# Transcranial magnetic stimulation in patients with epilepsy

Anil Dhuna, MD; John Gates, MD; and Alvaro Pascual-Leone, MD, PhD

**Article abstract**—We studied the effects of transcranial magnetic stimulation (TMS) applied in trains of 8- to 25-Hz stimuli on electroencephalographic epileptiform activity on eight patients being evaluated for epilepsy surgery. We performed the stimulation with a round water-cooled stimulation coil held flat on the scalp and centered over different positions of the International 10-20 System. We were unable to trigger seizures or induce epileptiform discharges arising from the epileptic focus in any of the eight patients with any of the stimulation protocols. However, we induced a partial motor seizure from the contralateral hemisphere to the exclusive temporal focus in the only patient stimulated with 100% maximal intensity. Precautions have to be taken when applying rapid TMS to patients because of the risk of seizure induction. Our results do not support the view that TMS specifically activates the epileptic foci.

NEUROLOGY 1991;41:1067-1071



TMS has been recently advocated as a noninvasive means of determining the language-dominant hemisphere,[1] and the selective activation of epileptic foci.[2] In order to use TMS for the former use, faster rates of stimulation (8 to 25 Hz) are required than those possible with commercially available stimulators (0.3 Hz). The lower rates of stimulation with commercial stimulators have been shown to be safe,[3-6] even for patients with epilepsy.[7-9] Kindling is a growing concern with rapid TMS (rTMS). However, kindling has never been documented in the large number of patients who have undergone electrical cortical stimulation (ECS) over the years, despite the use of stimulation rates of up to 60 Hz for 5 to 15 seconds in sessions of up to 3 hours for 3 to 5 consecutive days.[10,11] No danger of kindling should exist using rTMS at frequencies of up to 25 Hz since the maximum current density induced is approximately four times smaller than with ECS.[12] A single report of pathologic damage to the brain of rats with TMS[13] remains controversial, and other investigators have failed to demonstrate pathologic changes despite applying TMS at frequencies up to 8 Hz.[14]

Topectomies or lobectomies as surgical treatment for partial, medically intractable epilepsies are indicated mainly for patients with a single epileptic focus. To select suitable surgical candidates, long-term monitoring with video-EEG is required to record several characteristic ictal events. Despite tapering of the antiepileptic drugs (AEDs) to increase the seizure frequency, the prospective surgical candidates are generally subjected to several weeks of hospitalization. There are several proposed methods to activate epileptic foci and shorten the required monitoring time, but the usefulness of all these methods is limited since the induced epileptiform activity may arise from a site other than the patient's characteristic ictal focus. Recently, Huhnagel et al[2] found selective activation of the epileptic focus with TMS and suggested that TMS be used as an additional tool in presurgical evaluation. Their study was performed on patients with implanted subdural electrode arrays (SEAs) over the presumed epileptic focus.

The main aims of this study were to evaluate the safety of rTMS up to frequencies of 25 Hz in patients with epilepsy, and to investigate the possibility of using TMS to selectively activate the epileptic focus in patients with epilepsy undergoing presurgical evaluation.

**Methods.** The subjects for this study were volunteers among the patients hospitalized at MINCEP's long-term monitoring unit at Abbott-Northwestern Hospital (ANH) between January and March 1990. We studied eight adult patients with medically intractable partial epilepsy being evaluated for surgical treatment. Six of them were included in an additional study protocol aimed at determining hemispheric dominance of speech and language with rTMS.[1] The table summarizes the clinical characteristics of all the subjects. None had undergone brain surgery or had cochlear implants or cardiac pacemakers. Informed consent was obtained in all patients prior to enrollment into the study, which had been approved by the Human Ethics Committee at ANH and at the University of Minnesota.

rTMS was performed with a Cadwell Rapid-Rate Magnetic Stimulator specially designed to deliver stimuli at a frequency of up to 25 Hz.[1] This is a net-0-charge stimulator with a maximal output to the patient of approximately 0.2 mJ per pulse. The power of the discharges can be regulated in 20%

From the Department of Neurology (Drs. Dhuna and Pascual-Leone), University of Minnesota, and MINCEP Epilepsy Care PA (Dr. Gates), Minneapolis, MN.

Presented in part at the 115th annual meeting of the American Neurological Association in Atlanta, GA, in October 1990.

Received September 19, 1990. Accepted for publication in final form December 4, 1990.

