RESEARCH PAPER

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Effect of low-frequency repetitive transcranial magnetic stimulation on cognitive function in rats with medial temporal lobe epilepsy

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Epilepsy, especially the medial temporal lobe epilepsy (TLE), can result in cognitive impairment. Low-frequency repetitive magnetic stimulation (rTMS) has been verified to suppress neural excitability and reduce seizures. Given its potential in modifying cortical activity, we aimed to investigate its impact on cognitive function in the context of epilepsy, a condition where the use of rTMS has not been extensively explored. However, the influence on cognitive function has not yet been investigated. Therefore, this study aimed to investigate the effects of low-frequency rTMS on cognitive improvement in epileptic rats. Rats used in this study were randomly divided into five groups: the sham group, the epilepsy group, and three epilepsy groups treated with rTMS at different frequencies. Each group underwent the Morris water maze test to investigate hippocampus-dependent episodic memory, to evaluate their cognitive performance. Further assessments included patch clamp and western blot techniques to estimate the synaptic function in the hippocampus. Comparison between groups showed that low-frequency rTMS significantly reduced spontaneous recurrent seizures and improved spatial learning and memory impairment in epileptic rats. Additionally, rTMS remodeled the synaptic plasticity affected by seizures and notably enhanced the expression of AMPAR and synaptophysin. Low-frequency rTMS can antagonize the cognitive impairment caused by TLE, and promote synaptic connections.

Key words: epilepsy, low-frequency repetitive transcranial magnetic stimulation, cognition, synapse

INTRODUCTION

Epilepsy is a common neurological disease (Janmohamed et al., 2020), which is thought to be associated with the imbalance caused by over-excitation or insufficient inhibition of neurons (Ziemann et al., 1998). Temporal lobe epilepsy (TLE) is the most common type of focal epilepsies and represents more than 70% of drug-resistant epilepsy in adults. The most frequent pathological manifestation in patients with TLE is hippocampal sclerosis (HS), which is histologically characterized by segmental loss of main pyramidal neurons, synaptic reorganization, and reactive astrocyte proliferation in the hippocampus.

The well-established and clinically translatable lithium-pilocarpine model, which is one of the most popular and widely used rodent models of epilepsy, stimulates the entire process of initiation, spread, and development of human epilepsy and is consistent with the characteristics of temporal lobe epilepsy, the most common type of epilepsy in adults. It provides an ideal platform for studying the mechanism of epileptic occurrence and formation due to its easy operation and good repeatability (Curia et al., 2008).

Since it was first introduced in 1985, TMS has rapidly evolved as a powerful and non-invasive tool for human brain research (Barker et al., 1985). TMS pulse stimulation can generate electric fields in localized

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regions of the brain, leading to the depolarization of cell membranes and activation of neurons, which can excite or inhibit specific brain regions (Hallett, 2000). Repetitive magnetic stimulation (rTMS) refers to repeated pulse stimulation with varying frequencies or intensities, which can non-invasively change cortical excitability, and the effect continues even after the stimulation. Therefore, it has potential therapeutic value. Currently, it is widely used in the treatment of depression, pain, Parkinson's disease, Alzheimer's disease, dystonia, stroke, consciousness disorder, and other neuropsychiatric conditions (Lefaucheur et al., 2014, 2020; Perera et al., 2016; Yu et al., 2017; Lin et al., 2019; Shao and Luo, 2019; Xie et al., 2019).

Low-frequency rTMS can inhibit cortical excitability by acting directly on the cortex, and the inhibitory effect persists regardless of whether the stimulation is stopped or not. The mechanism may be related to the enhancement or attenuation of GABA activity or synaptic connectivity (Chen et al., 1997). Low-frequency rTMS is thought to inhibit epileptic activity, thereby reducing the frequency of seizures. However, several studies (Cantello et al., 2007; Joo et al., 2007) on rTMS treatment of intractable epilepsy reported diverse results, and relevant systematic reviews (Chen et al., 2016; Cooper et al., 2017; Mishra et al., 2020) have failed to reach a cohesive conclusion which may be due to the differences in research objectives, methodologies, and treatment parameters.

Recently, rTMS showed significance on the potential to modulate cognitive functions in AD and MCI. Numerous *in vitro* and *in vivo* models provide evidence that rTMS can increase long-term potentiation (LTP) and could promote good performance on hippocampal dependent spatial cognition (Wang et al., 2015; Huang et al., 2017; Chou et al., 2020). However, the usage of low-frequency rTMS on the cognitive function in TLE has not been widely investigated. Therefore, we induced TLE model, by receiving different frequency of rTMS, the cognitive behaviors and histological changes of hippocampus were detected.

