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Review Article

Repetitive transcranial magnetic stimulation in central post-stroke pain: current status and future perspective

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ABSTRACT

Central post-stroke pain (CPSP) is an incapacitating disorder that impacts a substantial proportion of stroke survivors and can diminish their quality of life. Conventional therapies for CPSP, including tricyclic antidepressants, anticonvulsants, and opioids, are frequently ineffective, necessitating the investigation of alternative therapeutic strategies. Repetitive transcranial magnetic stimulation (rTMS) is now recognized as a promising noninvasive pain management method for CPSP. rTMS modulates neural activity through the administration of magnetic pulses to specific cortical regions. Trials analyzing the effects of rTMS on CPSP have generated various outcomes, but the evidence suggests possible analgesic benefits. In CPSP and other neuropathic pain conditions, high-frequency rTMS targeting the primary motor cortex (M1) with figure-eight coils has demonstrated significant pain alleviation. Due to its associaton with analgesic benefits, M1 is the most frequently targeted area. The duration and frequency of rTMS sessions, as well as the stimulation intensity, have been studied in an effort to optimize treatment outcomes. The short-term pain relief effects of rTMS have been observed, but the long-term effects (> 3 months) require further investigation. Aspects such as stimulation frequency, location, and treatment period can influence the efficacy of rTMS and ought to be considered while planning the procedure. Standardized guidelines for using rTMS in CPSP would optimize therapy protocols and improve patient outcomes. This review article provides an up-to-date overview of the incidence, clinical characteristics, outcome of rTMS in CPSP patients, and future perspective in the field.

Keywords: Analgesics, Opioid; Central Post-Stroke Pain; Cerebral Cortex; Neuralgia; Pain; Pain, Intractable; Quality of Life; Stroke; Therapeutics; Transcranial Magnetic Stimulation.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive, effective alternative treatment for central post-stroke pain (CPSP). Several investigations that benefited from the application of rTMS have demonstrated this. Eleven to forty percent of stroke patients experience chronic pain, with CPSP being the most common variant [1,2]. Reportedly, chronic pain disorders following a stroke can diminish quality of life by impacting emotions,

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sleep, and the ability to socialize [3]. The incidence of CPSP in stroke patients can vary between one percent to thirty-five percent [4]. Damage to any part of the brain's somatosensory pathways, including the medulla, thalamus, and cerebral cortex, can result in CPSP [5]. Multiple research investigations show that the occurrence of CPSP differs depending on the area of the damage, with a notably high incidence following infarct of the lateral medulla or damage in the ventroposterior thalamic region [6]. In research by MacGowan et al. [5], 63 individuals with infarct of the lateral medulla were diagnosed retrospectively and prospectively, and 16 of them developed CPSP.

CPSP, like other neuropathic disorders, is frequently challenging to manage, and drug dosage can be limited due to adverse effects, especially in elderly people. In the clinical setting, pharmaceutical management for CPSP typically entails trying various drugs until alleviation of pain is achieved, frequently involving a combination of multiple medications [7]. Neurostimulation therapies, such as rTMS, have been developed recently in individuals with CPSP which are resistant to pharmaceutical therapy [6]. This review article provides an up-to-date overview of the incidence, clinical characteristics, and outcomes of rTMS in CPSP patients, as well as future perspectives in the field.

MAIN BODY

1. Current definition of CPSP

1) CPSP then and now

In 1891, Edinger introduced the idea of central pain for the first time. In a paper titled "Le syndrome thalamique" published 15 years later, Déjerine and Roussy provided a widely cited description of CPSP. A limited number of patients with multiple neurologic manifestations attributable to lesions in the optic thalamus were described. The thalamus and a portion of the posterior extremity of the internal capsule were affected in these three patients, as determined by their pathological examinations [6]. Twenty-four stroke patients who showed signs of thalamic optic lesions and central pain in 1911 were documented comprehensively by Head and Holmes for their sensory abnormalities and pain experiences. During the recovery of function, these neurologists observed that patients frequently experienced discomfort and hypersensitivity to stimuli [8]. In 1938, Riddoch [9] elaborated on the clinical characteristics of central pain originating from both thalamic and extra-thalamic origins. Although few individuals exhibit the traditional "Dejerine and Roussy syndrome," the word "CPSP" has become primarily used to characterize neuropathic pain following a stroke. Central pain can also be produced by vascular damage in parts of the central nervous system (CNS) other than the thalamus [6].

CPSP is one of the chronic pain disorders known as central neuropathic pain, which is brought on by damage or dysfunction of the CNS [10]. Due to the challenge of distinguishing this disease from various pain disorders linked to abnormalities of the CNS, a new description of central neuropathic pain has emerged in recent years. It refers to discomfort brought on by central somatosensory lesions or illness. Other pain conditions, including headaches, spasm pain, contracted muscles, hemiplegic pain in the shoulder, and various forms of musculoskeletal pain, can complicate the clinical manifestation of CPSP [11].

There are currently no pathognomonic indications for the diagnosis of CPSP. The elderly and post-stroke patients are prone to chronic pain, and many individuals may experience multiple forms of pain simultaneously. Nociceptive sources are frequently the main culprits in these patients' suffering, despite the fact that many of them meet the diagnostic requirements for neuropathic pain. It might be challenging to pinpoint the central neuropathic component in CPSP instances when symptoms like spasms, hemiplegic pain in the shoulder, and other musculoskeletal discomfort are present. Multiple forms of pain can sometimes manifest in the same area of the body [6]. Certain researchers characterize CPSP as a syndrome of post-stroke central neuropathic pain that affects the specific area of the body associated with cerebral and vascular damage. Pain and aberrant sensory perception are its defining features [12]. There are no longer any other identified sources of peripheral neuropathic, nociceptive, or psychogenic pain [13]. As a result, the alternative diagnosis must take into account sensory signals, the site of the lesion, and certain clinical examination conclusions, for example, a rise in muscle tone or shoulder muscle displacement [6].

Chronic pain in stroke patients was not always directly related to the stroke, as prior chronic pain syndromes are frequent in those with post-stroke pain [1]. Shoulder pain, CPSP, spasticity, and tension-type headaches are the most frequent types of chronic pain following a stroke. Some stroke patients may experience multiple types of discomfort [1,2]. Reportedly, chronic pain disorders following a stroke can diminish quality of life by impacting

emotions, sleep, and the ability to socialize [4]. Despite scant epidemiological research on CPSP, its prevalence among stroke patients ranges from 1% to 35% [6]. According to one study, people with sensory abnormalities are more likely to have CPSP (18%) than those without it [2]. CPSP is not an unusual illness, and the evaluation of sensory manifestations, especially pain, is an essential component of post-stroke patient monitoring, especially for geriatric people or those with aphasia [6].

2) Neuroanatomy of CPSP

A complicated network of axonal branches that connect to several brain areas makes up the pain mechanism. There are connections between the anterior pretectal nucleus, periaqueductal gray (PAG) matter, lateral and medial thalamus, ventral and dorsal medullary reticular formation, amygdala, and hypothalamus. The ascending route is made up of two distinct routes of pain known as the medial and lateral route [14]. The spinohypothalamic, spinoamigdala, medial spinothalamic, and spinoreticular tracts comprise the medial system. There are connections between these tracts and the limbic, prefrontal, and cingulate cortices. The medial system transmits information regarding affective, motivational, and autonomic pain responses [15]. The spinothalamic tract, which connects to the lateral thalamus and then to the primary and secondary somatosensory cortices, makes up the lateral system. These regions determine the nature, location, and intensity of the nociceptive stimulus [14]. Although the exact processes behind the development of CPSP are still unknown, neuroanatomical linkages are well understood. Nevertheless, it is widely recognized that CPSP has implications beyond structural damage [16].

Lesions caused by a stroke reduce M1 stimulation in the affected part of the brain. This decreases neuronal output, particularly interhemispheric inhibition (IHI) to M1 in the brain area that was unaffected by the stroke. As a result, the neuronal output and M1 excitability in the contralateral hemisphere both increase, enhancing the IHI from the contralateral M1 to the affected M1 and inhibiting excitability in the affected hemisphere [17].

