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Research Progress of Different Modes of Transcranial Magnetic Stimulation in Patients with Consciousness Disturbance

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Abstract

The diagnosis and treatment of disorders of consciousness have been major challenges for clinicians. Transcranial magnetic stimulation (TMS) is a non-invasive, low-risk technique that offers various advantages. It has been widely developed in the field of neuropsychiatry. This paper reviews the mechanism of action of TMS on consciousness disorders, the common stimulation sites of TMS, and the application of different modes of TMS in consciousness disorders. There is more evidence to support the improvement of consciousness disturbance by high-frequency repetitive transcranial magnetic stimulation (rTMS), while there is less research on low-frequency repetitive transcranial magnetic stimulation and theta burst stimulation (TBS). In the future, it is necessary to further explore the pathogenesis of consciousness disorders, identify the optimal target and treatment parameters of TMS for consciousness disorders, and develop personalized TMS treatment plans for patients with consciousness disorders.

Keywords

Disturbance of consciousness, Transcranial magnetic stimulation, Non-invasive neuroregulation

Various states of loss of consciousness caused by severe craniocerebral injury are called consciousness disorders, which mainly include coma, vegetative state, and minimally consciousness state, Recently, the concept of cognitive-motor dissociation (CMD) has been added to the diagnostic classification of disorders of consciousness, characterized by patients whose brain activity is detected by task-state-based fMRI and EEG, but whose behavioral diagnosis is coma, VS/UWS, or MCS [1]. At present, it is generally believed that the cause of consciousness disorders is mainly the breakdown of thalamic-cortex and cortical-cortex connections [2]. In the process of recovering brain function, The metabolic activity and functional connections of the middle forebrain circuit [3] and frontal-parietal network [4] were gradually increased. Clinically, the main treatment methods for consciousness disorders include drug therapy, rehabilitation therapy, hyperbaric oxygen therapy, etc., but the therapeutic effect is limited. Transcranial magnetic stimulation was first proposed by Barker in the 1980s [5]. In recent years, because of its non-invasive, low risk and other advantages [6], it has been widely developed in the neuropsychiatric field. TMS has a variety of stimulation modes, including single-pulse magnetic stimulation, double-pulse magnetic stimulation, repeated pulse magnetic stimulation, and theta burst stimulation. This article aims to review the mechanism and application of transcranial magnetic stimulation in the treatment of patients with consciousness disorders in recent years.

1. Mechanism of action of TMS in patients with disturbance of consciousness

Based on the principle of electromagnetic induction, TMS uses rapidly changing magnetic fields to generate induced current in a specific cortex of the brain to depolarize cortical neurons and thus regulate cortical excitability [7], The therapeutic mechanism of transcranial magnetic stimulation in patients with disturbance of consciousness is not well understood. Current studies suggest that rTMS may regulate synaptic plasticity through the activation of NMDA and AMPA receptors, regulation of the dopaminergic system, and regulation of neurotrophic factors and synaptic proteins [8-11], In addition, rTMS can promote the increase of cerebral blood flow and brain metabolism [12]. A study [13] divided 40 healthy subjects into the experimental group and the pseudo-stimulation group. Real and false rTMS stimulation at 20Hz was performed on the left dorsolateral forehead respectively, and arterial spin labeled perfusion MRI was used to measure quantitative cerebral blood flow. The study found that the relative cerebral blood flow in the left medial temporal cortex or hippocampus of the subjects subjected to high-frequency transcranial magnetic stimulation increased. However, there was no change in the sham stimulation group. This study suggests that the mechanism of action of high-frequency repetitive transcranial magnetic stimulation may be realized through the redistribution of cerebral blood flow. However, the mechanism of TMS in the treatment of consciousness disorders is still unknown to a large extent, and a large number of basic experiments and clinical trials are still needed to further study.

2. TMS is at the stimulation site of patients with consciousness disorders

The production of conscious activity requires the normal function of the ascending reticular activation system and the stimulation of specific parts of the cerebral cortex. Therefore, the selection of the stimulating location of TMS is crucial for the recovery of consciousness disorders. At present, the stimulation sites commonly used in clinical research mainly include the prefrontal lobe, primary motor cortex, parietal-occipital lobe, and so on.

The prefrontal lobe is an important node in the "central circuit" theory of consciousness disorder, an important brain region for higher cognitive function of human beings, and is the most used stimulating site in clinical research of consciousness disorder. A meta-analysis of non-invasive brain stimulation for the treatment of disorders of consciousness [14] suggested that left DLPFC rTMS may be the most effective form of stimulation.

