Safety of rapid-rate transcranial magnetic stimulation in normal volunteers

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Summary In 9 normal volunteers, we studied the safety of rapid-rate transcranial magnetic stimulation (rTMS) applied to different scalp positions at various frequencies and intensities. Pure tone threshold audiometry showed temporary threshold shifts in 3 subjects. In the subject stimulated at the highest intensity, rTMS induced a focal, secondarily generalized seizure despite the absence of definite risk factors for seizures. Rapid-rate TMS did not result in any important changes in the neurological examination findings, cognitive performance, electroencephalogram, electrocardiogram, and hormone levels (prolactin, adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone). In 10 additional subjects, the electromyographic activity in several contralateral muscles showed that trains of rTMS applied to the motor cortex induced a spread of cortical excitability. The spread of excitability depended on the intensity and frequency of the stimulus and probably constituted an early epileptogenic effect of rTMS. Guidelines for preventing the undesirable side effects of rTMS are offered.

Key words: Rapid-rate transcranial magnetic stimulation; Safety; Hormones; Electroencephalography; Audiogram; Seizure

The recent development of a magnetic stimulator capable of delivering stimuli at rates of up to 60 Hz promises to expand the applications of the commonly used magnetic stimulators, which are limited to rates of approximately 0.3–1 Hz (Burgess 1991). For example, with rapid-rate transcranial magnetic stimulation (rTMS), it may be possible to design a noninvasive test of language laterality that could replace the invasive Wada test (carotid artery injection of sodium amobarbital) (Pascual-Leone et al. 1991), develop a noninvasive technique for the localization of epileptogenic foci in patients with medically intractable epilepsy (Hufnagel et al. 1990a; Dhuna et al. 1991), and devise methods to improve the motor performance and alleviate akinesia in patients with Parkinson’s disease and related conditions (Pascual-Leone et al. 1992b). However, the safety of rTMS must be considered carefully (Pascual-Leone et al. 1991).

rTMS has only been used in a few normal volunteers (Amassian et al. 1990; Pascual-Leone et al. 1991) and patients with epilepsy (Dhuna et al. 1991; Pascual-Leone et al. 1991). The reported side effects of rTMS at frequencies of up to 25 Hz and trains of up to 10 sec in duration are muscular tension headaches, which remitted within 2 h of taking acetaminophen (Pascual-Leone et al. 1991), the induction of a skin burn under a surface electrode in one subject (Pascual-Leone et al. 1990), and the induction of a seizure in a patient with epilepsy (Dhuna et al. 1991). The neurological examination findings, mini-mental tests, and surface-recorded electroencephalograms (EEGs) were unchanged in all subjects studied with rTMS (Dhuna et al. 1991; Pascual-Leone et al. 1991). In patients with epilepsy, rTMS appeared to cause no changes in the frequency or types of seizures (Dhuna et al. 1991). Finally, there was no evidence of structural damage in the temporal lobes of patients with epilepsy who had rTMS before the operation (Gates et al. 1992).

Additional support for the safety of rTMS comes from the extensive experience with repetitive electrical stimulation of the human brain. Direct repetitive electrical cortical stimulation has become a standard diagnostic tool of neurosurgeons to help them decide which
SAFETY OF RAPID-RATE TMS

functional brain areas to remove and which to spare (Penfield and Jasper 1954; Engel 1987; Lesser et al. 1987). Routinely, 0.3 msec pulses applied at 50–60 Hz for 5–15 sec are used for this purpose.

In the present study, we systematically assessed the safety of rTMS in normal volunteers and defined stimulation parameters that can help prevent its undesirable side effects.

Methods

Subjects

Only adults without a medical history or physical evidence of neurological disease were eligible for the study. A medical history was taken from all candidates, and all had physical and neurological examinations. We excluded subjects who had a history of a neurosurgical procedure, recurrent fainting spells, seizures or spells suggestive of seizures, possible febrile seizures in infancy, or substance abuse, as well as women who could not rule out pregnancy. A family history of neurological disease, including seizures, was not considered reason for exclusion. Subjects with pacemakers, cochlear implants, medication pumps, or surgical clips were also excluded.

