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ORIGINAL PAPER

Prospects for Clinical Applications of Transcranial Magnetic Stimulation and Real-Time EEG in Epilepsy

Alexander Rotenberg

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Abstract Recent advances in methods for transcranial magnetic stimulation (TMS) enable its coupling to real-time EEG (TMS-EEG). Although TMS-EEG is applied largely in neurophysiology research, there are prospects for its use in clinical TMS practice, particularly in epilepsy where EEG is already in wide use, and where TMS is emerging as a diagnostic and therapeutic tool. In diagnostic applications, TMS-EEG may provide a useful measure of cortical excitability at baseline or after antiepileptic treatment. For therapeutic purposes, TMS-EEG may be of use in selection of appropriate TMS strength outside of the motor cortex where the threshold for cortical activation is more apparent with the aid of EEG. In other realistic clinical applications, TMS-EEG may be of use in real-time monitoring for epileptiform activity in vulnerable populations where TMS may trigger seizures, or as a component of a responsive neurostimulation setup in which TMS timing is determined by underlying EEG activity. Future trials and evolution of TMS-EEG methods are likely to provide answers as to the actual clinical value of TMS-EEG.

Keywords Transcranial magnetic stimulation · EEG · Epilepsy

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A. Rotenberg (✉)
Department of Neurology, Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Fegan 9, Boston, MA 02115, USA
e-mail: alexander.rotenberg@childrens.harvard.edu

A. Rotenberg
Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard Medical School, Boston, MA, USA

Introduction

Transcranial magnetic stimulation (TMS) is a quarter-century-old method for focal noninvasive cortical stimulation that is emerging as a novel clinical tool (Barker et al. 1985; Kobayashi and Pascual-Leone 2003). As a diagnostic procedure, single-pulse and paired-pulse TMS may be used to map cortical function and to measure cortical excitability (Krings et al. 2001; Staudt et al. 2004). In therapeutic applications, the capacity of repetitive TMS (rTMS) to induce a lasting change in cortical excitability has been tested in several disease states (Pascual-Leone et al. 1996; Topper et al. 2003; Boggio et al. 2006). The 2008 United States Food and Drug Administration (FDA) clearance of rTMS for treatment major depression is testament to its gain of acceptance in the clinical setting.

The clinical potential of TMS and rTMS (TMS/rTMS) also drives translational research where these methods may be tested in animal disease models. Translational work with TMS/rTMS, includes tests of its anti-depressant (Hargreaves et al. 2005; Kim et al. 2006; Vieyra-Reyes et al. 2008), anti-manic (Shaldivin et al. 2001), and anti-epileptic (Akamatsu et al. 2001; Anschel et al. 2003) potential, as well as experiments aimed to evaluate the safety of TMS/rTMS (Nishikiori 1996; Liebetanz et al. 2003; de Sauvage et al. 2008).

Recent advances that enable co-registration of TMS with EEG (TMS-EEG) in humans and in animals may enhance the clinical and translational TMS/rTMS applications (Ilmoniemi et al. 1997; Boutros et al. 2000; Bonato et al. 2006; Ives et al. 2006; Rotenberg et al. 2008a). At time of this writing, TMS-EEG is used mostly in human non-clinical studies of cortical excitability and connectivity, and has yet to be extensively studied in patient populations or in animal disease models. In particular, TMS-

EEG applications hold realistic promise in epilepsy: a prevalent disorder affecting 0.5–1.0% of the population (Hauser et al. 1991; Picot et al. 2008). The scalp EEG is essential in epilepsy management, and TMS/rTMS is increasingly recognized as a well-tolerated and potentially beneficial procedure to track cortical excitability as well as to suppress seizures (Theodore 2003; Schrader et al. 2004; Fregni et al. 2006; Bae et al. 2007). Also, TMS-compatible scalp EEG electrodes and electronic components designed to minimize TMS artifact are relatively inexpensive and can be adapted to most existing clinical and research EEG setups in order to permit real-time EEG recording during TMS/rTMS (Ives et al. 2006).

The present review summarizes some of the data relevant to plausible clinical applications of TMS-EEG in epilepsy. Broadly, the available publications and pilot data suggest that among indications for TMS-EEG in epilepsy may be: (1) diagnostic measures of cortical excitability, (2) real-time monitoring for epileptiform EEG activity during rTMS in vulnerable populations, and (3) modulation of therapeutic rTMS protocols. These prospects for TMS-EEG use are discussed below.