In order to explain how a person having lateral thalamic injuries misperceives painful and non-painful stimulation, Henry Head and Gordon Holmes developed the disinhibition theory in 1911. Their hypothesis states that damage to the lateral nucleus disrupts cortical control mechanisms, resulting in hyperactivity in the thalamus and increased reactions to stimuli [8]. According to a theory by Craig [18], injuries to the CNS cause the output of thermosensory regions in the insula and limbic networks to be out of balance. Damage in the lateral lamina I spinothalamocortical route, which is linked to the parietoinsular cortex through posterolateral thalamic inputs, cause polymodal nociceptive activity to stop being turned off [16]. In contrast, damage in the medial lamina I spinothalamocortical route, which is linked to the anterior cingulate cortex, results in thermosensory integration deficits. This loss manifests as a burning sensation and increased sensitivity to temperatures that were formerly innocuous [18]. The notion that injury to the spinothalamic route is an important process in CPSP is supported by additional research. Boivie et al. [19] discovered that damage at any site on this route can result in CPSP, and Vartiainen et al. [20] showed that disruption of the spinothalamocortical route is an independent predictor of the onset of central pain.

Using imaging techniques, researchers have also conducted investigations into CPSP. Using magnetic resonance imaging, the temporal cortex, secondary somatosensory cortex, insular cortex, ventrolateral prefrontal cortex, and nucleus accumbens have been identified as exhibiting characteristic cortical atrophy in CPSP patients [21]. These structural changes point to anatomical variances that might be responsible for maladaptive changes linked to the emotional aspect of pain and sensory discrimination impairment [22]. In another investigation employing diffusion tensor imaging (DTI), changes in white matter microstructure were detected in pain-processing regions, including the anterior cingulate cortex, posterior insula, thalamus, and somatosensory cortex. This research also revealed an increase in functional connection within the anterior cingulate cortex and a decrease within the somatosensory cortex [23]. Adopting a holistic strategy that combines neurophysiological measurements to comprehend the connection among areas of neuroanatomical damage and physiological states may therefore contribute to a more accurate diagnosis [24].

Since thalamic injuries are usually followed by CPSP, it is thought that the thalamus is crucial to understanding the mechanisms behind central pain. In one study, out of eleven patients with thalamic lesions and pure sensory stroke, nine were found to have minor infarcts in the thalamus, specifically in the posterolateral nucleus, which contained the damage [25]. Another study found that damage to the caudal ventral thalamic nucleus was enough to reduce temperature sensibility and cause CPSP without altering the posterior part of the medial ventral nucleus [26]. Positron emission tomography (PET) investigations have shown that CPSP patients with spontane-

ous pain at rest have lower blood circulation to the areas of the brain in the thalamus. This shows that the thalamus is less active, which could be connected with the cause of neuropathic pain. Through single-photon emission computerized tomography and PET imaging, thalamic hyperactivity was identified in allodynia [6]. Studies on primates and rodents with central pain suggest that an elevated excitability of thalamic nuclei is the result of abnormal homeostasis plasticity caused by the absence of normal ascending input through the spinothalamic tract [27]. Using microelectrodes, electrical stimulation of specific regions in the lateral and medial thalamus can induce pain [28]. As a pain producer or in the handling of aberrant ascending input, the thalamus likely performs an essential part in certain patients with central pain [6].

3) Pathophysiology of CPSP

Changes in brain plasticity can also cause CPSP in addition to physical injury to the pathway. This concept proposes that malfunctioning neural plasticity is the primary mechanism underlying CPSP and is supported in the pathophysiology of other neuropathic pain disorders, such that the abnormal condition of spontaneous pain is associated with inappropriate responses to cortical and thalamic hyperexcitability [22]. In a study with rats, Gritsch et al. [24] hypothesized that central pain is generated by hyperexcitability of the lateral thalamus, which is linked to the expression of calcium-voltage-dependent channels and alterations to the GABAergic inhibitory mechanism. Other animal investigations have shown that the occurrence of CPSP is associated with an increased connection between the mediodorsal (MD) nucleus of the thalamus and the amygdala in the affected hemisphere [29]. In addition, Kuan et al. [30] identified brain-derived neurotrophic factor (BDNF) as a possible mediator of abnormal neural activity in the circuit involving the medial thalamus and the cingulate cortex.

Central sensitization plays a part in the processing of pain in CPSP, just like it does in other kinds of neuropathic pain [31]. Central sensitization is an increased neuronal response to central signaling, primarily focused on the dorsal horn, although the thalamic and cortex areas can also be concerned. There are both homosynaptic and heterosynaptic processes involved in central sensitization. Homosynaptic processes involve identical inputs, while a heterosynaptic processes involve different inputs and can lead to allodynia [32]. Sensitization mechanisms, which fall into five categories—pre-synapse changes, post-synapse changes, interneuron changes, alterations in descending modulation, and immune/microglial mechanisms—involve higher discharge of excitatory neurotransmitters and/or improved synaptic effectiveness [33].

Several metabotropic G-protein-coupled receptors, such as μ-opioid receptors, GABA-b, and adenosine receptors, inhibit glutamate release pre-synaptically. After nerve damage, μ-opioid receptors are located simultaneously pre- and post-synapse, which may cause an increase in glutamate release [34]. Voltage-gated calcium channel activation at the terminals of the main afferent centers initiates the release of excitatory neurotransmitters. The dorsal root ganglion and spinal cord both experience elevation of the $\alpha 2$-δ subunit of these channels in response to nerve damage [35]. This could result in a rise in calcium influx and glutamate discharge, ultimately leading to neuropathic pain. Due to their ability to attach and inhibit this subunit, the anticonvulsant medications gabapentin and pregabalin are useful in treating neuropathic pain [33].

In some studies, the function of post-synaptic processes in central sensitization was found. Substance P and other peptides cause a gradual depolarization that leads to the activation of the glutamate N-methyl-D-aspartate (NMDA) channels, which then allow calcium entry [36]. Calcium can enter through α-Amino-3-Hydroxy-5-Methyl-4 Isoxazole Propionic Acid receptors, and this mechanism can play a role in long-term potentiation (LTP) of the dorsal horn, which ultimately causes hyperalgesia and allodynia [33].

The immune system, including cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), plays a role in neuropathic pain [37]. Microglia are activated, and respond with nociceptive inflammatory mediators, and activate pain-related neurotransmitter receptors. Through the overexpression of glutamate receptors and the downregulation of GABA, which both contribute to the pain effect, TNF-α and IL-1β are implicated in controlling the development of neuropathic pain [33]. **Fig. 1** illustrates the pathophysiology of CPSP.

4) Diagnostic criteria of CPSP

CPSP shares clinical characteristics with other central and peripheral neuropathic pain disorders [38]. There are no hallmark manifestations associated with the development, diagnosis, or severity of CPSP, and the symptoms and description of CPSP can differ considerably between patients [6]. Persistent or sporadic pain that is reported as searing, pulsating, pressing, or freezing can be a symp-

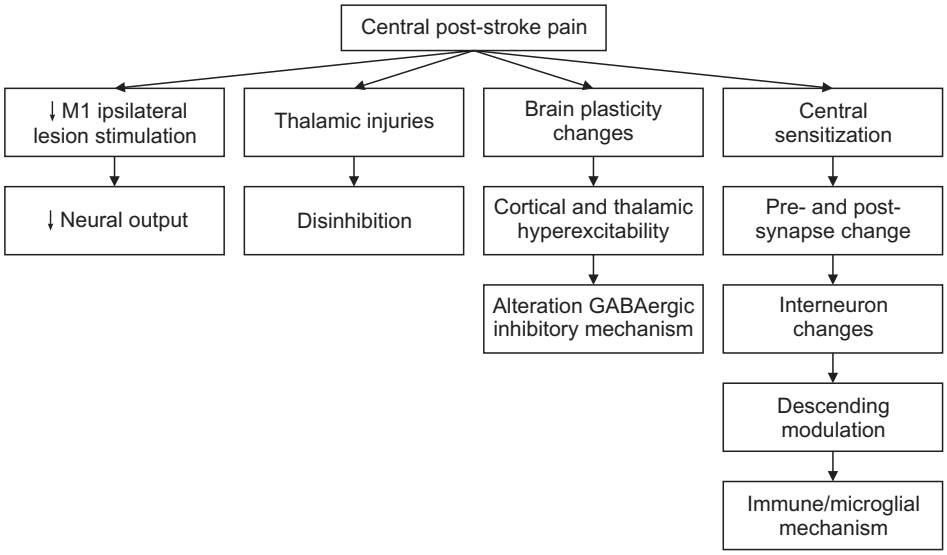

Fig. 1. Schematic illustration of the pathophysiology central post-stroke pain (CPSP). There are several structural and functional changes associated with the development of CPSP, including reduced M1 stimulation in the affected part of the brain, thalamic injuries, brain plasticity changes, and central sensitization.

tom of CPSP. Typically, the pain is localized to a specific anatomical location and is accompanied by somatosensory abnormalities and impairment in both proximal and distal body segments, which correspond to the anatomical site of the damage within the CNS [16].

