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Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat

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ABSTRACT

Objective: To test the anticonvulsive potential of a range of repetitive transcranial magnetic stimulation (rTMS) frequencies by novel methods for simultaneous EEG and rTMS in a rat seizure model.
Methods: Seizures were triggered by intraperitoneal kainic acid (KA; 10 mg/kg). Rats ($n = 21$) were divided into three groups in which individual seizures were treated with rTMS trains at one of three frequencies: 0.25, 0.5 or 0.75 Hz. EEG was continuously viewed by an operator who identified each seizure onset. Consecutive seizures in each animal were (1) treated with *active* rTMS, (2) treated with *sham* rTMS, or (3) were *untreated*. EEG was re-analyzed post hoc by visual inspection, and seizure durations were compared within and between treatment groups.
Results: KA-induced seizures were abbreviated by 0.75 Hz ($P = 0.019$) and 0.5 Hz ($P = 0.033$) *active* EEG-guided rTMS. In contrast, neither *active* 0.25 Hz rTMS nor the control conditions affected seizure duration ($P > 0.2$).
Conclusions: We demonstrate that EEG-guided rTMS can suppress seizures in the rat KA epilepsy model, and that the effect is frequency dependent, with 0.75 and 0.5 Hz rTMS being superior to 0.25 Hz rTMS.
Significance: These data support the use of rat seizure models in translational research aimed at evaluation and development of effective rTMS anticonvulsive protocols. We also offer a proof of principle that real-time analysis of EEG can be used to guide rTMS to suppress individual seizures.

1. Introduction

Transcranial magnetic stimulation (TMS) is a method for noninvasive focal cortical stimulation that is based on Faraday's principle of electromagnetic induction where small intracranial electrical currents are generated by a powerful fluctuating extracranial magnetic field (Barker et al., 1985; Kobayashi and Pascual-Leone, 2003). In the recent years, TMS has emerged as a potential therapeutic tool in epilepsy (Theodore, 2003). The widest use of TMS in epilepsy is based on the capacity of interictal prolonged trains of low frequency ($\leqslant$1 Hz) repetitive TMS (rTMS) to induce a lasting reduction in cortical excitability, thereby raising seizure threshold and reducing seizure frequency (Theodore et al., 2002; Fregni et al., 2006; Santiago-Rodriguez et al., 2008). The mechanisms for increasing seizure threshold by interictal rTMS are not completely characterized, but are likely similar to those of long-term depression (LTD) induced by electrical stimulation at low frequencies (Dudek and Bear, 1992; Kandel, 2001; Hallett, 2007).

In addition to altering seizure threshold by interictal trains of low frequency rTMS, there is also the potential for ictal rTMS is to terminate ongoing individual seizures. For abortive seizure therapy, rTMS anticonvulsive mechanisms may relate more to its capacity to interrupt ongoing neuronal activity as for instance can be seen with functional impairment of cortical function in human subjects (Amassian et al., 1989; Cohen et al., 1997). Ictal rTMS has been applied clinically in several cases of human epilepsia partialis continua (EPC), with seizures terminated in approximately half of the subjects (Graff-Guerrero et al., 2004; Misawa et al., 2005; Morales et al., 2005; Rotenberg et al., 2008). However, interpretation of data from these few human trials is limited since a broad range of rTMS protocols were used with a small and heterogeneous population of patients. Thus, the differential effect of altering ictal rTMS paradigms has not been formally tested, and remains a gap in knowledge.

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The partial efficacy of ictal rTMS in humans justifies translational use of animal seizure models systematic testing of rTMS protocols in groups of homogeneous subjects. Accordingly, we developed methods for high quality EEG combined with rTMS in seizing rats (Ives et al., 2006), and evaluated whether (1) rTMS could reliably attenuate ongoing ictal discharges, and (2) whether such effects are dependent on rTMS frequency in the rat intraperitoneal kainate (KA) seizure model. We also tested whether EEG-guided "closed loop" responsive rTMS that is administered when a seizure is detected on EEG is practical and effective in suppressing ictal discharges.