METHODS

Lithium-pilocarpine Model Establishment and Low-Frequency rTMS Treatment

In our experiments, the rTMS was specifically targeted towards the hippocampal CA1 region, believed to be associated with the effects observed. The choice of this region was based on observations that the LTP effect in the hippocampus of TLE rats was greatly suppressed, which could be partially reversed by rTMS of 0.3 Hz treatment. Forty male Sprague-Dawley (SD) rats obtained from Beijing Vital River Laboratory Animal Technology Co., (aged six to eight weeks and weighing 180–200 g) were placed into 5 groups at random. The study was admitted by the Research Ethics Committee of the Second Hospital of Hebei Medical University (approval NO.2022-AE004, dated 2022.1.7). Six rats were left for each group after modeling due to reasons such as natural mortality and modeling failures. In cases where the rats did not display the expected seizure levels or had other health complications, they were excluded from the study: Control group (healthy rats receiving normal saline injection), SE group (rats receiving Lithium-pilocarpine injection to establish status epileptic model), SE+0.3 Hz group (SE rats receiving rTMS stimulation of 0.3 Hz), SE+0.5 Hz group (SE rats receiving rTMS stimulation of 0.5 Hz), SE+1Hz group (SE rats receiving rTMS stimulation of 1 Hz). For the Lithium-pilocarpine model establishment (Qu et al., 2019), the rats were given a pilocarpine injection (50 mg/kg, dissolved in 0.9% saline) following a lithium injection (127 mg/kg) intraperitoneally. 30-60 min later, while the Racine scale, introduced in 1972, has its limitations, it remains a widely used method for evaluating seizure severity due to its simplicity and reproducibility. In this study, seizures were evaluated using the 5-stage Racine scale (McIntyre et al., 2002) as follows: Level 0: no reaction; Level I: shaking, blinking, whisker moving and chewing; Level II: rhythmic nodding and tail flicking; Level III: clonus of one forelimb; Level IV: clonus of bilateral forelimbs with standing; and Level V: total tonic clonic seizure with a fall. If the rats failed to meet the standard of Level IV or V with the duration of 1 hour for the first time, we tried again up to two times with 10 mg/kg pilocarpine each time until the standard was obtained. To eliminate the side effects of pilocarpine, atropine sulfate (1 mg/kg) was administered 30 min before pilocarpine injection. Seizures were terminated with 3% pentobarbital (1.5 mg/kg) after an ongoing epileptic attack of Level IV or V for 1 hour. On the next day of modelling, we applied a 70 mm figure-of-eight coil of a Magstim Rapid^2 TMS stimulator (Magstim Company Ltd., UK), positioned 1 cm above the head of the rats in the SE+0.3 Hz group, with the frequency of 0.3 Hz, 300 pulses, and the intensity of 40%. Similarly, the SE+0.5 Hz and SE+1 Hz groups were stimulated with the frequency of 0.5 Hz and 1 Hz, respectively, keeping other conditions unchanged. The treatment was administered once a day for 28 days. Rats in the Control group and SE group did not receive any treatment. All animal experiments were conducted in accordance with the Institutional Animal Ethics Committee guidelines.

Evaluation of SRSs of Lithium-Pilocarpine induced epilepsy

After one week of modelling, the rats were monitored with a high-definition camera all day to observe the spontaneous recurrent seizures (SRSs) for 28 days. The latency of SRSs, the frequency of SRSs, and incidence were calculated.

Spatial learning and memory evaluation

In the seventh week following SE, the MWM test was conducted (Xie et al., 2012; Qu et al., 2019), which consists of the following three components: (1) Visual platform: To exclude the differences in visual acuity and swimming speed of rats, the platform was placed in a quadrant and kept 1.5 cm above the water. Rats were plunged into the water from the opposite quadrant. Both the latency of escape and the average swimming speed were recorded. (2) Navigation test: The rats were placed in water in four different quadrants orderly every day to be observed whether they could find the platform 1.5 cm beneath the water. The so-called latency of escape, the time period from entering the water to standing on the platform, was then recorded. If the platform was not identified within 2 min, the experimenter would guide the rats to stand on the platform for 30 s, and the latency was recorded as 2 min. The above process was repeated for 5 days. (3) Spatial exploration: Following the navigation test, the submerged platform was withdrawn, and rats were put into water from opposite quadrant. The time spent in the platform's quadrant, as well as the number of crossing the platform, were recorded.

