which multilevel, brain-wide interactions between subcortical and cortical processing hubs produce the sensation of pain.[38,39]

Putative mechanisms of CPSP

In the context of an integrated, brain-wide model of pain, consistent clinical features of CPSP provide important clues about its pathogenesis. From an anatomical perspective, CPSP is typically associated with lesions at various points in the lateral spinothalamic tract, which transmits pain and temperature signals. Dorsal column pathways, which transmit somatic sensory signals, are concomitantly spared (Figure 1). As a result, the emergent pain is relatively localized to areas in which sensation is lost or disrupted. A combination of reduced and exaggerated sensory symptoms is often observed; thermal sensation is more frequently involved than somatic sensation, and the most characteristic symptom is cold hypersensitivity. This presentation strongly suggests that an imbalance of

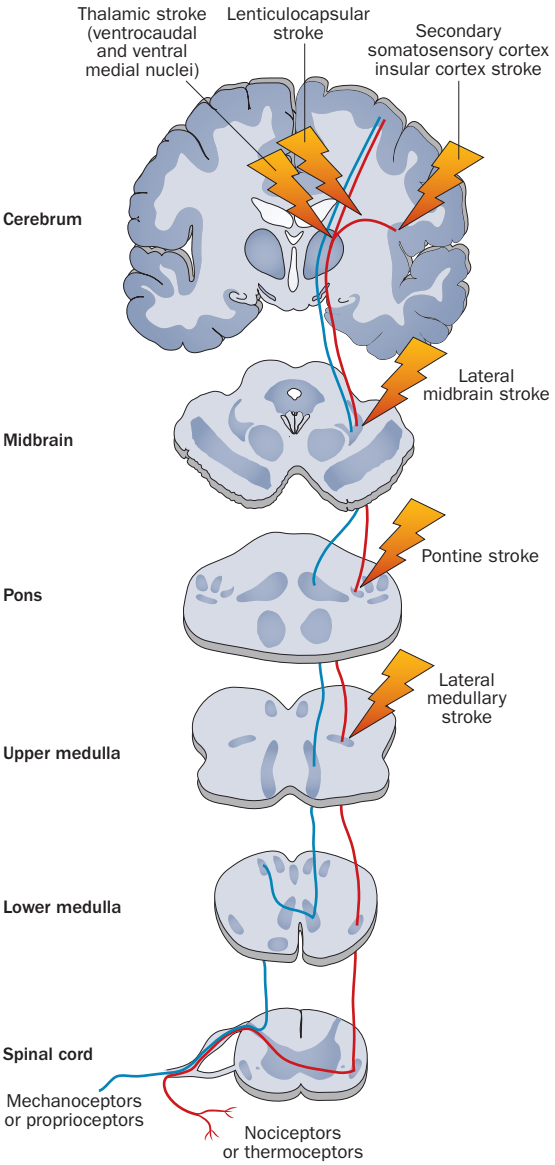

Figure 1 | Lesion sites associated with central poststroke pain. The spinothalamic tract (red) ascends from the dorsal horns of the spinal cord through the medulla and brainstem (pons) to the thalamus and cortex. In addition to spinal cord lesions, lesions at several other sites, particularly those caused by pontine, medullary, thalamic and cortical strokes, can lead to central poststroke pain. The somatic sensory system (dorsal columns; blue) are typically spared in central poststroke pain.

the interactions between different sensory pathways—in particular, thermal and pain pathways—contributes to the pathogenesis of CPSP. Pain can result from lesions at various sites in the spinothalamic tract and its projections, producing similar, but not necessarily identical, clinical phenotypes.[19,40,41] This observation is relevant to the mechanism of pain, as the physiological functions of each point along the interconnected pathways is distinct, yet lesions cause very similar symptoms.

