

Chapter 39

Epilepsy

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INTRODUCTION

Epilepsy is among the most common neurological disorders and affects approximately 1% of the world's population according to the [World Health Organization \(2009\)](#) factsheet on epilepsy. Notably, epilepsy is pharmacologically intractable in about one-third of all instances, a statistic that has not changed despite the introduction of more than 15 new antiepileptic drugs in the past quarter century ([Kwan and Brodie, 2000](#); [Loscher and Schmidt, 2011](#)). Accordingly, neurostimulation techniques are emerging as potentially valuable tools for seizure control; among these are two non-invasive techniques: transcranial magnetic stimulation (TMS) ([Fig. 39.1](#)) and, to a lesser extent, transcranial direct current stimulation (tDCS) (reviewed in [Nitsche and Paulus, 2009](#)). For both methods, the procedure basics, the rationale, and supportive data for application in epilepsy, and realistic future directions, are discussed below.

TRANSCRANIAL MAGNETIC STIMULATION IN SEIZURE SUPPRESSION

Repetitive TMS (rTMS), particularly low-frequency (0.3–1 Hz) rTMS, which can induce a lasting reduction in cortical excitability (see [Chapter 27](#)), has plausible antiseizure therapeutic potential ([Theodore, 2003](#); [Hallett, 2007](#)). If it is assumed that excess cortical excitability is a critical part of the epileptic pathophysiology, then it follows logically that suppression of regional cortical excitability might reduce seizure frequency. Thus, approximately 14 years of open-label trials and recent randomized controlled trial results show a potential for seizure reduction by rTMS

when applied over the epileptogenic region, or even when applied in a neutral scalp location, such as the vertex. Interestingly, the favorable response of some patients to stimulation outside of the epileptogenic zone, and in one series a favorable response of patients with primary generalized seizures to rTMS, raises the possibility of widespread therapeutic benefit elicited by focal stimulation (reviewed in [Nitsche and Paulus, 2009](#)). Here, if substantiated, the antiepileptic mechanism may not be as simple as local suppression of intracortical excitability, but rather a network effect of low-frequency rTMS.

Yet, despite the favorable data from open-label rTMS trials in epilepsy, four published placebo-controlled trials have yielded inconsistent results. The first found that the clinical effect of rTMS was a mild and short-lived reduction in seizure frequency in patients with temporal lobe epilepsy ([Theodore et al., 2002](#)). The second showed a significant seizure reduction and improvement of interictal electroencephalography (EEG) findings in patients with cortical dysplasia ([Fregni et al., 2006a](#)). The third, which investigated rTMS in a mixed group of patients with either focal or primary generalized seizures, concluded that active rTMS was no better than placebo for seizure reduction, but that active treatment significantly reduced interictal EEG epileptiform abnormalities ([Cantello et al., 2007a](#)). Last, a recent trial of low-frequency rTMS in patients with focal seizures demonstrated significant seizure and interictal epileptiform discharge suppression following 2 weeks of treatment ([Sun et al., 2012](#)).

These inconsistent findings with respect to seizure suppression in controlled rTMS trials, as well as discrepancy between the open-label and controlled data, suggest that further placebo-controlled trials of rTMS in epilepsy are necessary to characterize fully its antiepileptic