Recording of electrophysiology of hippocampus

LTP has been implicated as an important electrophysiological mechanism concerning the plasticity of synaptic transmission. Following the MWM test, the LTP levels in the left hippocampus of the four urethane-anesthetized groups were detected (Qu et al., 2019). Stimulating electrodes (4.0 mm posterior to the bregma and 3.8 mm lateral to the midline) were implanted at the Schaffer collateral pathway while recording electrodes were placed at the stratum radiatum of the CA1 region (3.7 mm posterior to the bregma and 2.9 mm lateral to the midline). The stimulus intensity was adjusted to 30-50% of the maximum amplitude of field excitatory postsynaptic potential (fEPSP) at 30 s intervals. The basic fEPSPs were recorded for 30 min, following which LTP was induced by three sets of high-frequency stimulation (HFS) at intervals of 30 s. Each set of HFS protocols was carried out using 20 pulses at a frequency of 200 Hz. The recording then continued for 1 hour.

Electron microscope observation

After LTP recording, the rats were anesthetized with 3% pentobarbital and perfused with saline solution at 4°C. The electron microscope perfusion solution was continued just until the bleeding stopped, and it came to an end with quivering muscle, a stiff tail, and other symptoms. A tissue block of 1-mm^3 was cut from the CA1 region of the hippocampus and sliced with an ultrathin microtome, and the ultrastructure of the synapse was observed using transmission electron microscopy. By the software of ImageJ, the synaptic cleft width and the thickness of postsynaptic density (PSD) were measured from randomly selected 10 visual fields with multi-point average method.

Western blotting

The bilateral hippocampus was separated from the brain tissue. The protein concentration of the hippocampus was precisely measured using a conventional bicinchoninic acid (BCA) kit. The protein was then passed on to polyvinylidene difluoride (PVDF) membranes (Millipore, CA, USA) for nearly 90 min after being detached on 10% sodium dodecyl sulfate-polyacrylamide gels. Next, the PVDF membranes were sealed with 5% skim milk at room temperature for 1 h. The PVDF membranes were then incubated in diluted antibodies, anti-AMPAR (1:2000 Abcam), anti-Syp (1:10000 Abcam), and anti-β-actin (1:5000 Bioworld) at 4°C overnight. The next day, the PVDF membranes were washed with 0.1% TBST three times for 5 min each. Finally, the membranes were incubated in the secondary antibody of goat anti-rabbit fluorescent (1:10000 Abbkine) at room temperature on a shaking table for an hour and then rinsed with TBST three times for five minutes each. The density of the target bands was measured by Odyssey imaging system scan film (LI-COR, America) and calculated by ImageJ software relative to that of the β-actin (the internal control).

Statistical analysis

All data were presented as mean ± standard deviation (SD). Comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by *post hoc* tests for multiple comparisons. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software version 25.0.

RESULTS

Low-Frequency rTMS Reduced the SRSs of Lithium-Pilocarpine Model Rat

The latency and frequency of SRSs were analyzed across the different groups to understand the therapeutic potential of low-frequency rTMS. Notably, the SE + 0.3Hz and SE + 0.5Hz groups demonstrated a longer latency to the onset of SRS and reduced frequency compared to the SE group, suggesting that the rTMS intervention was beneficial (Fig. 1A-C). The detailed comparisons and statistical significance are as described. The SE+1Hz group, however, showed a lesser improvement, indicating a potential optimal frequency range for rTMS intervention in this model.

Low-Frequency rTMS Enhanced Spatial Learning and Memory behaviors in Epileptic Rats

Our behavioral tests aimed to determine the efficacy of rTMS in improving cognitive deficits in the epileptic rats. While all groups demonstrated a learning curve in the navigation test, the SE + 0.3Hz group showed a faster rate of learning, suggesting a beneficial effect of rTMS at this frequency (Fig. 2A, 2B). The spatial exploration trial further cemented these findings, with the SE+0.3 Hz group outperforming the SE group (Fig. 2C).

Low-Frequency rTMS Partly Reversed the Synaptic Plasticity Induced by Epilepsy

Neurophysiological measurements provided insights into the changes in synaptic plasticity post rTMS treatment. The SE group displayed diminished synaptic responsiveness post-HFS, indicating impaired synaptic plasticity. The SE + 0.3 Hz group, however, showed an improvement in synaptic responsiveness, suggesting a protective or restorative effect of rTMS (Fig. 3A, 3B).

Low-Frequency rTMS remodeled the Ultrastructural Damage of Synaptic hippocampus

Ultrastructural analysis revealed changes in the synaptic architecture, with the SE group showing a thinner PSD compared to controls. The SE + 0.3 Hz group demonstrated a reversal of this trend, suggesting the potential of rTMS in preventing or reversing the structural changes induced by epilepsy (Fig. 4A, 4B).

