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Repetitive transcranial magnetic stimulation in the treatment of epilepsia partialis continua

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ABSTRACT

Objective: Repetitive transcranial magnetic stimulation (rTMS) is a technique for noninvasive focal brain stimulation by which small intracranial electrical currents are generated by a fluctuating extracranial magnetic field. In clinical epilepsy, rTMS has been applied most often interictally to reduce seizure frequency. Less often, rTMS has been used to terminate ongoing seizures, as in instances of epilepsia partialis continua (EPC). Whether ictal rTMS is effective and safe in the treatment of EPC has not been extensively studied. Here, we describe our recent experience with rTMS in the treatment of EPC, as an early step toward evaluating the safety and efficacy of rTMS in the treatment of intractable ongoing focal seizures.

Methods: Seven patients with EPC of mixed etiologies were treated with rTMS applied over the seizure. rTMS was delivered in high-frequency (20–100 Hz) bursts or as prolonged low-frequency (1 Hz) trains. The EEG was recorded for three of the seven patients.

Results: rTMS resulted in a brief (20–30 min) pause in seizures in three of seven patients and a lasting ($\geqslant$1 day) pause in two of seven. A literature search identified six additional reports of EPC treated with rTMS where seizures were suppressed in three of six. Seizures were not exacerbated by rTMS in any patient. Generally mild side effects included transient head and limb pain, and limb stiffening during high-frequency rTMS trains.

Conclusions: Our clinical observations in a small number of patients suggest that rTMS may be safe and effective in suppressing ongoing seizures associated with EPC. However, a controlled trial is needed to assess the safety and anticonvulsive efficacy of rTMS in the treatment of EPC.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been applied in several cases of intractable epilepsia partialis continua (EPC) to terminate the ongoing seizures. Here, we describe a case series summarizing our recent experience with rTMS in the treatment of EPC as an early step toward controlled trials testing the safety and efficacy of rTMS in the treatment of continuous focal seizures.

rTMS is a noninvasive method for focal cortical stimulation that is based on Faraday's principle of electromagnetic induction. During rTMS, small intracranial electrical currents are repetitively generated by a strong fluctuating extracranial magnetic field [1,2]. In recent years, the potential of low-frequency ($\leqslant$1 Hz) rTMS to induce a lasting decrease in cortical excitability has been used in clinical epilepsy, where interictal rTMS delivered over a neocortical seizure focus may reduce seizure frequency [3–5]. The precise mechanism underlying this antiepileptic property is unknown, but likely resembles that of long-term depression (LTD), which can be induced with direct, electrical, low-frequency cortical stimulation.

In contrast to the more common interictal application of rTMS, ictal rTMS may be aimed at interrupting ongoing seizures, rather than reducing seizure frequency in established epilepsy. The rationale for using rTMS to suppress seizures in real time relates to its potential to interrupt ongoing neuronal activity, as well as its potential to change focal cortical excitability (reviewed in [6]). Ictal application of rTMS, however, has not been extensively studied. Accordingly, we reviewed the published reports and report experience in our laboratory to summarize the available efficacy and safety data related to ictal rTMS in cases of EPC.

2. Methods

We reviewed laboratory records to identify patients with refractory EPC who were treated with rTMS at the Berenson–Allen Center of noninvasive brain stimulation (CNBS) and affiliated

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Table 1
Summary of cases of EPC treated with rTMS in the Berenson–Allen Center for noninvasive brain stimulation and affiliated institutions

