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.

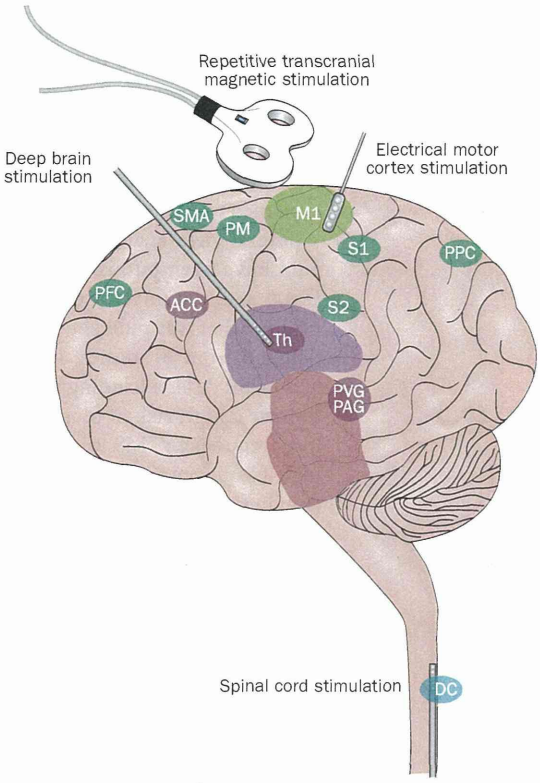

Figure 2 | Neurostimulation targets in the CNS. Deep brain stimulation targets the sensory thalamus (Th), periventricular grey matter (PVG) and periaqueductal grey matter (PAG), or anterior cingulate cortex (ACC). Electrical motor cortex stimulation targets the primary motor cortex (M1). Repetitive transcranial 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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Author contributions

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Topics

反復経頭蓋磁気刺激療法

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●経頭蓋磁気刺激とは

脳機能の解明，中枢神経系の障害の評価のみならず，難治性神経障害性疼痛（InNP）を含めた神経難病の治療において非侵襲法である反復経頭蓋磁気刺激（repetitive transcranial magnetic stimulation：rTMS）が注目を集めている．rTMSは1990年代後半に登場し，治療に応用する可能性が示された．その後，InNPなどさまざまな神経疾患に応用され，有効性が報告されている．米国食品医薬品局（FDA）が2008年，2013年にrTMS 2機種に対し，うつ病治療の認可を行った．InNPにおいて日本で治験を準備中である．

●一次運動野刺激療法

1990年，坪川博士らは一次運動野（M1）の電気刺激（electrical motor cortex stimulation：EMCS）が中枢性脳卒中後疼痛（CPSP）を改善させることを見出した．その後，EMCSはInNP全般に有効性が報告され，世界に広まった．EMCSの有効性は，大規模二重盲検試験は存在しないが，有効率は50％程度と考えられていた[1]．

われわれは平成21～23年に厚生労働研究補助金にて，多施設共同研究を行った．20歳以上の70例のInNPに対し全国7施設で，5Hz-rTMS（90％安静運動誘発閾値，500パルス）とシャム刺激のクロスオーバー試験を行った．70例をランダムに2群に割り付けて，本刺激とシャム刺激の間は2週間以上空けた．1次エンドポイントは疼痛尺度で，2次エンドポイントはマギル疼痛質問表とし，ベックうつスケール（Beck depression inventry：BDI），患者満足度（Patient global impression of change：PGIC）も検討した．結果として61例（男性39例，女性22例）が臨床研究を終えた．エントリーの大多数がCPSPであった．重大な有害事象はなかった．rTMS前後の短期効果では終了直後，60分後ともに疼痛尺度，マギル疼痛質問表ともに本刺激で有意な除痛効果がみられた（図1）．PGICスコアは本刺激中，シャム刺激に対して有意に改善がみられ，フォロー中は有意差がなかった（図2）．BDIでは，本刺激，シャム刺激の間に有意な差がなかった．シャム刺激に対して有意な除痛効果が得られた患者は21％であった．この多施設共同研究では，有意な短期除痛効果が認められ，有害事象がなかったことから，rTMSを繰り返すことで治療となると考えられた[2]．Cochrane ReviewにもrTMSによる除痛効果が報告されている[3]．