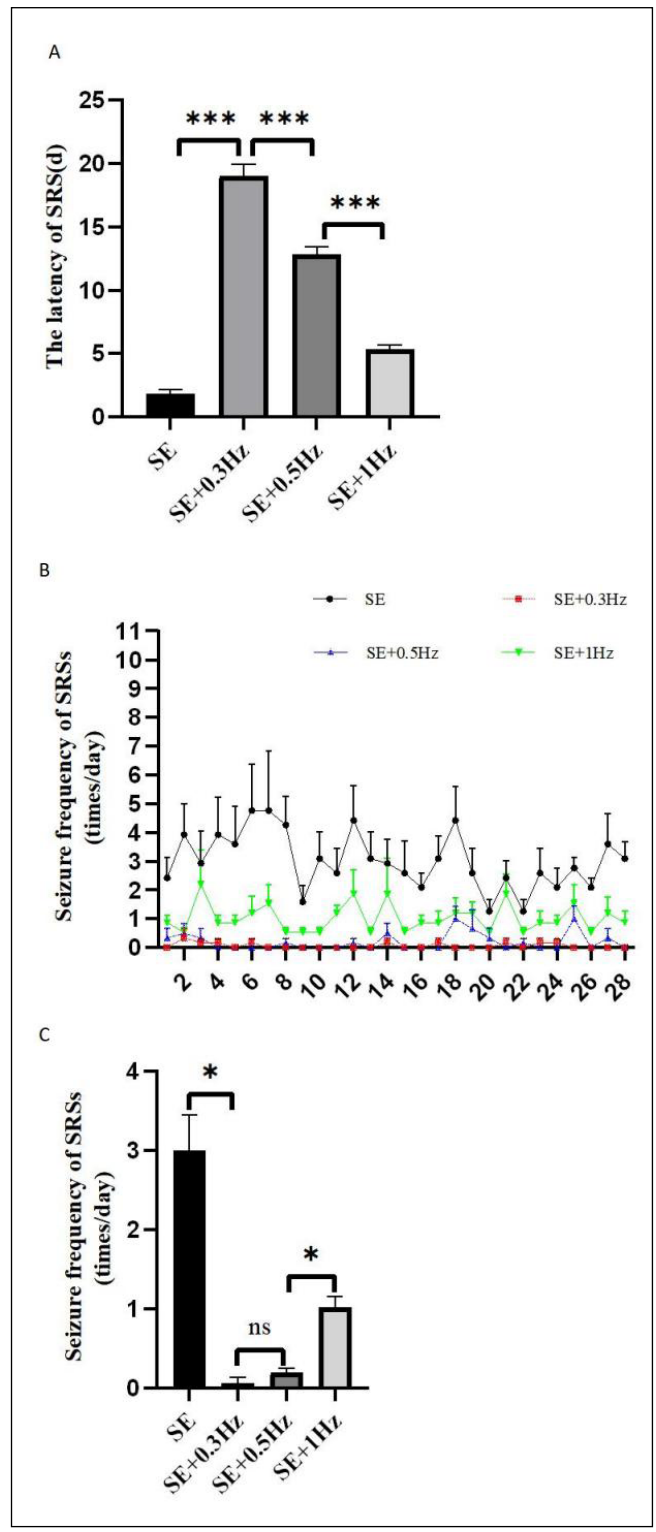

Fig. 1. Effect of rTMS on the frequency and latency of SRSs as determined by video monitoring. It's worth noting that while video monitoring provides visual evidence of seizure activity, it might not capture all the nuances of focal seizures. Combining this method with EEG recordings would offer a more comprehensive evaluation. (A) Latency of SRSs. (B, C) Seizure frequency of SRSs. Data were expressed as the mean ± SEM (n = 6/group) (*represent p<0.001).

