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Progress on Low-frequency Repetitive Transcranial Magnetic Stimulation Based on Cerebral Cortex Excitability Control in the Treatment of Alzheimer's Disease

Yanxiang Cheng

Nanjing Sport Institute, Nanjing, China

Abstract: *Low-frequency repetitive transcranial magnetic stimulation is a type of transcranial magnetic stimulation technology. Based on its high safety characteristics, researchers currently apply this technology to treat Alzheimer's disease and have achieved certain results. This paper summarizes low-frequency transcranial magnetic stimulation and its research progress in the treatment of Alzheimer's disease.*

Keywords: *Cerebral Cortex; Low Frequency Repetition; Transcranial Magnetic Stimulation; Treatment Progress; Alzheimer's Disease*

1. Introduction

Transcranial magnetic stimulation is a non-invasive electrical stimulation technique that acts on the cerebral cortex and spinal cord. It can regulate the function of various areas of the cerebral cortex by changing the excitability of neurons. At present, low-frequency rTMS has achieved certain progress as a new treatment method for Alzheimer’s patients,this technology has important application prospects.

2. Summary on Low-frequency Repetitive Transcranial Magnetic Stimulation

Transcranial magnetic stimulation technology is divided into three modes: single pulse magnetic stimulation, double pulse magnetic stimulation and repetitive transcranial magnetic stimulation. Among them, single-pulse magnetic stimulation and double-pulse magnetic stimulation can only temporarily activate the needed neurons, while rTMS, the TMS pulse stimulation with repeated sequence regularity, can continuously activate specific neurons and regulate the excitability of the cerebral cortex. Based on different frequency, rTMS includes low-frequency rTMS and high-frequency rTMS. The stimulation frequency of high-frequency rTMS is>1 Hz, mainly generates excitatory potential. The stimulation frequency of low-frequency rTMS≦1 Hz, mainly produces inhibitory potential, inhibits the function of the cortex, increases the threshold value of motor-evoked potential and reduces the amplitude. Figure 1 shows a schematic diagram of a navigating transcranial magnetic stimulation instrument. Transcranial magnetic stimulation promotes changes in the structure and function of cerebral cortex neurons in Alzheimer's patients, while low-frequency rTMS can inhibit the excitability of neurons, affect the stimulation site and the synergistic distal cortical function, stimulate the reconstruction of the data network function area of the cerebral cortex, and be used in the treatment of Alzheimer's disease.[1]

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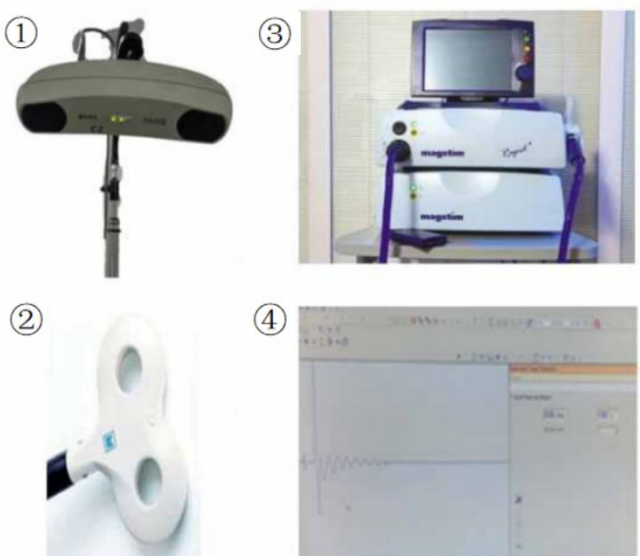

Figure 1: Schematic diagram of navigating transcranial magnetic stimulation instrument

①Infrared navigation device;

②Magnetic stimulation coil;

③Magnetic stimulation energy generator;

④EMG information detection system.

3. The Effect of Low-frequency Repetitive Transcranial Magnetic Stimulation on Alzheimer's Disease

Previous studies have proved that rTMS can be used as an auxiliary method for clinical treatment of Alzheimer's disease, delaying the deterioration of the disease, and improving the cognitive function and mental behavior symptoms of patients. The test on patients is shown in Figure 2.[2]

Figure 2 :Schematic diagram of low-frequency rTMS

①Repeated transcranial magnetic stimulation;

② Holder;

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③8 word coil;

④Test subject.

3.1 The Effect of Low-frequency Repetitive Transcranial Magnetic Stimulation on Cognitive Function in Alzheimer's Disease

Cognitive dysfunction in Alzheimer's patients includes abnormalities in memory, attention, thinking ability, reasoning ability, and intelligence. The main clinical manifestations are a decrease in cognitive rate, an increase in reaction time, a shrink in short-term memory capacity, and language disorder and visual spatial ability impairment. The effects of low-frequency rTMS on the cognitive functions of Alzheimer's patients are as follows.