The interval between a stroke and the onset of pain differs, with some patients experiencing pain immediately after the event and others developing it years later. Although the onset of CPSP can be delayed, the majority of cases manifest within the first few months following a stroke [6]. In a prospective trial with 16 CPSP patients, ten individuals experienced pain during their first month following their stroke, three during one and six months, and three after six months [12].

Despite the efforts of clinicians and researchers to establish standardized diagnostic criteria, CPSP remains difficult to classify due to the wide variety of clinical symptoms. **Table 1** outlines the diagnostic criteria used to evaluate individuals with CPSP, which have been proposed by a variety of researchers [6,39,40].

2. Current treatment guideline recommendations on CPSP

Similar to other neuropathies, the treatment of CPSP is frequently complicated and limited by the possibility of adverse effects, particularly among older people. In the clinical setting, pharmaceutical management for CPSP typically entails trying various drugs until alleviation of pain is achieved, frequently involving a combination of multiple medications. The only study done so far on CPSP prevention was a double-blind, prospective, placebo-controlled trial that looked at how well amitriptyline (75 mg per day) worked in 39 people who had just had an acute thalamic stroke. The study followed these patients for one year, but no significant preventive effect was discovered [7].

The initial therapy for neuropathic pain is tricyclic antidepressants, which are effective in a variety of neuropathic pain conditions [41,42]. Amitriptyline (75 mg/day) effectively decreased pain in CPSP patients. Many respondents had plasma values of more than 300 nmol/L of amitriptyline, which was associated with the impact. Fatigue and dry mouth were the most frequent adverse effects [43].

Anticonvulsant drugs are drugs whose analgesic mechanism acts in several ways, including reducing neuronal hyperexcitability. It is generally known that gabapentin and pregabalin are effective at treating both peripheral and central neuropathic pain [13,44]. In one pregabalin study, patients with central neuropathic pain experienced a significant therapeutic benefit in pain intensity [45]. The most frequently observed adverse effects were nausea, somnolence, intellectual function decline, and dizziness. Lamotrigine was tolerated effectively and had an adequate pain-relieving benefit in one study for CPSP [43,46]. A summary of neuropathic pain medications and how they work is provided in **Table 2** [47–49].

The most well-researched combination for the treatment of neuropathic pain is pregabalin or gabapentin combined with tricyclic antidepressants, and specialists have had positive clinical results with this approach. Pregabalin or gabapentin combined with tricyclic antidepressants is beneficial for people who cannot handle high

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Table 1. Diagnostic criteria for central post-stroke pain

Klit et al. (2009) [6]	Hansen et al. (2012) [39]	Scholz et al. (2019) [40]
Mandatory criteria: 1. Pain within an area of the body corresponding to the lesion of the CNS. 2. History suggestive of a stroke and the start of pain at or after stroke onset. 3. Confirmation of CNS damage by imaging or negative or positive sensory manifestations in the body part where the damage is located. 4. Other sources of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely. Supportive criteria: 1. No primary relation to movement, inflammation, or other local tissue damage. 2. Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and piercing needles, although any description of pain can be used. 3. Hypersensitivity to touch or cold.	1. Development of pain with onset at or after the stroke. 2. Location of pain on the stroke-affected side of the body. 3. No other apparent of the pain, including pain isolated to the shoulder joint and nearby origin.	1. Pain is caused by a cerebrovascular lesion, infarct or hemorrhage, of the brain or brainstem. 2. The pain may be spontaneous or induced, as an increased response to a painful stimulus (hyperalgesia) or a painful response to a normally non-painful stimulus (allodynia). 3. The diagnosis of central post-stroke pain requires a history of stroke and neuroanatomically plausible distribution of the pain, *i.e.*, pain experienced in the body area reflected in the central nervous tissues damaged by the stroke. 4. The pain may affect half of the body or a smaller region. 5. Negative or positive sensory symptoms or sign indicating the involvement of the brain have to be displayed in the body part impacted by the stroke.

CNS: central nervous system.

Table 2. Pharmacotherapy of neuropathic pain drugs

Drug	Mechanism of action
Tricyclic antidepressants (amitriptyline)	Inhibition of noradrenaline reuptake *via* α2-adrenergic receptors [42]
Calcium channel a2δ ligand (gabapentin, pregabalin)	Acts on the a2δ subunit of the voltage-gated calcium channel [44]
Serotonin-noradrenaline reuptake inhibitors (duloxetine, venlafaxine)	Inhibits the reuptake of serotonin and noradrenaline [47]
Lamotrigine	Inhibition of voltage-gated calcium channels [46]
Carbamazepine	Blocks sodium channels [48]
Opioids (tramadol, morphine)	μ-opioid receptor agonist [49]

doses of either medication or who require more than one medication to relieve their pain [50]. However, we must be aware of adverse effects, which may be more prevalent and severe in stroke patients [51]. Some of the side effects that often appear when using this combination of drugs include sedation, nausea, dyspepsia, dizziness, headaches, and blurred vision [52].

Various non-pharmaceutical treatments for CPSP have been investigated for their efficacy. Psychological therapies, such as relaxation techniques and biofeedback, as well as acupuncture and vestibular caloric stimulation, may be useful in the management of CPSP. In cases of CPSP that do not respond well to medications, neurostimulation therapies like motor cortex stimulation (MCS), deep brain stimulation (DBS), and rTMS can be considered [6]. Among the recommendations for post-stroke rehabilitation, only the American Heart Association/American Stroke Association have specifically addressed using neurostimulation therapy for CPSP [53]. **Table 3** summarizes the current post-stroke rehabilitation guideline recommendations for CPSP [53–55].

3. New evidence on the management of CPSP with rTMS

1) Development of rTMS

Galvani and Volta started the bioelectric movement in the late 17th and early 18th centuries, which is where transcranial magnetic stimulation (TMS) originated [56]. Since then, TMS has evolved into a non-invasive treatment for a variety of neurologic and mental health conditions. Michael Faraday made the scientific discovery of electromagnetic attraction in 1831, demonstrating that magnetic field variations can generate electricity [57]. The fundamental principles of TMS are derived from the Maxwell-Faraday formula and principle. Once the coil is "active," it generates a magnetic field through the flow of current. In the absence of a current, the magnetic field generates a perpendicular electric field that is higher at the edges and lower in the middle. This magnetic current depolarizes the transmembrane potential while also stimulating the nearby neurons [58]. There are several coil models, including circular, figure-eight, or butterfly coil, as well as H-coil shapes, available to designate the stimulation's focal point [56].

In 1985, Barker, Jalinous, and Freeston of Sheffield, United Kingdom, described the repetitive method. They used an over-the-head coil capable of generating action potentials in the arm muscles in conjunction with a ca-

Table 3. Summary of current clinical management guideline recommendations on CPSP

Royal College of Physicians (2016) [54]	A. Patients with central post-stroke pain ought to receive amitryptilline, gabapentin, or pregabalin as their initial treatments. B. Patients with central post-stroke pain who are unable to obtain adequate pain relief with initial pharmaceutical therapy at the maximum permissible dose should be given the option of receiving therapy with an alternative medication or medication in conjunction with the first medication.
American Heart Association/American Stroke Association (2016) [53]	- Amitriptyline and lamotrigine are acceptable first-line medications (Class IIa, LoE B) - Second-line therapies could include phenytoin, gabapentin, pregabalin, or carbamazepine (Class IIb, LoE B) - The efficacy of transcutaneous electrical nerve stimulation (TENS) as a therapy is yet to be proven (Class III, LoE B) - Motor cortex stimulation may be appropriate in the management of persistent central post-stroke pain that is unresponsive to other therapies in carefully selected patients (Class IIb, LoE B) - The efficacy of deep brain stimulation as a therapy is yet to be proven (Class III, LoE B)
Canadian Stroke Best Practice (2020) [55]	- Anticonsulvant (such as gabapentin or pregabalin) should be the initial therapy for central nervous system pain (LoE C) - As a second-line treatment, tricyclic antidepressant (*e.g.*, amitryptiline) or a Serotonin-norepinephrine Reuptake Inhibitor (especially duloxetine) should be administered to patients (LoE C) - Opioids and tramadol can be used to treat patients unresponsive to first- and second-line treatment (LoE C)

CPSP: central post-stroke pain, LoE: level of evidence.

