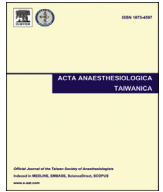




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Review Article

Efficacy and practical issues of repetitive transcranial magnetic stimulation on chronic medically unexplained symptoms of pain

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ABSTRACT

Chronic pain is a common issue worldwide and remains a big challenge to physicians, particularly when the underlying causes do not meet any specific disease for settlement. Such medically unexplained somatic symptoms of pain that lack an integrated diagnosis in medicine have a high psychiatric comorbidity such as depression, and will require a multidisciplinary treatment strategy for a better outcome. Thus, most patients deserted management in spite of being inadequately treated and even presented with high resistance to analgesic drugs. Noninvasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS), has been used to treat refractory neuropathic pain and the analgesic efficacy is promising. So far, some case series and randomized rTMS studies have reported on patients with certain medically unexplained symptoms (MUSs) of pain (e.g., psychogenic pain or somatic symptoms in major depression and fibromyalgia). However, there is still no review article that is specific to the efficacy of rTMS on chronic unexplained symptoms of pain. Therefore, in the present review, we ventured to clarify the terminology and summarized the analgesic effects of rTMS on chronic MUSs of pain.

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1. Introduction

1.1. Definition and clinical relevance of chronic pain

Chronic pain, traditionally defined as pain persisting for more than 6 months, is one of the most common symptoms in the general population. The prevalence rate of chronic noncancer pain in the adult general population is estimated to be 10–20% in the western world.^{1,2} Chronic pain is a public health issue worldwide,³ and the eastern population is no exception. A recent large-scale study carried out in Hong Kong ($N = 5001$) revealed that 34.9% of the adult general population suffered from pain lasting for more than 3 months, with the highest prevalence noted in women and middle-aged adults.⁴ More than one-third of the patients suffering from pain experienced pain in multiple sites, the most common of which is the head with the legs and back being oftentimes the collusive spots. Pain is an unpleasant sensory and emotional experience. Prolonged existence of bodily painful symptoms could

lead to worsened quality of life,⁴ significant economic loss, reductive productivity,^{1,4} higher comorbidity of physical and mental disorders,^{5,6} and even increased suicidal risks.^{7,8}

1.2. Medically unexplained symptoms of pain

One of the categories of chronic pain that could not be well explained by the existence of general medical conditions (e.g., cancer, arthritis, kidney stones, stroke, and trigeminal neuralgia) is defined as medically unexplained symptoms (MUSs) (Fig. 1). Many patients present with MUSs. Significant proportions of the somatic symptoms encountered in the primary settings, with a rate of at least 33%, are MUSs.^{9,10} Up to 25% of the MUSs are chronic or recurrent,¹⁰ of which pain is the most common.¹¹ Unexplained or multiple somatic symptoms are strongly associated with coexisting depressive and anxiety disorders.¹⁰ Physically painful symptoms are more likely to occur in patients with major depression.^{5,6,12} The presence of physically painful symptoms in depression may lead to ignoring seeking help for depression *per se*¹² and patients tend to mask or delay seeking help for depression.¹³ The severity of pain in depression is also a strong predictor of poor treatment outcome to antidepressants.¹⁴

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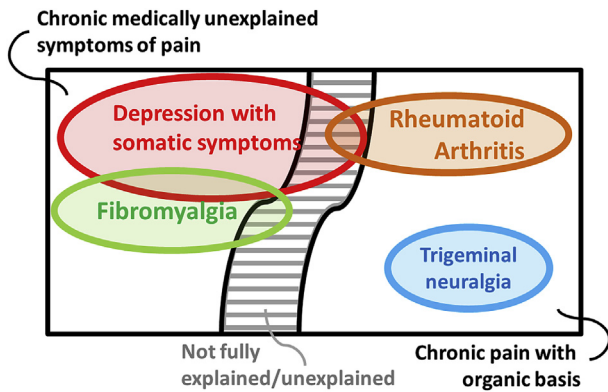


Fig. 1. Schematic diagram showing the causes of chronic pain. There is a wide overlap between most of syndromes with medically explained symptoms of pain (e.g., fibromyalgia and psychogenic or somatic painful symptoms in the context of depression). Trigeminal neuralgia is an example of chronic neuropathic pain with organic basis. Some chronic pain caused by specific diseases (e.g., rheumatoid arthritis) could present some symptoms that are not fully explained by the disease. One of the explanations goes to its high comorbidity with depression.