2. Materials and methods

2.1. Animals

Male Long Evans rats were used in this study (100–175 g). All animals were housed in a temperature-controlled animal care facility with a 12-h light-dark cycle. All procedures were approved by and in accordance with the guidelines of the Animal Care and Use Committee at Children's Hospital (Boston, MA) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize animal suffering and the number of animals used.

2.2. Seizure induction

Seizures were provoked by intraperitoneal KA (10 mg/kg) in 21 young male (100–175 g) Long Evans rats. KA resulted in the onset of relatively frequent discrete seizures in these animals. All seizures were apparent on EEG, and progressed through expected clinical stages from behavioral arrest to tonic–clonic convulsion (Ben-Ari, 1985; Hellier et al., 1998). Only the EEG response to rTMS was measured for the purposes of this study where the overall aim was to obtain a quantitative measure of the effects EEG-guided rTMS on KA-induced seizure duration.

2.3. EEG

All rats were unanesthetized and gently restrained on a platform with two broad Velcro® straps (Fig. 1) positioned over the torso behind the forelimbs and in front of the hindlimbs. Once the straps were secured, the animal was confined to the platform but retained full range of motion of the head, limbs and tail. An advantage of this gentle restraint is that it enables a continuous view of the animals' head and extremities, and thus clinical seizures can be observed. The platform restraint allows easy access to the rat's head for EEG electrodes and the TMS coil. The rats tolerate this restraint with minimal discomfort during placement, and no signs of distress afterward.

Continuous EEG was acquired with three thin silver/silver-chloride Teflon coated EEG subdermal wire electrodes [Ives EEG Solutions, Ontario] (impedance $12.5 \pm 6.5\ k\Omega$; mean ± SD), with a reference contact positioned over the dorsal snout at midline, and two active contacts in the scalp over the parietal regions bilaterally. A fourth electrode was placed in the skin of the torso to record EKG. We used the MRI-compatible subdermal wire electrodes, as pilot studies in our laboratory showed that these provide a consistent signal and are neither heated nor displaced by rTMS. Rats tolerated the electrodes without signs of local pain or discomfort after initial subcutaneous placement.

To minimize rTMS artifact, and to allow real-time assessment of the ictal pattern by the TMS operator, the EEG signal was processed through a limited slew rate pre-amplifier, according to our earlier-described methods (Ives et al., 2006). The EEG signal was digitized at 200 Hz, filtered 1–70 Hz, and displayed in a bipolar montage for online assessment and post hoc review (Gamma Reviewer, Grass-Telefactor, Providence, RI).

2.4. rTMS

EEG-guided TMS was delivered with a Cadwell MES 10 stimulator (Cadwell Laboratories, Kennewick, WA) and a modified 8 cm hand-held figure-8 coil centered overhead (Fig. 1). The stimulator and coil were essentially identical to those used in human work except that the casing around the capacitor and coil was removed in order to facilitate cooling and to enable longer rTMS trains without overheating. Maximal output of the stimulator was 2.1 T at 100% machine output (MO), identical to that used in human studies. TMS timing was recorded with two wire electrodes positioned near (but not in contact with) the animal. Signal from these leads bypassed the pre-amplifier, and was filtered 30–100 Hz to accentuate the high frequency and high amplitude artifact produced by each TMS pulse (Fig. 2). After KA injection, baseline EEG was collected for 60 min prior to start of rTMS. At 60 min following KA injection, EEG-guided rTMS was initiated.

An operator positioned to view the real-time EEG manually triggered the stimulator at the onset of an individual ictal EEG discharge. For each rat, rTMS was applied for seizures occurring in the period between 60 and 180 min after KA injection, which represented a period of stable intermittent seizure duration (see Section 3). This allowed us to apply different stimulation paradigms during a relatively constant electrographic state.

