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Original Research

Effects of low-frequency repetitive transcranial magnetic stimulation on depression- and anxiety-like behaviors in epileptic rats

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Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been considered as a treatment option for depression and anxiety. However, its role in epilepsy comorbid with depression and anxiety is unclear. Therefore, we evaluated whether low-frequency rTMS can alleviate depression- and anxiety-like behavior in epileptic rats. Forty-eight adult rats were allocated at random to four groups: Control, Pentylenetetrazol (PTZ), PTZ-rTMS and PTZ-Sham. The control group received intraperitoneal injections of normal saline, while the other groups received intraperitoneal injections of pentylenetetrazol (35 mg/kg/d) once a day for 15 days. Low-frequency rTMS or sham stimulation were administered to the PTZ-rTMS and PTZ-Sham group, respectively, over the two-week period. The open-field test (OFT), elevated plus-maze test (EPM) and forced swimming test (FST) were carried out before the experiment, on the 8th and 15th day to assess depression- and anxiety-like behavior in the rats. Two weeks of low-frequency rTMS treatment could not impair the increases of seizure severity in epileptic rats. However, relative to the PTZ and PTZ-Sham group, the two-week low-frequency rTMS treatment significantly reduced the immobility time in the forced swimming test and attenuated the progressive decrease in total distance traveled, frequency of rearing, velocity in the open-field test, number of entries in the open arms (%) and the time spent in the open arms (%) in the elevated plus-maze test of the PTZ-rTMS group. We proposed that low-frequency rTMS can benefit epileptic rats via amelioration of comorbid depression and anxiety, but it can not alleviate the seizure severity.

Keywords

Epilepsy; low-frequency rTMS; depression; anxiety; rat

1. Introduction

Epilepsy is a common neurological disorder characterized by unpredictable epileptic seizures and behavior or cognitive impairment. Approximately 50 million people worldwide are suffering from this disorder. It is commonly associated with advanced neurological dysfunctions leading to several psychiatric comorbidities, like depressive and anxiety. Almost one-third of the people with epilepsy (PWE) suffer from depression and anxiety (Cianchetti et al., 2018), and people with temporal lobe epilepsy or refractory epilepsy appear to be at greater risk than those with other types of epilepsy (Beyenburg and Damsa, 2005). Depression and anxiety lead to feelings of stigmatization and suicidal ideation or attempts. These experiences may also increase the adverse effects associated with anti-epileptic drugs and may lead to refractory epilepsy (Hamed, 2011; Smith et al., 2018). As a result, the quality of life of PWE with depression and anxiety may be worse than that of PWE without these disorders (Izci et al., 2016), which makes it imperative to manage the depression and anxiety in PWE appropriately.

Depression and anxiety in PWE often remains untreated due to concerns about anti-depressants potentially lowering the seizure threshold and exacerbating epilepsy (Pisani et al., 2017). Another reason is that many anti-epileptic drugs themselves may increase the risk of depression and anxiety (Grimaldi-Bensouda et al., 2017). Electro-convulsive therapy is another option for depression and anxiety. However, when electro-convulsive therapy is applied to treat PWE, depression and anxiety may be controlled while the frequency of seizures increases (Bog et al., 2018). All of these issues indicate that the treatment of depression in epilepsy has not been met without affecting the seizure threshold.

TMS is a kind of focal non-invasive brain stimulation method, which induces electrical currents through the fluctuating extracranial magnetic field (Tsuji, 1994). The effect of rTMS on neurological function is influenced by many parameters, one of which is stimulus frequency. It is widely believed that low frequency rTMS ($<$1Hz) inhibits neurons, while high frequency rTMS ($>$1Hz) excites neurons (Anand and Hotson, 2002). Low frequency rTMS can produce an inhibitory effect that could conceivably reduce epilepsy-related cortical excitability. However, the evidence for efficacy of rTMS for seizure reduction remains controversial (Joo et al., 2007; Theodore et al., 2002) despite reasonable evidence

