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Effect of chronic and acute low-frequency repetitive transcranial magnetic stimulation on spatial memory in rats

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a novel, non-invasive neurological and psychiatric tool. The low-frequency (1 Hz or less) rTMS is likely to play a particular role in its mechanism of action with different effects in comparison with high-frequency (>1 Hz) rTMS. There is limited information regarding the effect of low-frequency rTMS on spatial memory. In our study, each male Wistar rat was daily given 300 stimuli (1.0 T, 200 μs) at a rate of 0.5 Hz or sham stimulation. We investigated the effects of chronic and acute rTMS on reference/working memory process in Morris water maze test with the hypothesis that the effect would differ by chronic or acute condition. Chronic low-frequency rTMS impaired the retrieval of spatial short- and long-term spatial reference memory but not acquisition process and working memory, whereas acute low-frequency rTMS predominantly induced no deficits in acquisition or short-term spatial reference memory as well as working memory except for long-term reference memory. In summary, chronic 0.5 Hz rTMS disrupts spatial short- and long-term reference memory function, but acute rTMS differently affects reference memory. Chronic low-frequency rTMS may be used to modulate reference memory. Treatment protocols using low-frequency rTMS in neurological and psychiatric disorders need to take into account the potential effect of chronic low-frequency rTMS on memory and other cognitive functions.

Keywords: Repetitive transcranial magnetic stimulation; Morris water maze test; Reference memory; Working memory

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a novel neurological and psychiatric tool. Basing on its ability to non-invasively and relatively painlessly stimulate the cortex by a conducting coil, rTMS has both clinical and basic neuroscience applications [21]. rTMS has been developed a valuable tool in neuroscience because it could affect brain functions, including attention, memory, speech, etc. [13]. Moreover, rTMS had a significant potential as a treatment for several neuropsychiatric illnesses, such as depression, schizophrenia, obsessive–compulsive disorder and post-traumatic stress disorder [27,32]. In particular, it is not known what stimulation parameters (frequency, intensity, duration and number of pulses) are required for an optimal application.

The frequency of stimulation is likely to play a key role in its mechanism of action with different effects. There has been much interest in the various effects of rTMS delivered at different frequencies. In clinical studies, most investigations of rTMS for the antidepressant effect have used high frequencies (10–20 Hz) [11,22]. But high-frequency rTMS may induce some side effects, such as seizure, headache or other harmful potentials, which could be reduced by the application of low-frequency of rTMS. Compared with high-frequency rTMS, the low-frequency rTMS is of different characteristic. When delivered over the motor cortex, rTMS produces different effects depending upon the frequency of stimulation. At a frequency of 1 Hz, rTMS produces inhibition of subsequent cortical responses [4], whereas at frequencies of 5–20 Hz, it produces facilitation, as measured by its effect on the motor threshold [26,1]. Klein

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et al. [18] reported antidepressant effect with 1 Hz stimulation over the right prefrontal cortex, with the explanation that "inhibition" of the right prefrontal cortex had an effect similar to the "facilitation" of the contralateral side. A study of low frequencies for their neurological effects is of clinical importance. The rTMS treatement at lower frequencies is better tolerated, with a lesser likelihood of local pain or discomfort and a lower risk of seizures [20].

However, it is not quite clear whether administration of rTMS can disrupt or facilitate memory activity, especially after the long-term treatment of rTMS. The previous reports about effects of rTMS on memory function are not consistent [19,12,34,14]. In animal studies, a retrograde memory for conditioned taste aversions was diminished by 50 brief pulse TMS [19]. And in human study verbal recall was consistently significantly diminished only after rTMS applied during word list presentation [12]. However, clinical application of rTMS at high- and low-frequency manners revealed no detrimental effects on cognition, including learning and memory [14]. Similarly, in patients treated with rTMS, cognitive performance remained constant or improved and memory complaints alleviated [34]. On the other hand, rTMS treatment, similar to electroconvulsive therapy (ECT), generates an alternating electrical field in the brain, however, ECT could be a dramatic impact on cognitive function, especially on memory function [6]. It is unknown whether rTMS, especially low-frequency rTMS treatment, could impair memory similar to ECT.