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pacitor discharge device [59]. This extended the concept of the single pulse developed at the National Hospital in London by A. Merton and H. B. Morton [57]. They administered a short, high-voltage electric shock to stimulate the motor cortex and elicit the motor evoked potential, a relatively synchronous muscle response. Unfortunately, initial attempts at this technique failed, but in 1985, TMS was conducted for the first time painlessly or with minimal discomfort. To effectively employ TMS, pulses of varying frequencies must be administered repeatedly to stimulate or inhibit brain functions [56].

Dr. Alvaro Pascual Leone is a pioneer in demonstrating how rTMS may bring insight into brain function. In his studies involving blind people, he and his associates applied magnetic stimulation to the cerebral cortex and observed an improvement in Braille reading ability, indicating neural plasticity. His research has included epilepsy, stroke, Parkinson's disease, pain, autism, melancholy, and dementia, among others [60]. rTMS has emerged as a cost-effective, and repeatable method for researching the brain that is safe and non-invasive. Initially employed predominantly for cortical mapping, it is now being investigated as a treatment or potential treatment for a variety of conditions [56].

2) The mechanism of rTMS for CPSP

Utilizing the electromagnetic induction principle that Michael Faraday first introduced in 1831, TMS uses a wire coil to produce a brief and rapidly changing current. This current generates a fluctuating magnetic field of high strength (+1–2 Tesla) [61]. In 1985, Barker et al. [59] performed the initial demonstration of TMS on humans. Since then, the discipline has experienced rapid expansion and numerous technological adaptations, but the fundamental principle has remained unchanged. Conventionally, coils are positioned tangentially to the cranium, and magnetic pulses are delivered perpendicular to their plane. This pulse reaches the brain by penetrating the epidermis, scalp, and skull [61]. The magnetic pulse induces an electric current within the brain that is in line with the coil axis and perpendicular to the magnetic field. This induced current can induce action potentials in the designated brain region's neurons [62]. Recent developments have enhanced our comprehension of the neural elements activated by TMS. Scientists have tracked both "direct" and "indirect" stimulation of pyramidal V-layer neurons via mono- and polysynaptic interneuron circuits by utilizing epidural cervical electrodes to observe descending flow throughout the corticospinal tracts evoked by single-pulse TMS to the primary motor cortex [63]. Considering these advancements, the particular processes underlying TMS-induced neuronal activation continue to be inadequately understood and the subject of ongoing debate [61].

rTMS may share a similar mechanism with MCS, as suggested by research on MCS. These studies suggest that MCS could directly shut down parts of the brain that control the emotional response to pain and/or indirectly set off processes that make dorsal horn inhibitory pathways more active [64]. rTMS may also alleviate pain by increasing blood circulation to the damaged location. It has been shown that there is a relative decrease in cerebral blood flow (CBF) in chronic pain, and PET investigations have shown that rTMS administration in M1 substantially increases CBF in neuropathic pain patients [65]. rTMS activation via an interhemispheric pathway through the corpus callosum has been suggested as the cause of this extensive influence on CBF [66]. The researchers came to the conclusion that rTMS can cause bilateral increases in brain tissue oxygen consumption through sustained dilatation of small resistance arteries without documenting the effects of rTMS on hemodynamic variables (such as changes in pulse rate or blood pressure) [67].

Several functional magnetic resonance imaging investigations on CPSP patients treated with rTMS have demonstrated significant decreases in activity in the secondary somatosensory cortex (S2), insula, prefrontal cortex, and putamen [68]. Goto et al. [69] used DTI to track fibers from the corticospinal tract and thalamocortical tract in a functional imaging study. This suggests that the integrity of both tracts is important for rTMS [69]. Effective respondents to rTMS had greater delineation ratios of the corticospinal and thalamocortical tracts than ineffective responders (delineation ratio: cross section of the affected side divided by the unaffected side in a ratio) [69]. The meta-analysis conducted by Leung et al. [64] also supports the importance of the general integrity of pain modulation systems in determining the prospective therapeutic benefit of rTMS. Ohn et al. [68] discovered an important relationship between the functioning of superior thalamocortical tracts in the ipsilesional hemispheres and variations in visual analog scale (VAS) scores after rTMS. Ahmed et al. [70] found that the decrease in VAS scores that rTMS caused in M1 was linked to an increase in beta-endorphin in the brain, which is a neuronal analgesic factor. rTMS-induced plasticity changes in the function and structure of emotion-related cerebral regions may be associated with pain relief [71].

Research conducted on animals has shed light on

the workings of rTMS in CPSP. In studies of the Macaca fuscata monkey, the thalamocortical somatosensory pathway between the ipsilesional ventral posterolateral nucleus (VPL) of the thalamus and the primary and secondary somatosensory cortices (S1 and S2) was found to have fewer fibers [29]. This connectivity persisted despite thalamic lesions, suggesting a potential clinical effect of rTMS *via* this pathway [72]. Projections from VPL to S1/S2 are lateral pathways of pain, and they particularly communicate information about the position and intensity of pain stimuli [14]. In addition, the CPSP condition demonstrated greater functional connections within the MD thalamus and the amygdala than the control condition [73]. The 5-Hz rTMS treatment of the ipsilesional primary motor cortex of CPSP primates increased their pain threshold and caused a decrease in connectivity strength between the MD thalamus and amygdala, which normalized during rTMS stimulation. These findings indicate that abnormal connectivity between the MD thalamus and amygdala may contribute to CPSP following VPL lesions and that rTMS therapy may reduce aberrant connectivity, which may explain its therapeutic effect [29].

Although other cortical structures, like the dorsolateral prefrontal cortex and S2, were also targeted, M1 is the region most frequently linked to analgesic benefits [74]. There are three primary processes that may contribute to the analgesic benefits of rTMS. Initially, rTMS might make the cerebral cortex more excitable, resulting in top-down stimulation and descending inhibition of the brainstem [75]. Secondly, rTMS may stimulate the release of neurotransmitters, including BDNF and nerve growth factor [76]. Lastly, rTMS has the potential to stimulate pain-related emotions and sensory control regions [77].

The analgesic effect of M1 stimulation on chronic pain is thought to occur because of its anatomical and physiological relationship with the structure of the neuromatrix of pain [78]. M1 is anatomically connected to the S1 and S2, mid-cingulate cortex, thalamus, and PAG in a reciprocal way [79]. M1-induced analgesia is caused by two things. One is that the thalamus stops pain signals from going up, and the other is that the PAG turns on pain-blocking pathways that go down [80].

Reduced GABAergic neurotransmission in the CNS has been identified in multiple clinical trials as the primary cause of persistent neuropathic pain [81]. It is believed that M1's intracortical inhibition (ICI) reflects the activity of the interneurons. ICI and intracortical facilitation (ICF) may be indicators of GABAergic inhibitory interneurons, particularly GABA function [82]. High-frequency rTMS has been shown in prior research to raise ICI and ICF, and these changes are connected to pain alleviation in CPSP [83]. Thus, rTMS may alleviate CPSP through the mechanism of increasing GABAergic neuron transmission [71].

LTP and long-term depression (LTD) are the two main ways that rTMS has an impact on brain plasticity [84]. LTD is thought to be a significant factor in long-term alterations in synapse strength following exposure to rTMS. LTD causes a long-term decrease in synaptic strength, whereas LTP results in an increase in synaptic strength that can last for days, weeks, or months [71]. NMDA receptors may be connected to LTP and LTD induction. When the cell membrane is depolarized, the NMDA receptor's cationic channels—which are normally blocked by magnesium ions—are opened up, allowing calcium ions to enter the postsynaptic neuron and eventually inducing LTP [85]. LTD also involves NMDA receptor activation, although in a different way. LTD is brought on by a steady, small inflow of calcium ions as opposed to LTP, which is brought on by a sudden rise in postsynaptic calcium ion content [71].