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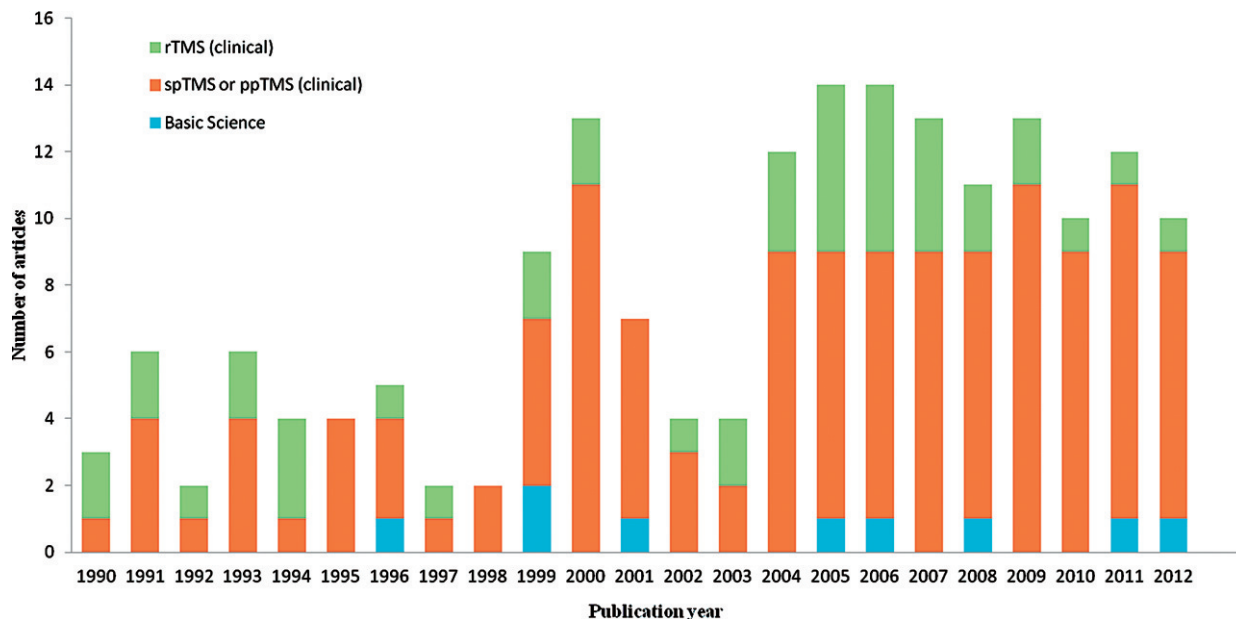


Fig. 39.1. Research activity relating to transcranial magnetic stimulation (TMS) in epilepsy. Bar graph shows annual publications where TMS was applied to humans with epilepsy, or experiments involving animal seizure models. Clinical experiments are further segregated into those involving single-pulse TMS (spTMS) or paired-pulse TMS (ppTMS), or repetitive TMS (rTMS). The increasing number of publications over time underscores the growing interest in TMS as an investigational and clinical tool in epilepsy. (Courtesy of Dr. Masoud Majed.)

potential. The design of such future controlled rTMS trials may be informed by both the controlled trial data and by meta-analysis of the open-label reports. One review of the pooled controlled trial data has provided an estimate to the rTMS placebo effect: a 0–2% median change in seizure frequency and a 16–20% responder rate attributable to placebo rTMS conditions where the appearance and sound of the stimulating coil is approximated without inducing appreciable intracranial electrical current (Bae et al., 2011). The same analysis also suggested that rTMS delivered directly over a neocortical seizure focus is more likely to suppress seizures than rTMS delivered outside the epileptogenic zone. This notion is supported by favorable outcomes in the two controlled trials where low-frequency rTMS was delivered over a neocortical seizure focus (Fregni et al., 2006a; Sun et al., 2012), and by a larger meta-analysis of the open-label and controlled trial data where, based on 11 eligible publications, the authors concluded that antiepileptic rTMS may be particularly beneficial in patients with neocortical epilepsy or cortical dysplasia (Hsu et al., 2011). Thus, whether rTMS will prove successful in seizure suppression remains in question, but published reports do support further investigation into its use in drug-resistant cases, and underscore the need for larger randomized controlled trials in well selected populations of patients with epilepsy.