2. Difficulties in diagnosis and treatment of chronic unexplained symptoms of pain

Because no underlying organic diseases could be identified to be responsible, the somatic symptoms sustained by patients with MUS are relegated to psychogenic, functional, or idiopathic cause. In fact, the term MUS is not a specific disorder but consists of syndromes such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and somatic symptoms in mood disorders.¹⁵ These syndromes have overlapping presentations and are believed to link with a common factor, despite not being synonymous.¹⁵ Likewise, MUSs induced by these disorders causes similar levels of physical dysfunction as in symptoms caused by identifiable organic diseases.⁹ In psychiatry, the diagnosis of somatoform disorders is defined in the current classification by both the text revision of the *Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV-TR)* and the 10th revision of the *International Classification of Diseases*. It is used in psychiatry to define a group of MUS patients with psychological distress associated with repeated treatment-seeking behaviors. Notably, most MUS are associated with depressive or anxiety disorders and, to a lesser degree, somatoform disorders.^{11,13} We even conducted a retrospective review in a medical center ($N = 1068$) and found that more than half of the patients with MUS referred to consultation–liaison psychiatry services were subjected to chronic painful symptoms. Most of the patients with MUS were females who complained of pain at multifocal sites, and had a high psychiatric comorbidity, especially of depression (35.6%) and anxiety disorders (29.7%), rather than somatoform disorders (9.9%).¹¹ The category of DSM-IV somatoform disorders includes pain disorders, hypochondriasis, somatization disorders, conversion disorders, and undifferentiated somatoform disorders. These disorders overlap widely and there is a lack of a clear boundary between these syndromes that patients with MUS presented to nonpsychiatric physicians. Physicians may find the diagnosis of somatoform disorders difficult to use. Therefore, in the coming DSM-5 (scheduled to be published in May 2013), somatoform disorders would be referred to somatic symptoms and related disorders in order to avoid overlapping of akin areas.¹⁶

Because clinical presentations of MUS vary widely and are often mixed up with high levels of emotional distress, patients with such atypical and nonspecific symptoms could hardly be diagnosed and treated properly by specialists. Without adequate explanations, patients with MUS being referred to psychiatrists felt that they are

disbelieved. Such referrals may further hinder patients to receive adequate evaluations and treatment. The management and treatment of chronic MUS are also challenging issues.^{17,18} As to evidence-based treatment, drawing conclusions from systemic reviews and randomized controlled studies have been found to be difficult, because of the inconsistent definitions of the disorders used by different authors and the wide presentations on the part of the patients.¹⁹ A personalized approach based on the bio–psycho–social elements by a multidisciplinary team would enhance treatment outcome in patients with chronic MUS.^{18–21} However, even by doing so, a significant proportion of patients with chronic MUS pain remain symptomatic.

3. Basic principles and clinical applications of repetitive transcranial magnetic stimulation treatment

3.1. Basic principles

There are some noninvasive forms of cortical stimulation such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation, and theta-burst stimulation. A large body of evidence has shown that rTMS is an effective neuromodulation method in treating intractable pain and brings new hopes to the treatment of the patients.²² The basic principle of TMS is electromagnetic mutual induction, in which a strong and brief electrical current is passed through a wire coil and the induction of magnetic fields could pass through the resistive layers of the head (i.e., the scalp, skull, meninges, and cerebrospinal fluids) into the brain without energy loss. The induced magnetic field could, in turn, induce an electrical field and then cause the underlying neurons to depolarize and generate action potentials. In clinical settings, the figure-of-eight coil is selected to generate an induced electrical field to the brain in a more spatially focused way.^{22,23} With the advent of stimulators, we could deliver TMS in a repeated way (so-called rTMS). The physiological effects of the rTMS pulses came from the rTMS studies in the motor cortex.²⁴ A facilitating and inhibitory effect on cortical excitability was demonstrated by an increase and decrease of the amplitude of the motor-evoked potentials, respectively, following high-frequency (≥ 5 Hz) and low-frequency rTMS pulse trains. Following safety guidelines,²⁵ rTMS is a safe and well-tolerated neuromodulation tool.