Effect on memory: Memory is the process of storing and reproducing various types of information in the brain and the core symptom of Alzheimer's patients is memory loss. Studies have found that rTMS stimulates the left parietal cortex of Alzheimer's patients to relieve the symptoms of short-term forgetting. Of course, some people use rTMS to stimulate DLPFC to conclude that stimulating the right DLPFC with low-frequency rTMS can enhance the abilities of healthy people and Alzheimer's patients to remember faces and words and regulate the excitability of brain neural networks. High-frequency rTMS will reduce this kind of memory capabilities. Zhang Liyong et al. found that rTMS can improve the MoCA and memory scores of Alzheimer's patients. In addition, some studies have shown that low-frequency rTMS can strengthen the plasticity of rat synapsin in Alzheimer's patients and improve their spatial learning and memory capabilities.

Effect on language function: Language ability is the main way of interpersonal communication, including language expression ability, written language ability, sign language and facial expressions. Language disorder is that people have difficulties in using language skills to communicate. Studies have shown that using low-frequency rTMS to inhibit specific parts of the right cerebral hemisphere, the patient's naming ability and language function are significantly improved. Some also use low-frequency rTMS to stimulate the DLPFC area of Alzheimer's patients. Three months after treatment, the patients' language ability index scores in the mental status checklist have been significantly improved. It can be seen that low-frequency rTMS can significantly improve the language ability of Alzheimer's patients. When studying the effects of low-frequency rTMS on Alzheimer's patients, the results show that low-frequency rTMS can effectively improve the scores of AS-Cog, language factors, memory factors and EEG indicators in Alzheimer's patients. It is clear that low-frequency rTMS can effectively enhance the language function of Alzheimer's patients and improve the symptoms of aphasia. Although low-frequency rTMS is applied to the recovery of language function, the number of samples in the study is small and the methods of evaluating language function in each study lack consistency. Therefore, the efficacy of low-frequency rTMS on the language function area of the cerebral cortex needs to be standardized and unified. Effect on Orientation: Orientation refers to people's spatial cognition ability, temporal cognition ability and cognition ability to their own current state. Similarly, after studying the effects of low-frequency rTMS on the right DLPFC and posterior parietal cortex of the cerebral cortex, it can be known that after the posterior parietal cortex inhibits stimulation, its alertness and orientation function decrease, while after DLPFC inhibits stimulation, its executive function decreases, the orientation function is improved. Researchers used low-frequency rTMS to stimulate the DLPFC area of Alzheimer's patients. Three months after treatment, the patients' orientation index scores in the mental status checklist were significantly improved. It is clear that low-frequency rTMS can significantly improve the orientation of Alzheimer's patients . Through literature search and analysis, we found rTMS has effects on the cognitive function of Alzheimer's patients. The results of systematic statistics showed that the spatial, temporal, and orientation abilities of Alzheimer's patients were significantly enhanced after low-frequency rTMS treatment. The above studies all prove that qq real low-frequency rTMS has a good effect on the orientation function of healthy people and Alzheimer's patients and has no side effects.

3.2 The Effect of Low-frequency Repetitive Transcranial Magnetic Stimulation on Mental and Behavioral Symptoms in Alzheimer's Patients

The main manifestations of mental and behavioral symptoms in Alzheimer's patients include personality change, delusion, depression, mania, hallucination, aggression, behavioral abnormality, sleep status and identity disorder. Psycho-behavioral symptoms can seriously affect patients' life quality,

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and can react on the cognitive function of patients, causing the disease to progressively worsen. Some studies have shown that using low-frequency rTMS to stimulate the DLPFC area of Alzheimer's patients significantly improves patients' mental state, life and depression scale scores three months after treatment. It can be said that low-frequency rTMS can significantly improve the mental behavioral symptoms and depression of Alzheimer's patients[3]. Relevant researchers used low-frequency rTMS to treat Alzheimer's disease for six weeks, and the patient's mental behavioral symptom score was significantly reduced with low adverse reactions. The above studies show that low-frequency rTMS has a good effect on improving the mental and behavioral symptoms of Alzheimer's patients.