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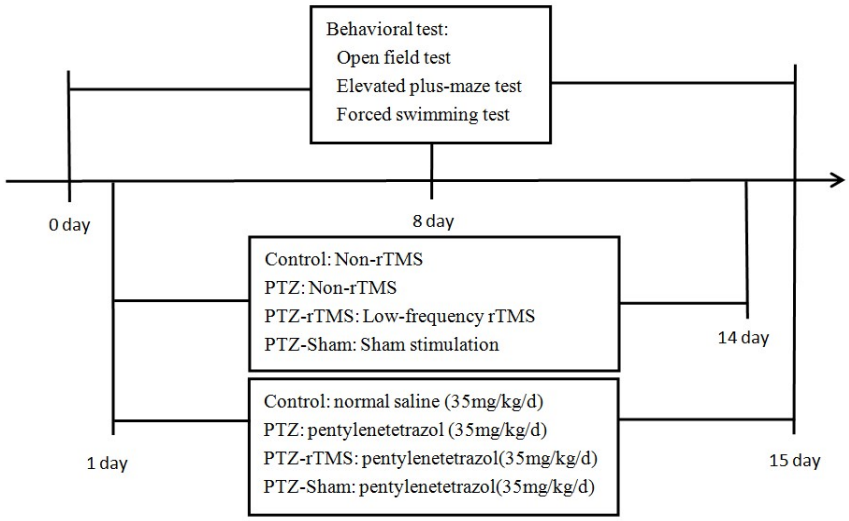

Figure 1. A schematic representation of experimental protocol. Behavioral test were carried out two hours after the PTZ injections on the 8th and 15th day. Low-frequency rTMS and sham stimulation without a magnetic field were delivered 4 hours after daily PTZ injections.

that it can effectively reduce epileptiform discharges (Fregni et al., 2006; Muller et al., 2014; Sun et al., 2012). Furthermore, rTMS is considered to be superior to electro-convulsive therapy (ECT) for the treatment of PWE. In recent years, some studies have found that low frequency rTMS has good efficacy and safety in the treatment of depression and anxiety, and has been applied in clinical practice. (Janicak and Dokucu, 2015; Jassova et al., 2018; Paes et al., 2013). The current view is that rTMS may play an anti-depressant and anti-anxiety role by regulating the activity and regeneration of neurons, affecting the expression of neurotransmitters (Kim et al., 2014; Tan et al., 2013). Its role in epilepsy comorbid with depression and anxiety, however, is unclear. Thus, this study was designed to investigate whether low-frequency TMS can reduce the seizure severity and alleviate the depression- and anxiety-like behavior in epileptic rats.

2. Materials and methods

2.1 Animals

Forty-eight adult male Sprague-Dawley (SD) rats (nearly two-month old, 180--220 g) were used in this study. Rats were obstained from Hunan Slack King of Laboratory Animals Company. Under a 12-h light/dark cycle, rats were kept in an environment-controlled animal care facility (22 $\pm$ 2°C; 50-55% humidity). Food and water were provided ad libitum during the adaptation period of one week before the experimentation.

2.2 Experimental design

A total of 48 animals were randomly allocated to the following four groups: Control (n = 12), PTZ (n = 12), PTZ-rTMS (n = 12), PTZ-Sham (n = 12). On day 0, 8 and 15, we carried out behavioral experiments on all groups to assess depression- and anxiety-like behavior in the following order: OFT, EPM and FST. The behavioral tests on the 8th and 15th day were carried out two hours after the PTZ injections. In the PTZ-rTMS group and the PTZ-Sham group, low-frequency rTMS and sham stimulation without a magnetic field, respectively, were delivered 4 hours after daily PTZ injections (Fig. 1).

2.3 Epilepsy induction

According to the method described by previous studies (Corda et al., 1991; Ito et al., 1977; Mason and Cooper, 1972), we employed the pentylenetetrazol-induced kindling model to induce epilepsy in rats. The control group received intraperitoneal injections of normal saline, while the other three groups received intraperitoneal injections of a subconvulsive dose of pentylenetetrazol (35 mg/kg/d) once a day for 15 days. After PTZ treatment, the behavior of rats was observed for 30 min to assess the seizure severity score according to Racine's scale as follows (Racine, 1972): stage 1, immobility, eye closure, ear twitching, twitching of vibrissae, sniffing, facial, and clonus; stage 2, head nodding associated with more severe facial clonus; stage 3, clonus of one forelimb; stage 4, bilateral clonus accompanied by rearing without falling; and stage 5, generalized clonic seizures accompanied with rearing and falling.