TMS-EEG in Measures of Cortical Excitability

While EEG is the most widely-used measure of cortical excitability in clinical epilepsy management, TMS can provide measures of regional cortical excitability as well. Yet without simultaneous EEG recording, direct measures of cortical excitability by TMS are limited largely to the motor cortex. With most common protocols, TMS is coupled with EMG (TMS-EMG) such that the motor cortex is stimulated and the magnitude of the evoked muscle contraction in a contralateral limb (typically a hand muscle) can be quantified by skin electrodes and the recording of a motor evoked potential (MEP) (reviewed in Kobayashi and Pascual-Leone 2003).

From the MEP, a number of measures can be derived to probe cortical excitability (Table 1). One is the threshold to muscle activation, or motor threshold (MT). The MT appears to reflect largely neuronal membrane excitability and is increased by anticonvulsants, such as phenytoin and carbamazepine that inhibit voltage-gated sodium channels. Additionally, paired-pulse TMS-EMG provides measures of γ-aminubutyric acid (GABA)-mediated cortical inhibition and glutamate-dependent cortical excitability. In the most common paired-pulse TMS-EMG protocols, a subthreshold conditioning stimulus is delivered before each succeeding TMS pulse (reviewed in Theodore 2003; Kobayashi and Pascual-Leone 2003; Chen 2004). Short (1–5 ms) interstimulus intervals lead to reduction of the MEP, and likely reflect $GABA_A$ receptor-mediated short-interval intracortical inhibition (SICI). Slightly longer (6–20 ms) interstimulus intervals augment the MEP, reflecting glutamate-mediated intracortical facilitation (ICF). Benzodiazepine ($GABA_A$ receptor agonist) anticonvulsants enhance SICI and suppress ICF (Ziemann et al. 1996; reviewed in Ziemann 2004). Still longer interstimulus (50–300 ms) paired pulse TMS-EMG protocols can also measure $GABA_B$,-receptor mediated long-interval intracortical inhibition (LICI) which is enhanced by the $GABA_B$ receptor agonist baclofen (Sanger et al. 2001; Florian et al. 2008). The extent of cortical inhibition may also be measured by the cortical silent period (CSP), a transient EMG silence observed when TMS is delivered to the motor cortex during an active motor contraction. The CSP too appears mediated by GABA receptors, although the contributions of $GABA_A$ and $GABA_B$ receptors to CSP is less defined than for paired-pulse measures (Roick et al. 1993; Ziemann et al. 1996; Fedi et al. 2008).

The TMS-EMG measures appear useful in detecting abnormalities in the inhibition:excitation ratio in patients with epilepsy. Data from published reports where parameters derived from TMS-EMG in patients with epilepsy were compared to values obtained from non-epileptic controls are summarized in Table 2 (*note*: for purposes of this review, findings from studies referenced in Table 2 were simplified to underscore comparisons in MT, SICI, ICF, LICI and CSP between epileptic and control groups—a detailed review of the diverse and interesting objectives and conclusions from the referenced experiments is beyond the scope of this discussion). Although findings vary somewhat between studies, and likely reflect subject and methodology differences, they provide an overall impression that either primary or compensatory abnormalities in cortical inhibition:exhitation ratio can be measure by TMS. In particular, pathologic suppression if intracortical inhibition (Table 2) as detected by paired-pulse stimulation appears to be a common finding in patients with epilepsy.

Detection of abnormalities in cortical inhibition by TMS-EMG suggests its possible utility in epilepsy, but also underscores a limitation as global cortical excitability must be inferred from stimulation of the motor cortex. However this anatomic limitation may be overcome by TMS-EEG where TMS-evoked surface potentials from any cortical region can be recorded with scalp electrodes and used to estimate regional excitability of the extramotor cortex (Kahkonen et al. 2005a, b; Lioumis et al. 2008).