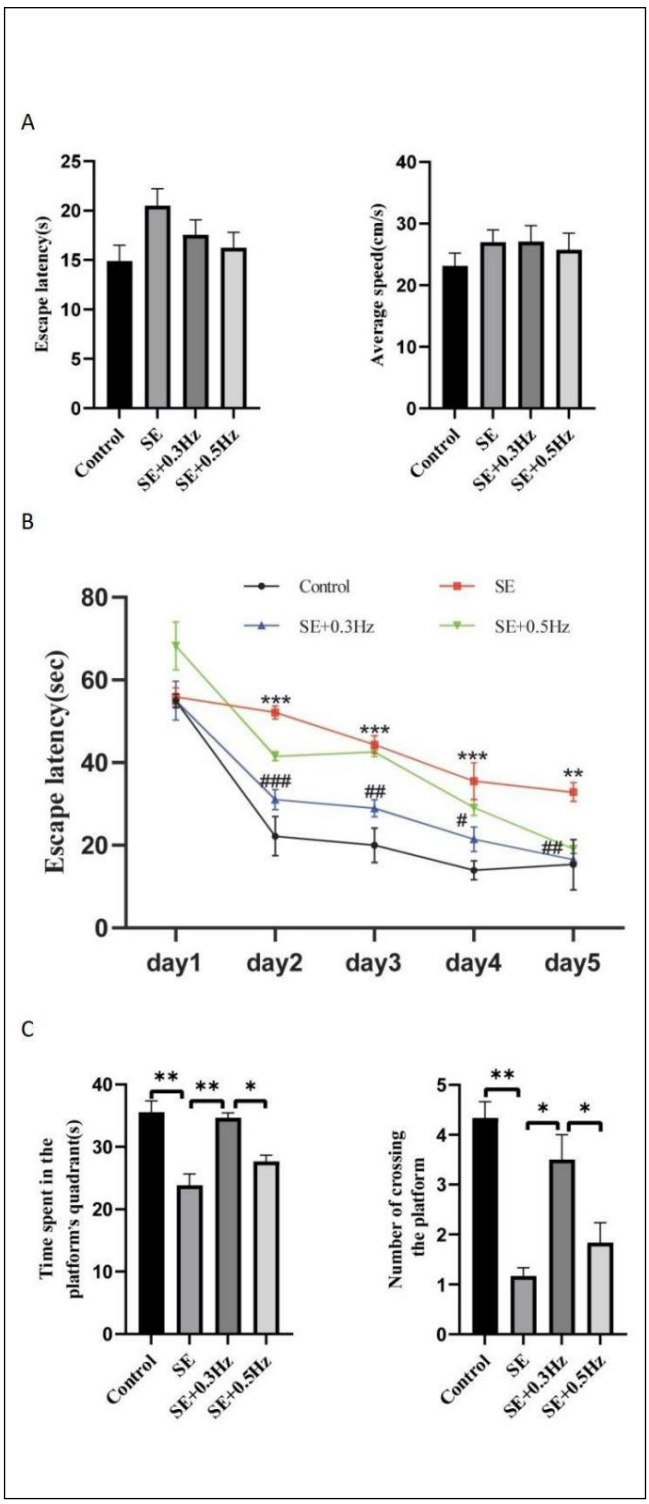

Fig. 2. Effect of low-frequency rTMS on the Morris water maze (MWM) test. All data were expressed as the mean±SEM. (*p<0.05, **p<0.001) (A) Escape latency recorded during the five days of hidden platform trials.(repeated-measures ANOVA with LSD test). (B) Time spent in the platform quadrant and the number of times crossing over the original platform location (one-way ANOVA with LSD test). (C) Similarities in escape latency and average swimming speed among the four groups (P>0.05).

Low-Frequency rTMS promoted the expression of synapse-associated proteins

Biochemical analyses revealed a decrease in the expression of AMPAR and Syp in the SE group, indicating potential synaptic dysfunction. Post rTMS treatment, the SE + 0.3 Hz group showed a marked increase in the levels of these proteins, suggesting a positive effect on synaptic health and function (Fig. 5A, 5B). The differential response between the SE + 0.3 Hz and SE + 0.5 Hz groups for AMPAR further points to a frequency-dependent effect of rTMS.