Patient	Age	Etiology	Coil position	rTMS intensity	rTMS frequency	Train duration	Number of trains	Outcome	Adverse Events
1	42	Hypoglycemia	Seizure focus	100% MT	1 Hz	1800 s	3	Clinical seizures stopped for 30 min after each train, then resumed	none
2	56	Stroke, Hypoglycemia	Seizure focus	100% MT	First session: 1 Hz	20 Hz: 2 s	First session: 1 (1 Hz)	First session: no effect	none
					Second session: 20 Hz, then 1 Hz	1 Hz: 1600 s	Second session: 40 at 20 Hz, then 1 at 1 Hz	Second session: clinical seizures stopped for 20 min, then resumed	
3	33	Unknown	Seizure focus	100% MT	6 Hz then 1 Hz	6 Hz priming, then 1 Hz for 1600 s	2	First session: clinical seizures improved during rTMS Second session: clinical seizures improved during stimulation, stopped for 20 min, then resumed	none
4	18	Unknown	Seizure focus	100% MT	1 Hz	2000 s	1	Clinical seizures stopped, and were absent for remainder of the 2-day inpatient stay[a]	none
5	46	Resected cortical vascular malformation	Seizure focus	90–100% MO	100 Hz, 1 Hz	100 Hz: 0.05–1.25 s	First session: 15 at 100 Hz[b], then 1 at 1 Hz	First session: clinical seizures improved after stimulation, but however, resumed within 3 months	none
						1 Hz: 1600–1800 s	Second session: 10 at 1 Hz, daily	Second session: clinical seizures improved and were suppressed at last follow-up (>4 months after rTMS)	
6 [7]	11	Rasmussen's encephalitis	Seizure focus	100% MT	1 Hz	1800 s	9, daily	Clinical and EEG seizures improved during stimulation, but returned to baseline within 30 min after each daily session	none
7	79	Stroke	Seizure focus	100% MT	20 Hz, 1 Hz	20 Hz: 4 s 1 Hz: 30 min	First session: >20 (20 Hz)	First session: no effect	Scalp, arm and leg pain with 20 Hz
							Second session: 1 (1 Hz)	Second session: clinical seizures involving face, arm, and leg improved slightly to involve arm and leg only[c]	

Note. MO, machine output; MT, motor threshold; age is in years.
[a] Further follow-up is not available.
[b] One-hundred-hertz trains were delivered at successively increasing durations ranging from 0.05 to 1.25 s.
[c] Patient sedated and intubated within 1 day of rTMS, thereafter lost to follow-up.

institutions. All patients presented with EPC lasting 1 day or longer. In all instances, the seizures were refractory to anticonvulsant medications, and a decision to treat the ongoing seizures with rTMS was made by the clinical team. rTMS was delivered by physicians trained in the clinical application of rTMS (A.P.L., A.R., J.M.T.), after informed consent was obtained. When available, accompanying video and EEG recordings were reviewed.

3. Results

3.1. Seizure suppression by rTMS

We treated seven patients with EPC of varying etiology (Table 1). In each instance, seizures were clinically apparent as repetitive myoclonic or clonic movements involving the face, hand, arm, or leg. The stimulating coil was positioned over the scalp region approximating the motor cortex contralateral to the side involved in the clinical movements. The EEG was recorded for some or all of the rTMS sessions for three of seven patients.

In these seven patients, we report one of three observations made during or immediately after rTMS: (1) seizures continued uninterrupted ($n = 2$ patients), or (2) seizures paused for 20–30 min and then resumed ($n = 3$ patients), or (3) seizures stopped and did not resume for the duration of follow-up ($n = 2$ patients). In total, ongoing seizures were disrupted after rTMS in five of seven patients. However, in three, the effect was short-lived, lasting only 20–30 min after an rTMS train before relapse of clinical seizures, whereas in two others, the anticonvulsive effect lasted days or longer.

In two patients who experienced a durable (>1 day) arrest in seizures, follow-up was limited to 2 days in one, and therefore, information about relapse in days after rTMS is not available. However, in one case where extensive follow-up was available, seizures originating near a resected vascular malformation, and characterized by continuous right-hand movements of approximately 20 years' duration, were initially disrupted by high-frequency (100 Hz) rTMS bursts, and a durable (> 4 months) EPC suppression was achieved with 10 daily 30-min sessions of 1-Hz rTMS delivered with a figure-8 coil over the seizure focus.

In the cases in which there was no appreciable pause in seizures after rTMS, some change in seizure was nevertheless observed. In one of the two patients, a child with Rasmussen's encephalitis, seizures were suppressed only for the duration of a 30-min 1-Hz rTMS train, but resumed immediately after rTMS on each of 9 days of daily treatment. Details related to this case were previously published by our group [7]. In the other patient, seizures most likely due to an acute stroke continued without pause, but changed in character immediately after the rTMS trains from a hemiconvulsion involving face, arm, and leg to slightly milder seizures involving arm and leg only.