2.4 Low-frequency rTMS treatments

In the PTZ-rTMS group and the PTZ-Sham group, low-frequency rTMS and sham stimulation without a magnetic field, respectively, were delivered four hours after daily injection. The rTMS apparatus was supplied by Wuhan Yiruide Medical Equipment Co., LTD (China). In accordance with the previous study (Tan et al., 2018), we adapted a parallel-wound solenoidal circular coil stimulator (Y064, height = 2.04 cm, 57-mm outer diameter, 18-mm inner diameter, wire cross-section = 18 mm^2, number of turns = 6 layers $\times$ 5 turns/layer = 30 turns), specifically designed for rodents. Rats were hand-restrained in a suitable cloth. When a circular coil is applied, while the maximum magnetic field is below the center of the coil, the maximum induced electric field is below the windings. When treated with rTMS, the circular coil was placed contiguously to the rat scalp. To stimulate the rat brain, we placed the center of the coil over the intersection of the interocular and midline line about 15 mm anterior to the Bregma. In this situation, the windings can cover the area between 13.5 mm posterior and 6 mm anterior to Bregma, which almost covers the whole rat brain. One rTMS session consisted of 41 burst trains,

with each train containing 10 pulses at 0.5 Hz with 2-s inter-train intervals,totaling 410 pulses, lasting 15 min and 2 s. The coil was turned by 90° and placed 5 cm away from the skull for the sham rTMS treatment.

2.5 Forced swimming test

We used a transparent glass circular cylinder about 80-cm-high with a 40-cm inner diameter. The height of the water in the cylinder was maintained at 30 cm, and its temperature was mainted approximately 20 °C. At a depth of 30 cm, rats could not easily stand at the bottom of the apparatus, so it is impossible for rats to modify the effects of the forced swim by producing behavioral adaptation. We placed the rats individually in the cylinder and each test lasted 6 min. The immobility time of rat was analysed and recorded by video recording system (EthoVision XT 11.5) in the last 4 min. Before the next test, the water will be exchanged.

2.6 Open field test

The apparatus used for OFT consisted of a dark grey plastic box (100 × 100 × 35 cm^3). The rat was individually placed in the center of the box and each test lasted 5 min. The total distance traveled, the frequency of rearing and the velocity of the animal were analysed and quantified by video recording system. Before the next test, the apparatus will be cleaned.

2.7 Elevated plus-maze test

The apparatus used for this test consisted of a central platform (10 × 10 cm^2), two enclosed arms (10 × 50 × 50 cm^3) and two open arms (10 × 50 cm^2). The height of the platform is maintained at 50 cm. At this height, rats could not easily jump off the platform, so it is impossible for rats to modify the effects of the test by producing behavioral adaptation. The rat was individually placed on the central platform facing the same side of the open arm at the beginning of the test and each test lasted 5 min. The following data are obtained through video monitoring system: 1) time (s) spent in the open arms as a percentage of total time; 2) the number of entries into the open arms (%). Before the next test, the apparatus will be cleaned.

2.8 Statistical analysis

Date are expressed as the mean ± SEM. All groups passed the Shapiro-Wilk omnibus normality test. Two-way repeated measures ANOVA and Tukey's test were used to determine the intraday significance of differences in the responses between the control, PTZ, PTZ-rTMS, and PTZ-Sham group. Statistical significance was set at P values < 0.05.

3. Result

3.1 Effect of low-frequency rTMS treatments on seizure severity score

There were no epileptic seizures in the control group. Compared with the control group, the seizure severity score of the PTZ group, PTZ-rTMS group, and PTZ-Sham group increased significantly with the increase of injection times ($F_{(14,490)} = 202.07$, $P < 0.001$). However, there was no significant difference in seizure severity between the PTZ group, PTZ-rTMS group, and PTZ-Sham group (Fig. 2).