In support of potential TMS-EEG application in measuring cortical excitability in patients with epilepsy, a recent experiment demonstrates that inhibition of the evoked EEG response over extramotor frontal and parietal cortex, analogous to LICI, can be recorded with a paired-pulse TMS-EEG paradigm (Fitzgerald et al. 2008; Fitzgerald et al. 2009). An interesting extension of these data may be to test

Table 1 TMS-EMG parameters

TMS-EMG parameter	Protocol	Likely mechanism	Examples of change with medication
Motor threshold (MT)	Single pulse stimulation: measure of stimulus strength necessary for a motor response	Corticomotor neuron membrane excitability	Increased by sodium channel antagonists (e.g. PHT, CBZ)
Short-interval intracortical inhibition (SICI)	Paired pulse stimulation: conditioning stimulus precedes test stimulus by 1–5 ms	$GABA_A$-mediated inhibition	Increased with $GABA_A$ agonists (LZP, DZP)
Intracortical facilitation (ICF)	Paired pulse stimulation: conditioning stimulus precedes test stimulus by 6–20 ms	Glutamate-mediated excitation	Decreased with $GABA_A$ agonists (LZP, DZP)
Long-interval intracortical inhibition (LICI)	Paired pulse stimulation: conditioning stimulus precedes test stimulus by 50–300 ms	$GABA_B$-mediated inhibition	Increased by $GABA_B$ agonists (baclofen; PGB)
Cortical silent period (CSP)	Single pulse stimulation: measure of pause in voluntary EMG activity after TMS	$GABA_B$-mediated inhibition	Increased by $GABA_B$ agonists (baclofen; PGB); decreased by $GABA_A$ agonists (LZP, DZP)

CBZ carbamazepine; *DZP* diazepam; *LZP* lorazepam; *PGB* pregabalin; *PHT* phenytoin

whether extramotor LICI-type TMS-EEG abnormalities are present in the epilepsy population. However, as number of TMS-EMG experiments show motor cortex abnormalities in patients with extra-motor and generalized epilepsies, further studies will be required to test whether interrogating focal cortical excitability outside of the motor cortex by TMS-EEG is of any greater clinical value than checking TMS-EMG measures (Cincotta et al. 2000; Loscher et al. 2007; Groppa et al. 2008).

Spike Provocation by TMS

An intriguing role for TMS-EEG in epilepsy may be as a neurologic stressor to provoke epileptiform activity in a vulnerable cortical region. Epileptiform discharge provocation by TMS has been demonstrated in human subjects in past, but the early results suggested that TMS was no more likely to activate the seizure focus on EEG than was hyperventilation in epileptic patients (Hufnagel et al. 1990; Schuler et al. 1993; Steinhoff et al. 1993). However, more recently, Valentin et al. (2008) applied single pulse TMS-EEG to patients with focal epilepsy and to a group of healthy controls. The authors identified two broad categories of electrographic evoked response: an early (<100 ms) slow wave response and a late (100–1000 ms) response which was either epileptiform in morphology (resembling a sharp wave or spike) or was characterized by rhythmic EEG activity. Notably, although the early responses were present in all subjects, the late epileptiform responses were detected only in patients with complex partial seizures. These late discharges often appeared similar to the patient's habitual spikes or sharp waves and were lateralized to the epileptogenic hemisphere in most cases. Moreover, in some instances where epileptiform abnormalities were triggered by TMS, the interictal scalp EEG was normal (Valentin et al. 2008). As Valentin and colleagues propose, these data raise the prospects for eventual applications of TMS-EEG to enhance the sensitivity of the scalp EEG in detecting epileptiform abnormalities.

An extension of the above-cited data showing epileptiform activity provoked by TMS-EEG and localized to one hemisphere, is toward more detailed seizure focus localization, as is necessary in cases where surgical seizure focus resection is considered. However, whether the sensitivity and spatial resolution of TMS-EEG will enable it to meaningfully enhance existing methods for presurgical seizure focus localization has yet to be determined. In current practice noninvasive localization methods employ surface EEG anatomic and functional imaging to identify a seizure focus with a resolution of 0.5–1.0 cm (Sarco et al. 2006; Cascino 2008). Perhaps with high density EEG and with co-registration of a subjects anatomic imaging with EEG responses, TMS-EEG spatial resolution can be enhanced sufficiently to localize a seizure focus in a patient with epilepsy (Esser et al. 2006).