4. The Mechanism of Low-frequency Repetitive Transcranial Magnetic Stimulation on Alzheimer's Disease

The typical neuropathological characteristics of Alzheimer's patients include: senile plaques caused by amyloid deposition in the cerebral cortex and hippocampus; double-stranded helix filaments and tangles caused by hyperphosphorylation of proteins in neurons. When Alzheimer's disease develops, there will be selective loss of neurons and synapses in the cerebral cortex and hippocampus, and the function of synaptic transmission will be weakened. The mechanism of low-frequency rTMS on Alzheimer's disease is not completely clear. Possible mechanisms include that low-frequency rTMS can inhibit the excitability of the cerebral cortex, enhance the plasticity of the cerebral cortex neurons and the interconnection between neurons, and increase the blood flow of the cerebral cortex, etc.

4.1 Low-frequency rTMS Regulates the Excitability and Receptor Expression of the Cerebral Cortex

The difference in rTMS stimulation frequency has different effects on the excitability of the cerebral cortex. High-frequency rTMS (>1 Hz) enhances the excitability of the cerebral cortex. Low-frequency rTMS (≤ 1 Hz) raises the inhibitory indicators in the cortical neural network, suppresses the excitability of the cerebral cortex, weakens the synaptic activity, and leads to long-term depression (LTD), and the inhibitory effect can last for a certain period of time. However, high-intensity low-frequency rTMS can enhance the excitability of the cerebral cortex. This requires in-depth research. Low-frequency rTMS mostly acts on the cerebral cortex outside the motor area of the first cortex, and acts on the prefrontal area to regulate mood, depression and cognitive functions. Low-frequency rTMS can effectively improve the mania of Alzheimer's patients, restrain the excessive activation of neurons, and adjust the neural network distribution of the language center. At the same time, low-frequency rTMS can increase the expression level of specific NMDA receptor proteins in the CA1 region of rat hippocampus, and enhance the learning and memory ability of in Alzheimer's rats. The expression levels of BDNF receptors in the hippocampus and frontal regions of Alzheimer's patients are significantly reduced, and low-frequency rTMS can lift the level of neurotrophic factor BDNF in the hippocampus of Alzheimer's rats, and enhance the learning and memory ability of Alzheimer's rats[4].

4.2 Low-frequency rTMS Regulates Neural Functional Connections

Alzheimer's Patients have abnormal neurological connections, including weakened functional connections between the frontal and parietal lobes, and excessively strong functional connections in the brain lobes. rTMS can regulate the synaptic plasticity and connectivity of neurons, and strengthen the function of neurons to remodel and restore functional connections, that is, long-term potentiation (LTP) and long-term inhibition. rTMS frequency have different effects on neuronal plasticity and connectivity regulation. High-frequency rTMS triggers LTP, while low-frequency rTMS can lower down MEP amplitude, trigger LTD, and regulate synaptic density, NMDAR activity, and AMPAR channels. However, high-intensity low-frequency rTMS can induce strong LTP. Low-frequency rTMS acts on the prefrontal lobe to repair the reticular system with cognitive functions such as memory coding. The low frequency can also achieve a balance between the cortical excitation regulating neural function in the stimulating side and contralateral hemispheres and Interhemispheric neural activity. Low-frequency rTMS not only inhibits the excitability of the cortex in the target area, but also changes the function of the distal cortex, revealing the remodeling effect of low-frequency rTMS on the cortical neural network. The specific effect of low-frequency rTMS on the neural connectivity between various parts of the cerebral cortex in Alzheimer's patients needs to be studied in depth.[5]

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5. Conclusion

At present, low-frequency rTMS has achieved certain progress as a new treatment method for Alzheimer's patients. However, there are still some problems that need to be solved urgently: (1) The physiological conditions of the cerebral cortex of people of different ages are different, so appropriate low-frequency rTMS intensity should be selected for different ages; (2) There are few studies on low-frequency rTMS applied to the recovery of language function, and the ways of evaluating language function in each study lack consistency. Therefore, the efficacy of low-frequency rTMS on the language function area of the cerebral cortex is in urgent needs for unified study; (4) There is a lack of correlation research on the treatment duration and efficacy of low-frequency rTMS; (5) Because Alzheimer's patients need long-term medication, there is a lack of research on the effects of low-frequency rTMS on drugs; (6) Applying low-frequency rTMS to Alzheimer's patients is much safer and less likely to cause adverse reactions such as epilepsy, headache and hearing impairment than high-frequency rTMS. However, due to the strong excitatory effect of high-intensity low-frequency rTMS, it may cause higher adverse reactions. Therefore, it is necessary to study the correlation between the intensity of low-frequency rTMS and adverse reactions. In summary, the low-frequency rTMS technology is painless, non-invasive, and highly safe, and has broad prospects for the treatment of Alzheimer's disease, but a comprehensive and in-depth study of the mechanism and clinical application of this technology is still needed.

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