SAFETY OF TMS IN EPILEPSY

As with any new technology in a vulnerable population, the threshold question of safety should be addressed before its implementation. This is particularly germane in patients with epilepsy, given that provoked seizures are the most serious reported adverse rTMS event, and that the population with epilepsy is by definition seizure-prone. rTMS safety and tolerability has been addressed in a few studies. A 2007 review of the literature identified a crude per-subject seizure risk approximating 1.4% in patients with epilepsy undergoing rTMS (Bae et al., 2007). A subsequent case series by the same group found that in-session seizures during rTMS were most likely in patients whose seizure frequency exceeded one per day, and in all instances were identical in semiology to the patient's typical seizures, and either typical or shorter in duration than the patient's native seizures (Rotenberg et al., 2009a). Further, any documented in-session seizures during rTMS thus far have not been correlated with either a poor neurological outcome or absence of a rTMS response. Seizure exacerbation in patients with epilepsy by rTMS has not been recorded, nor has any instance of rTMS-provoked status epilepticus. The absence of reported seizure exacerbation appears to be a common finding independent of whether rTMS is administered interictally or during an ongoing seizure, as in *epilepsia partialis continua*

(EPC) (Rotenberg et al., 2009b). The incidence of the remaining rTMS-related adverse events (headache, neck pain, tinnitus, etc.) is similar in patients with epilepsy to that described for healthy volunteers and for other patient populations (Bae et al., 2007). Finally, rTMS appears to be safe and well tolerated in specialized populations with implanted vagus nerve stimulators or titanium skull plates, both relatively prevalent in the population with drug-resistant epilepsy (Di Lazzaro et al., 2004; Rotenberg et al., 2007).

TMS AS A DIAGNOSTIC INSTRUMENT IN EPILEPSY

TMS is unique among the neurostimulation techniques that have been applied in epilepsy in its potential as either a diagnostic or a therapeutic tool. In particular, paired-pulse TMS (ppTMS) as a means to assess intracortical inhibition or facilitation (see Chapters 27 and 30) is emerging as a practical measure of the excitation:inhibition ratio (E:I) in patients with epilepsy, such that this technique may be used either to track disease severity or to measure the therapeutic effect of an antiepileptic intervention.

As discussed in more detail in Chapter 27, in its most common embodiment TMS is applied over the motor cortex and coupled with surface electromyography (EMG) such that TMS elicits an evoked muscle contraction in a contralateral limb (typically a hand muscle) which is quantified by skin electrodes and the recording of a motor evoked potential (MEP) (reviewed in Kobayashi and Pascual-Leone, 2003). This application, particularly if coupled with frameless stereotaxy, can be used to map motor cortical anatomy in patients who are candidates for epilepsy surgery (Zsoter et al., 2012; Vitikainen et al., 2013). Here, the common use of invasive subdural electrodes in presurgical monitoring offers a unique opportunity to validate the noninvasive motor map (Fig. 39.2).

Further, a number of TMS-dependent measures can be derived from the MEP to probe cortical excitability. One is the threshold to muscle activation, or motor threshold (MT). The MT likely reflects largely neuronal membrane excitability and is increased by anticonvulsants, such as phenytoin and carbamazepine, that inhibit voltage-gated sodium channels (see Chapter 32) (Ziemann et al., 1996a). Other measures can be obtained from ppTMS protocols. Specifically, ppTMS provides measures of γ -aminobutyric acid (GABA)-mediated cortical inhibition and glutamate-dependent cortical excitability. In the most common ppTMS protocols, a subthreshold conditioning stimulus is delivered before each succeeding TMS pulse (reviewed extensively in several chapters as well as in Kobayashi and Pascual-Leone,

2003; Theodore, 2003; Chen, 2004; Rotenberg, 2010). 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., 1996a, b). Still longer interstimulus (50–300 ms) ppTMS–EMG protocols can also measure GABA_B receptor-mediated long-interval intracortical inhibition (LICI), which is enhanced by the GABA_B receptor agonist baclofen, and in an animal TMS model is also enhanced by the GABA_A agonist pentobarbital, and in the same model suppressed by the GABA_A antagonist pentylene-tetrazole (Sanger et al., 2001; Florian et al., 2008; Hsieh et al., 2011). 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 also appears to be mediated by GABA receptors, although CSP pharmacology, particularly GABA_A and GABA_B receptor contributions, is less defined than for paired-pulse measures (Roick et al., 1993; Ziemann et al., 1996b; Fedi et al., 2008). See Chapter 32 for a full review of these pharmacological features.

