MRI study of human brain exposed to high-dose repetitive magnetic stimulation of visual cortex

Article abstract—T1-, T2-, and diffusion-weighted MRI was used to determine whether repetitive transcranial magnetic stimulation (rTMS) affects the blood–brain barrier or induces localized brain edema. In 11 healthy individuals, 1,200 to 3,800 stimuli were applied over the visual cortex of one hemisphere in series of 5-, 10-, or 20-Hz stimulus trains. MRI performed 6 minutes to 6 hours after rTMS did not show pathologic changes in conventional MRI sequences, after application of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA), or by determining apparent diffusion coefficients. **Key words:** Repetitive transcranial magnetic stimulation—MRI—Visual cortex—Phosphenes—Safety—Blood–brain barrier—Brain edema.

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Rapid-rate repetitive transcranial magnetic stimulation (rTMS) with ≤20 Hz is increasingly used to study complex brain functions and to treat mood disorders such as depression.[1-3] rTMS might have deleterious effects beyond the concern that it may induce seizures.[4,5] The synchronized excitation of neurons could lead to a release of excitatory amino acids with subsequent acute cellular swelling and other excitotoxic neuronal damage, as described for long-lasting epileptic seizures.[6]

T2- and diffusion-weighted imaging (DWI) was chosen to determine whether extensive magnetic stimulation with frequencies of 5 to 20 Hz causes brain edema or other structural alterations. Contrast-enhanced MRI additionally was performed to exclude alterations of the blood–brain barrier.

Methods. Eleven healthy volunteers (10 men, 26 to 38 years of age) with normal EEGs were studied with written informed consent and ethics committee approval. The investigated persons (including 3 of the authors) are all professionally engaged in the field of neurosciences or students of medicine or psychology. Eight of the persons did active research using TMS. All persons knew about the risk of eliciting epileptic seizures by rTMS. Studies were performed by neurologists familiar with the recognition and treatment of seizures in a room in which life-support equipment and anticonvulsive medication were available.

Magnetic stimulation. Focal rTMS was performed with biphasic stimuli (pulse duration, 300 μsec; Dantec MagPro stimulator, Dantec, Skovlunde, Denmark) and the center of an eight-shaped coil placed 2 cm lateral the inion over the visual cortex of one hemisphere. The table summarizes the details of the stimulation protocol.

Stimulation was performed with the 1.0- ± 0.2-fold (mean ± 1 SD; range, 0.6 to 1.3) of the thresholds for eliciting phosphenes with single pulses (threshold defined as the intensity at which phosphenes regularly occurred in the contralateral visual half-field). Because the thresholds were lower for eliciting phosphenes with repetitive pulses (43% ± 7% versus 54% ± 13% of the maximal stimulator output for single pulses), the individually used stimulus intensities lay at or above this threshold (1.2- ± 0.2-fold; range, 1.0 to 1.5). When relating stimulus intensities to motor thresholds,[5] they are between 1.0- and 1.6-fold of this threshold (1.3- ± 0.2-fold). Threshold is defined as intensity at which responses of 0.1 mV occurred in the relaxed first dorsal interosseous muscle in ~50% after motor cortex stimulation with single pulses. Trains of stimuli were applied with a precooled coil until the thermal-protection circuit stopped the stimulator, usually after 2,000 stimuli. Stimulation was continued after cooling the coil with ice bags.

MRI. All individuals had MRI before and at two variable intervals within 6 hours after rTMS (figure). MRI was performed on a 1.5-T superconductive system (Gyroscan NT 15; Philips, Best, the Netherlands) and a circular, polarized head coil. Transverse images of the whole brain were obtained by using a T1-weighted (TR/TE, 500/20 msec; acquisition matrix, 256 × 256; one excitation) and a T2-weighted (TR/TE, 3,789/120; acquisition matrix, 245 × 256; two excitations; turbo factor 13) spin-echo technique. Field of view was 23 × 23 cm, and section thickness was 4 mm. Diffusion-weighted images were acquired by using a cardiac-gated multishot spin-echo EPI sequence (TR/TE_{eff}, 4,800/145 msec; EPI factor, 13; b = 0/386/868 mm^2/sec; acquisition matrix, 128 × 128; two excitations). Apparent diffusion coefficient (ADC) maps were calculated on a pixel-to-pixel basis. Contrast-enhanced MRIs were additionally studied in three individuals after i.v. administration of double-dose gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA; 0.2 mmol/kg) at the end of the stimulation session.

T1-, T2-, diffusion-weighted studies, and ADC maps were visually inspected for signal changes. Measurements of ADC were done in corresponding regions of interest in the visual cortex ipsilateral and contralateral to stimulation and from the frontal cortex contralateral to stimulation as control. ADC ratios of stimulated to nonstimulated regions were computed to control individual differences in ADC. Statistical differences between the ADC ratios before and after stimulation were calculated with the paired Student's *t*-test.