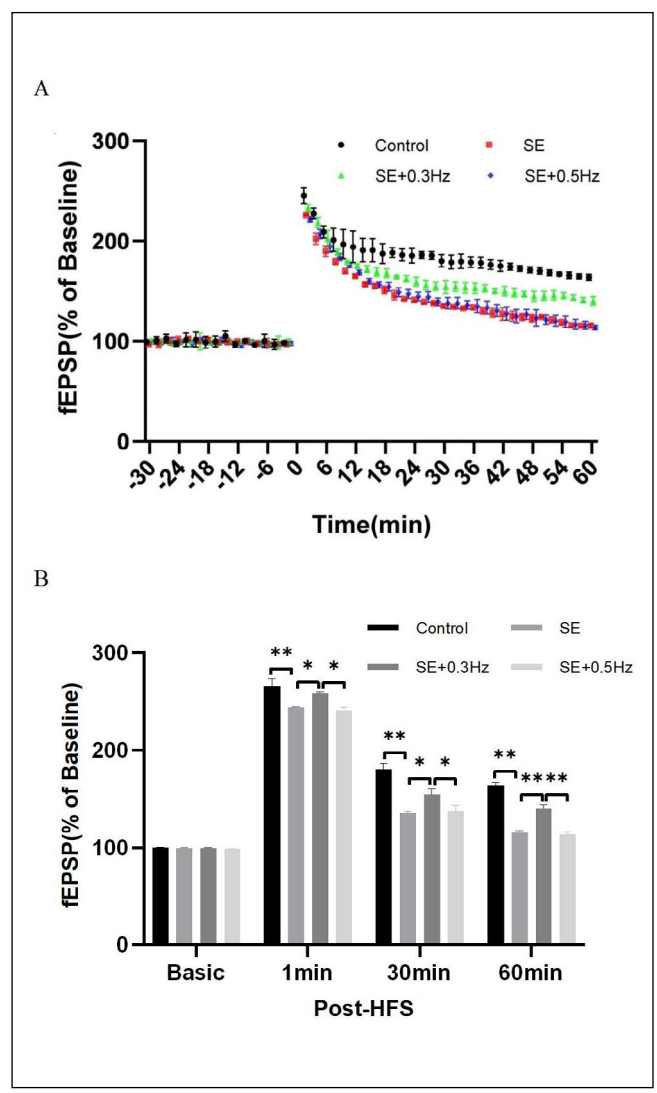

Fig. 3. Effect of rTMS treatment on E-LTP in the hippocampal CA1 region of epileptic rats. (A) Complete trend of fEPSP amplitudes before and after HFS with time. (B) Comparison of changes in average fEPSPs amplitudes before and after HFS in the form of a histogram (1 min, 30 min, and 60 min post-HFS). Data were presented as mean ± SEM (*p<0.05, **p≤0.001).

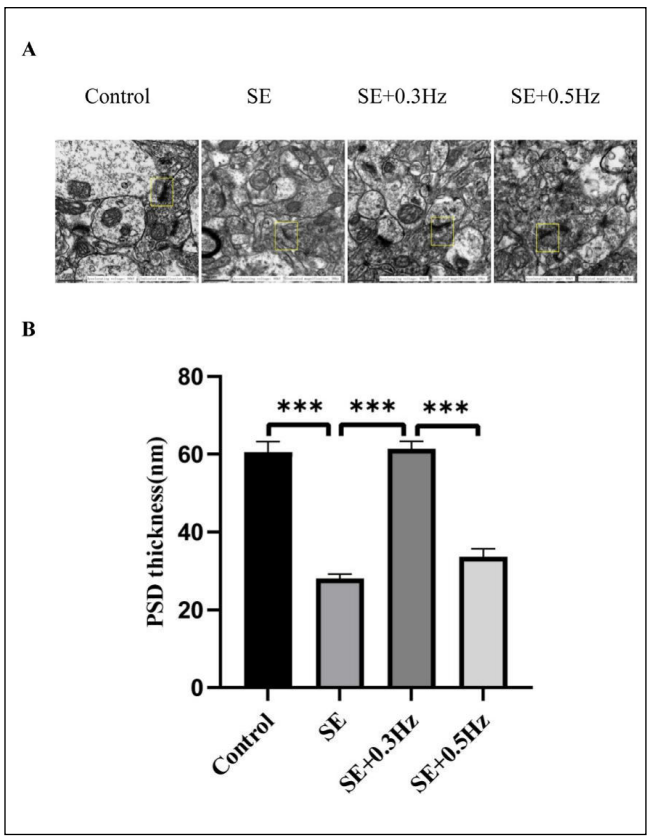

Fig. 4. Effect of rTMS on synaptic ultrastructure in the CA1 region of the hippocampus in epileptic rats. (A) Representative photomicrographs of synaptic ultrastructure in each group. (B) The thickness of PSD at the synapse. Results were expressed as mean ± SEM (**p<0.001).