3.2. Adverse events associated with rTMS

In our experience, as in published cases [8–11], side effects related to rTMS were generally mild and short-lived. The more commonly reported adverse events were transient head and limb pain, and limb stiffening during high-frequency rTMS. Notably, although seizures may be triggered by interictal rTMS in patients with epilepsy [12], in the available data, no instance of seizure exacerbation such as secondary generalization or increase in severity is identified.

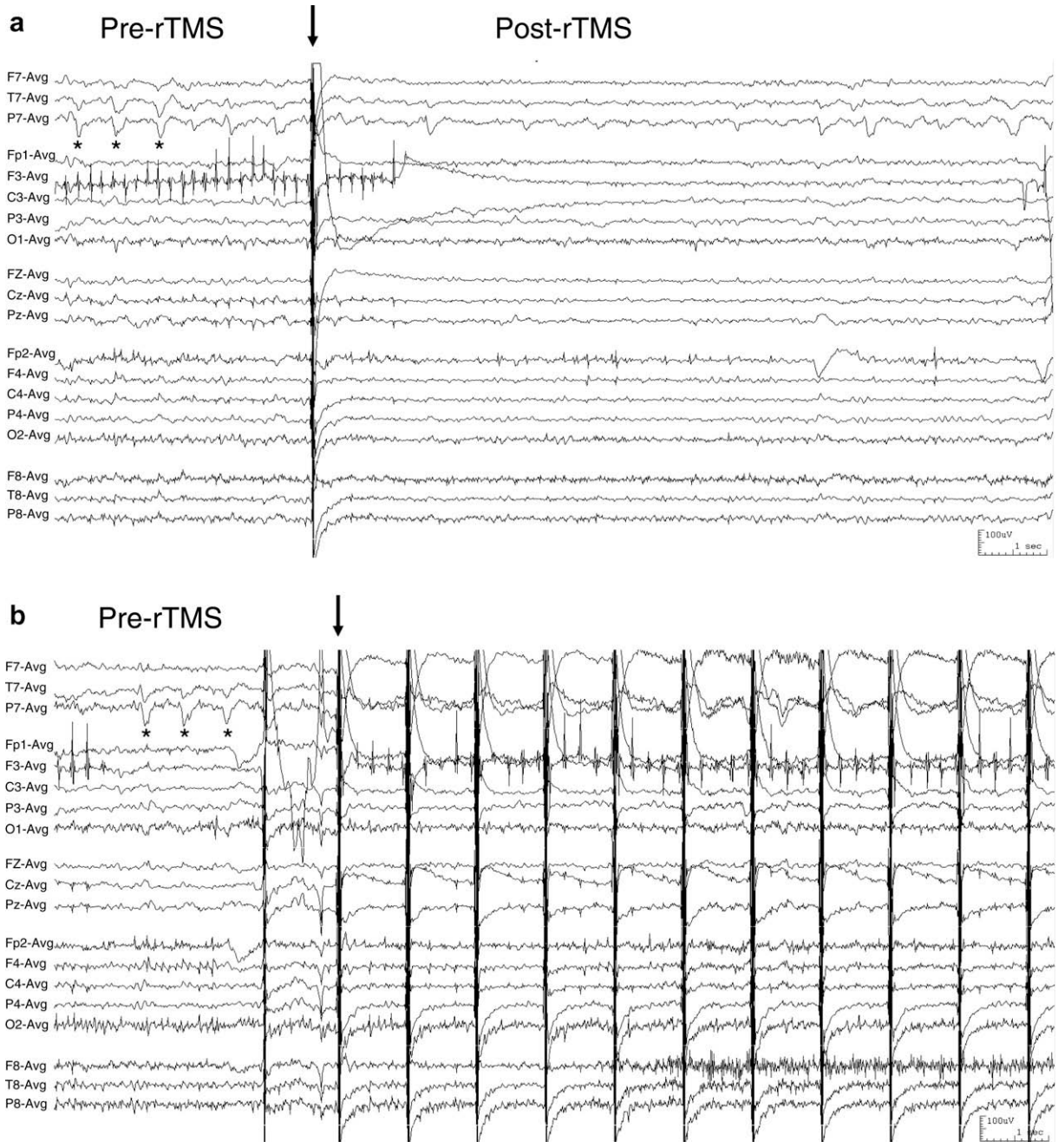

Fig. 1. EEG of a patient with EPC undergoing rTMS. The EEG was recorded with a conventional 10–20 international scalp electrode configuration, filtered 1–70 Hz, and displayed in a referential montage. * Typical left temporal sharp waves. (a) 100-Hz rTMS was at 100% machine output with figure-8 coil for 0.05 second (arrow). EEG following rTMS shows transiently reduced sharp wave frequency. Typical sharp waves (*) precede 1-Hz rTMS (b, arrow) and are absent (c) following rTMS. Note: prominant artifact of the F3 electrode is related to TMS coil positioning.