A neurotrophic factor that interacts closely with neural plasticity and neuropathic pain, in addition to NMDA, is BDNF. BDNF is a neurotrophin that is linked to pain and plays a part in sustaining the dorsal root ganglion neurons [86]. The dorsal root ganglion exhibits elevated BDNF expression in a number of pain types, including neuropathic pain. BDNF is delivered by the posterior horn of the spinal cord and functions there as a neuromodulator in response to pain stimulus [87]. The analgesic effects of BDNF are brought on through serotonergic and opiatergic pathways [88]. Patients with CPSP who received 3 weeks of rTMS treatment saw a significant rise in serum BDNF levels, according to Zhao et al. [74]. **Fig. 2** depicts the rTMS's workings in the management of CPSP [74].

3) New evidence on rTMS in patients with CPSP

The effectiveness of rTMS treatment depends on the choice of targeted areas of the cortex. rTMS is a noninvasive technique that stimulates specific cerebral cortex regions by inducing electrical currents through coils placed on the cranium [89]. M1 is a possible rTMS therapy target for neuropathic pain. Multiple studies have demonstrated that high-frequency (5–20 Hz) rTMS of the motor cortex alleviates chronic pain. The majority of these studies' findings centered on chronic pain syndromes like fibromyalgia, spinal cord injury, and mixed neuropathic pain [90]. Some studies have involved homogenous patient groups, particularly CPSP patients. The concept of CPSP

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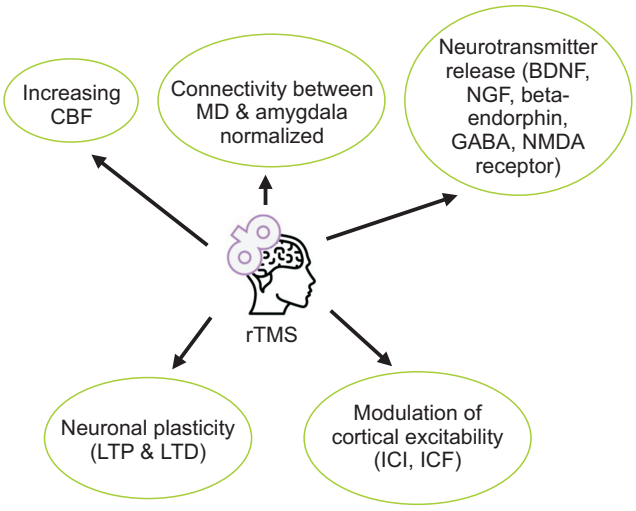

Fig. 2. The repetitive transcranial magnetic stimulation (rTMS) treatment mechanism in central post-stroke pain (CPSP). Schematic illustration showing the mechanisms behind the use of rTMS to treat CPSP includes increasing CBF, normalizing connectivity between MD and amygdala, increasing neurotransmitter release, altering neuronal plasticity, and modulating cortical excitability. CBF: cerebral blood flow, MD: mediodorsal, BDNF: brain-derived neurotrophic factor, NGF: nerve growth factor, GABA: gamma-aminobutyric acid, NMDA: N-methyl-D-aspartate, LTP: long-term potentiation, LTD: long-term depression, ICI: intracortical inhibition, ICF: intracortical facilitation.

encompasses thalamic pain, which is typically resistant to current pharmacological interventions [91].

rTMS is intended to induce analgesic benefits through noninvasive cortical stimulation in patients with CPSP. A magnetic coil stimulator is applied to the cranium and stimulates a specific cortical region. Figure-eight coil-based focused stimulation is required. In the excruciating region, the stimulation intensity is given as a percentage of the muscle's motoric threshold when it is at rest. Stimulation is administered just under the motor threshold [78].

The impact of rTMS on the human brain cortex is currently being investigated in a number of neurophysiological studies. Depending on the stimulation frequency, these effects may range from inhibition to facilitation [92]. rTMS at frequencies of 1 Hz or less can inhibit the motor cortex's excitability, whereas rTMS at frequencies above 5 Hz causes a transient increase in cortical excitability [93]. In controlling CPSP, it has been discovered that rTMS with a frequency greater than 5 Hz is more effective than low-frequency stimulation. This is because the aberrant cortical excitability has been restored [94,95]. According to a recent study, rTMS causes an increase in IHI from the damaged hemisphere to the contralateral hemisphere, which reduces pain [96]. As a result, high-frequency rTMS in the damaged hemisphere increases inhibition to the unaffected hemisphere, restoring the cerebral cortex's excitability to normal and ultimately producing the pain-relieving effect. Conversely, low-frequency rTMS in the unaffected hemisphere may result in a reduction in the inhibition of the affected hemisphere [71].

Migita et al. [97] published in 1995 that rTMS on M1 resulted in a 30% reduction in pain in two patients with central pain, one of whom had CPSP. Several additional investigations have shown the potentially positive effects of rTMS in CPSP patients, although with variable results [74,98,99]. In current research, Ojala et al. [100] looked at how 10 sessions of 10 Hz stimulation in areas S2 and M1 of CPSP patients affected their pain. A numeric rating scale (NRS) was used to gauge the severity of the patients' pain. Short-term analgesia was produced by targeted stimulation of S2 and M1, but the results were no different than those in the placebo group, demonstrating a potent placebo effect [100]. **Table 4** contains additional in-depth research concerning the influence of rTMS on CPSP [101–103].

Several studies that investigated the analgesic effect of rTMS on CPSP showed that multiple session interventions and long intervention durations could make the analgesic effects last longer than single sessions and short intervention durations [71,104]. In the Lefaucher et al. [105] study, a "real" 10 Hz rTMS session was observed to result in a substantial decrease in daily VAS scores from days 1 to 8 compared to sham stimulation. Days 9 through 12 didn't show a significant difference between the two procedures [105]. In the study by Ohn et al. [68] with rTMS administration for 5 days in a row, VAS scores decreased significantly after rTMS, then stabilized at 2 weeks after the procedure. Furthermore, Kobayashi et al.'s [94] study revealed a considerable decline in VAS scores three weeks following the initiation of the rTMS treatment. For 12 weeks, the rTMS session was repeated once a week. The average VAS score reduction was roughly 30 points during the eighth or ninth week, and the rTMS intervention was rated beneficial in 61.1% of patients, overall, after three months of intervention for this effect, which appeared to peak at that point [94].

A review of the post-stroke rehabilitation guidelines reveals a limited discussion of neurostimulation therapy in the CPSP, with no mention of TMS specifically. In 2007, the European Federation of Neurological Societies issued recommendations on neurostimulation therapy for neuropathic pain. These include peripheral nerve stimulation, spinal cord stimulation, DBS, epidural MCS, and

Table 4. rTMS study results on CPSP

Author, Year	Country	Study design	Number of patients	Stroke type	rTMS site	Frequency (Hz)	Intensity	Pulses	Intertrain interval	Session schedule	Outcome measure
Migita et al., 1995 [97]	Japan	Case report	2 (1 CPSP patient)	Hemorrhagic stroke	M1	NA	NA	NA	NA	NA	Pain relief (VAS)
Lefaucher et al., 2001 [105]	France	Cross-over	14 (7 CPSP patients)	Infarct and hemorrhagic stroke	M1	10	80% RMT	1,000	55 sec	Single session	Pain relief (VAS)
Khedr et al., 2005 [95]	Egypt	Parallel	48 (24 CPSP patients)	Infarct and hemorrhagic stroke	M1	20	80% RMT	2,000	NA	5 sessions	Pain relief (VAS)
Saitoh et al., 2007 [98]	Japan	Cross-over	13 (7 CPSP patients)	Infarct and hemorrhagic stroke	M1	1/5/10	90% RMT	5,000	50 sec	3 sessions	Pain relief in 5 Hz and 10 Hz (VAS)
Ohn et al., 2012 [68]	Republic of Korea	Open label trial	22 (All CPSP patients)	Infarct and hemorrhagic stroke	M1	10	90% RMT	1,000	55 sec	5 sessions	Pain relief (VAS)
Matsumura et al., 2013 [99]	Japan	Cross-over	20 (All CPSP patients)	Infarct and hemorrhagic stroke	M1	5	100% RMT	500	25 sec	Single session	Pain relief (VAS)
Hosomi et al., 2013 [83]	Japan	Cross-over	21 (All CPSP patients)	Infarct and hemorrhagic stroke	M1	5	90% RMT	500	50 sec	10 sessions	Pain relief (VAS)
Hasan et al., 2014 [101]	United Kingdom	Open label trial	14 (All CPSP patients)	Infarct and hemorrhagic stroke	M1	10	80%–90% MT	2,000	60 sec	5 sessions	Pain relief (NRS)
de Oliveira et al., 2014 [102]	Brazil	Parallel	21 (All CPSP patients)	Infarct and hemorrhagic stroke	PMC/DLPFC	10	120% RMT	1,250	25 sec	10 sessions	No effect pain relief (VAS)
Kobayashi et al., 2015 [94]	Japan	Open label trial	18 (All CPSP patients)	Infarct and hemorrhagic stroke	M1	5	90% AMT	500	50 sec	12 sessions	Pain relief (VAS)
Lin et al., 2018 [91]	China	Open label trial	7 (All CPSP patients)	Infarct and hemorrhagic stroke	M1	10	90% RMT	1,000	60 sec	10 sessions	Pain relief (VAS)
Zhao et al., 2021 [74]	China	RCT	38 (All CPSP patients)	Infarct and hemorrhagic stroke	M1	10	80% RMT	2,000	3 sec	18 days	Pain relief (NRS)
Malfitano et al., 2021 [103]	Italy	Case series	1 CPSP patient	Infarct stroke	M1	10	90% RMT	2,000	5 sec	10 sessions	Pain relief (NRS)
Ojala et al., 2022 [100]	Finland	RCT	17 (All CPSP patients)	Infarct and hemorrhagic stroke	M1/S2	10	90% MT	5,050	50 sec	10 sessions	Pain relief (NRS)