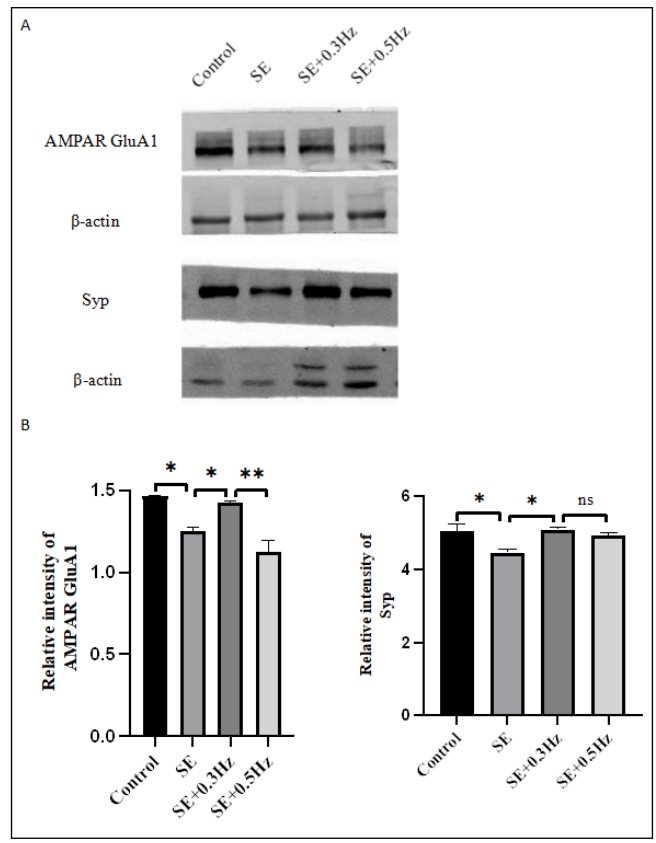

Fig. 5. Effect of low-frequency rTMS on the expression of synapse-related proteins in the hippocampus of epileptic rats. (A) Representative immunoblots of AMPAR and Syp in the hippocampus. (B) Relative intensity of AMPAR and Syp in the hippocampus in each group. The data represents the relative quantity compared with the control group. All results were expressed as mean ±SEM (*p<0.05).

DISCUSSION

While previous studies have explored the potential of rTMS in treating cognitive deficits in various neurological conditions, its effects in the context of epilepsy, especially in a rat model, are relatively underexplored. This study provides unique insights into this niche area, offering a novel perspective on the applicability of rTMS in treating cognitive impairments associated with epilepsy. This section investigated the impact of low-frequency rTMS on the cognitive function of rats with TLE. Using four experimental methods, namely MWM, LTP, fluoroscopic electron microscopy, and Western blot, we demonstrated that low-frequency rTMS could improve behavior, synaptic structure, and function, as well as synapse-related proteins. The present study using different frequency rTMS on the TLE rats, and found that the low-frequency rTMS could ameliorate the cognitive dysfunction after epilepsy, and promote synaptic remodeling. Moreover, rTMS of 0.3 Hz was considered to be more effective.

TLE is one of the most common types of epilepsy. The most vulnerable cognitive areas in patients with temporal lobe epilepsy are memory and language function. The medial temporal lobe (MTL), particularly the hippocampus, is involved in processing new information and creating new memories. Patients with bilateral MTL impairment show a significantly decreased ability to recall and remember new information (Schomaker et al., 2021). In our study, we also observed similar cognitive impairments in the rat model, aligning with these findings.

Learning and memory is a high-level process of brain activity that involves a complex process of interaction and connection between various neurons and synapses. Synaptic plasticity refers to the adaptability of information transmission between neurons, particularly the plasticity of the synaptic structure and transmission efficiency. Synaptic plasticity and learning and memory work together and are insep-

arable. The basis for modifications in learning and memory is synaptic plasticity. Learning and memory, in turn, increase the area, number, and volume of synapses, thereby forming new neural circuits. While measuring PSD thickness is not a standard method in the field, we chose this approach based on its potential to provide insights into synaptic deficits. The process of synaptic functional plasticity is often accompanied by structural changes, including changes in parameters such as PSD thickness and synaptic cleft width. PSD is a specialized structure with high electron density under the postsynaptic membrane that has irregularly shaped holes. We acknowledge the limitations of this method, especially when changes in protein expression are subtle, and emphasize the importance of considering multiple indicators for a comprehensive understanding. The main components of PSD include neurotransmitter receptors, cytoskeletal and regulatory proteins, and protein combinations of various enzymes (Opazo et al., 2012; Huganir and Nicoll, 2013). Our results, particularly the changes observed in synaptic plasticity, support this intertwined relationship. When information is being transmitted from the pre-synapse, the molecular composition and structure of the PSD can be dynamically altered to improve or impair the transmission efficiency at the synapse. Thus, PSD is one of the most important indicators of synaptic plasticity (Kennedy, 2000; Sheng and Kim, 2002; Yang et al., 2006). These structural changes were evident in our observations as well, further confirming the established knowledge. It is generally believed that the wider the synaptic cleft, the longer it takes for neurotransmitters to release from the presynaptic membrane into the synaptic gap and reach the postsynaptic membrane, resulting in a relatively lower synaptic function. The protocol for measuring PSD thickness and synaptic cleft width was adapted from Guldner (1980) and Jones (1978). Our study showcased the potential of this method in providing a deeper understanding of the synaptic changes in the rat model. Many animal studies have also confirmed that chronic seizures can cause changes in the structure and function of hippocampal synapses (Jackson et al., 2012; Yokoi et al., 2012).Consistent with these studies, our results also highlighted significant structural and functional changes in hippocampal synapses following chronic seizures.

