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Research report

Antidepressant efficacy of high and low frequency transcranial magnetic stimulation in the FSL/FRL genetic rat model of depression

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HIGHLIGHTS

- The total impulse amount is equivalent in both the high frequency and the low frequency rTMS groups.
- This enables us to exclude the impulse amount as a confounder and to focus on the effect of the frequency stimulation.
- We examine the antidepressant efficacy in a relevant animal model and the differences in choice of stimulus variables.
- The results are promising, but the optimal stimulus parameters need to be validated to gain clinical effect.

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ABSTRACT

Repetitive Magnetic Stimulation (rTMS) has appeared to be a potential non-invasive antidepressant method, which implies non-convulsive focal stimulation of the brain through a time varying magnetic field. The antidepressant potential of rTMS has been supported by animal studies showing a number of interesting similarities between magnetic stimulation and electroconvulsive stimulation (ECS). Despite these positive results, this method still contains many unknown issues. Importantly, there are fundamental uncertainties concerning the optimal combination of stimulus parameters (frequency, intensity, duration, and number of pulses) to obtain an antidepressant effect. Therefore, the present study aimed to qualify the choice of rTMS stimulus frequency in a well-validated genetic animal model of depression, the FSL/FRL rats. We compared the antidepressant effect of low frequency, high frequency rTMS and ECS to sham treatment in FRL and FSL rats using 6 parallel groups. We used the Forced Swim Test and the Open Field Test to screen the depression-like state in rats. We found that both the high frequency and the low frequency rTMS resulted in a significant antidepressant effect. However, this effect was inferior to the effect of ECS. The low frequency and high frequency groups, which received the same total impulse load and stimulus intensity, did not differ with respect to antidepressant efficacy in this study. In conclusion, this study provides robust evidence that both rTMS interventions are efficacious, although not as efficient as ECS.

1. Introduction

Previous research indicates that the antidepressant effect of rTMS is associated with specific stimulation of the dorsolateral prefrontal cortex [1]. Due to fewer side effects, rTMS may be a potential alternative to ECT. Both ECT and rTMS expose the brain to an electric current. However, ECT is associated with a global cerebral stimulation elicited by an epileptic seizure whereas the antidepressant effect of rTMS does not depend on seizure activity and consequently requires no anaesthesia. In addition, rTMS does not seem to be associated with cognitive disturbances. However, clinical research on the issue points to rTMS not as a first line substitute for ECT but rather as a treatment option for depressed patients intolerant to other types of treatment or not accepting ECT [2].

The antidepressant potential of rTMS has been supported by animal studies showing a number of interesting similarities between magnetic stimulation and ECS (the animal equivalent of ECT)

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; ECS, electroconvulsive stimulation; FSL/FRL, flinders sensitive line flinders resistant line rats; FST, forced swim test.

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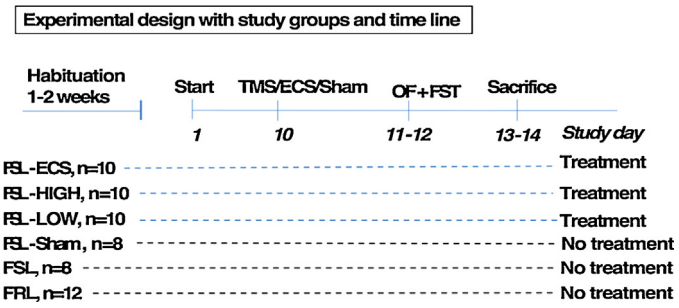

Fig. 1. An illustration of the time-line of the study. Approximate study days and group sizes with/without treatment are imaged.

[3–7]. Rats exposed to the two treatment modalities have shown identical changes in antidepressant behaviours and neurophysiological changes. Similar changes have shown to be associated with antidepressant effect of ECT and conventional antidepressants [4]. Furthermore, like ECT, low frequency rTMS has been demonstrated to inhibit the amygdala kindled seizures in animal studies, a phenomenon known to be of pathophysiological significance in depressive illness and probably of major importance to the antidepressant mechanism of ECT [8].