rTMS: repetitive transcranial magnetic stimulation, CPSP: central post-stroke pain, RCT: randomized control trial, M1: motor cortex, S2: secondary somatosensory cortex, PMC: premotor cortex, DLPFC: dorsolateral pre-frontal cortex, RMT: resting motor threshold, MT: motor threshold, AMT: active motor threshold, NA: not available, VAS: visual analog scale, NRS: numeric rating scale.

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rTMS. According to this recommendation, there is moderate evidence (level B) that high-frequency (5–20 Hz) rTMS targeting M1 with figure-eight coils can substantially reduce pain in CPSP and other neuropathic pain conditions. However, low-frequency (5 Hz) rTMS may not be effective in treating the same pain conditions (level B) [106].

4) Limitation of rTMS

TMS has been researched for more than 25 years in both healthy volunteers and patients all over the world. Meta-analyses evaluating TMS's overall safety and tolerability have been conducted on side effects gathered in both experimental and clinical settings [107]. The length of the side effects seems to change concurrently with the length of stimulation. Long-lasting negative outcomes are brought on by prolonged stimulation [108]. The TMS Safety Consensus Group of the International Federation of Clinical Neurophysiology has formally published the risks connected with TMS and complete safety protocol standards [109]. The most common side effect of TMS, in brief, is headache or neck pain. This side effect is thought to be related to muscle tension brought on by repeated muscle twitching, a tapping feeling on the skull, as well as from wearing a snugly fitting helmet or headband. The majority of the time, this discomfort subsides on its own or with over-the-counter medications [61].

Seizure induction is a rare but dangerous major adverse effect. Since Wassermann's initial safety recommendations were released in 1998, fewer than 20 occurrences of TMS-induced seizures have been documented, and the widely mentioned risk is lower than 1 in 1,000 [110]. The risk is larger in those who are susceptible, such as people who have epilepsy, but it is still only about 1%–2% [111]. There is no increased risk of epilepsy related with TMS-induced seizures, which are regarded as provoked events. Other infrequent side effects may include temporary cognitive, mood, or neuropsychiatric symptoms, syncope (due to anxiety or anticipation of TMS), and probable hearing loss connected with TMS clicking sounds that can be mitigated by using earplugs. The general conclusion is that as long as safety requirements and recommendations are followed, the chance of major side effects is quite low [61].

CONCLUSIONS AND FUTURE PERSPECTIVE

At this time, rTMS usage in CPSP is not clearly indicated. We can, however, synthesize the indications for rTMS in CPSP based on several previous studies. Patients with CPSP for more than six months, individuals whose pain remains uncontrolled despite the use of two or more medications, and those with NRS or VAS > 5 fall into this category. In addition, hemiparesis patients with manual muscle testing scores between 3 and 5 (determined prior to the rTMS procedure) are also potential candidates for rTMS treatment [68,69,91,100].

In general, rTMS is beneficial for alleviating pain temporarily in cases like CPSP. However, further study is required to ascertain the long-term effects of rTMS on pain alleviation, especially for periods longer than three months. There are presently available and necessary more randomized controlled trials to confirm the beneficial effects of rTMS on alleviating pain. In addition, elements such as stimulation frequency, location, and length of treatment may influence the outcomes of rTMS. Consequently, it is essential to conduct additional studies with more samples and extended follow-up times to ascertain the optimal rTMS treatment for CPSP.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Jönsson AC, Lindgren I, Hallström B, Norrving B, Lindgren A. Prevalence and intensity of pain after stroke: a population based study focusing on patients' perspectives. J Neurol Neurosurg Psychiatry 2006; 77: 590-5.
2. Kong KH, Woon VC, Yang SY. Prevalence of chronic pain and its impact on health-related quality of life in stroke survivors. Arch Phys Med Rehabil 2004; 85: 35-40.
3. Naess H, Lunde L, Brogger J. The effects of fatigue, pain, and depression on quality of life in ischemic stroke patients: the Bergen Stroke Study. Vasc Health Risk Manag 2012; 8: 407-13.
4. Oh H, Seo W. A comprehensive review of central post-stroke pain. Pain Manag Nurs 2015; 16: 804-18.
5. MacGowan DJ, Janal MN, Clark WC, Wharton RN, Lazar RM, Sacco RL, et al. Central poststroke pain and Wallenberg's lateral medullary infarction: frequency, character, and determinants in 63 patients. Neurology 1997; 49: 120-5.
6. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. Lancet Neurol 2009; 8: 857-68.
7. Lampl C, Yazdi K, Röper C. Amitriptyline in the prophylaxis of central poststroke pain. Preliminary results of 39 patients in a placebo-controlled, long-term study. Stroke 2002; 33: 3030-2.
8. Head H, Holmes G. Sensory disturbances from cerebral lesions. Brain 1911; 34: 102-254.
9. Riddoch G. The clinical features of central pain. Lancet 1938; 231: 1205-9.
10. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain 2008; 137: 473-77.
11. Seifert CL, Mallar Chakravarty M, Sprenger T. The complexities of pain after stroke--a review with a focus on central post-stroke pain. Panminerva Med 2013; 55: 1-10.
12. Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS. Incidence of central post-stroke pain. Pain 1995; 61: 187-93.
13. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289-305.
14. Westlund KN. Pain pathways: peripheral, spinal, ascending, and descending pathways. In: Practical management of pain. 5th ed. Edited by Benzon HT, Rathmell JP, Wu CL, Turk DC, Argoff CE, Hurley RW. Elsevier. 2014, pp 87-98.e5.
15. Sewards TV, Sewards MA. The medial pain system: neural representations of the motivational aspect of pain. Brain Res Bull 2002; 59: 163-80.
16. Betancur DFA, Tarragó MDGL, Torres ILDS, Fregni F, Caumo W. Central post-stroke pain: an integrative review of somatotopic damage, clinical symptoms, and neurophysiological measures. Front Neurol 2021; 12: 678198.
17. Gerges ANH, Hordacre B, Pietro FD, Moseley GL, Berryman C. Do adults with stroke have altered interhemispheric inhibition? A systematic review with meta-analysis. J Stroke Cerebrovasc Dis 2022; 31: 106494.
18. Craig AD. A new version of the thalamic disinhibition hypothesis of central pain. Pain Forum 1998; 7: 1-14.
19. Boivie J, Leijon G, Johansson I. Central post-stroke pain--a study of the mechanisms through analyses of the sensory abnormalities. Pain 1989; 37: 173-85.
20. Vartiainen N, Perchet C, Magnin M, Creac'h C, Convers P, Nighoghossian N, et al. Thalamic pain: anatomical and physiological indices of prediction. Brain 2016; 139: 708-22.
21. Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. PLoS One 2011; 6: e26010.
22. Krause T, Asseyer S, Taskin B, Flöel A, Witte AV, Mueller K, et al. The cortical signature of central poststroke pain: gray matter decreases in somatosensory, insular, and prefrontal cortices. Cereb Cortex 2016; 26: 80-8.
23. Li X, Feng Y, Gao F. Maladaptive reorganization in pain-related brain network contributing to the central post-stroke pain. Neuropsychiatry (London) 2019; 9: 2186-97.
24. Gritsch S, Bali KK, Kuner R, Vardeh D. Functional characterization of a mouse model for central post-stroke pain. Mol Pain 2016; 12: 1744806916629049.
25. Kim JS. Pure sensory stroke. Clinical-radiological