M1 region has traditionally been considered as a therapeutic target for exercise rehabilitation. However, studies have found that transcranial stimulation in M1 region has significant therapeutic effects on pain, swallowing disorders, sleep disorders, cognitive dysfunction, consciousness disorders, anxiety, depression, and other non-functional disorders [15]. Shen et al. [16] randomly divided 99 patients with VS after traumatic brain injury into three groups. 20HZ rTMS was used to stimulate the dorsolateral prefrontal cortex (DLPFC) in the control group and M1 region in the experimental group, respectively, and the sham stimulation in the placebo group was compared with that in the placebo group. However, there are also studies [17] that suggest that 20 Hz rTMS of M1 has no significant effect on VS patients.

According to information aggregation theory, the posterior parietal cortex (PPC) has been shown to be the largest cortical region associated with consciousness [18]. Xu et al. [19] performed 10 Hz rTMS on the left PPC of 24 VS patients and found that it could significantly improve the functional recovery of unresponsive DoC patients. The precuneus is part of the posterior parietal cortex and is located in the BA7 region [20, 21]. Due to its hidden location and lack of focal lesions, it has received little attention and has traditionally been considered to be a region of the visual cortex [22]. With the progress of imaging, recent studies have found that as an important component of the default network, the precuneus is involved in episodic memory, self-processing, motor imagination, highly integrated and associative information processing, and other processes [20]. Moreover, the precuneus appears to be an important region in distinguishing plant states from microconsciousness disorders and is involved in the restoration of consciousness levels [23-25], Other studies [26] have found that the central precuneus plays a key role in executive function. A study [27] conducted 10 Hz pulse stimulation of the anterior cuneus of 11 patients, and conducted CRS-R scale and EEG analysis, and found that it could improve behavioral scores and brain functional connectivity.

The underlying mechanism of the recovery of consciousness disorders is still unclear. The operation mechanism of the brain is very complex. Various regions of the brain, they are close to each other or separated from each other, work together and create common tasks.

3. Stimulation patterns of TMS in patients with disturbance of consciousness

3.1 Single-pulse magnetic stimulation and paired-pulse magnetic stimulation

Monopulse transcranial magnetic stimulation is a stimulation mode that outputs one pulse at a time. Paired pulse magnetic stimulation means that two pulse stimuli with a time-locking relationship occur in pairs, and different time intervals produce different biological effects [28]. Motor-evoked potentials after single or double-pulse transcranial magnetic stimulation in the cerebral cortex are an objective means to evaluate the excitability and pathway integrity of the motor cortex [29].

Clinical evaluation of the consciousness level of patients with consciousness disorder mainly adopts behavioral score [30], but its subjectivity is high and there is a high misdiagnosis rate [31]. Secondly, neuroimaging and neuroelectrophysiology have been gradually applied to the assessment and prediction of patients with consciousness disorders, including functional magnetic resonance imaging [32], positron emission computed tomography [33], and electroencephalography [34]. TMS-EEG is developed on the basis of electroencephalography and TMS [35]. It is a new non-invasive tool for evaluating cortical excitation and connectivity that does not require patient active cooperation and has high temporal resolution [36]. TMS-EEG uses a single pulse TMS to stimulate the cerebral cortex to generate evoked potentials (TEPs). Some studies [37] found that the complexity of TEP was positively correlated with the conscious state of DOC patients. Casali et al. [38] introduced and tested a level of consciousness index: Disturbance Complexity Index (PCI) in 2013. PCI quantifies an individual's level of consciousness during wakefulness, sleep, and anesthesia. Bai et al. [39] conducted 20 10Hz rTMS in the dorsolateral prefrontal cortex of a 47-year-old female patient with DOC, and calculated the TEP, PCI, and GMFP of the three times by using TMS-EEG assessment before treatment, after the first treatment, and after 20 treatment respectively. The study found that TMS-EEG could objectively evaluate the patient's state of consciousness. It is an effective tool for diagnosing DOC.

3.2 Transcranial magnetic stimulation

Recent studies have shown that repetitive transcranial magnetic stimulation is effective in the treatment of depression, neuropathic pain, post-stroke movement, aphasia, and Parkinson's disease [40]. At present, there are a variety of rTMS modes in the studies on the awakening of consciousness disorders, and the effect of the cortex is significantly related to the location, frequency, intensity, and time of stimulation [41-42]. rTMS can be divided into high frequency (> 1Hz) and low frequency (≤1HZ), which produce excitatory and inhibitory effects on the cerebral cortex of the stimulating brain region, respectively. The commonly used rTMS is based on the interhemispheric competitive inhibition model. According to the mutual inhibition between the hemispheres of the brain through the corpus callosum, high-frequency stimulation can improve the excitability of the affected cortex, and low-frequency stimulation can inhibit the excitability of the healthy cortex, so as to restore the balance of interhemispheric inhibition [43-45].

