Lack of Pathologic Changes in Human Temporal Lobes After Transcranial Magnetic Stimulation

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Summary: Most animal studies have failed to demonstrate pathologic changes in the brain after transcranial magnetic stimulation (TMS). Nevertheless, vacuolar lesions in the cortex of rats after TMS have been reported. We report the first histopathologic studies of human brains after TMS in 2 patients with epilepsy who underwent temporal lobectomies. They had been involved in a study to determine the speech-dominant hemisphere by TMS and had received ~2,000 stimuli centered over the resected temporal lobe. Histologic study of the surgical specimens did not show any lesions attributable to TMS in these 2 patients. Key Words: Transcranial magnetic stimulation—Equipment safety—Epilepsy—Brain pathology—Temporal lobe.

Since introduction of the magnetic stimulator as a clinical tool in 1985 (Barker et al., 1985), more applications for transcranial magnetic stimulation (TMS) in clinical neurophysiology and research are being developed (Chokroverty, 1989). The magnetic stimulator is a capacitor discharge system: Storage capacitors are charged to a voltage determined by the stimulus strength required and can then be discharged into the stimulating coil through solid-state switches. The flow of current in the coil generates a magnetic field pulse which is oriented perpendicularly to the wire windings in the coil. This magnetic field induces a secondary current in the tissue which is perpendicularly oriented to the magnetic field, i.e., parallel to the primary current in the coil (Barker et al., 1985; Jalinous, 1988; Cadwell, 1989). TMS is noninvasive and does not transmit any electrical current directly to the tissue, but the potential dangers of the eddy currents induced in the brain must be considered (Barker et al., 1985; Agnew and McCreery, 1987). Most studies have failed to demonstrate any pathologic changes in the brain of animals repeatedly stimulated with TMS (Sgro et al., 1989; Tsubokawa et al., 1989), but Matsumiya et al. (1989) described vacuolar lesions in several cortical layers in rats after TMS stimulation. We report the first pathologic studies of humans stimulated repeatedly with TMS.

METHODS

Subjects of this report are 2 patients with medically intractable epilepsy who were part of a study to determine the speech-dominant hemisphere using TMS (Pascual-Leone et al., 1991) and who have in the meantime undergone anteromesial temporal lobectomy. Informed consent was obtained before patients were enrolled in the study, which had been approved by the Human Ethics Committee at Abbott Northwestern Hospital and at the University of Minnesota. Both patients were experiencing multiple daily partial complex and secondarily generalized seizures despite use of multiple antiepileptic drugs (AEDs). Table 1 summarizes the ages, seizure types and frequencies, localization of seizure foci, and surgical treatment of both patients. At the time of the TMS study, both were being tapered on AEDs for the purpose of preoperative characterization of the ictal focus. Location of the ictal focus was based on video-surface EEG recording of 12 and 16 seizures, respectively.

TMS was performed with a Cadwell Rapid-Rate Magnetic Stimulator. This is a net-0 charge stimulator specially designed to deliver stimuli at a frequency of ≤25 Hz (Gates et al., 1990). The power of the discharges can be regulated for an output of 0–100% maximal output intensity. Each sinusoidal
stimulus has a pulse width of 50 μs. The peak voltage gradient is ~6 V/cm, and the calculated charge density/phase is 1-2 μCoulombs/cm² (personal communication, Dr. John Cadwell). A water-cooled, round stimulation coil of 11-cm inner diameter was used in the study.

In both patients, TMS was performed with the outer edge of the coil centered over the point of stimulation and the coil held in a sagittal plane angulated toward the vertex so that it lay flat on the scalp. Stimulation was performed over F7(8), F3(4), T3(4), C3(4), T5(6), and P3(4), and nine other points over each hemisphere defined by dividing in halves the distances between the above 10-20 International Electrode System positions (Pascual-Leone et al., 1991). The stimulation parameters used in the patients are summarized in Table 1.