3.2. rTMS clinical application

The rTMS could generate long-lasting effects on cortical excitability and is able to modify neuronal activity not only regionally but also at distant brain regions. Therefore, rTMS has shown its great potentials in treating a variety of psychiatric and neurological disorders. For example, abundant evidence has shown that rTMS is an efficacious treatment for treatment-resistant major depressive disorders.^{26–28} Commonly adopted parameters for rTMS to treat depression are high-frequency rTMS (e.g., 10 Hz) at the left prefrontal cortex, low-frequency rTMS (e.g., 1 Hz) at the right prefrontal cortex, and a combination of both in a session.^{26,27} Longer treatment duration (e.g., 4–6 weeks)²⁷ and more total stimulation pulses²⁹ are associated with better antidepressant effects, but the clinical antidepressant efficacy could be found even after 10 sessions of rTMS treatment (i.e., 2 weeks). Based on a large multicenter randomized, sham-controlled study ($N = 301$),³⁰ the U.S. Food and Drug Administration (FDA) in 2008 approved the use of TMS for the treatment of adult patients with a major depressive disorder who have unsatisfactory improvement from one previous antidepressant medication. A recent review by George²⁸ pointed out that daily left prefrontal rTMS is effective not only in the clinical trials, but also in the real-world settings, with remission in 30–40% of patients.

4. Therapeutic application of rTMS in chronic neuropathic and MUS pain

4.1. Experiences from the usefulness of chronic neuropathic pain

The motor cortex is the most common target for rTMS to treat chronic neuropathic pain. The idea came from an early report by Tsubokawa et al,³¹ in which they found the analgesic effects of motor cortex stimulation by dural implanted electrodes on a small group of patients ($N = 12$) with chronic central neuropathic pain that was resistant to morphine treatment. Since then, accumulating evidence supported that the alternative, noninvasive procedure by targeting rTMS at the motor cortex could be also effective in the treatment of chronic neuropathic pain,^{32–34} despite noninvasive procedures appearing to be less effective than invasive motor cortex stimulation.³³ High-frequency rTMS targeted at the primary motor cortex is evidenced to have analgesic efficacy,^{32,35} particularly the side contralateral to the painful site (Fig. 2). The primary motor cortex (M1), instead of the adjacent premotor area, the primary sensory cortex, or the supplementary motor area, could be the better choice of target for rTMS application.³⁶ Poststroke pain and limb pain seemed to respond poorly to rTMS, whereas trigeminal neuralgia and a presence of sensation in the painful region seemed to predict better responses to rTMS.³⁷ A growing number of evidence indicated that the left prefrontal cortex is involved in pain modulation.^{38–40} A recent preliminary study has shown that slow-frequency rTMS (1 Hz) delivered to the right dorsolateral prefrontal cortex had positive analgesic effects on patients with chronic refractory neuropathic pain.⁴¹ The effects of prefrontal rTMS for chronic neuropathic pain warrant further investigations.

4.2. rTMS therapeutic efficacy on chronic unexplained somatic symptoms of pain

We did a PubMed search to look up articles published over the past 15 years using the following keywords: “medically unexplained symptoms,” “somatoform pain,” “functional pain,” “atypical pain,”