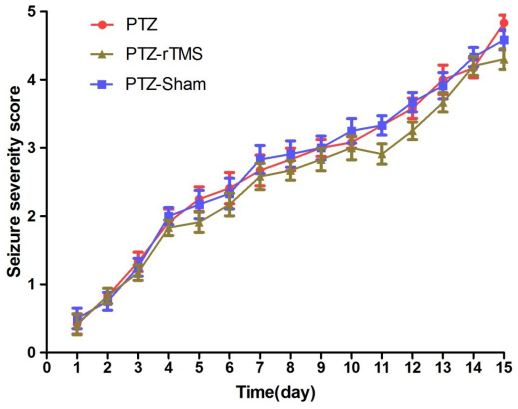

Figure 2. Effect of low-frequency rTMS treatments on seizure severity score. No epileptic seizures were found in the control group, which was not shown here. Date are expressed as mean ± SEM and $P < 0.05$ (Tukey's test) was considered to be significant.

3.2 Effect of low-frequency rTMS treatments on depressive-like behavior in the forced swimming test

As showen in Fig. 3. No significant difference was found in the immobility duration between the groups on day 0 and day 8. However, on day 15, the immobility duration of the PTZ, PTZ-Sham and TMS group increased significantly compared with the control group ($F_{(2,88)} = 19.79$, $P < 0.001$). On day 15, there was a significant difference in immobility duration among the groups ($F_{(3,44)} = 10.4$, $P < 0.001$). The immobility duration of the TMS group was significantly lower than that of the PTZ ($t_{22} = 2.113$, $P = 0.04$) and PTZ-Sham group ($t_{22} = 2.652$, $P = 0.015$), yet it was higher than that of the control group ($t_{22} = -2.693$, $P = 0.013$), and there was no difference between the PTZ and PTZ-Sham group ($t_{22} = -0.286$, $P = 0.779$).

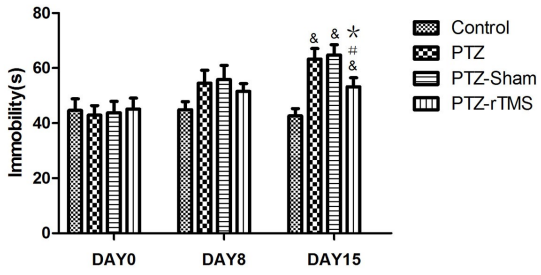

Figure 3. Effect of low-frequency rTMS treatments on depressive-like behavior in the forced swimming test. Date are expressed as mean ± SEM and $P < 0.05$ (Tukey's test) was considered to be significant. *: as compared to PTZ group; #: as compared to PTZ-Sham group; &: as compared to control group.

3.3 Effect of low-frequency rTMS treatments on depressive-like behavior in the open field test

At day 0, there was no significant difference in the distance traveled, rearing frequency and velocity among the four groups. A significant difference among the four groups was, however, found at day 8 and day 15 ($F_{(2,88)} = 44.48$, $P < 0.001$; $F_{(2,88)} = 42.45$,