Address correspondence and reprint requests to Dr. Anil Dhuna, Department of Neurology, University of Minnesota, P.O. Box 295 UMHC, 420 Delaware Street SE, Minneapolis, MN 55455.

Table. Summary of the clinical histories, rTMS stimulation frequencies and intensities, and the EEG and MRI results of the eight patients studied with rTMS

| Pt no. | Age/Sex (yrs) | Seizure types | AEDs (μg/ml) | EEG | | MRI | Frequencies (Hz) | Intensities (% max. output) | Approximate no. stimuli/ position |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Ictal focus (electrode) | Interictal activity (electrode) | | | | |
| 1 | 30/M | PS, PC<br>PS-2° GTC<br>PC-2° GTC | PHT (3.4) | Rt. temporal (Sp2) | None | Rt. anterior temporal vascular malformation | 8, 16, 25<br>8 | 60<br>80 | 570 |
| 2 | 32/F | PC<br>PC-2° GTC | PHT (9.0) | Lt. temporal (F7, T3, Sp1) | Occasional spikes (F7, Sp1) | Normal | 8, 16<br>8, 16<br>16<br>16 | 40<br>60<br>80<br>100* | 800 |
| 3 | 38/F | PC<br>PC-2° GTC | CBZ (6.9) | Lt. temporal (F7, T3, T5) | Bitemporal independent spikes | Normal | 8, 16, 25<br>0.1, 0.3, 1<br>8, 16, 25 | 40<br>60†<br>60 | 980 |
| 4 | 49/M | PC<br>PC-2° GTC | CBZ (10.4) | Rt. temporal (Sp2, F8) | Rt. mesio-temporal sharp waves (Sp2) | Normal | 8, 16, 25<br>8, 16 | 60<br>80 | 730 |
| 5 | 24/F | PC | VPA (123) | Lt. temporal (Sp1, F3) | Lt. temporal slowing (max. at Sp1) | Normal | 8, 16, 25<br>8, 16, 60<br>8 | 40<br>80 | 820 |
| 6 | 34/M | PC<br>PC-2° GTC | PHT (11)<br>VPA (100) | Rt. temporal (Sp2, F8) | Bitemporal independent sharp waves and spikes | Normal | 8, 16, 25<br>8, 16, 25<br>8 | 40<br>60<br>80 | 1,060 |
| 7 | 23/M | PC | VPA (80.5) | Lt. and rare Rt. temporal | Sharp-and-slow waves (Sp1, T3, rarely Sp2) | Lt. temporal arachnoid cyst | 8, 16, 25 | 60 | 490 |
| 8 | 34/F | PC<br>PC-2° GTC | PHT (8.2) | Lt. temporal (Sp1, F7, T3) | Bitemporal independent sharp waves | Normal | 8, 16, 25<br>8, 16 | 60<br>80 | 730 |

Patients 1-6 had been included in another study.[12]

AEDs Antiepileptic drugs.
MRI Cranial magnetic resonance imaging.
PS Partial simple seizures.
PC Partial complex seizures.
2° GTC Secondarily generalized tonic-clonic seizures.
PHT Phenytoin.
CBZ Carbamazepine.
VPA Valproate.
Rt Right.
Lt Left.
* Applied only over P4.
† 50 stimuli with each frequency over each electrode position.

Electrodes refer to the electrode positions according to the International 10-20 System.



increments for an output of 0 to 100% maximal output intensity. Each stimulus produced by this device is similar to that by the Cadwell commercial stimulator, with a pulse width of 50 μsec, peak voltage gradient of approximately 6 V/cm, and a calculated charge density/phase 1 to 2 μC/cm². A water-cooled, round stimulation coil of 9.5-cm inner and 11-cm outer diameter was employed.

rTMS was performed by investigators blinded to the localization of the patient's epileptic focus. At stimulation, the coil was held flat on the scalp (tangential coil orientation) with the outer edge centered successively over F7(8), F3(4), T3(4), C3(4), and T5(6) according to the International 10-20 System. In the six patients included in the speech lateralization study,[1] rTMS was performed over additional scalp areas. In four randomly selected patients (patients 1, 3, 4, and 8) stimulation was begun over the right hemisphere, and over the left in the other four. The rTMS stimulation frequencies and intensities for each patient are summarized in the table. During the stimulation the patients were continuously monitored with video-surface EEG and ECG. The baseline EEG (5 minutes before rTMS was begun) was compared with the poststimulation EEG (5 minutes immediately after completion of the entire rTMS protocol) to establish the effects of the stimulation on the epileptiform and background activities. In addition, 10-second EEG epochs recorded before and after each rTMS train were compared.