The absence of a proconvulsive side effect of stimulation is underscored in three instances where EEGs were recorded simultaneously with rTMS. In these cases, we reviewed the EEGs and found no evidence of subclinical exacerbation such as generalization or spike provocation with either high- or low-frequency rTMS. Representative EEGs from one patient are shown in Fig. 1, and another EEG has been previously published by our group [7].

4. Discussion

We present an overview of our experience with use of rTMS for treatment of EPC. A major limitation of the current study is that the data obtained were from a small and heterogeneous group of patients with EPC who were treated with rTMS. Accordingly, conclusions with respect to anticonvulsive efficacy cannot be made at this point. Patient characteristics, seizure mechanisms, and rTMS protocols that are best associated with EPC suppression need to be addressed in future studies. Interactions of rTMS with anticonvulsants and other medications that may facilitate or interfere with its anticonvulsive potential also have to be investigated. However, the transient (minutes) seizure suppression in three of seven patients and the durable (days to months) seizure suppression in two of seven patients suggest that there may be utility in future controlled trials of rTMS in EPC

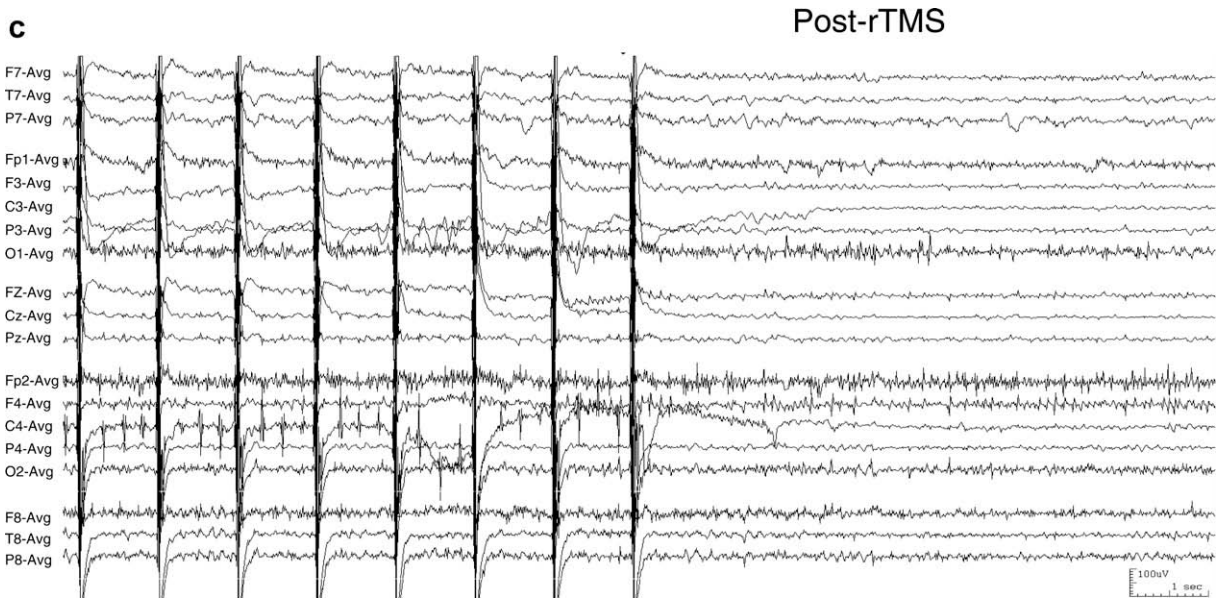

Fig. 1 (*continued*)