As with other technologies, the clinical potential of TMS-EEG may be investigated by translational research. For this purpose, we recently adapted TMS-EEG methods to gently-restrained unanesthetized rats. Our approach has been to record scalp EEG with subdermal silver wire electrodes which can be easily placed into an animal, have little magnetic property, and are neither heated nor displaced by TMS. To minimize TMS artifact we are using a low slew-rate operational pre-amplifier which limits the TMS artifact to about 30 ms (Ives et al. 2006). Our group is testing the diagnostic potential of TMS-EEG in a rat seizure model where we find that EEG spikes can be provoked by TMS in seizure-prone rats (Fig. 1). Whether such spikes can be provoked focally, and which TMS parameters favor

Table 2 TMS-EMG findings in patients with epilepsy

Study	Subjects (n)	Findings (relative to control); comments				
		MT	SICI	ICF	LICI	CSP
Akgun et al. (2009)	JME(21); AS(21); C(20)	↑; all on AED	NT	NT	NT	↓
Badawy et al. (2009)	JME(10); GE(10); FE(10); C(10)	=	↓ / = ; reduced in early morning in JME, but not other GE / normal in FE	↑	↓; reduced in early morning in all GE; normal in FE	NT
Brodtmann et al. (1999)	JME(3); GTC(3); JAE(1); C(16)	=	NT	NT	↓	NT
Cantello et al. (2000)	FE(18); C(11)	↑; all on AED	↓; reduced in a subset of patients with FE	↑; increased in a subset of patients with FE	NT	NT
Caramia et al. (1996)	JME(7); GTC(2); C(6*) *1 non-epileptic subject on PB	↑ / = ; increased in JME / normal in GTC; all on AED	↓; reduced in JME	NT	NT	NT
Cicinelli et al. (2000)	FE(16); C(16)	↑	NT	NT	NT	↓; reduced in hemisphere ipsilateral to seizure focus
Cincotta et al. (1998)	FE(18); C(16)	↑; all AED	NT	NT	NT	↑; increased in subgroup with clonic seizures
Danner et al. (2009)	EPM1(24); C(24)	↑; majority on AED	NT	NT	NT	↑
Di Lazzaro et al. (2004)	E(5); C(11)	↑; all on AED	=; increased with VNS	NT	NT	NT
Ertas et al. (2000)	GE(14); FE(11); C(14)	NT	NT	NT	NT	↑
Fedi et al. (2008)	GE(14, all with *GABRG2(R43Q)* mutation); C(24)	=	↓	↑	NT	=
Hamer et al. (2005)	FE(23); C(20)	↑; majority on AED	=	=	NT	=; reduced in hemisphere ipsilateral to extramotor seizure focus
Klimpe et al. (2009)	GE(10); FE(10); C(20)	=	↓	=	NT	=
Macdonell et al. (2001)	JME(9);JAE(1);GE(11); C(19)	=	NT	NR	NT	↑
Manganotti et al. (2000)	JME(15);C(12)	=	↓	=	=	=
Manganotti et al. (2006)	JME(10); C(10)	=	↓; reduced further with sleep deprivation	=	NT	=
Manganotti et al. (2004)	JME(9); C(20)	=	↓	=	NT	NT
Molnar et al. (2006)	FE(3); SGE(2); C(9)	↑; all on AED	↓	=	↓; at 50 ms ISI	=

Table 2 continued

Study	Subjects (n)	Findings (relative to control); comments				
		MT	SICI	ICF	LICI	CSP
Munchau et al. (2005)	JME(1); FE(1); GTC(5); C(6)	↑; majority on AED	=	=	NT	↑
Nezu et al. (1997)	BECTS(13); C(10)	↓ / ↑; decreased in untreated patients; / increased in treated patients	NT	NT	NT	NT
Reutens and Berkovic (1992)	GE(45); C(71); 34 GE patients treated	↓ / ↑; reduced in untreated patients; / increased in treated ptients	NT	NT	NT	NT
Salih et al. (2007)	FLE(3); C(7)	NT	↓; reduced in NREM sleep	=; not uniformly altered	NT	NT
Valzania et al. (1999)	PME(12); C(8)	=	NT	NT	↓	=
van Rootselaar et al. (2007)	FCMTE(8); C(15)	=	↓	=	NT	=
Varrasi et al. (2004)	FE(21); C(15)	=	↓; reduced in a subset of patients with FE	=	NT	=
Werhahn et al. (2000)	FE(15); C(17)	=	↓	↑	NT	=

↓: reduced; ↑: increased; =: unchanged; *AED* antiepileptic drugs; *BECTS* benign epilepsy of childhood with centrotemporal spikes; *C* control subjects; *EPM1* progressive myoclonic epilepsy type 1; *FCMTE* familial cortical myoclonic tremor with epilepsy; *FE* focal epilepsy; *FLE* frontal lobe epilepsy; *GE* generalized epilepsy, not otherwise specified; *GTC* generalized tonic-clonic seizures; *JAE* juvenile absence epilepsy; *JME* juvenile myoclonic epilepsy; *NREM* non-rapid eye movement; *NT* not tested, or not compared between epilepsy and control groups; *PB* phenobarbital; *PME* progressive myoclonic epilepsy