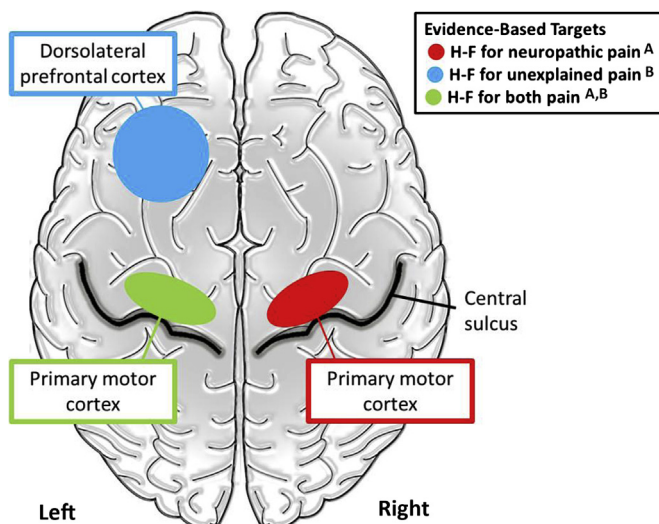


Fig. 2. Evidence-based rTMS target for the treatment of chronic neuropathic pain and chronic unexplained pain. (A) For chronic neuropathic pain, high-frequency (H-F) rTMS targeted at the primary motor cortex, particularly the side contralateral to the neuropathic pain site, is evidenced to be effective [please see Lefaucheur (2006)³² and Mylius et al (2012)³⁵ for details]. (B) For chronic unexplained symptoms of pain, a growing body of evidence supported that H-F rTMS has promising analgesic efficacy, particularly targeting at the left prefrontal cortex and the left motor cortex. rTMS = repetitive transcranial magnetic stimulation.

“fibromyalgia,” “chronic fatigue syndrome,” “psychogenic pain,” “complex regional pain syndrome,” “repetitive transcranial magnetic stimulations,” “rTMS,” and “TMS.” Notably, complex regional pain syndrome (CRPS) type I, formerly known as reflex sympathetic dystrophy, is characterized as chronic pain in the absence of any nerve lesions. It develops mostly after minimal trauma, but the severity of symptoms is disproportionate to the causative event. The CRPS type I frequently presents with abnormal psychological features, and many symptoms in CRPS type I are suggested to be psychogenic.⁴² Therefore, in the search for therapeutic efficacy of rTMS on MUS, CRPS type I was also included as a target of interest. Relevant references cited by the identified papers were also checked. Surprisingly, much less research had been done to investigate the therapeutic effects of rTMS on medically unexplained pain, as compared with the treatment of chronic neuropathic pain. Only 10 studies were found, including two case series (mostly unexpected findings in sham-controlled studies with depression as primary outcome measurement),^{43,44} one controlled pilot study with CRPS as part of their research targets,⁴⁵ and seven controlled studies with chronic unexplained pain as primary research target.^{46–52} The studies identified are summarized in Table 1. Most of these studies focused on patients with fibromyalgia or unexplained painful somatic symptoms associated with major depression. There were two studies that investigated painful symptoms in patients with simultaneous major depression and fibromyalgia.

Despite only a small amount of research available, the results so far supported that rTMS, in particular the high frequency rTMS, which targets the left prefrontal and the left primary motor cortex, has promising analgesic effects on medically unexplained pain.

Low-frequency rTMS at the right prefrontal cortex seemed to have inconsistent results. In a double-blind, sham-controlled rTMS study for treating depression in 2006, Sampson et al⁴³ reported an unexpected finding of great pain relief in four patients with refractory major depression who had comorbidities with fibromyalgia and borderline personality. However, Carretero et al⁴⁸ conducted a randomized, sham-controlled study in 2009 using a different rTMS machine, and reported that both groups of active and sham rTMS acting at the right dorsolateral prefrontal cortex showed no analgesic effect in treating patients with major depression and fibromyalgia. They explained that the discrepancy might be in part due to the differences in the delivered pulses/session (Carretero, 1200 pulses/session versus Sampson, 1600 pulses/session).

As to the prefrontal cortex as the treatment target for rTMS, the therapeutic effects on unexplained pain also came from unexpected findings while conducting a large, multisite, double-blind, sham-controlled study for refractory depression.³⁰ In this trial for the FDA approval for 10-Hz rTMS at the left dorsolateral prefrontal cortex in treating depression, O’Reardon et al⁴⁴ published an unexpected finding of great improvement of psychogenic headaches in two patients, who sustained drug-resistant major depression. In addition, Avery et al⁴⁶ conducted a double-blind sham-controlled study in drug-resistant major depression using 10-Hz rTMS delivered to the left dorsolateral prefrontal cortex. They reported that in a subgroup of patients with prominent somatic painful symptoms, rTMS was associated with a significant reduction of self-reported pain severity.

