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Repetitive transcranial magnetic stimulation for neuropathic pain

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Noninvasive stimulation of the nervous system for treating chronic neuropathic pain has received attention because of its tolerability and relative efficacy. Repetitive transcranial magnetic stimulation (rTMS) is a representative method of noninvasive brain stimulation. Evidence-based guidelines on therapeutic use of rTMS have been proposed recently for several neurological diseases. These guidelines recommend treating neuropathic pain by applying high-frequency (≥ 5 Hz) rTMS to the primary motor cortex contralateral to the painful side. This review summarizes the mechanisms and guidelines of rTMS for treating neuropathic pain, and proposes directions for future research.

Key words: Transcranial magnetic stimulation; Neuropathic pain; Guideline

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INTRODUCTION

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system."[1] It is one of the most-common causes of chronic pain, with approximately 40% of patients with chronic pain suffering from neuropathic pain.[2] Pharmacological treatments for neuropathic pain show limited efficacy, with no medicine available that can completely relieve neuropathic pain.[3] Several guidelines recommend nonpharmacological treatments for neuropathic pain, including noninvasive brain stimulation, spinal cord stimulation, radiofrequency ablation, and nerve blocking.[4,5] There are two main stream of noninvasive brain stimulation: (1) repetitive transcranial magnetic stimulation (rTMS) and (2) transcranial direct-current stimulation.[6] Evidence-based guidelines on the therapeutic use of rTMS in several neurological diseases have been proposed recently.[7] Here we review the basic technique and mechanism of rTMS and discuss guidelines and future directions of rTMS in neuropathic pain treatment.

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BASIC TECHNIQUE AND MECHANISM OF rTMS

Basic technique of rTMS

Transcranial magnetic stimulation (TMS) is based on Faraday's principle of electromagnetic induction. A TMS coil is placed on the scalp, and current is passed through it that generates a rapidly fluctuating magnetic field that in turn induces electrical current flow toward the intracranial space. Activities of the cortical neurons are modulated by the electrical field produced by the magnetic field.[8] There are several configurations of TMS coils, with circular and figure-of-eight coils being the two main models. Circular coils are the simplest, and they provide diffuse stimulation. In contrast, figure-of-eight or 'butterfly' coils are the most commonly used because they can induce highly focused electrical fields.

The five parameters of location, focality, frequency, pulse intensity, and duration should be considered when conducting TMS.[8] There are several ways to ensure that the correct location is stimulated. When the eloquent cortex is stimulated, the induced response is expected to be based on functional mapping. A single pulse of TMS will induce muscle activation by stimulating the primary motor cortex (M1). Perception of a phosphene is expected if the primary visual cortex (V1) is stimulated. Stereotactic navigation techniques been recently become popular for stimulating more-complex cortical areas, such as the dorsolateral prefrontal cortex (DLPFC). The depth and focality of stimulation are critical functional parameters, and they are interlinked, with an increased depth resulting in reduced focality. The pulse intensity is correlated with the depth of stimulation, with a larger pulse intensity increasing the depth but reducing the focality.

TMS can modulate brain activities in various ways depending on the stimulation pattern and frequency. Single-pulse TMS can induce an immediate response, but it exerts no sustained effect on the stimulated cortex. This modality is normally used to record motor evoked potentials and to determine the motor threshold (MT).[8] Paired-pulse TMS applies two pulses in rapid succession, and is used in basic and clinical neurophysiological research to measure inhibitory and excitatory central mechanisms.[6,9] In contrast, rTMS can induce long-lasting neuroplastic changes, and is used for treating several neurological diseases. Low-frequency (1 Hz) stimulation has an inhibitory effect, while high-frequency (≥ 5 Hz) stimulation has an excitatory effect on the underlying cortex. Theta-burst stimulation (TBS) is another form of rTMS, which also has two protocols: (1) continuous TBS with an inhibitory effect and (2) intermittent TBS with an excitatory effect.[10,11] TBS should induce longer lasting neuroplasticity compared with rTMS.[8]

Mechanism of motor cortex stimulation in neuropathic pain treatment

The mechanism underlying the effects of applying rTMS to M1 in treating neuropathic pain is unclear. The motor cortex has connections to the thalamus,[12] and motor cortex stimulation can inhibit thalamic activity that then indirectly activates the descending pain inhibitory pathway.[13] These connections might explain the analgesic effect of rTMS on M1 against neuropathic pain.[14] Another postulated mechanism of action is endogenous opioid release induced by M1 stimulation.[14] A positron-emission tomography (PET) study evaluating the activity of opioid receptors found decreased signals after 7 months of direct electrical stimulation to M1, suggesting that endogenous opioids released by M1 stimulation could occupy opioid receptors.[15] A recent PET study also demonstrated significant release of endogenous opioids within a hemispheric brain network by applying single session of 10-Hz rTMS to M1 in 10 healthy subjects.[16]

rTMS FOR NEUROPATHIC PAIN

Evidence-based protocol of rTMS in neuropathic pain

The International Federation of Clinical Neurophysiology and the European Federation of Neurological Societies reached a consensus on the therapeutic use of rTMS and reported evidence-based guidelines in 2014.[17] They subsequently updated the recommendations taking into account all publications related to rTMS, including data prior to 2014 as well as currently reviewed literature until the end of 2018.[7] They recommended level A evidence (definite efficacy) for high-frequency rTMS of M1 contralateral to the painful side for neuropathic pain. High-frequency rTMS of the left M1 or DLPFC for improving the quality of life or pain was relevant for level B evidence (probable efficacy).[7]

Since the early report on the effects of M1 stimulation by

Tsubokawa et al.,[18] many studies have been performed to define the appropriate rTMS parameters for treating neuropathic pain. Most studies demonstrating good efficacy of rTMS against neuropathic pain have applied similar rTMS parameters: high-frequency stimulation (10-20 Hz), 1,600 to 3,000 stimulations per session, intertrain interval of 10 to 84 seconds, intensity of 70% to 90% of the MT, and using a figure-of-eight coil (Table 1). The most significant results for the good efficacy of rTMS against neuropathic pain were obtained following M1 stimulation.