correlates of 21 cases. Stroke 1992; 23: 983-7.
26. Kim JH, Greenspan JD, Coghill RC, Ohara S, Lenz FA. Lesions limited to the human thalamic principal somatosensory nucleus (ventral caudal) are associated with loss of cold sensations and central pain. J Neurosci 2007; 27: 4995-5004.
27. Wang G, Thompson SM. Maladaptive homeostatic plasticity in a rodent model of central pain syndrome: thalamic hyperexcitability after spinothalamic tract lesions. J Neurosci 2008; 28: 11959-69.
28. Lenz FA, Weiss N, Ohara S, Lawson C, Greenspan JD. The role of the thalamus in pain. In: Supplements to clinical neurophysiology. Edited by Hallett M, Phillips LH, Schomer DL, Massey JM. Elsevier. 2004, pp 50-61.
29. Kadono Y, Koguchi K, Okada KI, Hosomi K, Hiraishi M, Ueguchi T, et al. Repetitive transcranial magnetic stimulation restores altered functional connectivity of central poststroke pain model monkeys. Sci Rep 2021; 11: 6126.
30. Kuan YH, Shih HC, Shyu BC. Involvement of P_2X_7 receptors and BDNF in the pathogenesis of central poststroke pain. Adv Exp Med Biol 2018; 1099: 211-27.
31. Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: epidemiology, etiology, and treatment options. Arch Neurol 2001; 58: 1547-50.
32. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009; 10: 895-926.
33. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006; 52: 77-92.
34. Kohno T, Ji RR, Ito N, Allchorne AJ, Befort K, Karchewski LA, et al. Peripheral axonal injury results in reduced mu opioid receptor pre- and postsynaptic action in the spinal cord. Pain 2005; 117: 77-87.
35. Li CY, Song YH, Higuera ES, Luo ZD. Spinal dorsal horn calcium channel alpha2delta-1 subunit upregulation contributes to peripheral nerve injury-induced tactile allodynia. J Neurosci 2004; 24: 8494-9.
36. Yoshimura M, Yonehara N. Alteration in sensitivity of ionotropic glutamate receptors and tachykinin receptors in spinal cord contribute to development and maintenance of nerve injury-evoked neuropathic pain. Neurosci Res 2006; 56: 21-8.
37. Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci 2005; 6: 521-32.
38. Attal N, Fermanian C, Fermanian J, Lanteri-Minet M, Alchaar H, Bouhassira D. Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion? Pain 2008; 138: 343-53.
39. Hansen AP, Marcussen NS, Klit H, Andersen G, Finnerup NB, Jensen TS. Pain following stroke: a prospective study. Eur J Pain 2012; 16: 1128-36.
40. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al.; Classification Committee of the Neuropathic Pain Special Interest Group (NeuPSIG). The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 2019; 160: 53-9.
41. Kim MS, Kim BY, Saghetlians A, Zhang X, Okida T, Kim SY. Anti-nociceptive effects of dual neuropeptide antagonist therapy in mouse model of neuropathic and inflammatory pain. Korean J Pain 2022; 35: 173-82.
42. Obata H. Analgesic mechanisms of antidepressants for neuropathic pain. Int J Mol Sci 2017; 18: 2483.
43. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007; 132: 237-51.
44. Offord J, Isom LL. Drugging the undruggable: gabapentin, pregabalin and the calcium channel $\alpha 2\delta$ subunit. Crit Rev Biochem Mol Biol 2015; 51: 246-56.
45. Vranken JH, Dijkgraaf MG, Kruis MR, van der Vegt MH, Hollmann MW, Heesen M. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain 2008; 136: 150-7.
46. Stefani A, Spadoni F, Siniscalchi A, Bernardi G. Lamotrigine inhibits Ca2+ currents in cortical neurons: functional implications. Eur J Pharmacol 1996; 307: 113-6.
47. Sansone RA, Sansone LA. Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. Innov Clin Neurosci 2014; 11: 37-42.
48. Jo S, Bean BP. Sidedness of carbamazepine accessibility to voltage-gated sodium channels. Mol Pharmacol 2014; 85: 381-7.
49. Edinoff AN, Kaplan LA, Khan S, Petersen M, Sauce E, Causey CD, et al. Full opioid agonists and tramadol: pharmacological and clinical considerations. Anesth Pain Med 2021; 11: e119156.
50. Holbech JV, Jung A, Jonsson T, Wanning M, Bredahl C, Bach FW. Combination treatment of neuropath-

ic pain: Danish expert recommendations based on a Delphi process. J Pain Res 2017; 10: 1467-75.
51. Kim JS. Pharmacological management of central post-stroke pain: a practical guide. CNS Drugs 2014; 28: 787-97.
52. Banerjee M, Pal S, Bhattacharya B, Ghosh B, Mondal S, Basu J. A comparative study of efficacy and safety of gabapentin versus amitriptyline as coanalgesics in patients receiving opioid analgesics for neuropathic pain in malignancy. Indian J Pharmacol 2013; 45: 334-8.
53. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al.; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016; 47: e98-169. Erratum in: Stroke 2017; 48: e78. Erratum in: Stroke 2017; 48: e369.
54. Intercollegiate Stroke Working Party. National clinical guideline for stroke. 5th ed. Royal College of Physicians. 2016, pp 1-178.
55. Teasell R, Salbach NM, Foley N, Mountain A, Cameron JI, Jong A, et al. Canadian stroke best practice recommendations: rehabilitation, recovery, and community participation following stroke. Part one: rehabilitation and recovery following stroke; 6th edition update 2019. Int J Stroke 2020; 15: 763-88.
56. Iglesias AH. Transcranial magnetic stimulation as treatment in multiple neurologic conditions. Curr Neurol Neurosci Rep 2020; 20: 1.
57. Vidal-Dourado M, Conforto AB, Caboclo LO, Scaff M, Guilhoto LM, Yacubian EM. Magnetic fields in noninvasive brain stimulation. Neuroscientist 2014; 20: 112-21.
58. Diana M, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. Rehabilitating the addicted brain with transcranial magnetic stimulation. Nat Rev Neurosci 2017; 18: 685-93.
59. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985; 1: 1106-7.
60. Marcos Z. Álvaro Pascual-Leone: a pioneer of non-invasive brain stimulation. Lancet Neurol 2013; 12: 853.
61. Burke MJ, Fried PJ, Pascual-Leone A. Transcranial magnetic stimulation: Neurophysiological and clinical applications. Handb Clin Neurol 2019; 163: 73-92.
62. Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000; 406: 147-50.
63. Di Lazzaro V, Profice P, Ranieri F, Capone F, Dileone M, Oliviero A, et al. I-wave origin and modulation. Brain Stimul 2012; 5: 512-25.
64. Leung A, Donohue M, Xu R, Lee R, Lefaucheur JP, Khedr EM, et al. rTMS for suppressing neuropathic pain: a meta-analysis. J Pain 2009; 10: 1205-16.
65. Jin Y, Xing G, Li G, Wang A, Feng S, Tang Q, et al. High frequency repetitive transcranial magnetic stimulation therapy for chronic neuropathic pain: a meta-analysis. Pain Physician 2015; 18: E1029-46.
66. Pecuch PW, Evers S, Folkerts HW, Michael N, Arolt V. The cerebral hemodynamics of repetitive transcranial magnetic stimulation. Eur Arch Psychiatry Clin Neurosci 2000; 250: 320-4.
67. Vernieri F, Maggio P, Tibuzzi F, Filippi MM, Pasqualetti P, Melgari JM, et al. High frequency repetitive transcranial magnetic stimulation decreases cerebral vasomotor reactivity. Clin Neurophysiol 2009; 120: 1188-94.
68. Ohn SH, Chang WH, Park CH, Kim ST, Lee JI, Pascual-Leone A, et al. Neural correlates of the antinociceptive effects of repetitive transcranial magnetic stimulation on central pain after stroke. Neurorehabil Neural Repair 2012; 26: 344-52.
69. Goto T, Saitoh Y, Hashimoto N, Hirata M, Kishima H, Oshino S, et al. Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation. Pain 2008; 140: 509-18.
70. Ahmed MA, Mohamed SA, Sayed D. Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. Neurol Res 2011; 33: 953-8.
71. Pan LJ, Zhu HQ, Zhang XA, Wang XQ. The mechanism and effect of repetitive transcranial magnetic stimulation for post-stroke pain. Front Mol Neurosci 2023; 15: 1091402.
72. Lin RL, Douaud G, Filippini N, Okell TW, Stagg CJ, Tracey I. Structural connectivity variances underlie functional and behavioral changes during pain relief induced by neuromodulation. Sci Rep 2017; 7: 41603.
73. Mitchell AS, Chakraborty S. What does the mediodorsal thalamus do? Front Syst Neurosci 2013; 7:

37.
74. Zhao CG, Sun W, Ju F, Jiang S, Wang H, Sun XL, et al. Analgesic effects of navigated repetitive transcranial magnetic stimulation in patients with acute central poststroke pain. Pain Ther 2021; 10: 1085-100. Erratum in: Pain Ther 2021; 10: 1101-3.
75. Garcia-Larrea L, Peyron R. Motor cortex stimulation for neuropathic pain: from phenomenology to mechanisms. Neuroimage 2007; 37 Suppl 1: S71-9.
76. Attal N, Ayache SS, Ciampi De Andrade D, Mhalla A, Baudic S, Jazat F, et al. Repetitive transcranial magnetic stimulation and transcranial direct-current stimulation in neuropathic pain due to radiculopathy: a randomized sham-controlled comparative study. Pain 2016; 157: 1224-31.
77. Lindholm P, Lamusuo S, Taiminen T, Pesonen U, Lahti A, Virtanen A, et al. Right secondary somatosensory cortex-a promising novel target for the treatment of drug-resistant neuropathic orofacial pain with repetitive transcranial magnetic stimulation. Pain 2015; 156: 1276-83.
78. Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. Neurophysiol Clin 2006; 36: 117-24.
79. Kisler LB, Weissman-Fogel I, Sinai A, Sprecher E, Chistyakov AV, Shamay-Tsoory S, et al. Bi-phasic activation of the primary motor cortex by pain and its relation to pain-evoked potentials - an exploratory study. Behav Brain Res 2017; 328: 209-17.
80. Cha M, Ji Y, Masri R. Motor cortex stimulation activates the incertothalamic pathway in an animal model of spinal cord injury. J Pain 2013; 14: 260-9.
81. Yang L, Liu X, Yao K, Sun Y, Jiang F, Yan H, et al. HCN channel antagonist ZD7288 ameliorates neuropathic pain and associated depression. Brain Res 2019; 1717: 204-13.
82. Lanza G, Aricò D, Lanuzza B, Cosentino FII, Tripodi M, Giardina F, et al. Facilitatory/inhibitory intracortical imbalance in REM sleep behavior disorder: early electrophysiological marker of neurodegeneration? Sleep 2020; 43: zsz242.
83. Hosomi K, Kishima H, Oshino S, Hirata M, Tani N, Maruo T, et al. Cortical excitability changes after high-frequency repetitive transcranial magnetic stimulation for central poststroke pain. Pain 2013; 154: 1352-7.
84. Hoogendam JM, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimul 2010; 3: 95-118.
85. Cooke SF, Bliss TV. Plasticity in the human central nervous system. Brain 2006; 129: 1659-73.
86. Obata K, Yamanaka H, Dai Y, Tachibana T, Fukuoka T, Tokunaga A, et al. Differential activation of extracellular signal-regulated protein kinase in primary afferent neurons regulates brain-derived neurotrophic factor expression after peripheral inflammation and nerve injury. J Neurosci 2003; 23: 4117-26.
87. Ikeda K, Hazama K, Itano Y, Ouchida M, Nakatsuka H. Development of a novel analgesic for neuropathic pain targeting brain-derived neurotrophic factor. Biochem Biophys Res Commun 2020; 531: 390-5.
88. Siuciak JA, Altar CA, Wiegand SJ, Lindsay RM. Antinociceptive effect of brain-derived neurotrophic factor and neurotrophin-3. Brain Res 1994; 633: 326-30.
89. Chail A, Saini RK, Bhat PS, Srivastava K, Chauhan V. Transcranial magnetic stimulation: a review of its evolution and current applications. Ind Psychiatry J 2018; 27: 172-80.
90. Treister R, Lang M, Klein MM, Oaklander AL. Non-invasive transcranial magnetic stimulation (TMS) of the motor cortex for neuropathic pain-at the tipping point? Rambam Maimonides Med J 2013; 4: e0023.
91. Lin H, Li W, Ni J, Wang Y. Clinical study of repetitive transcranial magnetic stimulation of the motor cortex for thalamic pain. Medicine (Baltimore) 2018; 97: e11235.
92. Najib U, Bashir S, Edwards D, Rotenberg A, Pascual-Leone A. Transcranial brain stimulation: clinical applications and future directions. Neurosurg Clin N Am 2011; 22: 233-51, ix.
93. Machado S, Arias-Carrión O, Paes F, Vieira RT, Caixeta L, Novaes F, et al. Repetitive transcranial magnetic stimulation for clinical applications in neurological and psychiatric disorders: an overview. Eurasian J Med 2013; 45: 191-206.
94. Kobayashi M, Fujimaki T, Mihara B, Ohira T. Repetitive transcranial magnetic stimulation once a week induces sustainable long-term relief of central poststroke pain. Neuromodulation 2015; 18: 249-54.
95. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 2005; 76: 833-8.

96. Alhassani G, Liston MB, Schabrun SM. Interhemispheric inhibition is reduced in response to acute muscle pain: a cross-sectional study using transcranial magnetic stimulation. J Pain 2019; 20: 1091-9.
97. Migita K, Uozumi T, Arita K, Monden S. Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurgery 1995; 36: 1037-9.
98. Saitoh Y, Hirayama A, Kishima H, Shimokawa T, Oshino S, Hirata M, et al. Reduction of intractable deafferentation pain due to spinal cord or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex. J Neurosurg 2007; 107: 555-9.
99. Matsumura Y, Hirayama T, Yamamoto T. Comparison between pharmacologic evaluation and repetitive transcranial magnetic stimulation-induced analgesia in poststroke pain patients. Neuromodulation 2013; 16: 349-54.
100. Ojala J, Vanhanen J, Harno H, Lioumis P, Vaalto S, Kaunisto MA, et al. A randomized, sham-controlled trial of repetitive transcranial magnetic stimulation targeting M1 and S2 in central poststroke pain: a pilot trial. Neuromodulation 2022; 25: 538-48.
101. Hasan M, Whiteley J, Bresnahan R, MacIver K, Sacco P, Das K, et al. Somatosensory change and pain relief induced by repetitive transcranial magnetic stimulation in patients with central poststroke pain. Neuromodulation 2014; 17: 731-6.
102. de Oliveira RA, de Andrade DC, Mendonça M, Barros R, Luvisoto T, Myczkowski ML, et al. Repetitive transcranial magnetic stimulation of the left premotor/dorsolateral prefrontal cortex does not have analgesic effect on central poststroke pain. J Pain 2014; 15: 1271-81.
103. Malfitano C, Rossetti A, Scarano S, Malloggi C, Tesio L. Efficacy of repetitive transcranial magnetic stimulation for acute central post-stroke pain: a case study. Front Neurol 2021; 12: 742567.
104. Yang S, Chang MC. Effect of repetitive transcranial magnetic stimulation on pain management: a systematic narrative review. Front Neurol 2020; 11: 114.
105. Lefaucheur JP, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiol Clin 2001; 31: 247-52.
106. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol 2007; 14: 952-70.
107. Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A. Safety of rTMS to non-motor cortical areas in healthy participants and patients. Clin Neurophysiol 2006; 117: 455-71.
108. Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med 2015; 58: 208-13.
109. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015; 126: 1071-107.
110. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol 1998; 108: 1-16.
111. Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello JJ Jr, Pascual-Leone A, et al. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav 2007; 10: 521-8.