●除痛のメカニズム

疼痛認知には複数の脳領域の関与が考えられており，その脳活動はPETやfMRIや誘発電位などのいくつかの機能的画像研究により解析されている．M1や前頭葉と視床との連絡がMCSにより活性化されるとも推察している．加えて帯状回や前頭葉眼窩面の活性化によるInNPのaffective-emotional componentに変化を与えること，あるいは上位脳幹の活性化によりpain impulseの下行性抑制に影響を与えているのかもしれないとも考察している．

CPSPにおいて，視床病変と被殻病変症例でMRIのdiffusion tensor imageから，運動線維と感覚線維を描出し，健常側に対する患側の描出率を計算した．また，rTMSによる除痛効果との相関を検討したところ，除痛効果は運動線維，感覚線維の描出率に相関し，感覚線維により高い相関を示した[4]．つまり運動線維とともに感覚線維が保たれていることが，M1刺激の除痛効果発現に重要であることが示された．

またCPSPにおいて，患側のM1興奮性を2連発磁気刺激法で検討したところ，ICF（intracortical facilitation）が低下している患者において，rTMSによって，ICFが正常化する場合に，高頻度rTMSによる除痛効果が認められる結果が得られた．ICI（intracortical inhibition）変化の方が重要であるとの報告もある．ともあれ，M1興奮性に異常があって，高頻度rTMSを施行することで，興奮性が修飾されて除痛効果が得られるようである[4]．以上から脳内での複合的な除痛メカニズムが，現状では示唆されている．

●今後の展望

rTMSによる疼痛治療の現状について概括した．現在，患者が求めているのは非侵襲治療である．その点ではrTMSはぴったりである．プレガバリンが爆発的に使用されているが，すべての難治性疼痛患者の除痛が得られているわけではない．そこで，rTMSを在宅治療に持ち込むことは大変意味のある新たな治療戦略と考えられる（図3）．また技術進歩により，一段と効果の高い非侵襲なrTMS治療が可能になると考えられる．

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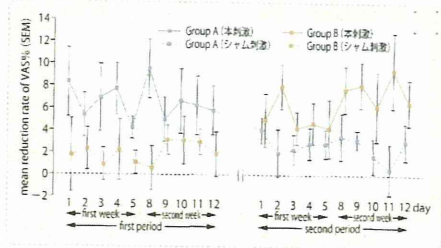

図1　連日rTMSによる除痛効果
一次運動野に対する5Hz rTMSを2週間連日施行し，シャム刺激と比較したところ，疼痛尺度において本刺激は有意に除痛効果を示した．

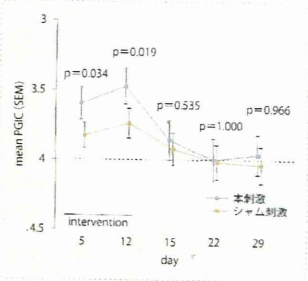

図2　連日rTMSによる患者満足度
患者満足度では，5Hz rTMS施行中は，シャム刺激に対して，有意な満足度が得られているが，刺激終了2週間後には消失している．

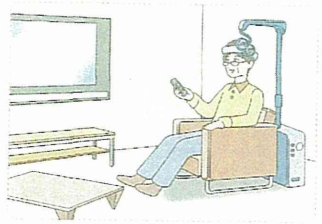

図3　在宅でのrTMS治療のイメージ
在宅において，症状改善を目的としたrTMSが可能となれば，図のように自宅でマッサージチェアに腰掛けて，テレビを見ながら，rTMSを繰り返すことになろう．

E インターベンション治療

7 大脳皮質刺激による除痛

ポイント

一次運動野刺激が一般的であるが，左前頭前野刺激の報告もある．電極を埋め込む方法と，反復経頭蓋磁気刺激の2法があって，前者は保険適応であるが，開頭術が必要なため，施行ケースが限られる．後者は研究中であり，治験が計画されている．

1 除痛のための刺激ターゲット

1990年，坪川らは一次運動野（M1）の電気刺激（EMCS）が中枢性脳卒中後疼痛（CPSP）を改善させることを見出した．EMCSの有効性は，大規模二重盲検試験など存在しないが，有効率は50％程度と考えられていた．