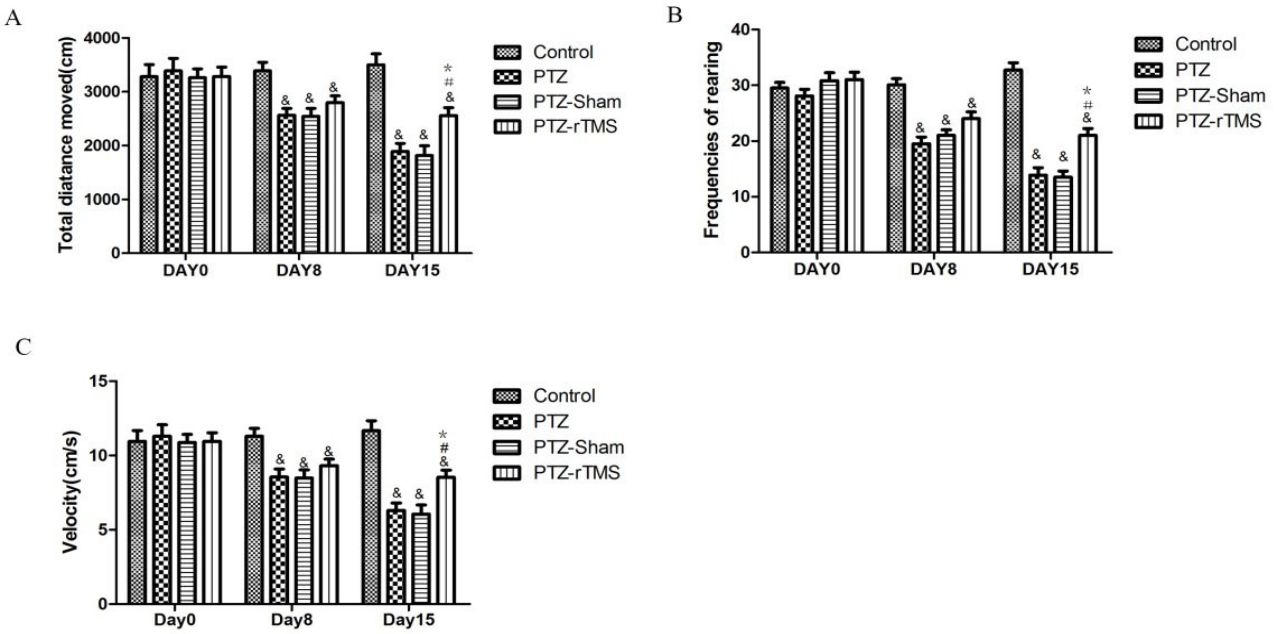

Figure 4. Effect of low-frequency rTMS treatments on depressive-like behavior in the open field test. Total distance moved (A), frequencies of rearing (B) and velocity (C) are shown. Date are expressed as mean ± SEM and $P < 0.05$ (Tukey's test) was considered to be significant. *: as compared to PTZ group; #: as compared to PTZ-Sham group; &: as compared to control group.

$P < 0.001$; $F_{(2,88)} = 41.45$, $P < 0.001$). On the 8th and 15th day, the distance traveled ($F_{(3,44)} = 7.73$, $P < 0.001$; $F_{(3,44)} = 20.52$, $P < 0.001$), rearing frequency ($F_{(3,44)} = 7.71$, $P < 0.001$; $F_{(3,44)} = 20.15$, $P < 0.001$, and velocity ($F_{(3,44)} = 7.59$, $P < 0.001$; $F_{(3,44)} = 20.3$, $P < 0.001$) in the PTZ-rTMS, PTZ, and PTZ-Sham group were significantly lower than those in the control group. But on the 8th day, there were no significant differences in the distance traveled (PTZ-rTMS *vs.* PTZ: $t_{22} = 1.29$, $P = 0.212$; PTZ-rTMS *vs.* PTZ-Sham: $t_{22} = 1.30$, $P = 0.208$; PTZ *vs.* PTZ-Sham: $t_{22} = 0.10$, $P = 0.92$), rearing frequency (PTZ-rTMS *vs.* PTZ: $t_{22} = 1.38$, $P = 0.181$; PTZ-rTMS *vs.* PTZ-Sham: $t_{22} = 0.817$, $P = 0.423$; PTZ *vs.* PTZ-Sham: $t_{22} = -0.607$, $P = 0.55$), and velocity (PTZ-rTMS *vs.* PTZ: $t_{22} = 1.286$, $P = 0.213$; PTZ-rTMS *vs.* PTZ-Sham: $t_{22} = 1.301$, $P = 0.208$; PTZ *vs.* PTZ-Sham: $t_{22} = 0.103$, $P = 0.902$) between the PTZ-rTMS, PTZ, and PTZ-Sham group. On day 15, the distance traveled, rearing frequency, and velocity of the PTZ-rTMS group were significantly higher than those of the PTZ ($t_{22} = 3.162$, $P < 0.05$; $t_{22} = 4.163$, $P < 0.05$; $t_{22} = 3.162$, $P < 0.05$), and PTZ-Sham group ($t_{22} = 3.081$, $P < 0.05$; $t_{22} = 7.112$, $P < 0.05$; $t_{22} = 3.081$, $P < 0.05$). No significant difference between the PTZ and PTZ-Sham group was found ($t_{22} = 3.320$, $P = 0.751$; $t_{22} = 0.072$, $P = 0.944$; $t_{22} = 0.320$, $P = 0.751$) (Fig. 4).