We studied 19 normal volunteers in 2 experiments. In experiment 1, we studied 9 subjects (6 men, 3 women), aged 22–64 years (mean, 45 years), who had a battery of tests before and immediately after rTMS, which was applied at various frequencies and intensities over 6 different scalp positions. In experiment 2, we studied 10 subjects (8 men, 2 women), aged 27–54 years (mean, 40 years) in order to assess the spread of cortical excitability after the application of rTMS at increasing intensities and frequencies to a single scalp position overlying the motor cortex. This group included three of the investigators.

Precautions and informed consent

The protocol was approved by the clinical research subpanel, and the Cadwell Rapid-Rate Magnetic Stimulator (CRRMS) was used under an investigational-device exemption from the Food and Drug Administration. The subjects gave their written informed consent for the study after its nature and possible consequences were fully explained to them. They were explicitly told that the purpose was to evaluate the safety of rTMS and that side effects, including generalized tonic-clonic convulsions, may occur. We shared with them the results of previous studies and encouraged them not to participate in the study if they had any reservations. All the subjects had previously participated in studies using single-pulse TMS.

In experiment 1, the subjects did not wear ear-plugs during rTMS so that we could study any temporary threshold shifts induced by the acoustic artifact associated with the discharge of the stimulation coil. We discussed with the subjects the significance of the shifts and shared with them the reports of hearing loss in rabbits exposed to TMS (Counter et al. 1990, 1991) and of the absence of hearing loss in humans after repeated exposure to TMS (Pascual-Leone et al. 1992b). We asked the subjects to report the occurrence of tinnitus, hearing loss, or aural fullness during the study, and considered this an endpoint of the stimulation. Stimulation was also immediately terminated if afterdischarges or epileptiform activity were detected on the EEG.

The studies were performed in a room equipped for neurological monitoring and were conducted by neurologists familiar with TMS, as well as the treatment of seizures. An Ambu bag oxygen, materials for placement of an intravenous line and antiepileptic medications were available at all times. The stimulation sessions were recorded on video tape.

Magnetic stimulation

The CRRMS is a net-0-charge stimulator with a maximal input of 325 J/pulse and a maximal output to the patient of approximately 0.2 ml/pulse. According to the manufacturer, Cadwell, Inc., the peak voltage gradient is approximately 6 V/cm, and the calculated charge density/phase is 1–2 μcoulombs/cm². The multiple pulse capability of the CRRMS is implemented by using storage capacitors half the size of the ones commonly used in standard magnetic stimulators and increasing the power supply from 450 W to approximately 2500 W (personal communication, Dr. J. Cadwell). We measured the wave shape delivered by the CRRMS as a single cosine with a period of approximately 200 μsec. The discharge of the coil causes an acoustic artifact of 119.8 dB(A) peak sound pressure level, 30 μsec rise time, and 260 μsec multiphasic ringing.

The stimulus rate was set externally by a Grass stimulator. At rates above 25 Hz, the power supply is incapable of fully charging the CRRMS's capacitors, and so the amplitude of the output will drop. At rates above 60 Hz, a lookout circuit will only recognize every other trigger pulse, so that effectively maximal stimulation rates of 30 Hz or less are achievable (personal communication, Dr. J. Cadwell).

To prevent overheating of the wire windings in the stimulation coil, we used a specially designed 8-shaped coil that allows continuous water cooling. Each loop of the coil measures approximately 7.5 cm at its smallest inner diameter and 10 cm at its largest outer diameter. The coil consists of 10 wire windings per loop, which are tightly bound in approximately 0.4 cm.

Experiment 1. rTMS was applied to 6 different scalp positions: the motor cortex bilaterally, from which
motor evoked potentials (MEPs) of maximal amplitude were elicited in the contralateral abductor pollicis brevis; 5 cm anterior to the motor cortex bilaterally; and 5 cm posterior to the motor cortex bilaterally. The following frequencies were used, with two subjects randomly assigned to testing at each frequency: 1 Hz, 5 Hz, 10 Hz, 20 Hz, and 25 Hz.

The stimulus intensity was always 100% of the stimulator's maximal output. In order to compare the stimulus intensity across subjects, however, we determined the motor threshold intensity for each subject and expressed the stimulus intensity as a percentage of the threshold intensity (considered to be 100%). The motor threshold intensity was determined by applying single-pulse TMS to the motor cortex and recording the surface electromyogram (EMG) from the relaxed abductor pollicis brevis. Motor threshold intensity was defined as the lowest stimulus intensity that in 10 trials elicited in the contralateral abductor pollicis brevis 5 or more MEPs with a peak-to-peak amplitude of at least 50 \mu V. Threshold intensity was determined separately for each hemisphere, and when different the lower intensity was used in calculating the stimulus intensity. Therefore, in some cases, the stimulus intensity was slightly overestimated for one hemisphere.