Results. No differences were found when comparing the baseline with the poststimulation EEG, except in patient 2. Analysis of the 10-second epochs after each rTMS train did not demonstrate any changes in background activity or frequency of epileptiform discharges. However, this analysis was limited by up to 2 to 3 seconds of poststimulus artifact.

Patient 2, who had a well-documented left mesial temporal epileptic focus, was the only subject to receive rTMS at 100% maximal output intensity. Applying rTMS at this intensity and 16-Hz frequency with the coil centered over P4 induced afterdischarges phase-reversing at P4 (figure 1). Following a second train of stimulation over the same site, she experienced a clinical right simple motor seizure with jacksonian march, which secondarily generalized on EEG. After the convulsion, no further rTMS was performed on this patient.

The seizure frequency was recorded in all patients for 10 days prior to, and in most patients after, rTMS by continuous video-EEG monitoring. The interpretation and significance of these results are limited, since most of the subjects were undergoing changes in their AEDs during the hospitalization. Despite this medication

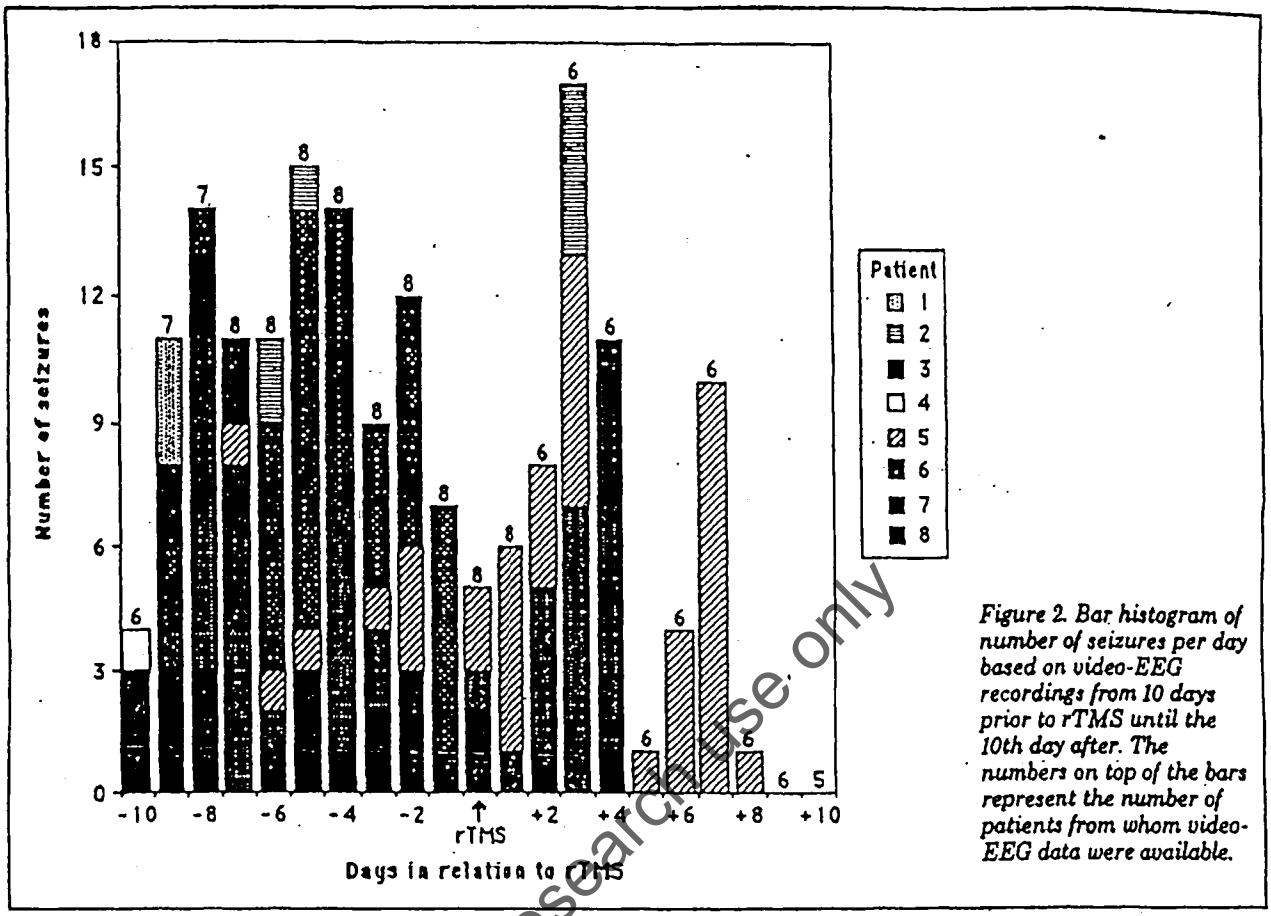


*Figure 2. Bar histogram of number of seizures per day based on video-EEG recordings from 10 days prior to rTMS until the 10th day after. The numbers on top of the bars represent the number of patients from whom video-EEG data were available.*