One candidate integrative mechanism for the pathogenesis of CPSP is an inhibitory interaction between pathways that transmit sensory signals of cold and pain. According to the influential disinhibition hypothesis,[42,43] lesions of spinothalamic pathways that normally transmit cold signals release the physiological inhibition of spinothalamic pathways that transmit pain signals and project to the cortex, causing a characteristic burning pain similar to that experienced in the thermal grill illusion (an experimental model in which pain is induced by a grill plate of alternating warm and cold bars).[44–46] The proposed anatomical basis for this disinhibition involves a medial spinothalamic pathway that transmits temperature and pain signals and projects to the VMpo and then to the anterior cingulate cortex and insular cortex. However, the involvement of the VMpo in CPSP is still unclear, as some studies suggest that lesions restricted to the ventrocaudal thalamus in classic sensory pathways are sufficient to cause CPSP.[47]

CPSP as a network reorganization disorder

One important complexity of CPSP is the combination of two distinct aspects of pain: stimulus-evoked acute pain (hyperaesthesia and allodynia), and spontaneous chronic pain.[48] Both types of pain frequently develop after a considerable period of time following a stroke rather than immediately, suggesting that the pathophysiology is not an immediate release phenomenon but a progressive, adaptive mechanism that involves plasticity and reorganization of a pain network.

Several lines of evidence are in keeping with this suggested progressive mechanism. First, studies of rats and humans have shown an increase in baseline excitability and abnormal burst firing of thalamic (ventral posterior lateral nucleus) neurons alongside the development of chronic pain in the days after a lesion occurs.[49,50] Second, functional imaging studies in humans have shown that activity in a broad network of brain regions differs between individuals with and without central pain, both in the resting state and in response to evoked pain.[48,51–53] These results suggest that an adaptive process induces a spontaneous dysrhythmic or hyperexcitable pattern of neural activity that causes chronic pain, possibly driven by the thalamus. Third, after the development of CPSP, structural changes occur in multiple brain regions, including a distinct pattern of morphometric change in grey matter in temporal, parietal and frontal lobes.[54] Last, some reports show that CPSP can be resolved by additional lesions, most notably those in the ipsilateral or contralateral parietal cortex.[55,56] We suggest that, taken together, these observations indicate a model of CPSP as a complex process of network reorganization rather than a simple process of focal disinhibition or hyperexcitability.

The difficulty with any theory of adaptive cortical reorganization is to determine which aspects of the reorganization generate pain, which are downstream sequelae of pain, and which relate to other manifestations of the central lesion. Studies of other chronic pain disorders have applied theoretical network-level approaches to human functional imaging data so as to identify relevant components of brain networks,[57,58] but this approach has not yet been applied to CPSP. Ultimately, network-level models must incorporate several aspects: the baseline

Table 1 | Randomized controlled trials of pharmacological treatments for CPSP

Study	Drug	Administration route	No. of patients with CPSP	Primary outcome
Leijon *et al.* (1989)[60]	Amitriptyline	Oral	15	Positive
	Carbamazepine	Oral	14	Negative
Bainton *et al.* (1992)[137]	Naloxone	Intravenous	20	Negative
Attal *et al.* (2000)[62]	Lidocaine	Intravenous	6	Positive
Vestergaard *et al.* (2001)[61]	Lamotrigine	Oral	30	Positive
Attal *et al.* (2002)[138]	Morphine	Intravenous	6	Negative
Canavero *et al.* (2004)[63]	Propofol	Intravenous	22	Positive
Vranken *et al.* (2005)[139]	Ketamine	Transdermal	15*	Negative
Vranken *et al.* (2008)[64]	Pregabalin	Oral	19	Positive
Kim *et al.* (2011)[65]	Pregabalin	Oral	219	Negative
Jungehulsing *et al.* (2013)[66]	Levetiracetam	Oral	42	Negative

*Calculated as the sum of patients with stroke (24%), thalamus lesion (9%) and brainstem infarction (12%) from a total of 33 patients. Abbreviation: CPSP, central poststroke pain.

functional topology of the pain network, which could be evaluated by resting state functional MRI (fMRI); the rapid synchronized neuronal firing that the networks support, which could be evaluated by electrophysiology and magnetoencephalography; and the subjective behaviour that the networks cause. A model that incorporates all three aspects, which would hold the promise of identifying targets for treatment, is currently lacking.

Pharmacological treatment

The pharmacological management of CPSP has previously been summarized elsewhere.[2,3,5,59] Several agents have been tested for the treatment of CPSP in double-blind, randomized, placebo-controlled trials (Table 1).