Relevant to epilepsy and antiepileptic interventions, single-pulse TMS (spTMS) and ppTMS measures appear useful in detecting abnormalities in the E:I ratio in patients with epilepsy, and comparisons of TMS-derived E:I ratios between patients with epilepsy and healthy controls have been published in numerous studies (reviewed in Rotenberg, 2010). Although findings vary among the published reports, and likely reflect subject and methodology differences, they provide an overall impression that either primary or compensatory abnormalities in cortical E:I ratio can be measured by TMS. In particular, pathological suppression of intracortical inhibition as detected by ppTMS appears to be a common finding in patients with epilepsy, and may in some instances reflect disease severity (Brodtmann et al., 1999). Moreover, such gain in the E:I ratio appears more prominent in the preictal period in patients with epilepsy, and suggests prospects for TMS in identifying periods of seizure vulnerability and prognosticating the timing and likelihood of seizure (Wright et al., 2006; Badawy et al., 2009a, b).

The capacity to probe the E:I ratio by TMS may address an important unmet need for patients undergoing antiepileptic therapies for which there are presently few, if any, biomarkers to guide dosing or to identify a favorable therapeutic effect in advance of a change in seizure count. Vagus nerve stimulation (VNS), for instance, results in a significant increase in intracortical

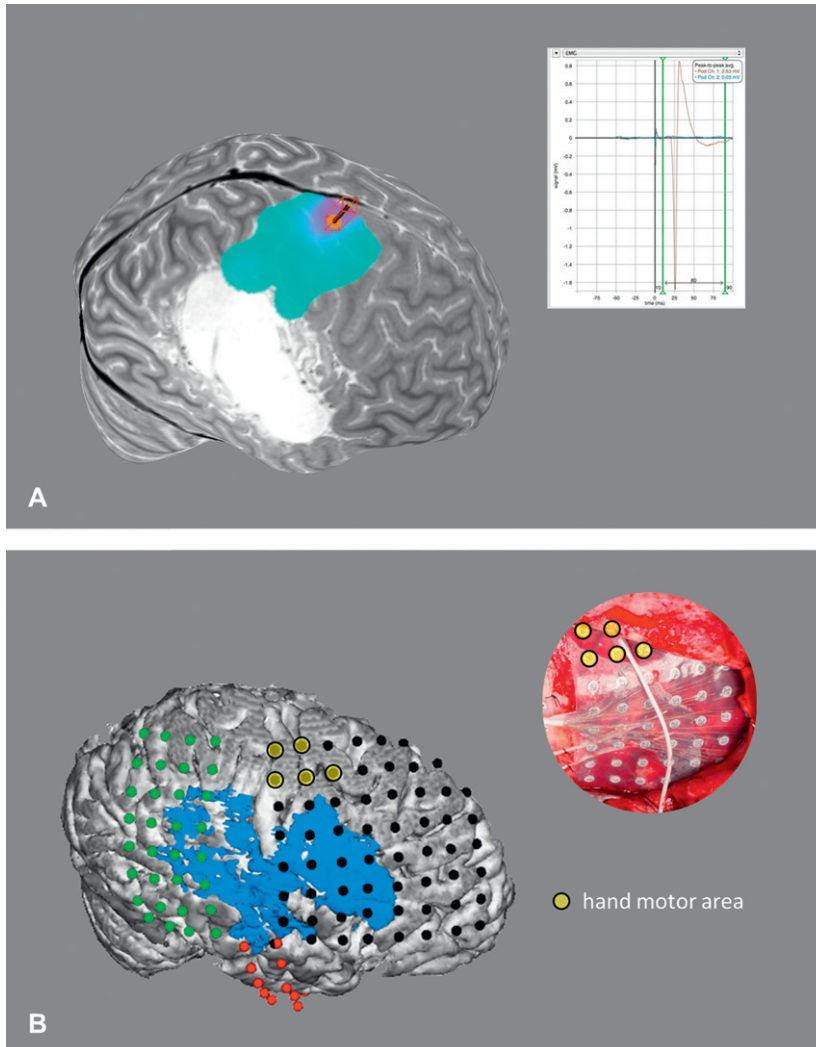


Fig. 39.2. Presurgical motor mapping by transcranial magnetic stimulation (TMS) in patients with epilepsy. (A) First dorsal interosseous (FDI) map obtained during presurgical workup in a patient with lesional intractable focal seizures. Reconstructed brain image shows a region of right frontotemporal encephalomalacia with the FDI map superior and anterior to the lesion margin. Bar marker indicates the region of peak left FDI MEP (inset). (B) Reconstructed subdural electrode map for the same patient. The lesion and its subcortical extension are shaded blue. Electrodes are depicted as solid circles. The area mapped to hand function by presurgical cortical stimulation is marked by yellow circles. Inset shows position of the hand motor area mapped onto the intra-operative electrode photograph. (Courtesy of Drs Chelamani Harini, Joseph R. Madsen, Jurriaan Peters, and Vauhid Taimouri.)