To date, the evidence-based efficacy of rTMS on chronic unexplained pain mostly came from the investigations on the treatment of fibromyalgia. A systemic review reported that most rTMS sham-controlled studies (80%) found significant decreases in fibromyalgia pain.⁵³ Fibromyalgia is a chronic widespread pain disorder. It shares much epidemiological and clinical similarity with other unexplained painful syndrome (e.g., somatic depression and somatoform pain disorders), such as female predominance, multifocal

Table 1
Effects of rTMS on chronic unexplained somatic symptoms of pain.

Authors	Patients	Study design	rTMS parameters	Target	Findings
<i>Prefrontal cortex stimulation</i>					
Sampson et al (2006) ⁴³	Refractory MDD with fibromyalgia and borderline personality (<i>N</i> = 4)	Observational, unexpected finding in a double-blind, sham-controlled study for depression Add-on	TMS machine: Magstim Super Rapid repetitive stimulator (Magstim Company Ltd., Spring Gardens, Wales, United Kingdom) 1 Hz, 110% MT 1600 pulses/session, 20 sessions in 4 wks	Right DLPFC (5-cm estimation method)	Pretreatment pain averaged 8.2 (7–9.5) and reduced to 1.5 (0–3.5) after treatment (<i>p</i> < 0.009). 4/4: pain improvement. 2/4: complete resolution of pain. 1/4: antidepressant response.
O'Reardon et al (2007) ⁴⁴	MDD (nonresponsive to previous ATDs) with psychogenic pain (<i>N</i> = 2)	Observational, unexpected finding in a double-blind sham-controlled study for depression Medication-free	TMS machine: Neuronetics Model 2100 (Neuronetics Inc., Malvern, PA, United States) 10 Hz, 120% MT, 3000 pulses/session, five times/wk for 4–6 wks	Left DLPFC (5-cm estimation method)	Psychogenic headache improved, not related to depression outcome.
Avery et al (2007) ⁴⁶	MDD (nonresponsive to previous ATDs × one to four times) with or without somatic painful symptoms (<i>N</i> = 68)	Double-blind, sham-controlled Add-on	TMS machine: Dantec MagPro Magnetic Stimulator (Medtronic Inc., Minneapolis, United States) 10 Hz, 110% MT, 1600 pulses/session, 15 sessions in a 4-wk period	Left DLPFC (5-cm estimation method)	A significant (<i>p</i> < 0.05) reduction in the systematic assessment for treatment emergent pain item, independent from depression.
Carretero et al (2009) ⁴⁸	MDD + fibromyalgia (American College of Rheumatology 1990 criteria) (<i>N</i> = 28)	Double-blind, sham-controlled 8 wks of follow-up	TMS machine: Dantec Medical MegLite model (Medtronic Inc., Minneapolis, United States) 1 Hz, 110% MT, 1200 pulses/session, 20 sessions in 4 wks	Right DLPFC (5-cm estimation method)	Negative findings. Both treatment groups (real and sham): improvement in fibromyalgia scale (FibroFatigue) and clinical global impression, yet no differences between active and sham groups. No improvements in the Likert pain scale.
Short et al (2011) ⁵¹	Fibromyalgia (American College of Rheumatology 1990 criteria) (<i>N</i> = 20)	Double-blind, sham-controlled	TMS machine: NeoPulse Neotonus Model 3600 (Neotonus Inc., Atlanta, GA, United States) 10 Hz, 120% MT 4000 pulses/session, five times/wk for 2 wks	Left prefrontal cortex (6 cm anterior to the motor cortex target)	Active TMS: mean 29% reduction in pain. Sham TMS: mean 4% nonsignificant reduction in pain.
Lee et al (2012) ⁵²	Fibromyalgia women (American College of Rheumatology 1990 criteria) (<i>N</i> = 14)	Double-blind, sham-controlled Follow-up for 1 mo Active (10 Hz, 1 Hz) Sham	TMS machine: Magstim Rapid Magnetic Stimulator (Magstim Company Ltd, Dyfed, United Kingdom) Active: 10 Hz, 80% MT, 2000 pulses/session 1 Hz, 110% MT 1600 pulses/session Sham: same as 1 Hz, but coil 90° perpendicular to the skull 10 sessions in 2 wks	1 Hz and sham to right DLPFC (5-cm estimation method) 10 Hz to the left motor cortex	1-Hz group: depression improved significantly from baseline to 1 mo after rTMS. Pain scores significantly decreased immediately after rTMS. 10-Hz group: depression and pain scores significantly decreased immediately after rTMS.
<i>Motor cortex stimulation</i>					
Rollnik et al (2002) ⁴⁵	Treatment-refractory chronic pain syndrome <i>N</i> = 12 (CRPS, <i>N</i> = 2; phantom limb pain, <i>N</i> = 1; spinal cord injury, <i>N</i> = 2; osteomyelitis, <i>N</i> = 1; peripheral nerve lesion, <i>N</i> = 6)	Double-blind, sham-controlled	TMS machine: Magstim Rapid Magnetic Stimulator (Magstim Co., Witland, United Kingdom) 20 Hz, 80% MT, 800 pulses for 20 min	M1	Negative findings. Active versus sham stimulation: not significantly different (active rTMS: mean VAS reduction $-4.0 \pm 15.6\%$; sham rTMS: $-2.3 \pm 8.8\%$).
Passard et al (2007) ⁴⁷	Fibromyalgia (American College of Rheumatology 1990 criteria) (<i>N</i> = 30)	Double-blind, sham-controlled Followed 15, 30, and 60 d after the rTMS study	TMS machine: Magstim Super Rapid Stimulator (Magstim Co., Witland, United Kingdom) 10 Hz, 80% MT, 2000 pulses/session, 10 sessions in 2 wks	Left M1	Active rTMS significantly reduced pain and improved quality of life. The analgesic effects are not related to changes in mood or anxiety.
Picarelli et al (2010) ⁴⁹	Complex regional pain syndrome (CRPS) type I <i>N</i> = 23	Double-blind, sham-controlled Add-on	TMS machine: Dantec MagPro Magnetic Stimulator (Medtronic Inc., Minnesota, United States) 10 Hz, 100% MT	M1	Active rTMS group: mean VAS reduction of 4.65 cm (50.9%). Sham rTMS: 2.18 cm (24.7%). Active add-on rTMS