Consecutive seizures in each animal were treated per one of three conditions: (1) *active* rTMS where the stimulating coil was discharged at 90% MO and positioned parallel with the dorsum of

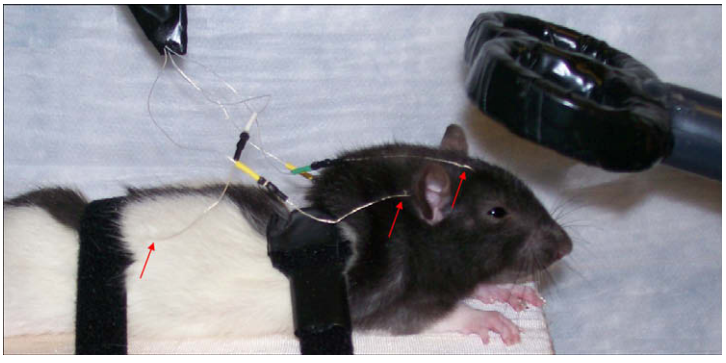

Fig. 1. *Rat with torso restraint.* Torso restraint permits clinical observation of seizures and full access of head to the TMS coil. Access to the rat's tails for *sham* TMS is also available. Subdermal wire EEG electrodes (arrows) were placed after restraint. In our experience, unanesthetized rats tolerate the restraint and electrode placement with minimal discomfort.

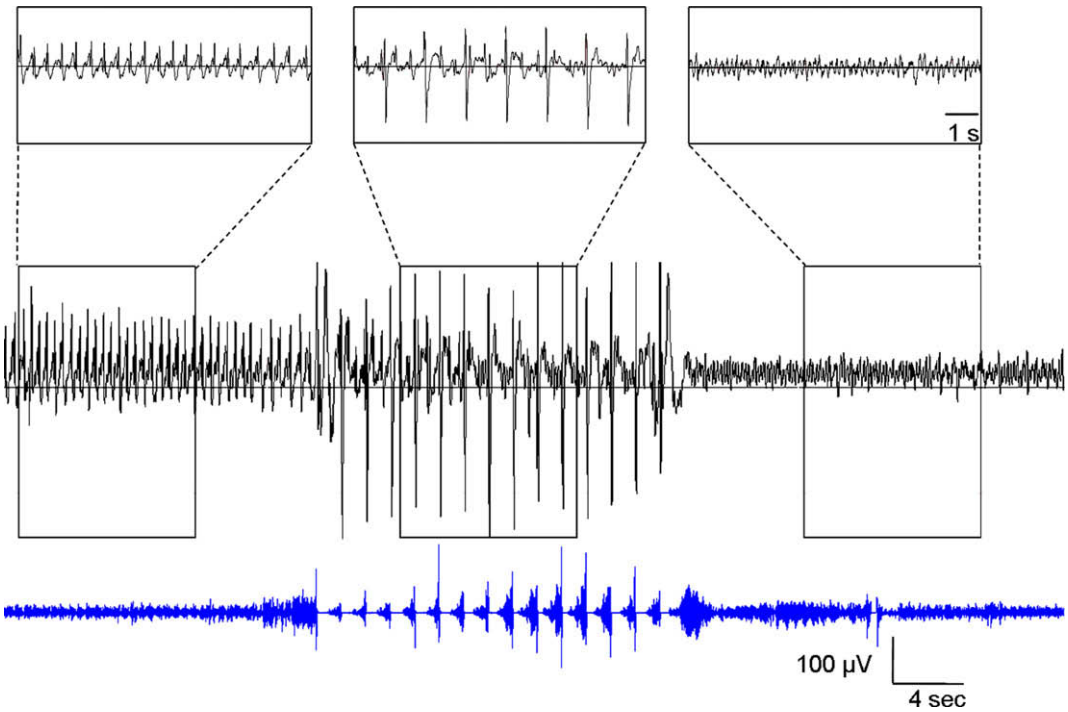

Fig. 2. *Seizure treated with rTMS.* A 60-s tracing shows a representative KA-triggered seizure terminating with a 0.75 Hz rTMS train. Typical spikes of KA seizures (left inset) were readily recognized by the TMS operator. Once a seizure was detected, rTMS (main figure, bottom tracing) was initiated, and continued until spikes were no longer evident between the prominent rTMS artifact (center inset). After rTMS the EEG returned to baseline (right inset).

the head, centered and in light contact with scalp and with the handle oriented away from the head (2) *sham* rTMS where the coil was discharged in contact with the tail at 70% MO, or (3) *untreated* where no rTMS was delivered. The purpose of *sham* stimulation was to control for the noise and somatosensory input associated with rTMS.