Stimulation was applied in 10 sec trains, and 4 trains were applied to each scalp position, with a 5 min pause between trains. Table I shows the stimulation parameters used in experiment 1. After each train, the subjects were requested to describe in detail any sensations induced by rTMS.

**Experiment 2.** rTMS was applied to the dominant hemisphere at different intensities and frequencies, with the coil centered over the scalp position on the motor cortex from which MEPs of maximal amplitude could be elicited in the contralateral abductor pollicis brevis. The coil was rotated (Pascual-Leone et al. 1992a) so that TMS at 110% of threshold intensity elicited MEPs only in the abductor pollicis brevis and not in the other muscles recorded. This effect could not be achieved in 7 subjects, and therefore the coil was held at the orientation that maximally activated the abductor pollicis brevis. Stimulus intensity was expressed as a percentage of threshold intensity, as defined earlier. Stimulus frequencies were 1 Hz, 3 Hz, 5 Hz, 10 Hz, 15 Hz, 20 Hz and 25 Hz. At each frequency, we began TMS at the threshold intensity (considered to be 100%) and then progressively increased it in steps of 10% up to the stimulator's maximal output. The maximal stimulus intensity ranged from 140% to 220% of threshold intensity across the subjects.

**Electroencephalography**

All subjects in experiment 1 had an EEG, which was recorded with Grass gold-plated silver electrodes applied according to the 10–20 international system of electrode placement and affixed to the scalp with collodion and filled with conducting gel. In order to prevent the induction by rTMS of a skin burn underneath a surface electrode (Pascual-Leone et al. 1990), the electrodes expected to be under the coil were either removed for the stimulation or special electrodes with a cut were used (Roth et al. 1992). The EEG was recorded (Nihon-Kohden electroencephalograph) for approximately 30 min before and after stimulation. The montages, transverse and longitudinal bipolar and referential to a linked ears reference, were those routinely used in the EEG Laboratory. The electrocardiogram (ECG), recorded concurrently with the EEG, was used to identify any cardiac effects of rTMS. In addition, the EEG was monitored continuously (referential montage) during the stimulation session. However, we interrupted the recording during the rTMS trains, because the current induced by the discharge of the stimulation coil would have blocked the amplifiers. Immediately after the completion of a train, recording was resumed for 1 min until the next train.

The EEGs were read by an experienced electroencephalographer (S.S.), who was unaware of the stimulation parameters.

**Electromyography**

In experiment 2, the EMG was recorded (DISA 1500C electromyograph) from the abductor pollicis brevis, the extensor carpi radialis, the biceps brachii, and the deltoid muscles with pairs of surface electrodes (DISA 13K60) taped over the muscle belly. Bandpass was set at 30 Hz–5 kHz and sensitivity ranged from 50 to 1000 \mu V/division. The MEPs were printed on heat-sensitive paper for off-line measurements of peak-to-peak amplitude.

**Neurological examination**

All subjects had a complete neurological examination by a board-certified neurologist (A.P.-L) shortly before and after rTMS. Blood pressure and pulse were measured, and grip and thumb-index finger pinch strength were quantified with an adjustable hand dynamometer (Jamar Model 1) and a spring-pincher dynamometer (BL). Two-point discrimination in the tips of both index fingers was quantified with a caliper of variable interpoint distance (1–20 mm). Gait was quantified by timing the speed at which the subject could cover a marked distance of 15 m when asked to walk "normally" and "as fast as possible without running." Balance was quantified by counting the missteps when the subject was asked to tandem-walk backwards along a 5 m straight line.

In addition, the subjects were specifically questioned about headache, visual disturbances, vertigo, tinnitus, hearing loss, aural fullness, weakness, paresthesias, and instability, and were encouraged to report any other sensations induced by rTMS.
TABLE I
Parameters and complications of rapid-rate transcranial magnetic stimulation (rTMS) in experiment 1.