The adrenergic antidepressant amitriptyline was proven effective for relief of CPSP in a three-phase crossover study, in which carbamazepine was not effective.[60] Lamotrigine—an antiepileptic drug that inhibits presynaptic voltage-gated sodium channels and supresses glutamate release—was also reported to be moderately effective for the treatment of CPSP.[61] Intravenous lidocaine or propofol and oral pregabalin have also been reported to be effective for treatment of central neuropathic pain, including CPSP.[62–64] However, the largest randomized controlled trial (RCT) of pregabalin, which included 219 patients with CPSP, failed to demonstrate a significant positive effect on the primary outcome (mean score on the Daily Pain Rating Scale), even though marked improvements were seen in sleep, anxiety and the clinician global impression of change.[65] Furthermore, a recent crossover study showed that levetiracetam was not effective in the treatment of CPSP.[66]

The few drugs that are moderately effective for the treatment of CPSP often have adverse effects, and their impact on the condition is frequently insufficient. No universal guidelines for pharmacological management of CPSP exist, but commonly used approaches include adrenergic antidepressants such as amitriptyline, antiepileptics such as lamotrigine, or a combination of the two types of drug.[5]

Nonpharmacological treatment

In the absence of adequate pharmacological treatments, several nonpharmacological approaches, such as neurostimulation and neuromodulation therapies, have been administered to patients with CPSP. If a network reorganization model of CPSP is applied, such neurostimulatory approaches might hold great promise, as identification of network nodes could allow specific targeting of these regions to alleviate pain. Below, we review these treatments and their mechanisms of action.

Deep brain stimulation

DBS was first used in 1961 to treat neuropathic pain associated with sensory deafferentation.[67] The technique targets several deep brain structures, including the sensory thalamus (the ventroposterior nucleus),[68] the posterior limb of the internal capsule, periventricular grey matter (PVG), periaqueductal grey matter (PAG), and the anterior cingulate cortex (Figure 2).[69–79]

The mechanisms by which DBS might relieve pain remain unclear, and various hypotheses have been proposed elsewhere.[80,81] Briefly, PVG and/or PAG stimulation might influence ascending and descending pathways by causing release of endogenous opioids, and through opioid-independent mechanisms. Similarly, thalamic stimulation might influence broad sensory cortico-cortical and cortico-subcortical networks,[81] probably through opioid-independent mechanisms.

Most reports of the use of DBS for intractable pain have included several types of pain disorders and only a small number of patients with CPSP. Moreover, efforts to keep patients blinded to the on–off status of their electrode are hindered by the fact that stimulation is perceptible. Owing to such limitations, no individual studies have provided high-quality evidence that DBS is effective for the treatment of CPSP.

Several substantial reviews have summarized the efficacy of DBS for the treatment of neuropathic pain.[80–82] Meta-analyses have suggested that DBS is more effective for nociceptive pain than for neuropathic pain (63% versus 47% long-term success), and more effective for peripheral neuropathic pain than for central pain (51% versus 31% long-term success).[82] According to pooled case series, comparison of PVG and/or PAG stimulation with sensory thalamus stimulation shows that the former is more effective for treatment of nociceptive pain, whereas the latter is more effective for the treatment of deafferentation pain.[81]

We have identified nine case series that reported on the long-term outcomes of DBS treatment for CPSP, with a long-term success rate estimated at 30% (Table 2, Supplementary Table 1 online). Published expert consensus is that the evidence for the efficacy of DBS in treating CPSP is weak and, therefore, inconclusive.[80,83] Furthermore, one report suggests that intracranial haemorrhage, which can cause permanent neurological deficits, occurs in 2–4% of patients who are treated with DBS.[84] Therefore, the risks and benefits should be carefully considered before proceeding with DBS for the treatment of CPSP.