For patients with consciousness disorders, high frequencies commonly used in current studies include 5hz, 10hz, and 20hz. Chen et al. [46] divided 50 patients into the stimulation group and the control group, and conducted true and false 10HZ rTMS respectively. The study found that 10Hz rTMS could effectively regulate the neural connectivity of patients with bilateral N20 consciousness disorders. Zhang et al. [47] randomly divided 48 patients with PVS into treatment group and control group. The treatment group received 5hz rTMS and the control group received false stimulation. 60 days later, rTMS was found to be conducive to the recovery of conscious function in PVS patients. Other studies [48] have found that 20hz rTMS stimulation can improve awareness and arousal in patients with consciousness disorders, and another study [49] found that 20 Hz rTMS applied to the left angular gyrus improved total coma recovery Scale scores in patients with minimal consciousness. Many studies have suggested that high-frequency rTMS can promote the recovery of consciousness in patients with DOC, but patients with MCS may benefit more from high-frequency rTMS [50-52]. However, in clinical studies of transcranial magnetic stimulation in patients with disturbance of consciousness, there are few studies on low frequencies. Lv Chao et al. [53] divided 62 patients with persistent vegetative state after craniocerebral injury into the observation group (conventional rehabilitation treatment) and the control group (conventional rehabilitation treatment and 0.5Hz rTMS), and found that low-frequency transcranial magnetic stimulation was helpful for the recovery of consciousness in patients with persistent vegetative state. Another study [54] also suggested that 0.5Hz rTMS had a stimulating effect on patients with persistent vegetative states after head injury. In summary, high-frequency rTMS can help promote the recovery of consciousness in patients with consciousness disorders, but patients with MCS may be more beneficial. Few studies have used low-frequency rTMS to stimulate patients with consciousness disorders to observe the efficacy. Although some studies have found that low-frequency repetitive transcranial magnetic stimulation has a stimulating effect on patients with vegetative state after craniocerebral injury, the sample size is small, and further expansion of the sample size is needed. At present, there is still no uniform standard for the optimal selection of rTMS stimulation site, stimulation duration and other parameters, which needs more research to explore.

3.3 Theta burst stimulation

Theta burst stimulation (TBS) is a new stimulation mode of rTMS discovered by Huang et al. [55] in 2005. Similar to the effect of high-frequency stimulation (> 1Hz) and low frequency stimulation (≤1Hz) in rTMS mode, iTBS mode can induce long-term increased excitability of nerve function. Theta burst stimulation is characterized by cluster stimulation and is set to simulate the nerve discharge frequency in the hippocampus, which is closer to the physiological state of neural activity, with reduced stimulation duration and fewer side effects [56, 57].

Theta burst stimulation stimulation has a credible therapeutic effect in the fields of depression and post-multiple sclerosis spasticity [58]. Recently, more and more studies have been conducted in the fields of Parkinson's disease, post-stroke movement disorder, and aphasia hemineglect. Wu et al. [59] performed left dorsolateral prefrontal iTBS stimulation on 8 patients with MCS or UWS, and conducted CRS-R evaluation and EEG collection evaluation on before treatment, 5 days after treatment, and 1 week after treatment, respectively. Finally, it was found that most patients showed lasting improvement after treatment. iTBS may be a safe and effective treatment. Huang Shaochun et al. [60] divided 56 patients with DOC caused by CNS injury into a control group and an observation group. The observation group was treated with iTBS in addition to the control group and found that the clinical and neuroelectrophysiological evaluation of the observation group was higher than that of the control group after treatment. iTBS has great potential for the recovery of consciousness disorders, but due to the lack of relevant studies and insufficient sample size, it can be further elucidated in future related studies.

4. Conclusions

At present, the pathogenesis of consciousness disorder is not very clear, and the diagnosis and treatment of consciousness disorder is still a difficult problem for clinicians. Transcranial magnetic stimulation has developed rapidly with its advantages of being noninvasive, simple, and effective, TMS-EEG is a combination of EEG and single-pulse transcranial magnetic stimulation, and its PCI provides an objective index for the diagnosis of patients with consciousness disorders, Combined application with other neuroelectrophysiology and neuroimaging in the evaluation of patients with consciousness disorders may reduce the misdiagnosis rate. Different modes of transcranial magnetic stimulation, including high-frequency rTMS, low-frequency rTMS, and iTBS, have been studied in the efficacy of patients with consciousness disorders. At present, it is found that high-frequency rTMS can promote the recovery of consciousness in patients with consciousness disorders, but there are few studies on the efficacy of low-frequency rTMS and iTBS in patients with DOC. This field should be further explored in the future, and more randomized controlled trials with large samples should be conducted to provide more basis for clinical application, and the pathogenesis of consciousness disorders should be further explored. To construct an accurate evaluation system, so as to achieve individualized accurate rehabilitation treatment.

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