inhibition (Di Lazzaro et al., 2004). Similarly, intracortical inhibition is enhanced by the ketogenic diet (Cantello et al., 2007b). Although the clinical utility of these findings will have to be determined in future trials, these data do underscore a potential for diagnostic TMS to guide existing treatments.

Analogous to motor cortex TMS, TMS coupled with scalp EEG (TMS–EEG) can also be applied to estimate regional excitability of the extramotor cortex (Nikulin et al., 2003; Kahkonen et al., 2005; Lioumis et al., 2009). In support of a realistic TMS–EEG role in measuring cortical excitability in patients with epilepsy, inhibition of the evoked EEG response over extramotor

frontal and parietal cortex, analogous to LIC1, has been recorded with a ppTMS–EEG paradigm (Fitzgerald et al., 2008, 2009). Increased cortical excitability in patients with juvenile myoclonic epilepsy has been shown by a spTMS–EEG protocol, and an interesting extension of these data may be to test whether extramotor LIC1 TMS–EEG abnormalities are present in the epilepsy population (Del Felice et al., 2011). However, as number of TMS–EMG experiments show motor cortex abnormalities in patients with extramotor and generalized epilepsies, further studies are 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

Another interesting role for TMS–EEG in epilepsy may be as a neurological stressor to provoke epileptiform activity in a vulnerable patient or in a vulnerable cortical region. Epileptiform discharge provocation by TMS has been demonstrated in human subjects, but the early results suggested that TMS was no more likely to activate the seizure focus on EEG than was hyperventilation in patients with epilepsy (Hufnagel et al., 1990; Schuler et al., 1993; Steinhoff et al., 1993). However, more recently, evoked EEG responses were evaluated by a spTMS–EEG protocol in patients with focal epilepsy. In this study, the authors identified two broad categories of electrographic evoked response: an early (<100 ms) slow wave response and a late (100–1000 ms) response that was either epileptiform in morphology (resembling a sharp wave or spike) or 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 the authors of this study propose, these data raise the prospects for eventual applications of TMS–EEG to enhance the sensitivity of the scalp EEG in detecting epileptiform abnormalities.