Cortical target of rTMS

The most-effective M1 location at which to apply stimulation remains to be defined. Andre-Obadia et al.[19] reported that rTMS was more efficacious when it is delivered over the hand motor area than the face area regardless of the pain location (hand or face). However, Ayache et al.[20] showed that anatomical targeting using magnetic-resonance-imaging-guided navigation may provide a better effect than the motor hotspot. That study included patients with neuropathic pain at various locations, which is more likely to reflect real situations.

The second-most-studied cortical target for rTMS in chronic pain has been the DLPFC. Unfortunately, rTMS of the DLPFC showed a very weak effect on chronic pain in a recent randomized multicenter sham-controlled trial.[21] Parieto-opercular cortex stimulation for treating orofacial pain produced significantly better analgesia than stimulation of the primary sensorimotor cortex or sham.[22,23] However, these studies were based on the short-term effect of a single rTMS session, and so long-term results need to be investigated further. Stimulating other cortical areas such as insular cortex[24] or middle cingulate cortex[25] failed to improve chronic neuropathic pain.

Safety of rTMS

rTMS is relatively safe. The most-common adverse effects of rTMS are headache, pain at the site of stimulation, increased

Table 1. Stimulation parameters of rTMS for treating neuropathic pain

Study	Frequency (Hz)	Motor threshold (%)	Number of pulses	Number of session	Pain control outcome
André-Obadia et al.[33] (2006)	1 or 20	90	1,600	2	20 Hz provided significant relief, whereas 1 Hz increased pain
André-Obadia et al.[34] (2014)	20	90	1,600	1	Trial of rTMS for epidural stimulation, pain significantly reduced vs. sham
Andre-Obadia et al.[19] (2018)	20	90	1,600	2	Stimulation over hand area provides significant relief vs. stimulation over face area
Attal et al.[35] (2016)	10	80	3,000	6	rTMS provided significant pain reduction vs. tDCS
Attal et al.[21] (2021)	10	80	3,000	15	M1-rTMS reduces peripheral neuropathic pain vs. sham but, not DLPFC-rTMS reduced peripheral neuropathic pain vs. sham
Khedr et al.[36] (2015)	20	80	3,000	10	Significant decrease in pain immediately and at day 15 after stimulation but not at 1 month: 80-87% responders (> 30% pain relief)
Lefaucheur et al.[37] (2011)	10	90	2,000	1	Response to rTMS correlates with response to epidural stimulation
Mori et al.[38] (2022)	5 or 10	90	500 or 2,000	1	The highest stimulation settings group reported best pain reduction vs. lower settings
Ma et al.[39] (2015)	10	80	1,500	10	Reduction of pain score up to 3 months after the last session: 50% responders (> 50% pain relief)
Nurmikko et al.[40] (2016)	10	90	2,000	5	Reduction of pain score vs. control 1 week after the lase session: 30% responders (> 30% pain relief)

rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; M1, primary motor cortex; DLPFC, dorsolateral prefrontal cortex.

bodily pain or paresthesia, fatigue, sleep disorders, nausea, anxiety/irritability/cognitive impairment, and muscle sensations during the stimulation.[21] No serious treatment-related adverse effect has been reported. Serious adverse events such as seizures are rare, especially when utilizing focused coils and an intensity of 70% to 80% of MT.

FURTHER PERSPECTIVES

Long-term effects of rTMS

Long-term effects of rTMS for maintenance treatment have not been clearly elucidated. The cumulative effect of rTMS sessions over the long term has been reported for various protocols of maintenance treatment. However, further study is needed to clarify the long-term effects of rTMS for maintenance treatment.[26,27]

New cortical targets of rTMS

Identifying new stimulation targets for rTMS would also be useful. The posterior insular cortex and anterior cingulate cortex are involved in central integration of the sensory-discriminative aspect of pain processing.[28] Deep brain stimulation of the posterior insular can lead to antinociceptive effects dependent on endogenous opioids and cannabinoids in experimental models of peripheral neuropathic pain.[29,30]

Theta-burst stimulation

Regarding the mechanism of action, TBS is a better method than high-frequency rTMS for inducing long-lasting effects with a lower stimulation intensity. However, published data on TBS have only been related to experimental or acute provoked pain,[31,32] and so further studies of TBS for chronic neuropathic pain treatment are needed.

CONCLUSION

Noninvasive brain stimulation has received attention for treating neuropathic pain because of its noninvasiveness and tolerability. High-frequency rTMS of M1 is a promising treatment methodology for chronic neuropathic pain. However, more data are needed on other cortical targets for stimulation and the effects of various stimulation patterns on neuropathic pain with diverse causes.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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