Table 1 (continued)

Authors	Patients	Study design	rTMS parameters	Target	Findings
Mhalla et al (2011) ⁵⁰	Fibromyalgia (American College of Rheumatology 1990 criteria) (N = 40; all female)	Double-blind, sham-controlled Add-on Followed 25 wks after the initiation of rTMS treatment	2500 pulses/session, 10 sessions in 2 wks TMS machine: Dantec MagPro X100 machine (Magventure Tonika Elektronik; Farum, Denmark) 10 Hz, 80% MT, 1500 pulses/session, 14 sessions (induction phase of five daily sessions → maintenance phase of three sessions a week apart → three sessions a fortnight apart → three sessions a month apart)	MagPROX100 machine (Magventure Tonika Elektronik, Farum, Denmark) Left M1	is effective in treating different aspects of pain (sensory–discriminative and emotional–affective). Active rTMS significantly reduced pain intensity from day 5 to week 25. These analgesic effects were associated with a long-term improvement in items related to quality of life.

ATDs = antidepressants; CRPS = complex regional pain syndrome; DLPFC = dorsolateral prefrontal cortex; M1 = primary motor cortex; MDDs = major depressive disorders; mo = months; MT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; VAS = visual analog scale; wks = weeks.

painful sites in distributions,¹¹ fatigue, and sleep disturbances.⁵⁴ According to the American College of Rheumatology (ACR) 1990 criteria, the diagnosis of fibromyalgia needs to meet both criteria of chronic widespread pain for at least 3 months and the presence of pain at more than 11 of the 18 specified tender points. In addition, the pain has to be present in the left and right side of the body, above and below the waist, and in the axial skeleton.⁵⁴ This previous criterion using tender points at specific body regions seemed to place fibromyalgia syndrome as a somewhat specific disease. However, the ACR 2010 fibromyalgia diagnostic criteria dismissed the tender points and the presence of pain in each quarter of the body, as well as placing much emphasis on patient symptoms such as widespread pain, fatigue, nonrestorative sleep, and subjective cognitive declines. The changes in the diagnostic criteria further echo the clinical difficulty in categorizing patients with unexplained symptoms into one specific disease category. The problem in the diagnosis is even bigger in patients presenting simultaneous chronic unexplained pain and mood symptoms.¹¹ The comorbidity of chronic pain and depression is very common.