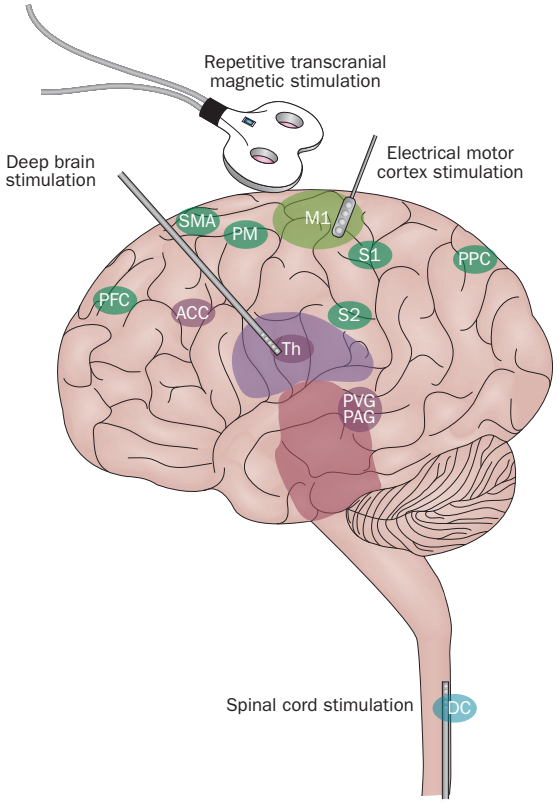

Figure 2 | Neurostimulation targets in the CNS. Deep brain stimulation targets the sensory thalamus (Th), periventricular grey matter (PVG) and periaqueductal grey matter (PAG), or anterior cingulate cortex (ACC). Electrical motor cortex stimulation targets the primary motor cortex (M1). Repetitive transcranial magnetic stimulation targets the M1, prefrontal cortex (PFC), supplementary motor cortex (SMA), premotor area (PM), primary somatosensory cortex (S1), secondary somatosensory cortex (S2) and posterior parietal cortex (PPC). Spinal cord stimulation targets the dorsal column (DC) of the spinal cord.

Motor cortex stimulation

Electrical motor cortex stimulation

EMCS for the treatment of intractable chronic pain was developed in the early 1990s,[85–87] and was subsequently adopted worldwide. The procedure involves implanting epidural or subdural electrodes over the primary motor cortex (M1) via a small craniotomy or burr hole, followed by subcutaneous implantation of a pulse generator that is connected to the electrodes.

Numerous case series of EMCS treatment of chronic pain have been published. We have extracted articles that report on the long-term efficacy of EMCS for the treatment of CPSP (Table 2).[88–100] Most of these studies reported a reduction of at least 40–60% in pain scores after follow-up periods of 1–4 years; the average success rate in 13 nonoverlapping studies was 50% (64 of 126 patients), similar to that reported in previous reviews that included some of these studies.[80,101,102] Peripheral neuropathic pain tended to respond better to EMCS than did central neuropathic pain, but the differences in efficacy seemed less marked than in the case of DBS.[81]

Complications of EMCS reported in one study included hardware-related problems (5.1%), infections (5.7%), seizures during the intraoperative or trial stimulation periods (12%), epidural or subdural haematomas, (1.9%) and transient neurological deficit (1.3%), but not chronic epilepsy.[101] EMCS is considered to be intrinsically safer than DBS because it rarely causes intracranial haemorrhage.[81,102] In addition, EMCS seems to be more effective than DBS:[75] only the clinical response to preoperative rTMS tests equals the response to EMCS.[81,96,103–105] The European Federation of Neurological Societies (EFNS) guidelines on neurostimulation therapy for neuropathic pain suggest that EMCS is effective for the treatment of CPSP (recommendation level C),[80] whereas another expert recommendation states that evidence of its effectiveness is inconclusive.[83]

To avoid the ethical difficulties of conducting sham surgery, several studies have employed double-blind evaluations of EMCS in a randomized controlled manner. These studies reported marked pain relief in the on-stimulation condition compared with the off-stimulation condition.[97,98] To reinforce the evidence for an analgesic effect of EMCS in the treatment of CPSP, however, multicentre prospective trials with double-blind evaluations in large numbers of patients will be needed.

Repetitive transcranial magnetic stimulation

rTMS is a noninvasive technique in which electromagnetic induction is used to stimulate the cortex through the scalp. The technique was first administered to patients with CPSP who were candidates for EMCS treatment.[106] Subsequently, the analgesic effect of high-frequency rTMS (≥5 Hz) that mainly targets M1 has been studied in various types of chronic pain. Other cortical targets have been tested, including the supplementary motor area, premotor area and primary somatosensory area, but only M1 rTMS has produced substantial pain relief in patients with neuropathic pain (Figure 2). rTMS of the left premotor cortex and dorsolateral prefrontal cortex did not have an analgesic effect in patients with CPSP.[107]