Morris water maze (MWM) test, described to investigate spatial learning and memory in the laboratory rat in 1981, has become one of the most frequently used laboratory tools in behavioral neuroscience [7]. The device consists of a large circular basin filled with opaque water and a small escape platform hidden below the surface of water and invisible to rats. During a number of training trials, animals learn to escape from the water by locating and climbing onto a platform. Although basic procedure is relatively simple, it has been used in some of the most sophisticated experiments in the study of the neurobiology and neuropharmacology of spatial learning and memory as well as in the validation of rodent models for neurocognitive disorders [7]. Behavioral tasks requiring reference memory emphasize relevant information applicable to all trials, whereas tasks requiring working memory emphasize relevant information applicable to a specific trial that does not apply to others [25]. For example, when rats seek food, the geographical information about the environment may be constantly useful for several days, that is, this kind of memory can be regarded as reference memory, and the information, such as, where the food is, may be applicable only to the task, in this way, this kind of memory may be working memory. According to this view, if the platform position is kept constant throughout all training trials, the task could be defined as a reference memory task. Additionally, if the position of the hidden platform is different on each training session, the particular spatial information will apply only to that specific session; thus, it could be considered a behavioral task for working memory [38]. Moreover, we want to distinguish the possible significance between the parts of memory structure, such as acquisition and retrieval in the reference memory process.

No study has yet addressed whether chronic/acute low-frequency rTMS administration induces spatial memory deficits. We hypothesized that chronic low-frequency rTMS would affect the spatial reference or/and working memory, but acute low-frequency rTMS might not. In order to test the hypothesis, the effect of low-frequency rTMS on spatial memory was examined in MWM task on reference and working memory versions, respectively.

2. Materials and methods

2.1. Animal

Naïve male 180–200 g rats of the Wistar strain, originally obtained from Medical Laboratory Animal Center, Sichuan University, were 10–12 weeks old. All animal studies were conducted, according to the guideline for the care and use of laboratory animals approved by Chinese government. The rats were housed in controlled temperature ($21 \pm 1\,^{\circ}C$) and light was set on 12 h dark:12 h light cycle referring light off at 07:00 h. Rats were housed five per cage, with food and water ad libitum.

2.2. Chronic and acute rTMS treatment

Rats were treated with rTMS daily for chronic and acute condition. An available stimulator manufactured by Biomedical Engineering Unit, West China Medical Center, Sichuan University, was used for rTMS. The conscious rats received the simulation by a round prototype coil (55 mm diameter, 15 windings). Each rat was daily given 300 stimuli resulting from 6 trains (1.0 T, 200 μs) at a rate of 0.5 Hz. The stimulus waveform was a biphasic cosine pulse. The initial current direction was clockwise. The trains were separated by 30 s intervals to cool the coil. The coil was tangentially placed above the vertex of skull and handled parallel to the line of the vertebral column, inducing mild motor tremor of the head caused by direct effects on muscle. The control rats received the similar stimulations by placing the coil on the low lumbar spine region, but no rTMS on brain.

Rats received chronic rTMS were subjected to daily rTMS treatment for 10 days and the behavior test was carried out 24 h after the last rTMS. Rats received acute rTMS were treated by rTMS before each daily training session, i.e., rats received acute rTMS which were tested in reference memory task were accepted daily rTMS during the training for 3 days and rats subjected to working memory task just received rTMS one time before the acquisition trial. The control rats received the sham stimulations according to relevant procedures described above.

3. Behavioral procedures

3.1. Apparatus

All rats were put into the Morris water maze to assess learning and memory performance on a spatial orientation task [23]. In particular, the rats were gently placed in a circular water basin, which was 50 cm high, 120 cm diameter and filled up to a level of 30 cm with $25 \pm 1\,^{\circ}C$ water. The animals could find the platform and escape from the pool. This platform, which consisted of a round platform (9 cm diameter) invisible for the rats, was hidden 2 cm below the surface of opaque water in one of the four quadrants of the basin. Clearly visible visual cues outside the basin were provided for orientation. The behavior of rat was recorded by a ceiling-mounted automatic tracking system (MI-200, Chengdu Taimeng Technology & Market Co., Ltd., China).