Stimulus intensity for *active* rTMS was based on pilot data which identified motor threshold at approximately 80% MO, a high value relative to human TMS studies which likely reflects poor electromagnetic coupling between a large coil and a small rodent head (Liebetanz et al., 2003). For purposes of this study, we chose to increase MO to 90% to accommodate for the extra distance between the magnetic coil and the limbic structures which lie deeper than the motor cortex, and are therefore likely exposed to lower amplitudes of induced current as suggested by recent electric field models in the rat head (Zheng et al., 2005).

To compare the anticonvulsive potential between a range of low frequencies, rats were divided into three treatment groups: 0.25 Hz (n = 8 rats), 0.5 Hz (n = 6 rats) and 0.75 Hz (n = 7 rats). Each rat received *active* or *sham* rTMS at only one frequency, depending on group assignment. Each animal served as an internal control where consecutive seizures were treated with rTMS of a single frequency (0.25, 0.5 or 0.75 Hz, as above) alternating with *untreated* seizures and with *sham* frequency-matched rTMS. For each seizure where *active*or *sham* rTMS was delivered, stimulation was continued until the end of the seizure on EEG.

2.5. EEG analysis

All ictal EEG segments were reviewed by a clinical neurophysiologist (AR) post hoc by visual inspection to identify the timing of each seizure onset and termination. Seizures were operationally defined as paroxysmal rhythmic sharp waves or spikes occurring in runs of >10 s.

In each of the three rTMS frequency groups (0.25, 0.5 and 0.75 Hz), average durations of seizures treated with *active* or *sham* rTMS were compared separately to average durations of *untreated* seizures with a two-tailed t-test. Additionally, per rTMS frequency, all seizure durations were normalized to average duration of untreated seizures in that group, and the values (% duration of untreated control) were compared by one-way ANOVA.

Only seizures with clear EEG onsets and terminations were considered for analysis. Those seizures where the timing of the initial or final components was ambiguous (such as those where spikes were obscured by motion artifact) were eliminated form analysis.

3. Results

3.1. KA-induced EEG seizures

As reported widely, the response to KA was subject to individual variation. Generally, seizures were evident on EEG within 30 min after injection. The electrographic component of initial untreated seizures that occurred within 60 min of KA injection was brief (39 ± 7 s; mean ± SEM)). However, seizure duration tended to reach a steady state (121 ± 4 s) at 60–180 min after KA injection. Beyond 180 min, seizures generally tended to be prolonged (>300 s) or continuous. For this reason, we limited the rTMS application to the time window of 60–180 min, where individual seizure duration was relatively constant.

3.2. Online seizure detection and EEG-guided TMS

Our experimental closed-loop setup enabled the operator to view the real-time EEG, rapidly identify seizures and initiate rTMS. A representative KA-induced seizure abbreviated by 0.75 Hz *active* rTMS is shown in Fig. 2. Based on similar ictal EEG changes, the operator would trigger the TMS device while positioning the coil over the animal's head or tail. The TMS output signal was recorded

in dedicated channels, and thus was available for post hoc review. *Active* or *sham* positioning of the coil was also event-marked on the EEG. The average time to TMS stimulation (*active* or *sham*) per seizure was (10.4 s ± 8.1 s, mean ± SD), and this did not significantly differ between the *active* and *sham* treatment conditions.

3.3. Seizure suppression by EEG-guided rTMS in KA-treated rats

EEG-guided rTMS trains at the higher frequency paradigms (0.5 and 0.75 Hz) resulted in significant decreases in seizure duration. However, seizure duration was not affected by 0.25 Hz rTMS.