Currently, the rTMS method is uncertain. We do not know the optimal combination of stimulus parameters (frequency, intensity, duration and number of pulses) to obtain an antidepressant effect. The stimulus frequency probably plays a key role in the mechanisms of action of rTMS [3,9–11]. Previous animal studies have shown that low frequency rTMS is associated with long-term inhibition of neuronal activity (long-term depression), whereas high frequency stimulation is followed by prolonged activation (long-term potentiation) [12–14]. Since comparing multiple rTMS frequencies in clinical studies is difficult because of the large sample seize required and the ethical constraints in the recruitment of patients for such studies, we could directly and efficiently examine multiple rTMS frequencies on a large group of animals using an animal model of depression (FSL/FRL). We compared the antidepressant effect of low and high frequency rTMS with electroconvulsive stimulation (ECS) as well as with Sham-stimulation in the Flinders Sensitive Line (FSL) rat, a genetic animal model of depression [15]. The study was carried out with the overall aim of qualifying the choice of rTMS stimulus frequency. First, as a behavioural examination of the possible antidepressant effect of rTMS using the modified Porsholt's swim test (FST) and the Open Field test and second, as a comparison of the efficacy of the two frequency rTMS modalities.

2. Materials and methods

2.1. Animals

Male Flinders Sensitive and Resistant Line rats (FSL/FRL, mean age 66, 4 ± 8 days) were derived from our colony at Translational Neuropsychiatry Unit (TNU), Aarhus University, Risskov, Denmark. The animals were housed individually at 20 °C ± 2 °C in a 12-h light/dark cycle (light on at 6.00 a.m.). Tap water and chow pellets were available ad libitum, and the animals were kept two per cage. All animal procedures were accepted by the Danish National Committee for Ethics in Animal Experimentation (2012-15-2934-00254).

2.2. Study design

Fifty-eight rats (46 FSL 12 FRL) divided into six groups (see Fig. 1) prior to testing were used. The six groups consisted of three intervention groups (all FSL) and three control groups (2 FSL and 1 FRL). The intervention groups consisted of ECS, high frequency rTMS, and low-frequency rTMS. The control groups were rTMS sham, and animals were only subjected to daily handling (FSL and FRL).

2.3. Treatments: rTMS

A Magstim Rapid stimulator, MEQNordic, Ltd Withland, UK was used for rTMS, using a double coil (s1165-00, MEQNordic) with an outer diameter of 25 mm for stimulation. The type of coil and the experimental set-up were chosen to achieve a stimulation pattern analogous to the stimulation pattern used in patients in standard clinical treatment [2,16]. During treatment, the coil was placed tangentially to the head of the animal with the center of the coil held immediately over the stimulus area, allowing no space between the coil and the skin of the animal. In the present study we positioned the coil to allow maximal field intensity over the prefrontal cortex. The animals were handheld throughout their individual treatments.

Motor thresholds were determined by visual inspection of the lowest degree of stimulation being able to release bilateral movement of the limbs of the animal. A qualified TMS expert assisted in determination of the threshold before beginning the experiment. Eight FSL animals were used to determine the exact response for motor response, resulting in a threshold value/median power level of 70% (range ±2.6). A distance below 1 cm between the coil and the animal's scalp was accepted.

The high and low stimulation regimes were computerized and separated in two runs.

In the high frequency group (n = 10), each animal received two 9 s 20 Hz stimulus trains at 110% fixed magnetic field intensity relative to its resting motor threshold, and an intertrain interval of 40 s. We conducted one rTMS session per day in 10 days, a total of 3600 magnetic pulses.

The low frequency group (n = 10) received rTMS using a stimulus model which has previously revealed a significant antidepressant effect in a clinically controlled, randomized outpatient trial [2]. Briefly, the animals received two 180-s 1 –Hz trains delivered at an intensity of 110% of the motor threshold with a 60 s. intertrain interval. The sessions were given for 10 days. In total, the animals received 3600 magnetic pulses per day.

The handling of the Sham group (acoustic stimulation) (n = 8) was identical to that of the actively stimulated animals, but with the coil being switched off and placed 10 cm above the head of the rat. The Sham group was exposed to the digitally recorded sound of active rTMS.

The ECS was given via ear-clip electrodes without anaesthetics (UGO Basile, Biological research apparatus, Italy). The stimulation parameters for the ECS apparatus were: electrical current 90 mA, shock duration 0.5 s, pulse width 0.5 ms and frequency 100 pulses/s. The manufacturer's instructions were followed carefully. The condition of the animals after the ECS treatment was closely monitored immediately after treatment (30–60 min after ECS, 3 h and 24 h later). The seizure activity was either tonic or clonic convulsions.

2.4. Behavioural testing

The studies were initiated with 1–2 weeks of scheduled habituation for the animals. The habituation period consisted of adjustment to the new surroundings, i.e. the stimulation sound of the TMS apparatus, and the handling experience by the experimenter. All behavioural testing took place between 09.00 and 13.00 a.m. in an area of the laboratory free from noise and other disturbances. The animals were moved to the experimental room to habituate one