一方，非侵襲な反復経頭蓋磁気刺激療法（rTMS）が2000年頃からスタートした．rTMSであれば大脳の想定される有効部位を刺激して，効果を比較することが可能である．われわれは光学式ナビゲーションシステムを使用して，大脳皮質の主要な部位を刺激してみることを考えた．同一の難治性神経障害性疼痛（InNP）の患者で，M1，一次感覚野，補足運動野，前運動野をターゲットとしてrTMSを行うとM1のみが有意に除痛可能であった．

現在，痛み治療目的のrTMSのターゲット部位は，前頭前野またはM1が選択される．米国では，前頭前野を刺激して，InNP，術後痛，線維筋痛症において有効性が報告されている．一方，M1といっても細長い不整な形状をしており，最も普及しているSの字コイルの刺激でM1全体をカバーすることは困難である．手が痛い場合にはM1の手の領域，足が痛い場合には足の領域を刺激するのが一般的である．

2 rTMSの刺激条件

一般に大脳を興奮させるとされる高頻度刺激（1Hz＜）が選択され，安静時（力を抜いた状態）運動閾値の100％以下で刺激することが推奨される．電気痙攣療法は，電気刺激によって脳内に痙攣波を起こすが，rTMSにおいては，脳内に痙攣波を起こさない．電気痙攣療法も除痛効果があるが，やはり効果が一時的であり，副作用としての認知症が問題となる．一方，rTMSには有害事象がない．国際ガイドラインに沿った使用が望ましい．

3 M1刺激による除痛のメカニズム

痛み認知には複数の脳領域の関与が考えられており，その脳活動は機能的画像研究により解析されている．M1や前頭野と視床との連絡がEMCSにより活性化されることも推察している．加えて帯状回や前頭葉眼窩面の活性化によるInNPの情動系に変化を与えること，あるいは上位脳幹の活性化によりpain impulseの下行性抑制に影響を与えているのかもしれないことも考察されている．

CPSPにおいて，視床病変と被殻病変症例でMRIのdiffusion tensor imageから，運動線維と感覚線維を描出し，rTMSによる除痛効果との相関を検討したところ，除痛効果は運動線維，感覚線維の描出率に相関し，感覚線維により高い相関を示した．

またCPSPにおいて，患側のM1興奮性を2連発磁気刺激法で検討したところ，ICF（intracortical facilitation）が低下している患者において，rTMSによって，ICFが正常化する場合に，高頻度rTMSによる除痛効果が認められる結果が得られた．M1興奮性に異常があって，高頻度rTMSを施行することで，興奮性が修飾されて除痛効果が得られるようである．以上から脳内での複合的なメカニズムによる除痛メカニズムが，現状では示唆されている．

4 治療の現状

保険適応はEMCSである．埋め込んだら，オンデマンドで患者が刺激を繰り返す．ドラッグチャレンジテストで，ケタミンで除痛される患者が適応との報告もあるが，実際には，電極をテスト留置しないと有効性が判定できない．rTMSで有効性を占うこともできるが，装置が高額である．米国では重症うつ病に対して，2008年NeuroStarが，2013年H-coilが治療器として認可された．これらはクリニックに通院して使用するものであるが，InNPの場合，1回の刺激で除痛効果が数時間から1日程度であるので，継続的なrTMSが必要となる．よって在宅でのrTMS機器が必要となり，現在，その機器を企業とともに共同開発しており，医師主導治験準備中である．

（齋藤洋一）

Cell-sheet Therapy With Omentopexy Promotes Arteriogenesis and Improves Coronary Circulation Physiology in Failing Heart

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Cell-sheet transplantation induces angiogenesis for chronic myocardial infarction (MI), though insufficient capillary maturation and paucity of arteriogenesis may limit its therapeutic effects. Omentum has been used clinically to promote revascularization and healing of ischemic tissues. We hypothesized that cell-sheet transplantation covered with an omentum-flap would effectively establish mature blood vessels and improve coronary microcirculation physiology, enhancing the therapeutic effects of cell-sheet therapy. Rats were divided into four groups after coronary ligation; skeletal myoblast cell-sheet plus omentum-flap (combined), cell-sheet only, omentum-flap only, and sham operation. At 4 weeks after the treatment, the combined group showed attenuated cardiac hypertrophy and fibrosis, and a greater amount of functionally ($CD31^+$/$lectin^+$) and structurally ($CD31^+$/α-SMA^+) mature blood vessels, along with myocardial upregulation of relevant genes. Synchrotron-based microangiography revealed that the combined procedure increased vascularization in resistance arterial vessels with better dilatory responses to endothelium-dependent agents. Serial ^{13}N-ammonia PET showed better global coronary flow reserve in the combined group, mainly attributed to improvement in the basal left ventricle. Consequently, the combined group had sustained improvements in cardiac function parameters and better functional capacity. Cell-sheet transplantation with an omentum-flap better promoted arteriogenesis and improved coronary microcirculation physiology in ischemic myocardium, leading to potent functional recovery in the failing heart.