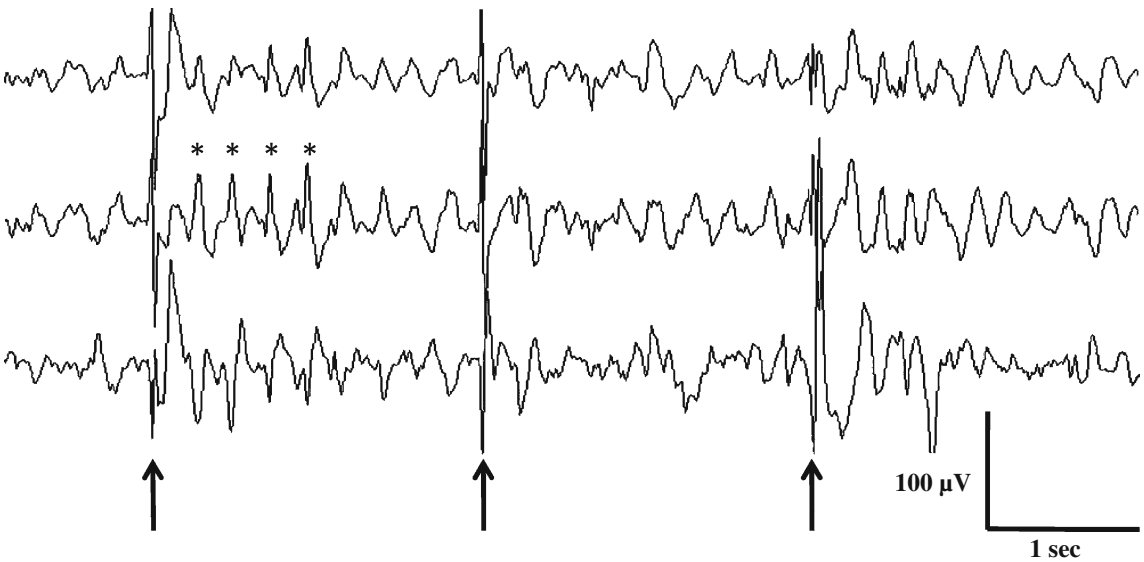

Fig. 1 EEG spikes provoked by TMS in rat. Scalp EEG demonstrates epileptic spikes (*) provoked by TMS (*arrow*) in one of three instances in a rat pre-treated with intraperitoneal pentylenetetrazole. (Rotenberg, Pascual-Leone, Jensen, unpublished data)

evoking spikes, but not seizures, is the work of ongoing experiments.

TMS-EEG in Selection of Stimulus Strength

Therapeutic applications of rTMS may also benefit from TMS-EEG methods. The mechanisms that underlie the beneficial clinical effects of rTMS are not entirely known, but appear to resemble those of long-term depression (LTD) and long-term potentiation (LTP) of synaptic strength that result from low or high frequency electrical brain stimulation, respectively (Bliss and Lomo 1973; Dudek and Bear 1992). In epilepsy, it is the inhibitory effect of low ($\leq$1 Hz) rTMS that is most widely-used to suppress seizures with encouraging antiepileptic results in open-label trials (Tergau et al. 1999; Fregni et al. 2005; Santiago-Rodriguez et al. 2008). Yet, results from placebo-controlled trials are mixed, with one trial demonstrating a reduction in seizures and improvement of (off-line) EEG (Fregni et al. 2006), and two others showing insignificant clinical improvement, or improvement of the EEG without a significant reduction of seizures (Theodore et al. 2002; Cantello et al. 2007).

Among factors contributing to the inconsistent findings in antiepileptic rTMS trials may be the difficulty in selecting an appropriate strength of extra-motor TMS. Over the motor cortex, where the MEP provides a reliable marker of cortical activation, TMS strength can be adjusted until the threshold for evoking the MEP is reached. For targets outside the motor cortex, such dosing is difficult and restricted to the primary visual cortex can be stimulated to elicit a phosphene (a subjective sensation of a flashing light (Kammer et al. 2005). Nevertheless in common practice the motor threshold is used to determine stimulation strength, despite data showing poor correlation between thresholds for activation of the motor and visual cortices (Stewart et al. 2001). By analogy to pre-frontal rTMS for treatment of mood disorders where data suggest a lower likelihood of clinical improvement after subthreshold rTMS (Padberg et al. 2002; Kahkonen et al. 2004), sub-threshold stimulation of the epileptic focus may account for some of the inconsistency in outcomes of clinical antiepileptic rTMS trials.