A substantial number of randomized sham-controlled trials of high-frequency rTMS of M1 have investigated its analgesic effect in patients with neuropathic pain, around half of whom had CPSP (Table 2, Supplementary Table 2 online).[103–105,108–118] All but one study reported positive results, with various degrees of pain relief, although the proportion of patients who responded well to rTMS ranged from 20% to 79%, and the reduction in pain score ranged from 7% to 45%. Pain relief after a single session of rTMS lasted for periods of hours to days,[109,112,114,115] so repeated administration of rTMS—possibly daily stimulation—might be necessary for practical clinical use. A multicentre, double-blind RCT assessed the safety and efficacy of multisession rTMS.[118] In this study, 64 patients with neuropathic pain (52 with CPSP, seven with spinal neuropathic pain, and five with peripheral neuropathic pain) received 10 daily sessions of rTMS that targeted M1. A significant short-term improvement in pain scores was seen in patients

Table 2 | Success of neurostimulation treatment of CPSP and neuropathic pain

Study	Patients with CPSP	Total no. of patients*	Success rate in CPSP (%)	Overall success rate (%)
Deep brain stimulation				
Richardson *et al.* (1977)[70]	2	30	50	66
Turnbull *et al.* (1980)[71]	1	18	100	67
Hosobuchi *et al.* (1986)[72]	13	122	46	67
Levy *et al.* (1987)[73]	25	141	24	31
Kumar *et al.* (1997)[74]	5	68	20	62
Katayama *et al.* (2001)[75]	12	12	25	25
Hamani *et al.* (2006)[76]	8	21	0	24
Owen *et al.* (2006)[77]	15	15	60	60
Rasche *et al.* (2006)[78]	11	56	18	46
Electrical motor cortex stimulation				
Katayama *et al.* (1998)[88‡]	31	31	48	48
Nguyen *et al.* (1999)[89‡]	11	32	73	75
Nandi *et al.* (2002)[90‡]	6	6	17	17
Pirotte *et al.* (2005)[94]	6	18	67	61
Brown *et al.* (2005)[91]	2	10	0	60
Gharabaghi *et al.* (2005)[92]	5	6	100	100
Nuti *et al.* (2005)[93‡]	23	31	48	52
Rasche *et al.* (2006)[95]	7	17	43	47
Hosomi *et al.* (2008)[96‡]	18	32	28	36
Velasco *et al.* (2008)[97]	1	11	100	73
Tanei *et al.* (2011)[99]	8	11	75	82
Lefaucheur *et al.* (2011)[98]	6	6	83	83
Sachs *et al.* (2014)[100]	2	14	0	14
rTMS				
Lefaucheur *et al.* (2001)[108]	12	18	Not reported	39
Lefaucheur *et al.* (2001)[109]	7	14	57	57
Lefaucheur *et al.* (2004)[110]	24	60	Not reported	27
Khedr *et al.* (2005)[111]	14	28	79	75
André-Obadia *et al.* (2006)[104]	9	12	44	42
Hirayama *et al.* (2006)[112]	12	20	42	50
Lefaucheur *et al.* (2006)[113]	10	22	Not reported	55[§]
Saitoh *et al.* (2007)[114]	7	13	57	62
André-Obadia *et al.* (2008)[115]	13	28	Not reported	18
Lefaucheur *et al.* (2008)[116]	13	46	Not reported	43[§]
André-Obadia *et al.* (2011)[117]	Not reported	45	Not reported[‖]	Not reported[‖]
Lefaucheur *et al.* (2011)[103]	20	59	Not reported	36
Hosomi *et al.* (2013)[118]	52	64	20	20
André-Obadia *et al.* (2014)[105]	11	20	Not reported[¶]	Not reported[¶]
Spinal cord stimulation				
Simpson *et al.* (1991)[128]	11	60	64	70
Katayama *et al.* (2001)[75]	45	45	6.7	6.7
Aly *et al.* (2010)[129]	30	30	23	23

*Includes those with types of neuropathic pain other than CPSP. ‡Analysis was based on data from multiple previous studies. §Data unavailable from cited study but extracted from Lefaucher, J. P. *et al. Clin. Neurophysiol.* **125**, 2150–2206 (2014). ‖A mean improvement of 10% on a numerical rating scale was reported. ¶Subjective pain relief (14.6%) on a numerical rating scale was reported after rTMS.
Abbreviations: CPSP, central poststroke pain; rTMS, repetitive transcranial magnetic stimulation.