Average duration of seizures treated with *active* 0.75 Hz rTMS ($n = 28$; 49 ± 5 s, mean ± SEM) was significantly shorter than average *untreated* seizure duration in the 0.75 Hz group ($n = 113$; 76 ± 5 s) ($t = 2.41$; $P = 0.019$). In contrast, seizure duration for *sham* 0.75 Hz rTMS ($n = 30$; 74 ± 9 s) did not differ significantly from *untreated* control ($t = 0.18$; $P = 0.86$). Similarly, the average duration of seizures treated with 0.5 Hz *active* rTMS ($n = 34$; 65 ± 5 s) was significantly shorter than average *untreated* seizure duration in the 0.5 Hz group ($n = 65$; 90 ± 8 s) ($t = 2.16$; $P = 0.033$), whereas average duration of seizures treated with *sham* 0.5 Hz rTMS ($n = 30$; 100 ± 12 s) did not differ from untreated control ($t = 0.71$; $P = 0.48$). In contrast to the 0.5 and 0.75 Hz rTMS paradigms, average seizure durations of 0.25 Hz *active* ($n = 26$; 87 ± 14 s) or 0.25 Hz *sham* ($n = 25$; 100 ± 15 s) rTMS did not differ significantly from *untreated* ($n = 73$; 82 ± 7) control ($t < 0.65$; $P > 0.51$).

Fig. 3 shows the data expressed as the percent of average *untreated* control seizure duration in each rTMS frequency group (% untreated control ± SEM). One-way ANOVA (within group df = 2) performed for each frequency group reveals selective reductions of average seizure frequency by *active* 0.75 Hz (64 ± 7%; $F = 3.60$; $P = 0.030$) and *active* 0.5 Hz (72 ± 5%; $F = 3.39$; $P = 0.037$), but no significant reduction of seizure duration by *active* 0.25 Hz rTMS (106 ± 17%; $F = 0.77$; $P > 0.2$). *Sham* stimulation did not result in seizure reduction in any of the three frequency groups.

In addition, given the inherent variability in the duration of KA-induced seizures in rats, we repeated the one-way ANOVA with data restricted to values falling within 95% CI of mean seizure duration for each treatment group. There, reduction in average seizure duration (mean % untreated control ± SEM) by 0.5 Hz *active* rTMS (73 ± 5%; $F = 9.01$; $P = 0.003$), and in the 0.75 Hz *active* rTMS (62 ± 5%; $F = 18.51$; $P = 2 \times 10^{-5}$) is underscored, but again no effect is seen with 0.25 Hz rTMS (94 ± 12%; $F = 2.28$; $P = 0.12$).

Although individual seizure durations were shortened in many instances by *active* 0.5 Hz, and *active* 0.75 Hz EEG-guided rTMS, average seizure durations for *sham*-treated and *untreated* seizures across the three frequency groups did not show any significant difference ($P > 0.2$, one-way ANOVA). Thus, with the present paradigm for short EEG-guided rTMS trains we did not identify an overall increase in seizure threshold. Since altering rTMS frequency did not significantly affect the durations of seizures in the control conditions, the anticonvulsive effect in this study appears restricted to the time window of an individual ictal epoch rather to the overall epileptic state that follows KA injection.

4. Discussion

Here we report that EEG-guided 0.5 and 0.75 Hz rTMS can suppress seizures in the KA rat epilepsy model. In contrast, 0.25 Hz rTMS was not effective in reducing seizure length. These data suggest potential efficacy of responsive rTMS in suppressing acute seizures in unanesthetized rats, and this effect appears to be at least in part dependent on the frequency of the rTMS train.