Synaptic functional plasticity can be divided into long-term and short-term synaptic plasticity. The former involves LTP and long-term depression (LTD). LTP is thought to be completed in three steps (Hayashi, 2022): induction, expression, and maintenance. "Induction" refers to the process in which a powerful stimulus acts on cells, and if the resulting signal transmission takes place at the synapse, it is referred to as synaptic transmission or "expression". Once the transmission effect increases, the "maintenance" mechanism continues in this state. This powerful stimulus activates the NMDAR, triggering calcium ion influx into the postsynaptic complex, ultimately leading to structural changes in AMPAR (Malenka and Bear, 2004). LTP inhibition has been observed in several animal epilepsy model experiments (Postnikova et al., 2019, 2021), suggesting that LTP reduction may be an electrophysiological mechanism of cognitive impairment in epilepsy. In this experiment, LTP was induced in the pyramidal cells of the CA1 region of the hippocampus in each group by stimulating the Schaffer collateral in the CA3 region of the hippocampus. The results demonstrated that the LTP effect in the hippocampus of TLE rats was greatly suppressed, which could be partially reversed by rTMS of 0.3 Hz treatment. In short, low-frequency rTMS had some protective effect on synaptic functional plasticity.

The expression of synapse-related proteins was detected in order to clarify the molecular mechanism of low-frequency rTMS regulating synaptic plasticity. Synaptophysin (Syp) is a vesicle-adsorbing protein closely related to the structure and function of synapses. It is widely present in all nerve endings of the body, specifically on the presynaptic vesicle membrane, participates in the release of Ca^{2+} dependent neurotransmitters and the circulation of synaptic vesicles, and is recognized as an essential marker of synaptogenesis and synaptic remodeling. Its location and quantification can accurately reflect the distribution and functional state of synapses, indicating their plasticity. Several animal experiments of epilepsy models have confirmed that Syp expression is increased in the hippocampus of epileptic animals (Proper et al., 2000; Wang et al., 2008; Li et al., 2002), suggesting that it is involved in synaptic remodeling, thus causing epileptic seizures.

AMPARs are glutamate-gated ion channels that mediate most of the fast excitatory synaptic transmissions in the brain. The four subunits, glua1-glua4, assemble to form a tetramer, which is the core functional ion channel. Different combinations result in unique cell transport behavior and biophysical characteristics. The phosphorylation of GluA1 S831 and S845 is closely linked to LTP (Lee et al., 2003). NMDAR-dependent LTP requires Ca^{2+} influx, which leads to CaMKII/PKC activation, then directly phosphorylates GluA1 S831, and increases GluA1 single channel conductance; thereby promoting GluA1 targeting PSD (Malenka and Bear, 2004; Kristensen et al., 2011). Zhou et al. (2018) created a GluA1C2KI mouse line by replacing the C-terminus of mouse AMPAR GluA1 with the C-terminus of

GluA2. The results demonstrated that the basic synaptic transmission in these mutant mice was unchanged, and LTP was completely abolished in GluA1C2KI mice, indicating that the C-terminus of GluA1 was essential for LTP. It can be observed that AMPARs play a vital role in brain function, and the change in AMPAR abundance following a synapse is the core mechanism for most forms of synaptic plasticity.

Our study's results, especially concerning behavior and incidence rates, show similarities and differences with the findings of other prominent studies in the field. (Fregni et al., 2006; Sun et al., 2012), indicating that low-frequency rTMS has a potential therapeutic effect on epilepsy. However, our findings also contrast with the observations (Rotenberg et al., 2009), where the effects of rTMS were found to be minimal or negligible. Such disparities highlight the need for continued research and exploration in this domain

LIMITATIONS

It's crucial to note the limitations in translating our findings directly to clinical applications. The hippocampus, being deep within the brain, presents challenges for direct stimulation with rTMS. While our experiments targeted the hippocampal CA1 region, in humans, rTMS effects are often achieved by targeting well-defined cerebral cortical areas associated with the hippocampus. Future studies could explore the mechanisms by which rTMS affects regions associated with the hippocampus, offering more insights into its potential therapeutic effects in epilepsy-associated cognitive impairments.

CONCLUSION

Our findings demonstrated that low-frequency rTMS had a significant influence on the synaptic function and cognitive performance of lithium-pilocarpine-induced epileptic rats, suggesting its potential as a treatment for epilepsy. This mechanism could be attributed to the neuroprotective effect on synapse-related proteins by increasing the expression of AMPAR and Syp.

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