clusively from the left temporal lobe. She was the only patient who received rTMS at 100% maximal output intensity. A first 10-second rTMS train at this high intensity resulted in an afterdischarge, and the seizure developed during a second train at the same intensity over the same area. A similar problem is encountered with ECS, which induces seizures in up to 10% of patients when applied to sites distant from the patient's epileptic focus.[11]

rTMS has the potential of eventually being a means of noninvasively mapping speech-related cortical areas, and possibly clinically replacing the intracarotid sodium amobarbital test.[1] We recommend that rTMS testing be done on days when the subject has been relatively seizure-free, that there be continuous on-line EEG monitoring, and that stimulation be discontinued immediately following the appearance of afterdischarges. Despite this, induction of seizures is possible and has to be anticipated. Therefore, rTMS studies should be conducted in a hospital setting and by investigators familiar with the diagnosis and treatment of seizures. Although we did not find any significant complications of rTMS, further work aimed at addressing safety issues is needed.

The second aim of our study was to evaluate the possibility of selective activation of the epileptic focus with TMS. Hufnagel et al,[2] using TMS with the commercially available Magstim 200-Novametrix stimulator, were able to activate the epileptic focus in 12 of 13 patients with medically intractable epilepsy. At the time of TMS, the AEDs had been reduced in their patients for the purpose of ictal event recording. In all their patients, TMS was applied with SEAs implanted over the suspected epileptic focus. They documented by electrocorticography facilitation of epileptiform afterdischarges with sequential stimulation, but were unable to elicit epileptiform potentials outside the epileptic foci. In one of their patients, they induced a complex partial seizure identical to the patient's habitual seizures.

Our patient population is similar to that studied by Hufnagel et al[2] with the sole exception that none of our patients had undergone a craniotomy or had sphenoidal or subdural electrodes in place. In contrast to that study,[2] we were unable to document selective activation of the seizure focus in any of our patients. Furthermore, we induced a partial simple motor seizure from the hemisphere contralateral to the single epileptic focus in one patient. These conflicting results could be related to a number of methodologic aspects. First, the TMS stimulators and stimulation coils employed were different, which would result in different magnetic fields and induced current in the tissue. Particularly important may be that Hufnagel et al[2] used a stimulator with a "critical damped" current output; the possibility therefore exists of polarization of the tissue with repeated stimulation. Second, Hufnagel et al[2] used stimulation frequencies of 0.1 to 0.3 Hz, whereas we stimulated our patients at 8, 16, or 25 Hz. The activation of the epileptic focus could conceivably occur preferentially at low stimulation fre-