who received rTMS compared with those who received sham treatment, and no serious adverse events were seen. Although cumulative improvements in pain scores did not reach statistical significance, this study suggested that daily high-frequency rTMS of M1 was tolerable and provided transient but modest pain relief in patients with CPSP. The modesty of the effect might be partially explained by cerebral lesions interfering with rTMS.[114,119]

Several meta-analyses of rTMS treatment for chronic pain have been published.[120–123] The latest Cochrane Database systematic review,[120] which updates the original that was published in 2010, included 746 participants from 30 studies, approximately 40% of whom had CPSP. After excluding studies that were considered to have a high risk of bias, the review concluded that low-frequency rTMS was ineffective (six studies), and high-frequency rTMS of M1 had a short-term effect on pain in single-dose studies (12 studies). This short-term positive effect equated to a 12% reduction in pain. EFNS guidelines published in 2007 suggested that rTMS has a transient effect in the treatment of central and peripheral neuropathic pain (Level B recommendation).[80] Guidelines based on the latest evidence and published in 2014 by a group of European experts stated that high-frequency rTMS of M1 contralateral to the site of neuropathic pain presentation has a definite analgesic effect (Level A recommendation).[121]

The effects of rTMS are transient, modest, and variable between individuals, but its noninvasive nature means that it is beneficial when weighed against the difficulties involved in treating CPSP, the reduction in quality of life that the condition causes, and the risks of invasive techniques such as DBS and EMCS. However, unlike implantable EMCS devices, the chronic repetition of rTMS that is required with current devices and stimulus conditions is not easy to continue. To establish rTMS as a practical neuromodulation therapy for CPSP, better stimulation conditions and improvement of rTMS devices (for example, adaptation for domestic use) are needed.

Mechanisms

The mechanisms by which EMCS and high-frequency rTMS modulate neuropathic pain and CPSP are often investigated and discussed together. The two techniques produce comparable neuronal stimulation,[124] and their analgesic effects have many shared features,[96,103,105] so the mechanisms of pain relief might also be similar.

Approximately 10 studies, including electrophysiological, neuroimaging and cortical excitability studies, have investigated CNS alterations that are associated with motor cortex stimulation for the treatment of chronic pain conditions. Of these studies, only three were limited to individuals with CPSP.[119,125,126] An fMRI study showed that pain relief resulting from M1 rTMS in patients with CPSP is associated with modulation of activity in multiple pain-related cerebral structures.[126] Diffusion tensor imaging in patients with CPSP showed that preservation of thalamocortical and corticofugal motor tracts predicted the efficacy of M1 rTMS in relieving pain.[119,126] Involvement of inhibitory and facilitatory intracortical

and interneuronal circuits within M1 has also been suggested.[81,113,125] Taken together, the evidence from these studies suggests that pain relief from stimulation initially involves local effects on M1, followed by modulation of various interconnected neural structures and pathways, probably as a consequence of orthodromic activation of corticofugal pathways and antidromic activation of thalamocortical pathways.[81,125,127] This hypothesis is consistent with a network-level neuromodulatory mechanism rather than a restricted effect on an individual area. Future studies might determine the core topology of network changes that lead to pain relief.[57]

Spinal cord stimulation

Only three case series have investigated the efficacy of SCS in the treatment of CPSP (Table 2).[75,128,129] On the basis of the first two studies,[75,128] the EFNS guidelines recommended that SCS should not be offered routinely for treatment of CPSP (Level D recommendation),[80] as only a limited number of patients experienced substantial reductions in pain with this technique.

Subsequent work retrospectively reviewed clinical outcomes of SCS treatment in 30 patients with CPSP.[129] Percutaneous trial stimulation produced good pain relief (≥50% reduction in visual analogue scale [VAS] score) in nine patients (30%), fair pain relief (30–49% reduction in VAS score) in six patients (20%), and poor pain relief (<30% reduction in VAS score) in 15 patients (50%). In 10 of the 30 patients, one or two quadripolar electrodes were implanted after the trial stimulation. After a follow-up period of at least 6 months, seven of nine patients who were monitored in the long term (mean follow-up period 28 months, range 6–62 months) reported good or fair pain relief (five and two patients, respectively). The median VAS score among the nine patients decreased significantly from 8.6 to 4.5 ($P = 0.008$), and no severe complications were reported.