We delivered rTMS in short trains which were sufficiently brief that a durable change in cortical excitability would not be expected. That is, individual rTMS trains applied during seizures in this study were generally <2 min in duration, and were not long enough to expect a reduction in excitability that is seen after low frequency rTMS typically delivered for longer periods (Chen et al., 1997; Gangitano et al., 2002; Daskalakis et al., 2006; Fitzgerald et al., 2006). This is supported by the selective reduction of seizures by active 0.5 and 0.75 Hz rTMS, and the relatively

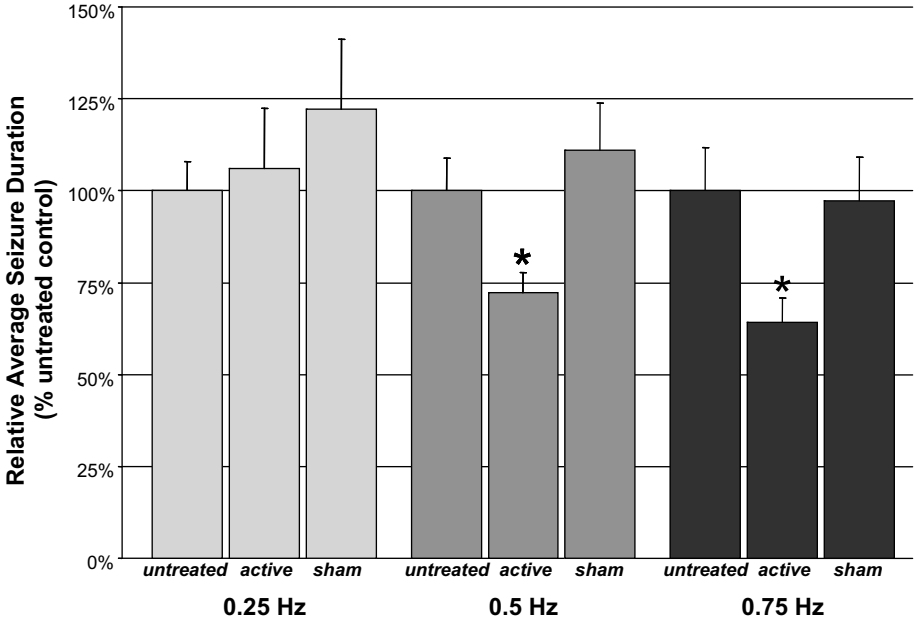

Fig. 3. *Average seizure duration by rTMS frequency.* Values are normalized to average untreated seizure duration in each frequency group. Bar graph illustrates significant suppression of seizures (*) treated with *active* 0.5 Hz ($P = 0.037$) or *active* 0.75 Hz ($P = 0.030$) EEG-guided rTMS. Average durations (mean % untreated control ± SEM) for the 0.25 Hz treatment group are *active* 106 ± 17%, *sham* 122 ± 19%, *untreated* 100 ± 8%; for the 0.5 Hz treatment group are *active* 72 ± 5%, *sham* 111 ± 12%, *untreated* 100 ± 9%; for the 0.75 Hz treatment group are *active* 64 ± 7%, *sham* 97 ± 12%, and *untreated* 100 ± 7%.

constant seizure duration in the control conditions. Accordingly, we hypothesize that the anticonvulsant mechanism of action in our study is related to the capacity of rTMS to disrupt ongoing neuronal activity (Amassian et al., 1989), rather than to an LTD-like change in cortical excitability that would be expected with the more widely used prolonged modulatory low frequency rTMS trains. In this regard, the better efficacy of the 0.75 and 0.5 Hz trains relative to 0.25 Hz may reflect the greater total number of stimuli per seizure that was delivered with the higher frequencies. Plausibly, such effect is similar to that observed with other forms of acute cortical stimulation that are aimed at interrupting seizure activity rather than inducing a durable change in synaptic strength (Kossoff et al., 2004).