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INTRODUCTION

Heart failure following myocardial infarction (MI) is a major cause of death and disability worldwide. Despite advances in drug and device therapy, recovery of cardiac function and prevention of transition to heart failure in MI patients remain unsatisfactory, indicating the need for development of novel therapeutic alternatives.[1] Myocardial regenerative therapy with cell-sheet transplantation has been shown to induce angiogenesis via paracrine effects in a chronic MI model.[2,3] However, the proangiogenic effect of the stand-alone cell-sheet treatment may be insufficient to fully relief ischemia in the chronic MI heart that involves a large territory of the left ventricle (LV), since the coronary inflow of the ischemic/infarct myocardium is dependent upon collateral arteries from other territories.[4,5] In addition, microvascular dysfunction is present in critical chronic MI heart across a wide range of the peripheral coronary tree.[6] This highlights the need for a comprehensive understanding of the mechanism of angiogenesis induced by a cell-sheet therapy in ischemic hearts.

For successful therapeutic neovascularization of ischemic tissues, it is essential to induce robust angiogenic responses (angiogenesis), and establish functionally and structurally mature arterial vascular networks (arteriogenesis) that show long-term stability and control perfusion.[5] Establishment of mature vessels is a complex process that requires several angiogenic factors to stimulate vessel sprouting and remodeling (endothelial tubulogenesis accompanied with a pericyte recruitment) of the primitive vascular network. Endothelial vasodilator function of coronary microvessels (resistance arterial vessels) is also an important determinant of myocardial perfusion in response to increased myocardial oxygen demand, playing a critical role in neovascular therapies.[6–8] The attenuated therapeutic effects observed in the previous clinical trials were caused by multiple factors including

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generation of unstable blood vessels that regress over time or functionally immature vessels accompanied with endothelial dysfunction in ischemic areas.[5,9]

The omentum (OM), historically used in surgical revascularization for patients with ischemic heart disease, is also known to release a number of angiogenic cytokines and attenuate inflammation.[10–14] In addition, the gastroepiploic artery involved in the OM-flap can play an important role as an extracardiac blood source with high perfusion capacity for developing effective collateral vessels for advanced coronary artery disease. We established a combination strategy of cell-sheet transplantation covered with a pedicle OM-flap in porcine models, allowing us to implant large numbers of cells and improve cell survival.[13,14] However, data are scarce regarding the therapeutic effects of such combined treatment on vessel maturity and coronary microcirculation physiology in ischemic territory. We hypothesized that cell-sheet transplantation with a pedicle OM-flap will better promote arteriogenesis and stabilize blood vessels in ischemic myocardium along with improved coronary microcirculation physiology, consequently enhancing the therapeutic effects of cell-sheet therapy. Herein, we focused on vessel maturation induced by cell-sheet therapy with an OM-flap and evaluated the physiological benefits in coronary microcirculation utilizing modern modalities such as *in vivo* synchrotron-based microangiography and positron emission tomography (PET).

RESULTS

Histological analysis of host myocardium

Four weeks after treatment, myocardial structural components, collagen accumulation and cardiomyocyte hypertrophy, were assessed by hematoxylin-eosin, Masson trichrome, and Periodic acid-Schiff staining (n = 11 for each group). LV myocardial structure was better maintained in the combined group as compared with the others (**Figure 1c**). The combined group had a significantly thickened anterior LV wall (anterior wall thickness, control 392 ± 31 versus combined 912 ± 34 versus sheet-only 688 ± 27 versus OM-only 500 ± 28 μm) (**Figure 1d**). That group also had a significantly attenuated collagen accumulation (percent fibrosis, 18 ± 1 versus 8 ± 4 versus 13 ± 6 versus 14 ± 1%, respectively) (**Figure 1e**) and cardiac hypertrophy (myocyte size, 23 ± 1 versus 16 ± 1 versus 20 ± 3 versus 21 ± 2 μm, respectively) (**Figure 1f**) in the peri-infarct regions (ANOVA $P < 0.001$ for all).