TMS-EEG in epilepsy may enable the operator to adjust the strength of the TMS pulse until an EEG response indicating regional cortical activation is recorded. Such an approach has been proposed for rTMS of the prefrontal cortex for the treatment of mood disorders where TMS of identical intensity resulted in distinct TMS-EEG responses in the prefrontal and motor cortex in healthy volunteers (Kahkonen et al. 2005a, b). In that study, the authors evaluated the global mean field amplitude (GMFA) of the EEG response. Future work may address whether regional activation for purposes of selecting rTMS strength is best reflected the GMFA or discrete TMS-evoked potentials (TEPs) such as the N100 which is presumed to reflect an evoked focal inhibitory response around the stimulated cortical volume and which has been demonstrated in extra-motor regions (Ilmoniemi et al. 1997; Bonato et al. 2006; Miniussi and Thut 2009). Further, the concept of "threshold" stimulus intensity may need to be better-developed in the TMS-EEG field where the amplitude of the TMS-evoked EEG response varies continuously with TMS strength (Komssi et al. 2004) in contrast to an all-or-none MEP response that is used to determine motor threshold by traditional TMS methods.

TMS-EEG in Seizure Monitoring

In clinical epilepsy where the majority of TMS/rTMS work has focused on the interictal state, TMS-EEG can be applied in the ictal state to identify real-time EEG changes induced by rTMS.,TMS-EEG may be of use to detect either improvement or exacerbation of seizure—both potentially valuable findings in the clinical setting. TMS-EEG was recently applied in a small number of cases of epilepsia partialis continua (EPC) to detect seizure suppression as well as to exclude seizure exacerbation during rTMS (Rotenberg et al. 2008b, c). Encouragingly, seizure exacerbation by rTMS was not seen, while seizure suppression was detected in some instances. Similar TMS-EEG methods may be of use to monitor for evoked epileptiform activity (as in Fig. 1) when rTMS is administered to treat non-epileptic symptoms such as mood disorder, motor dysfunction or chronic pain in seizure-prone patients, such as those with recent stroke, neurodegenerative disease or underlying epilepsy.

In contrast to patients with central nervous system disorders who are at increased risk for seizure, rTMS in healthy subjects appears safe. To date there is no apparent need to monitor for provocation of epileptic activity by rTMS either in healthy volunteers or in patients with neurologic or psychiatric disorders that do not markedly lower their seizure threshold as will indicated in safety guidelines which are in final review before print at time of this writing (Rossi, Hallett, Rossini, Pascual Leone, et al., Clinical Neurophysiology, accepted for publication).

TMS-EEG in Seizure Treatment

TMS-EEG may also have use in EEG-guided responsive neurostimulation where a seizure can be identified by EEG and treated with an anticonvulsive rTMS protocol such as a train of low frequency stimulation. The feasibility of such