management. In particular, the lasting response of some patients to low-frequency rTMS trains raises the possibility that repetitive stimulation protocols that lead to reduced cortical excitability, perhaps by induction of long-term depression-like changes in synaptic strength, may be of benefit in terminating ongoing seizures as well as in preventing their relapse.

Our observations are inline with published reports that also demonstrate relatively inconsistent efficacy of rTMS in the treatment of EPC. A literature search, as well as a search of the American Epilepsy Society's online abstract archive, identified six additional reports of EPC treated with low-frequency (0.5–1 Hz) or high-frequency (6–20 Hz) rTMS trains (Table 2). Clinical seizures were suppressed in three of six reported cases. As in our experience, published cases were of EPC due to mixed etiology in a heterogeneous group of patients. Consistent patient characteristics that favored seizure suppression by rTMS were not identified in our review of the literature, although the few instances where a clinical benefit lasting days or longer was achieved were associated with low-frequency rTMS trains. Similarly, in instances where seizures continued after rTMS, there were no consistent findings with respect to EPC etiology.

Adverse events in our small series were relatively mild and stopped immediately after stimulation. Encouragingly, seizure exacerbation, which is a concerning potential side effect of rTMS [12], was not seen by our group and was not reported elsewhere. There thus appears to be no evidence that using rTMS during active seizures will lead to an increase in severity or in generalization of the seizure. Indeed, in cases where rTMS was combined with real-time EEG, provoked spikes or subclinical seizure exacerbation was not observed (Fig 1, and published in [7]). As with efficacy, the safety of rTMS in EPC treatment will have to be the focus of future controlled trials.

A natural extension of the work with EPC may be the application of rTMS to other forms of intractable status epilepticus. The above-described suggestion of clinical efficacy and the relatively benign safety profile of rTMS in patients with epilepsy [12] suggest that rTMS warrants consideration, perhaps, in cases of primary or secondarily generalized seizures, where rTMS may be used to disrupt organized cortical activity. We anticipate that near-future work with patients as well as with animal status epilepticus models will provide more insight into the clinical applications of this method.

Table 2
Summary of published cases of EPC treated with rTMS

Patient	Age	Etiology	Coil position	rTMS intensity	rTMS frequency	Train duration	Number of trains	Outcome	Adverse events
1 [8]	7	Unknown, focal cortical atrophy on MRI	Seizure focus	50% MO	20 Hz	2 s	15	Clinical seizures became intermittent and stopped in 24 h	None reported
2 [8]	11	Unknown, focal cortical atrophy on MRI	Seizure focus	128% MT	20 Hz	2 s	15	No change in clinical seizures, improved EEG	None reported
3 [11]	48	Unknown Normal MRI	Seizure focus	100% MT	0.5 Hz	900 s	16 (2 trains/session, biweekly, for 4 weeks)	Clinical seizures decreased during rTMS, and decreased further on follow-up	None reported
4 [9]	31	Cortical dysplasia	Seizure focus	90% MT	0.5 Hz	200 s	1	Clinical seizures stopped, resumed in 2 months, and stopped again with rTMS	None reported
5 [10]	8	Neuronal ceroid lipofuscinoscis (probable)	Seizure focus	100% MO	6 Hz then 1 Hz	6 Hz: 5 s 1 Hz: 600 s	3 (1 Hz, one preceded by four trains at 6 Hz)	No change	None reported
6 [10]	16	Perinatal stroke	Seizure focus	76% MO	6 Hz, then 1 Hz	6 Hz: 5 s 1 Hz: 900 s	2 (1 Hz, one preceded by 4 trains at 6 Hz)	No change	Mild headache and leg pain

Note. MO, machine output; MT, motor threshold.

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