To date, published randomized studies on rTMS in treating fibromyalgia used the ACR 1990 criteria. Short et al⁵¹ conducted a randomized sham-controlled study by evaluating the efficacy of the left prefrontal cortex stimulation on fibromyalgia (N = 20) and replicated the efficacy of rTMS on fibromyalgia. As for the prefrontal cortex as the treatment target, Lee et al⁵² investigated a small group of women with fibromyalgia (N = 14) and found that upon active rTMS treatment, whether 10 Hz to the left motor cortex or 1 Hz to the right dorsolateral prefrontal cortex, pain and depression scores significantly decreased and to some degree the symptomatic relief was maintained for another 1 month. With regard to motor cortex stimulation, active 10-Hz rTMS delivered to the left primary motor cortex in two separate double-blind sham-controlled studies reduced fibromyalgia pain significantly and improved quality of life.^{47,50}

The CRPS type I is also an unexplained pain syndrome. Rollnik et al⁴⁵ conducted a pilot study investigating 20-Hz rTMS in treating a group of patients with drug-resistant chronic pain (N = 12, including two patients with CRPS), but failed to see that active rTMS was more effective than sham rTMS. However, they adopted low intensity (80% resting motor threshold) and only applied rTMS for 20 minutes. Later on, Picarelli et al⁴⁹ conducted a randomized sham-controlled study in patients with CRPS type I (N = 23) and reported that active 10-Hz rTMS at the primary motor cortex reduced pain more significantly than sham rTMS.

5. Potential mechanisms of rTMS's efficacy on chronic unexplained symptoms of pain

The left prefrontal rTMS-induced analgesia for chronic unexplained pain may involve endogenous opioid releases from the brain. Taylor et al⁵⁵ conducted a sham-controlled, double-blind, crossover study in 24 healthy volunteers. As compared with the sham, active rTMS reduced hot pain, and allodynia and naloxone pretreatment significantly reduced the analgesic effects of real rTMS. These results suggest that rTMS targeted at the left dorsolateral prefrontal cortex could drive endogenous opioid releases for pain relief. A complex interaction between several brain regions in response to pain has been identified, which is the so-called pain matrix of brain.^{56,57} The prefrontal cortex is particularly important as a critical brain region for pain processing in patients.⁵⁶ However, which part in the brain pain matrix is responsible for the development and persistence of chronic unexplained symptoms of pain remains elusive. With regard to the possible analgesic mechanisms for psychogenic pain, a ¹⁵O-H₂O-positron emission tomography (PET) study that adopted hypnotic suggestions to test changes in heat pain in 10 healthy participants could give us a clue. The hypnotic modulation of the intensity of the pain sensation led to significant changes in pain-evoked activity within the primary sensory cortex, but not in the anterior cingulate cortex.⁵⁸ By contrast, another study that adopted a similar PET design with hypnotic suggestions and noxious stimuli found that hypnotic modulation of pain unpleasantness (affect) produced specific changes within the anterior cingulate cortex, but not in the primary sensory cortex.⁵⁹ The findings provide evidence that fronto-limbic activity is involved in pain affect. In our previous study using left prefrontal rTMS to treat drug-resistant depression, we found that the left prefrontal rTMS increased prefrontal glucose uptakes and led to an improvement of fronto-limbic circuit.⁶⁰ Overall, the actual mechanisms of rTMS's analgesic effects on chronic unexplained pain are unknown, but may involve endogenous opioid releases and the functional improvement in the brain regions such as the prefrontal cortex, the anterior cingulate cortex, and the primary sensory cortex.

In conclusion, findings from early case series and randomized sham-controlled rTMS study on fibromyalgia provided evidence to support analgesic effects of rTMS on chronic unexplained symptoms of pain. Although the most optimal parameters warrant further research, existing evidence supports that high-frequency rTMS that target the left prefrontal cortex or the left primary

motor cortex has promising analgesic effects. The mechanisms of the analgesic effects may involve an improvement of functions in the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the sensory cortex, possibly by boosting endogenous opioid releases. However, the specific mechanisms warrant further studies to disentangle.

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