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Table *Conditions of rTMS of the visual cortex*

Individual	Motor threshold,* %	Phosphen threshold,† %	Stimulus intensity, %	Stimulation frequency, Hz	Train duration, sec	Intertrain interval, sec	Total no. of stimuli	Duration of TMS session, min	Cumulative pause,‡ % of whole session
1	41	67	55	5	10	5	1,500	18	72
2	40	85	55	5	10	5	1,500	22	77
3	38	38	45	10	5	10	1,500	25	90
4	35	65	55	10	5	10	1,550	34	92
5	31	40	50	10	5	10	1,600	37	93
6	41	53	54	10	5	10	1,700	32	91
7	37	46	50	10	5	10	1,800	34	91
8	40	49	61	10	5	10	2,000	39	91
9	50	50	51	20	2	30	1,200	18	94
10	44	53	55	20	2	30	1,200	19	95
11	37	51	43	20	2	30	3,800	52	97
Mean ± SD	39 ± 5	54 ± 13	52 ± 5				1,759 ± 716	31 ± 11	89 ± 8

* For EMG responses in contralateral hand muscles elicited by single stimuli.
† For phosphenes in the contralateral visual field elicited by single stimuli.
‡ Inter-train-intervals plus pause necessary to cool the stimulation coil.

TMS = transcranial magnetic stimulation; EMG = electromyographic.

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Results. In all individuals, rTMS of the visual cortex with 43% to 63% of maximal stimulator output elicited gray or white phosphenes. Poststimulation T1- and T2-weighted images did not show any signal changes in cortex regions underlying the stimulation coil or in remote regions. No pathologic enhancement of brain tissue was seen after application of contrast medium in T1-weighted scans obtained immediately and 43 to 75 minutes after stimulation in three individuals.

In DWI, no regional hyperintensity suggestive of decreases in water mobility was found. Quantitative maps of ADCs were symmetric in both hemispheres. No areas of reduced or increased ADCs were detected. The ADC ratio of the stimulated to nonstimulated visual cortex regions did not change significantly after rTMS. The range was 0.99 ± 0.11 before rTMS, and 1.01 ± 0.15, and 1.01 ± 0.12 in the first and second DWI study after rTMS. None of the individuals had symptoms or signs of a seizure or recognized visual disturbances during or after rTMS.

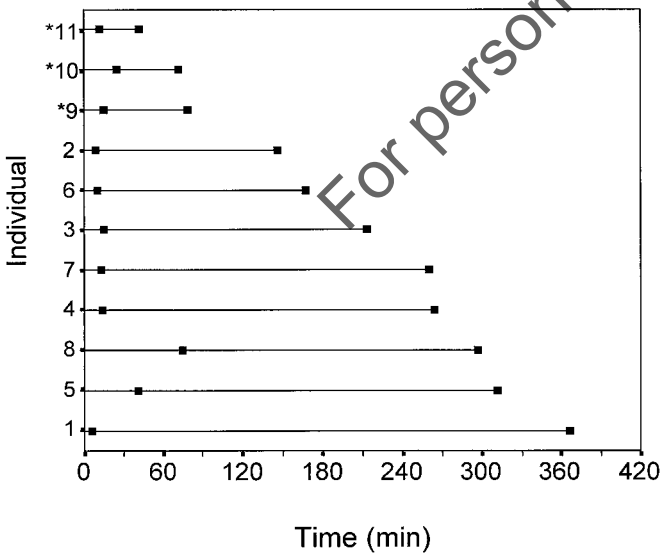

Figure. Time interval of the first and second MRI relative to the end of stimulation. MRI examination included T1- and T2-weighted spin-echo sequences and echo planar diffusion-weighted imaging. Contrast-enhanced scans were additionally obtained in three individuals after i.v. application of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA; see asterisks).

Discussion. One pathoanatomic study of the brain was performed 2 and 4 weeks after rTMS in two patients who underwent epilepsy surgery.[7] No lesions attributable to TMS were found in the resected temporal lobes previously exposed to ≤1,200 stimuli. In our study, conventional and diffusion-weighted MRI techniques were applied to detect transient edema or alterations of the blood–brain barrier in humans after rTMS. The visual cortex was chosen as the stimulation site instead of the prefrontal cortex in therapeutic trials of mood disorders,[1-3] because the activation of the visual cortex produces phosphenes as accessible stimulation effects.[8]

We found no signal changes in T1- and T2-weighted images after rTMS with ≤3,800 stimuli. Furthermore, contrast-enhanced MRI did not reveal an alteration of blood–brain barrier. It is possible that rTMS could lead to cytotoxic edema similar to a focal status epilepticus, which in the early stage is

not visible in conventional MRI sequences.[9] Therefore we applied DWI to detect cytotoxic edema, as demonstrated in experimental status epilepticus.[10] ADCs have been reported to decrease within minutes after onset of epileptic activity.[10] In our study, DWI did not show diffusion abnormality at intervals of 6 minutes to 6 hours between end of stimulation and imaging in areas repeatedly excited by rTMS trains. The findings did not indicate diffusion changes that outlast rTMS for minutes or develop with a delay. However, rapid reversible diffusion changes occurring during stimulation or biochemical alterations were beyond the scope of the study.

Duration and frequencies of the rTMS trains applied to the visual cortex were similar to those given over the prefrontal cortex with therapeutic intention in mood disorders.[1-3] In contrast to subthreshold stimulation—when stimulus intensity was related to motor thresholds—in those therapeutic trials, we stimulated with intensities above motor threshold and at or above the threshold for eliciting phosphenes with repetitive pulses. In relation to motor thresholds, the investigated combination of stimulus intensity, train duration, and frequency are outside the range suggested for a safe use of rTMS.[5] The risk of inducing a seizure might have been reduced by the long pause in the stimulation session necessary to cool the stimulation coil. For 10- and 20-Hz rTMS, the cumulative intertrain intervals (including the pause) was >90% of the duration of the whole stimulation session.

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