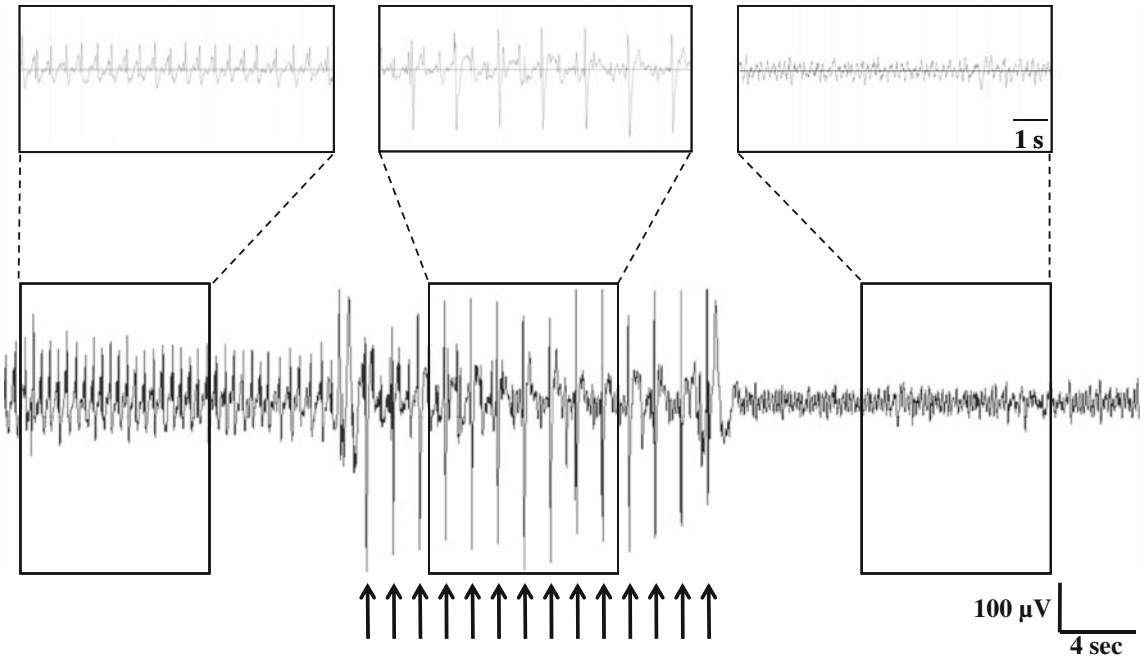

Fig. 2 Seizure treated with rTMS in rat. A 60-s tracing shows a representative KA-triggered seizure terminating with a 0.75 Hz rTMS train. Typical spikes of a KA seizures (*left*) were readily recognized by the TMS operator. Once a seizure was detected, rTMS (*arrow*) was initiated, and continued until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

applications with TMS-EEG was recently demonstrated in rat seizure models (Ives et al. 2006; Rotenberg et al. 2008a) where real-time EEG was used to identify the start of a seizure by visual inspection, to trigger stimulation, and to identify when the seizure has terminated. A representative seizure induced by intraperitoneal kainic acid (KA) and treated with 0.75 Hz rTMS train in a rat is shown in Fig. 2. Given that TMS-EEG equipment is relatively cumbersome, it does not seem that responsive TMS-EEG can offer a practical solution to patients' seizures in real-world applications. However, the rat data suggest that TMS-EEG may have potential as an experimental method to noninvasively test seizure detection algorithms in combination with abortive stimulation patterns, perhaps as a tool that will aid in the design other forms of responsive cortical stimulation.

Although EEG-guided TMS has not been applied in clinical practice, the potential for using real-time EEG to direct TMS/rTMS is suggested by several reports which demonstrate that the EEG state predicts the cortical response to TMS. For example, MEP amplitudes correlate with EEG power in the alpha and beta frequency range recorded with electrodes positioned over the motor cortex (Lepage et al. 2008; Sauseng et al. 2009). This preferential state-dependent response to TMS in healthy volunteers suggests that studies of EEG guidance in patient populations is warranted, and perhaps well-suited for epilepsy where the ictal and interictal EEG states are often easily distinguished by visual inspection or by an automated EEG algorithm.

On a finer temporal scale, TMS-EEG may enable gating of TMS to a specific phase of an underlying EEG signal. In somewhat speculative but plausible applications, TMS-EEG may be used to target a specific phase of the spike-and-wave complex during epileptic seizures. Similarly, during clinical TMS/rTMS outside of epilepsy, TMS-EEG gating may be of use in optimizing clinical protocols. It is possible that the variability in clinical response to rTMS is in part related to variability of the EEG state at the time that each TMS pulse is delivered. That is, TMS-EEG may enable delivery of the stimulating pulse to be timed expressly to a phase of the underlying EEG background rhythm. Of course, whether this is the case and whether improving the EEG-stimulation relationship will lead to desired clinical outcomes has yet to be tested.

Conclusions

At this time, the clinical role of TMS-EEG in epilepsy is not certain, and a discussion of its applications in the clinical arena is necessarily speculative. However, recent data suggest that exploration in patient populations is warranted, and the adaptation of TMS-EEG to translational research may help to clarify its role as a diagnostic or therapeutic tool. Especially attractive in clinical epilepsy are prospects for TMS-EEG to test regional cortical excitability, to more accurately detect threshold for activation of extramotor

cortex, and to detect an anticonvulsive effect or a proconvulsive side-effect of repetitive stimulation. As technology for TMS-EEG is now widely-available meaningful clinical and translational trials in the near future seem likely.

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