TRANSCRANIAL DIRECT CURRENT STIMULATION IN EPILEPSY

In parallel with TMS, tDCS is also emerging as a potential therapeutic tool in epilepsy, particularly for patients with drug-resistant seizures. During tDCS, cortical activity is modulated by prolonged (minutes) conductance of low-amplitude direct electrical current delivered through scalp electrodes. Applied to the mammalian cerebral cortex, cathodal tDCS induces a durable reduction in cortical excitability, whereas anodal tDCS predictably increases excitability after a single session (Bindman et al., 1964; Nitsche and Paulus, 2000). In epilepsy, the capacity of cathodal tDCS to reduce cortical excitability has prompted research into the antiepileptic potential of this technique (Nitsche and Paulus, 2009). Notably, in contrast to other neurostimulation methods, tDCS intensities are insufficient to generate action potentials in the stimulated cortex (Purpura and McMurtry, 1965), suggesting a mechanism of action more reliant on modulation of ongoing neuronal activity than the induction of

new neuronal activity (Cambiaghi et al., 2011; Fujiwara et al., 2011). The relatively low intracranial currents associated with tDCS likely, at least in part, account for its favorable safety profile. In contrast to TMS, seizures have not been associated with tDCS in patients with epilepsy, and the remaining side-effects are limited largely to skin irritation at the electrode sites (Brunoni et al., 2011).

However, also in contrast to TMS, the antiepileptic efficacy and overall clinical utility of tDCS in epilepsy are also less established. The observation that cathodal tDCS induces a long-term depression (LTD)-type depression in cortical excitability suggests that the hyperexcitability of a seizure focus may be suppressed by tDCS. This hypothesis is supported in part by preclinical data that show an antiepileptic effect in an in-vitro isolated hippocampus seizure model, and in in-vivo rodent focal seizure and status epilepticus models (Bikson et al., 1999; Lian et al., 2003; Liebetanz et al., 2006; Kamida et al., 2011).

Yet in humans with epilepsy, tDCS clinical data are limited. In one randomized controlled trial, cathodal tDCS delivered over the seizure-onset zone in patients with cortical dysplasia was effective in reducing EEG epileptiform discharges, but showed only a statistical trend toward seizure reduction (Fregni et al., 2006b; Auvichayapat et al., 2013). Notably, the favorable EEG response and the trend toward seizure reduction lasted as long as 1 month in some patients. However, in a more recent study, cathodal tDCS applied over a seizure focus failed to suppress continuous focal spikes during sleep (Varga et al., 2011). As with other emerging antiepileptic treatments, further study with rigorous patient stimulation parameter selection is necessary to identify whether and to what extent cathodal tDCS can improve the quality of life of patients with epilepsy.

CONCLUSION

Given that the rate of drug-resistant epilepsy has not changed much in recent years, TMS and tDCS offer plausible noninvasive and nonpharmacological options to improve seizure control in patients with intractable seizures. Although the antiepileptic effects of both procedures need to be substantiated in well selected patient populations, their benign side-effect profile suggests a favorable risk:benefit ratio and a high likelihood of implementation in clinical epilepsy in the near future. TMS, particularly as a diagnostic supplement to epilepsy workup, is further advanced with respect to clinical implementation. At present, TMS combined with frameless stereotaxy has been cleared by the US Food and Drug Administration for presurgical motor mapping, and is already in use for this purpose in some tertiary epilepsy

centers (Najib et al., 2011). Mapping of regional cortical excitability and the implementation of such data in the epilepsy workup seem like the next logical extensions of this work, which is anticipated to run in parallel with further clinical trials of rTMS antiepileptic efficacy. tDCS technology is also evolving, and improved protocols for focal and patient-specific stimulation may soon enable superior targeting of the seizure focus, and are expected to be tested in clinical trials (Sunderam et al., 2009; Datta et al., 2011; Bikson and Datta, 2012). Finally, as with other antiepileptic therapies, mechanistic basic science data and data from preclinical TMS and tDCS trials in animal seizure models are expected to inform some aspects of TMS and tDCS implementation in clinical research. As shown above, the favorable safety profile of these procedures favors rapid translation of preclinical data to clinical trials.

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