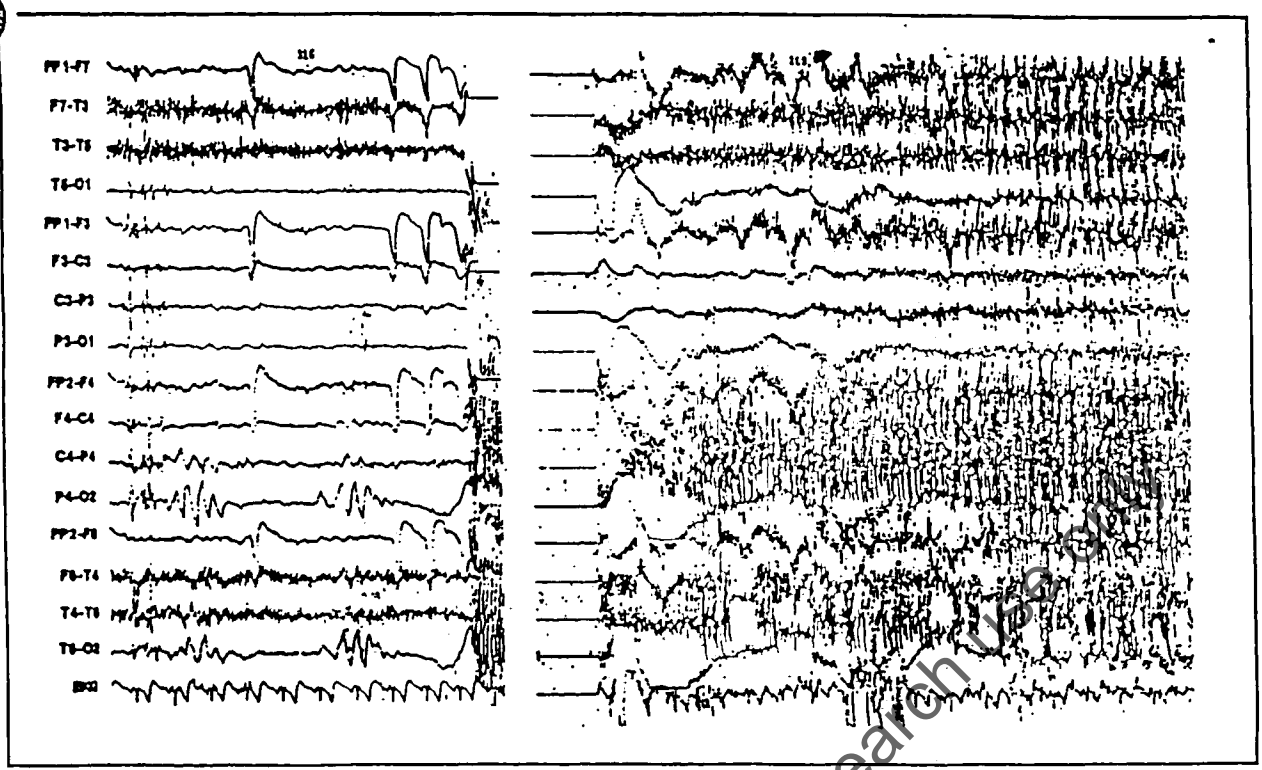


*Figure 1. Surface-recorded EEG on patient 2 during rTMS session. (Left) Afterdischarges phase-reversing at P4 after first 10-second rTMS train at 100% maximal output intensity over the right hemisphere. (Right) Following a second rTMS train stimulation at 100% intensity over the same location, the patient had a right hemispheric simple motor seizure with electroencephalographic generalization.*

change, the overall trend showed no evidence of seizure frequency exacerbation following rTMS (figure 2). Patient 5 represents an exception; around the time of rTMS her valproic acid was being tapered. Following this reduction, she had a dramatic increase in seizure frequency (no seizures on day −4 to 11 seizures on day +7). The seizures were controlled with a valproic acid load and the addition of felbamate. The typical seizures recorded prior to the rTMS stimulation protocol were not altered following stimulation. This was true even for patient 2 who was recorded for 25 days after the atypical rTMS-induced seizure. No increase in seizure frequency or further right-hemispheric seizures were documented. Subsequently, this patient underwent a left temporal lobectomy, and histopathologic analysis of the resected anterior temporal lobe and hippocampus was normal.[15]

In patient 3, additional stimulations were performed at low frequencies. Fifty stimuli were given with the coil centered over T3 and T4 at 0.1, 0.3, and 1 Hz. No EEG changes were demonstrated following these stimulations.

All the subjects tolerated the procedure very well, although when the stimulating coil was placed anterior the ear on the scalp, the subjects experienced a painful ipsilateral facial contraction. Similarly, stimulation of the occiput produced neck muscle contraction. Patient 1 developed, during rTMS, a skin irritation under an EEG scalp-recording electrode. The lesion was round and limited to the area within the electrode cup. Allowing sufficient time for gel cooling between stimulation periods precluded recurrence. Also, several of the subjects complained of a mild transient headache following the stimulation protocol.

**Discussion.** Several studies have reported on the lack of epileptogenicity of TMS at frequencies up to 0.3 Hz. Claus[6] reported that in over 2,000 TMS examinations at the National Hospital for Nervous Diseases, London, no seizures occurred. Michelucci et al[9] failed to show changes in seizure frequency or induction of seizures in epileptic patients. Only three seizures have been reported to be possibly related to TMS. Hömberg et al[16] reported on a patient with a 6-month-old stroke who developed a first tonic-clonic seizure during TMS. Subsequently, he had further spontaneous seizures; TMS may have only precipitated the manifestation of postinfarction epilepsy. Hufnagel et al[2] comment on the induction of a partial complex seizure identical to the patient's habitual spontaneous seizures while stimulating at low frequencies (up to 0.1 Hz) over the patient's epileptic focus. Tassinari et al[8] stimulated 58 epileptic patients; only one had a seizure, which occurred 20 seconds after TMS and was not different from the patient's characteristic convulsions. In all these cases it remains uncertain whether the seizures were induced by TMS or coincidental with it.