Gene expressions in peri-infarct myocardium during acute treatment phase

The myocardial gene expressions related to angiogenesis, vessel maturation, and anti-inflammation were analyzed at 3 days after each treatment using real-time PCR (n = 6 for each group). As compared to the others, the combined group showed substantially higher gene expressions of *vascular endothelial growth factor (VEGF)-A*, *VEGF receptor-1*, *VEGF receptor-2*, *Akt-1*, *platelet-derived growth factor (PDGF)-β*, *angiopoietin (Ang)-1*, *Tie-2*, *vascular endothelial (VE)-cadherin*, *platelet endothelial cell adhesion molecule (PECAM)-1*, and *stromal cell-derived factor (SDF)-1* in peri-infarct myocardium at the early stage of transplantation (**Figure 2**).

Vessel recruitment in transplanted cell-sheets and donor cell survial

To evaluate the effect of adding OM-flap to the cell-sheet therapy on the vessel recruitment (angiogenesis) in the transplanted area that should be related to the donor cell survival, we serially assessed the number of functional blood vessels with patent endothelial layers (CD31/lectin double-positive cells) in the transplanted area of the sheet-only and combined groups at 3, 7, and 28 days after each treatment (n = 6 for each group and each time point) (**Figure 3a–f**). At 3 days after treatment, in the sheet-only group, several blood vessels were just located at the border between the sheet and infarct area (**Figure 3a**), whereas a large number of functional vessels was detected proximal to the border between the cell-sheet and OM and within the sheet in the combined group (**Figure 3d**), suggesting that the cell-sheet received blood supply directly from the infarct myocardium and OM. Consequently, the combined group had greater numbers of functional blood vessels in the cell-sheet than the sheet-only group at any follow-up point, although both groups showed steady decrease in the number of vessels during the 28 days (**Figure 3g**).

The quantitative assessments of the donor (GFP-positive) cell presence were also serially performed to elucidate the donor cell dynamics in the sheet-only (**Figure 3a–c**) and combined (**Figure 3d–f**) groups. We traced the transplanted donor cells and found that there was no significant difference in the engrafted area at 3 days after transplantation between the groups, while the subsequent changes in each group were apparently distinctive (**Figure 3h**). During the 7days after the treatment, the amount of decrease in the engrafted area was substantially smaller in the combined group than that in the sheet-only group, resulting in 4.3-fold increased retention of donor cells in the former group. This led to the greater donor cell presence in the combined group persistently (at least until day 28), which was consistent with the amount of vessel recruitment in the cell-sheet.

Vessel remodeling and maturation in peri-infarct myocardium

We serially assessed neovascular vessel maturity in peri-infarct areas at 3 (n = 6 for each group) and 28 days (n = 11 for each group) after treatment (**Figure 4**). Vessel density and structural maturity were quantified as the number of CD31 positive and CD31/α-smooth muscle actin (SMA) double-positive vessels per mm^2, respectively. A maturation index was calculated as the percentage of CD31/α-SMA double-positive vessels to total vessel number. Functionally mature vessels with patent endothelial layers were assessed by lectin injection, which binds uniformly and rapidly to the luminal surface of endothelium, thus labeling patent blood vessels. Vessels positive for CD31 but negative for lectin were regarded as functionally immature and undergoing regression, or that had lost patency.[15,16]

In general, α-SMA signals were located at the outer edges of CD31 staining, indicating pericyte attachment to newly formed endothelium. Three days after treatment, there was no difference in number of CD31-positive cells among the groups, though the combined group showed a trend of greater number of functional blood vessels with patent endothelial layers (CD31/lectin double-positive) and structurally (CD31/α-SMA double-positive) mature vessels, with a higher maturation index (**Figure 4a–g**). Notably, the percentage without lectin staining (CD31$^+$/lectin$^-$) was significantly smaller in the combined group.