3.4 Effect of low-frequency rTMS treatments on anxiety-like behavior paradigms in the elevated plus-maze test

On day 0, there were no significant differences in the number of entries into the open arms (%) and the time spent in the open arms (%) among the groups, but there was significant difference in the number of entries into the open arms (%) and the time spent in the open arms (%) among the groups on days 8 and 15 ($F_{(2,88)} = 38.41$; $F_{(2,88)} = 23.01$, $P < 0.001$). On days 8 and 15, the number of entries in the open arms (%) ($F_{(3,44)} = 3.38$; $F_{(3,44)} = 11.11$; $P < 0.001$) and the time spent in the open arms (%) ($F_{(3,44)} = 7.68$; $F_{(3,44)} = 24.51$, $P < 0.001$) in the PTZ-rTMS, PTZ and PTZ-Sham group were lower than in the control group. On day 8, however, there was no statistical difference between the PTZ-rTMS and PTZ-Sham group ($t_{22} = 3.321$, $P = 0.743$; $t_{22} = 0.885$, $P = 0.386$). On day 15, the number of entries into the open arms (%) and the time spent in the open arms (%) in the PTZ-rTMS group were higher than those in the PTZ ($t_{22} = 2.479$, $P < 0.05$; $t_{22} = 3.078$, $P < 0.05$), and PTZ-Sham group ($t_{22} = 2.331$, $P = 0.029$; $t_{22} = 2.915$, $P = 0.008$), yet there was no statistical difference between the PTZ and PTZ-Sham group ($t_{22} = 0.147$, $P = 0.884$; $t_{22} = 0.183$, $P = 0.856$) (Fig. 5).

4. Discussion

Our study aimed to understand the effect of low-frequency rTMS on depression- and anxiety-like behavior in epileptic rats. The results suggest that depression- and anxiety-like behavior were present in the epileptic animals, and that low-frequency rTMS treatment for 2 weeks may have ameliorated this behavior.

rTMS is a brain stimulation method widely used in brain function research, which has the characteristics of focal non-invasive. It has made significant progress in neuropsychiatric and rehabilitation fields such as depression, anxiety, cognitive impairment (Padala et al., 2018), Parkinson's disease (Yokoe et al., 2018) and epilepsy (Chen et al., 2016). In some countries, is regarded one of the standard treatments for depression. Both high-frequency rTMS and low-frequency rTMS have good efficacy and safety, but the efficacy and safety of rTMS in the treatment of epilepsy remain controversial. In additon, no studies have evaluated the effects of low-frequency rTMS on epilepsy

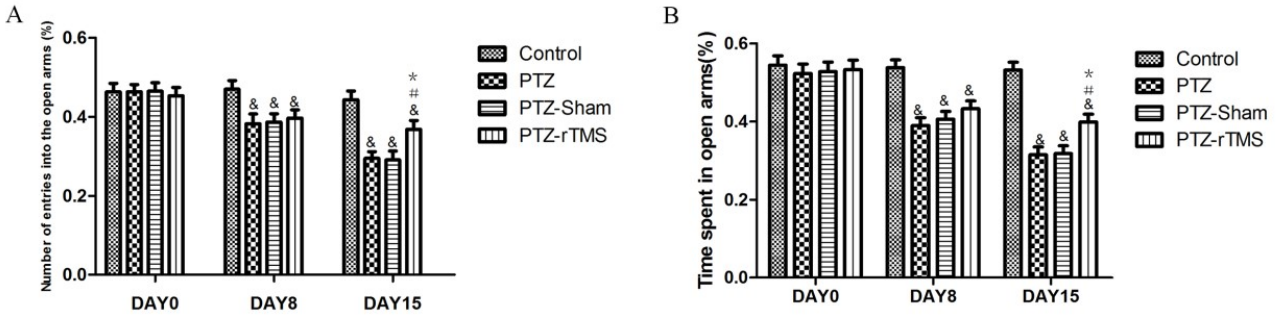

Figure 5. Effect of low-frequency rTMS treatments on anxiety-like behavior paradigms in the elevated plus-maze test. Number of entries in the open arms (%) (A) and the time spent in the open arms (%) (B) are shown. Date are expressed as mean ± SEM and $P < 0.05$ (Tukey's test) was considered to be significant. *: as compared to PTZ group; $^{\#}$: as compared to PTZ-Sham group; $^{\&}$: as compared to control group.

comorbid with depression and anxiety. Therefore, for the first time, in the pentylenetetrazol-kindled epilepsy model in rats, we explored whether low-frequency rTMS can alleviate the comorbid depression- and anxiety-like behavior in these epileptic rats. Pentylenetetrazol-induced kindling is a well-established animal model of temporal lobe epilepsy, which is mainly used to uncover the neurobiology of associated comorbidities. In humans, temporal lobe epilepsy is often associated with depression and anxiety comorbidity (Bragatti et al., 2010), which further proves the applicability of this animal model. In this study, an subconvulsive pentylenetetrazol doses were injected every 24 hours to challenge the epileptic animals and to evaluate the effect of low frequency rTMS on seizure severity score. Anti-depressant and anti-anxiety effects were evaluated employing the FST, OFT, and EPM, which are well-established behavioral tests in rodents.