Among our eight patients, one had a seizure during rTMS. This case is unique, since the seizure during rTMS arose from the right hemisphere, which was being directly stimulated at the time, whereas her spontaneous seizures were partial complex arising ex-

quencies, since they may not interfere with the development of epileptiform afterdischarges.[2] However, we failed to show activation of epileptiform discharges in patient 3 who was stimulated at 0.1, 0.3, and 1 Hz. Third, the protocol used by Hufnagel et al[2] involved stimulation over craniotomy sites, which may channel current flow and create a more focal stimulation with higher charge density.[17] Finally, Hufnagel et al[2] applied TMS over SEAs, which may have induced much higher charge densities under the subdural electrodes than is otherwise obtainable with TMS. One of our patients developed a round skin irritation with TMS under an EEG scalp-recording electrode. This raises concerns about the safety of TMS over SEAs, with the risk of similar complications at SEA-brain interface. Studies are required to document the induced charge densities and possible pathologic changes in the brain after TMS over SEAs.

In summary, we believe that rTMS is a useful technique for cortical functional mapping, although we do not consider it useful for delineating the epileptic focus or for selective activation.

## References


1. Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 1991;41:697-702.
2. Hufnagel A, Elger CE, Durwen HF, Böker DK, Entzian W. Activation of the epileptic focus by transcranial magnetic stimulation of the human brain. Ann Neurol 1990;27:49-60.
3. Bridgers SL, Delaney RC. Transcranial magnetic stimulation: an assessment of cognitive and other cerebral effects. Neurology 1989;39:417-419.
4. Cohen LG, Hallett M. Cortical stimulation does not cause short-term changes in the electroencephalogram. Ann Neurol 1987;21:512-513.
5. Levy WJ, Oro J, Tucker D, Haghighi S. Safety studies of electrical and magnetic stimulation for the production of motor evoked potentials. In: Chokroverty S, ed. Magnetic stimulation in clinical neurophysiology. Boston: Butterworth, 1989:165-172.
6. Claus D. Die transkranielle motorische Stimulation. Stuttgart: Gustav Fischer Verlag, 1989.
7. Kandler R. Safety of transcranial magnetic stimulation [Letter]. Lancet 1990;335:469-470.
8. Tassinari CA, Michelucci R, Forti A, et al. Transcranial magnetic stimulation in epileptic patients: usefulness and safety. Neurology 1990;40:1132-1133.
9. Michelucci R, Rubboli G, Plasmati R, Salvi F, Forti A, Tassinari CA. Transcranial magnetic stimulation of the cerebral cortex in epilepsy [Abstract]. Neurology 1989;39(suppl 1):414.
10. Lesser RP, Lüders H, Klem G, et al. Extraoperative cortical functional localization in patients with epilepsy. J Clin Neurophysiol 1987;4:27-53.
11. Engel J. Surgical treatment of the epilepsies. New York: Raven Press, 1987.
12. Agnew WF, McCreery DB. Considerations for safety in the use of extracranial stimulation for motor evoked potentials. Neurosurgery 1987;20:143-147.
13. Matsumiya Y, Yamamoto T, Miyauchi S, Yarita M, Kling JW. Effect of pulsed magnetic stimulation of the head II: neuropathological changes in the rat [Abstract]. J Clin Neurophysiol 1989;6:354.
14. Sgro JA, Stanton PC, Emerson RG, Ghatak NR. Repetitive high magnetic field stimulation: the effect upon rat brain [Abstract]. J Clin Neurophysiol 1991 (in press).
15. Gates JR, Dhuna A, Pascual-Leone A. Lack of pathological changes in human temporal lobe after transcranial magnetic stimulation [Abstract]. Epilepsia 1990;31:646.
16. Hömberg V, Netz J. Generalized seizures induced by transcranial magnetic stimulation of motor cortex [Letter]. Lancet 1989;2:1223.
17. Cadwell J. Principles of magnetoelectric stimulation. In: Chokroverty S, ed. Magnetic stimulation in clinical neurophysiology. Boston: Butterworth Publishers, 1989:13-32.