These results indicate that SCS could benefit patients with CPSP. SCS has the advantage of being less invasive than DBS and EMCS, owing to the use of percutaneous trial stimulations to screen patients for suitability before permanent implantation. Development and improvement of SCS systems, such as increasing the number of electrical contacts, is ongoing. Together, these factors suggest that further studies of SCS treatment for CPSP should be encouraged.

As in the case of central neurostimulation, the mechanisms of pain relief provided by SCS are poorly understood. SCS was initially used on the basis of gate control theory, which proposes that, owing to interactions between large and small diameter fibres and interneurons, transmission of non-nociceptive input by large-diameter fibres prevents nociceptive transmission to the brain, thereby 'closing the gates'.[36] However, this theory might not entirely explain the mechanisms. Experiments on animal models of neuropathy have demonstrated that SCS inhibits hyperexcitability of dorsal horn neurons, induces release of γ-aminobutyric acid and acetylcholine, and suppresses glutamate release in the dorsal horn.[130,131] Moreover, involvement of the descending inhibitory system has been proposed.[130] Studies that used PET, fMRI, or neurophysiological tests of cortical excitability have detected functional alteration at the supraspinal level after SCS,[132] and another study that used $H_2{}^{15}O$ PET revealed activation in brain areas that have been associated with emotional and cognitive aspects of pain, such as the anterior cingulate cortex and prefrontal areas, as well as in the somatosensory system.[132] Together, these result show that modulation of spinal activity can influence brain-level activity at multiple sites. Given the reciprocal ascending and descending connections between dorsal horn and brainstem sites, spinal processing should, therefore, be considered as a node in the central pain network.[75,129]

Other nonpharmacological treatments

Pituitary radiosurgery has been used to treat pain in a case series of 24 patients with thalamic pain. Although marked pain reduction was seen in 17 patients (71%), pain recurred within 6 months in most of them; by the end of the follow-up period, only five patients (21%) reported continued pain control, and 10 patients (41%) experienced adverse effects, such as hormone deficiency.[133]

Transcranial direct current stimulation (tDCS) has also been used to treat chronic pain. A Cochrane Database review revealed that tDCS of M1 did not significantly affect chronic pain, including various types of neuropathic and non-neuropathic pain.[120] A subsequent clinical trial reported that tDCS with anodal stimulation over M1 significantly improved temperature perception and provided pain relief for patients with CPSP.[134] Overall, the efficacy of tDCS for treatment of CPSP remains unclear.

Conclusions

The understanding of CPSP and its treatment with conventional pharmacological analgesics remains inadequate, even though the high incidence and severity of the condition make it an important area of unmet clinical need. We argue that the available evidence suggests that CPSP is best understood as a problem of central pain network reorganization rather than as a problem that is restricted to a single site or neurochemical pathway. This hypothesis offers a new theoretical framework in which to understand and evaluate pain in CPSP, and presents the opportunity to predict how modulation of network nodes (that is, specific brain regions) might be beneficial in treatment with neurostimulation.[135] In this context, it is encouraging that evidence already supports the use of invasive and noninvasive neurostimulation to provide at least moderate relief from chronic pain. However, invasive methods must be balanced with the concomitant risks, meaning that noninvasive rTMS is currently the treatment of choice for many patients.

The proposed theoretical framework highlights three key areas to be considered in future research. First, understanding of the core pathophysiology of CPSP would be improved by multimodal and longitudinal measurement of global brain activity, theoretical analysis of network processing, and evaluation of how this processing relates to symptoms and predicts outcomes.[136]

Second, existing treatment methods, especially non-invasive stimulation, could be improved by identification of new stimulation sites (for example, through network simulation), development of improved technology such as rTMS systems suitable for domestic use, and consideration of approaches that combine simultaneous stimulation and pharmacological treatment. Finally, technological innovation could provide substantially enhanced methods for neuromodulation, for example, multisite synchronous or asynchronous stimulation, or technologies such as optogenetic stimulation that target specific cells.

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