However, a cumulative effect of repeated brief low frequency trains leading to an LTD-like change cannot be excluded, particularly as the range of rTMS frequencies in this study is within that used in traditional LTD induction in vitro (Steele and Mauk, 1999). The possible antiepileptic effect of low frequency rTMS that outlasts the stimulus train (and thus resembles LTD) is also demonstrated by reduced seizure susceptibility after pentylenetetrazole injection in rats with that are pre-treated 0.5 Hz rTMS (Akamatsu et al., 2001). Additionally, modulation of excitability in the human motor cortex by short (<2 min) low frequency rTMS trains has been reported, and contribution of similar mechanisms to our findings cannot be excluded (Fitzgerald et al., 2006). The potential contributions of LTD-like processes to seizure control by low frequency rTMS in animal models will have to be the subject for future experiments.

The frequency-dependent discrepancy in response to rTMS suggests that ranges of rTMS paradigms may be systematically tested by translational work with the use of animal models, and perhaps matched to seizure mechanisms. Our data are limited by rTMS equipment in our laboratory which restricts rTMS to low frequency trains, but testing high frequency rTMS bursts in future trials may yield results that more closely resemble those seen with electrical cortical stimulation (Kossoff et al., 2004; Osorio et al., 2005). Similarly, a capacity for high frequency rTMS in rats may enable testing of the anticonvulsive potential of theta burst stimulation where at similar frequency and intensity distinct patterns of stimulation can lead to either facilitation or depression of cortical excitability (Huang et al., 2005).

Stimulus intensity is another variable that can be systematically varied in future experiments. In this study, intensity was deliberately in excess of motor threshold in order to assure activation of the relatively deep limbic structures where KA seizures likely originate. However, as with human rTMS, the true threshold for neuronal activation outside of the primary motor and sensory systems is difficult to measure, and this is further complicated in the current experiment by exposure to KA, and by the ictal state during stimulation. Empiric measurements of current distribution and thresholds for the activation of intracranial structures in the rat by direct extracellular recording may be useful in future studies.

As we relied on visual inspection of the EEG to trigger rTMS trains, there was considerable variability in latency from electrographic seizure onset to the first rTMS pulse (median: 8 s; range: 1–48 s). The natural (and unplanned) variability in the latency from seizure start to rTMS onset provides an opportunity to test whether rTMS onset earlier in the seizure corresponded to shorter seizure duration. Here, we found a slight trend toward longer seizures with longer latency to rTMS in the 0.5 Hz ($r = 0.19$) and 0.75 ($r = 0.20$), however, linear regression for these data did not demonstrate statistical significance in either group ($P > 0.3$). An extension of this work is to improve EEG-guided rTMS by supplanting the human operator by automated seizure detection in a closed-loop system that controls rTMS delivery to a seizure focus. This may improve on the current methods which incorporate a variable delay from seizure onset to treatment. As with electrical brain stimulation, automating rTMS delivery may provide a means to formally test whether latency from seizure onset to rTMS factors into the anticonvulsive efficacy The earlier delivery relative to ictal onset may enhance the anticonvulsive capacity of responsive rTMS, as a similar benefit from earlier stimulation has been shown in work with electrical brain stimulation (Lesser et al., 1999; Motamedi et al., 2002; Osorio et al., 2005).

Among limitations in this preliminary study is the relatively non-focal nature of rTMS in the rat as compared to human, and likely distinct mechanisms of seizure genesis in KA-treated rats as compared to human subjects. Certainly, in future work the intracranial distribution of electrical current induced by rTMS in rats will have to be assessed formally and applied to focal cortical seizure models that more closely resemble human epilepsies that have responded to rTMS (Fregni et al., 2005, 2006; Santiago-Rodriguez et al., 2008). However, for the KA model where seizures originate broadly in the limbic structures and then generalize (Ben-Ari, 1985), the likely broad distribution of the electromagnetic field in the rat head approximates coverage of the seizure focus in the present experiment.

Based on our findings of anticonvulsive effect of EEG-guided rTMS in an established epilepsy model, we expect that continued translational studies of EEG-guided rTMS in seizure control using rodent models are feasible. We anticipate near-future work to optimize the spatial resolution of rTMS in rat seizure models in order to extend experiments to additional rat seizure models of focal and generalized epilepsies.

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