Our results suggested that two weeks of low-frequency rTMS treatment could not impair increases of seizure severity in epileptic rats, which is inconsistent with previous studies (Kinoshita et al., 2005; Yadollahpour et al., 2014). In Kinoshita's study, a figure-of-eight coil was used, and the stimulation areas selected were where the most prominent epileptiform discharge had been recorded by long-term video electroencephalogram monitoring. Yadollahpour et al. (2014) found that application of circular coil showed a weaker anti-epileptogenic effect compared with the figure-of-eight coil. We speculate that the choice of coil type and stimulation area may be one of the reasons for the difference in study findings, and that the potential mechanism may be closely related to the amygdala. Recently, researchers have revealed that the amygdale pays a preponderant role in the pathogenesis of epilepsy (Cota et al., 2016). Although magnetic stimulation can cover the amygdala in our study, the circular coil has a disadvantage of poor targeting compared with a figure-of-eight coil. We speculate that the amygdala of rats in this study has not been effectively stimulated so the low-frequency rTMS treatment in this study could not impair increases of seizure severity in epileptic rats. Compared with the PTZ and PTZ-Sham group, the two-week low-frequency rTMS treatment significantly reduced the immobility time of the PTZ-treated rats in the FST and reduced the progressive decrease in distance traveled, rearing frequency, velocity, the time spent in the open arms (%) and number of entries into the open arms (%) in the OFT and EPM. The results also confirmed that epilepsy often cooccurs with depression and anxiety. Researchers have suggested many mechanisms to elucidate the pathophysiological relationship between epilepsy, depression, and anxiety. Abnormal structural changes, amygdale dysfunction, interleukin-1b, cerebral glucose metabolism, monoamine pathways, and the hypothalamic-pituitary-adrenal axis may all play potential roles in the pathogenesis of these conditions (Kwon and Park, 2014). In addition, previous studies have confirmed the anti-depressant and anti-anxiety effects of low-frequency rTMS (Janicak and Dokucu, 2015; Jassova et al., 2018; Paes et al., 2013), but this is the first time that this effect has been found in an animal model of epilepsy.

Previous studies have found that the anti-depressant and anti-anxiety effects of low-frequency rTMS may be related to the following mechanisms: low-frequency rTMS treatment can alter the expression levels of neurotransmitters and receptors in the brain, activate the cerebellum-thalamic-cortical pathway and the limbic system-thalamic-cortical neural network, remodel synaptic structure, inhibit cytokines, and regulate neuroendocrine systems (Chervyakov et al., 2015; Lisanby and Belmaker, 2000). In this study, behavioral studies have found the effects of low-frequency rTMS on comorbid depression- and anxiety-like behavior in epileptic rats. The next step is to further explore the underlying complex mechanisms.

One limitation of this study is that we only evaluated the effect of low-frequency rTMS on seizure severity, but did not record its impact on kindling rate, seizure duration, and latency to seizure. Future research should evaluate the anti-epileptogenic effect of low-frequency rTMS more comprehensively. Another limitation is that our study is based solely upon behavioral assessment. It is warranted to carry out research on neuroelectrophysiology and related biological markers in the future.

5. Conclusion

Based on our results, we proposed that low-frequency rTMS can benefit epileptic rats via amelioration of comorbid depression and anxiety, but it cannot alleviate the seizure severity. Therefore, we suggest that low-frequency rTMS can be used as an adjunctive treatment with anti-epileptic drugs and provide some ideas and reference for the treatment of epilepsy comorbid with depression and anxiety.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Renmin Hosptial of Wuhan University (No.WDRM 20171201).

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Conflict of interest

The authors declare no conflict of interest.

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