The 2 patients underwent temporal lobectomy 2 and 4 weeks after TMS study, respectively. The surgical procedure was decided based on the combined results of long-term neurodiagnostic monitoring with video-EEG, neuropsychologic assessment, intracarotid sodium amytal (Wada) testing, and intraoperative electrocorticography (Gates, 1986). After removal, the temporal lobe specimens were immediately fixed in 10% neutral formalin for 1-2 weeks. Thereafter, sections were embedded in paraffin and thin sections for microscopy were obtained with a microtome. Only H&E stains were performed.

RESULTS

Patient 1 underwent a standard left anterotemporal lobectomy without resection of the amygdala-hippocampus complex. Patient 2 had a standard right temporal lobectomy with limited resection of the hippocampus. All resected portions of the temporal lobe of patient 1 were normal (Fig. 1). Patient 2 was known to have an area of increased T2 signal on cranial magnetic resonance imaging (MRI) in the anterior right temporal lobe. Histopathologic examination of the surgical specimen showed a vascular malformation most likely a cavernous hemangio-

![Figure 1: Patient 1. H&E-stained section of left temporal cortex (original magnification ×10). No pathologic changes were evident.](image-url)
ma. anterior in the temporal lobe beneath the meninges in the gray matter (Fig. 2). The hemangioma appeared to be degenerating, and there was evidence of old hemorrhage with hemosiderin-laden macrophages in the adjacent cortex. No evidence of recent hemorrhages surrounding the hemangioma was noted. The rest of the resected temporal lobe cortex (Fig. 3) and the hippocampus (Fig. 4) were normal.

Patient 1 did have a seizure, an uncharacteristically isolated, partial motor event as a consequence of stimulation, as documented by simultaneous EEG monitoring. Neither patient had a significant increase in ictal events of any type, however, while under observation on the epilepsy unit for several days or by report after discharge (Khuna et al., 1991).

**DISCUSSION**

Direct cortical electrical stimulation with a charge density of about 0.05 μCoulombs/cm² applied at 50 Hz continuously for 24 h will not cause any detectable brain damage (Agnew et al., 1983). TMS of 60% maximal intensity with the Cadwell Rapid-Rate Magnetic Stimulator used in this study causes a calculated cortical charge density/phase of only 1–2 μCoulombs/cm² (personal communication, Dr. John Cadwell). Thus, there is a large safety margin between the estimated currents required to yield histologic damage with direct electrical stimulation and those induced in the brain with TMS (Agnew and McCreery, 1987). Nevertheless, Matsumiya et al. (1989) reported minute vacuolar lesions in cortical layers 3–4 and sometimes in layers 1–2 and 5–6 in

**FIG. 2.** Patient 2. H&E-stained sections of the vascular malformation (original magnification ×5). Details provided in text.

**FIG. 3.** Patient 2. H&E-stained section of the right temporal lobe cortex distant from the vascular malformation (original magnification ×10). No pathologic changes were evident.
rats after >700 TMS at 2.8 T. These findings are very controversial because other researchers have failed to show any pathologic changes with TMS. Sgro et al. (1989) stimulated rats with TMS for 20 min at a rate of 7 Hz (~10,000 stimuli) and failed to demonstrate pathologic changes with either H&E staining or with electronmicroscopy. Similarly, Tsubokawa et al. (1989) stimulated cats 1,000 times transectionally with maximum magnetic field pulses of 4,000 A and did not observe extravasation of Evans blue (indicating lack of damage to the blood-brain barrier) or pathologic changes on histologic or electronmicroscopic studies. No previous reports of pathologic studies in humans who underwent TMS are available.

The histopathologic study of the surgical specimens in our patients did not show any lesions attributable to TMS although they had received ~2,000 stimuli with the coil centered directly over the studied anterotemporal lobe (F7 or F8, T3 or T4, and intermediate position). No statements about delayed pathologic injury from TMS can be made, and continued observation is required. When epileptic patients who have undergone TMS undergo operation, the surgical specimens should be studied carefully.

REFERENCES


FIG. 4. Patient 2. H&E-stained section of the hippocampus (original magnification ×10). No pathologic changes were evident.