<table>
<thead>
<tr>
<th>Subject</th>
<th>rTMS intensity (% of threshold)</th>
<th>rTMS frequency (Hz)</th>
<th>Number of stimuli</th>
<th>Complications</th>
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<tr>
<td></td>
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<td>Each scalp position</td>
<td>Total</td>
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<tr>
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<td>172</td>
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<td>9</td>
<td>208</td>
<td>10</td>
<td>300</td>
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* Six scalp positions were stimulated in each subject.
* In addition, each subject had 10–20 single stimuli delivered over the motor cortex for determination of the motor threshold.
* Subject had a seizure after the third train of stimuli was delivered to the motor cortex (the first position stimulated).

Neuropsychological testing
All subjects in experiment 1 had neuropsychological testing just before and within 2 h after rTMS. The tests were administered by a research assistant (C.H.), who was unaware of the stimulation parameters and the potential side effects of rTMS. The following tests were used: story recall (revised Wechsler Memory Scale, WMS-R), selective reminding, word fluency (letter), Boston naming test, serial reaction time test (random blocks), and letter identification task (Pegboard paradigm). In order to reduce practice effects, only one story from the WSM-R was administered during each testing session. The Boston naming test was administered in two versions: even numbered and odd numbered pictures. Poststudy testing of 60 sec word fluency included both the “FAS” letter production task and an equivalent “CJM” task. The serial reaction time and letter identification tasks were administered randomly in each testing session. The subject’s score after rTMS was more than 1 S.D. below the prestudy score on any of the tasks, the subject was tested again 24 h later. The results of the neuropsychological tests were analyzed and interpreted by a neuropsychologist (J.G.), who was also unaware of the stimulation parameters. Statistical analysis included paired t tests and individual poststudy z score profiles normalized for prestudy scores.

Audiometry
All subjects in experiment 1 had pure tone threshold audiometry immediately before and within 5 min after rTMS. The testing was done by an audiologist (L.I.S.), who was unaware of the stimulation parameters. The following frequencies were tested: 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz, and 8000 Hz. Testing after rTMS began with 2000 Hz so that the study would have the highest possible sensitivity to temporary threshold shifts, which are typically of high frequency. All measurements were made in a double-walled, sound-isolated suite (Industrial Acoustics Company). The audiometer was either a Grason-Stadler 1701 with TDH-49 headphones or a Grason-Stadler 10 with TDH-50 headphones, recently calibrated to ANSI standards (ANSI 1989).

Fig. 1. Differences in grip strength and gait speed in all 9 subjects before and after rTMS as a function of stimulus frequency. Negative values express decreased strength or gait speed after rTMS. Asterisk indicates subject 9, who had a seizure. Fitted lines show the means for differences in the grip strength of the left hand (dashed line) and the right hand (solid line) and in the gait speed: fast (dashed line) and normal (solid line).
Hormone determinations

In experiment 1, we monitored the levels of prolactin, adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone to determine if there was a transient disturbance of hormone secretion secondary to rTMS. Approximately 8 ml of venous blood was drawn from each subject before and after stimulation. The first sample was obtained less than 1 h before rTMS to avoid the effects of circadian variations on the hormone level. The second sample was obtained approximately 30 min after rTMS, because this is the time of peak hormonal rises after a seizure (Pritchard 1991).

Results

Experiment 1

None of the subjects reported headache, visual disturbances, vertigo, weakness, paresthesias, or instability after rTMS. The subjects’ blood pressure, pulse, and ECG were unaffected (Table II). The effects of rTMS on the neurological examination and EEG were unremarkable, except in subject 9, who had a seizure (see details below). The tendency for a decrease in grip strength and gait speed (Table II) was independent of the frequency and total number of stimuli (Fig. 1) and may be related to the long duration of the experiment, rather than to rTMS. Hormone levels were unaffected by rTMS (Table II). However, subject 9 had a postictal rise in prolactin.

Neuropsychological testing in subjects 3, 8 showed no adverse effects of rTMS on attention, language, or memory. In fact, subjects 3, 5, 7, and 8, who had the highest stimulus frequencies and greatest number of stimuli, apparently had an improvement in reaction time and verbal memory (Fig. 2).

Subject 5 experienced “dizziness of the right ear” in the absence of tinnitus, and subject 8 described tinnitus in the left ear after rTMS. Both of these complications lasted for less than 30 min. In subject 5, the complaint was associated with 5 dB threshold shifts in the right ear at frequencies of 3000 Hz or higher and a 10 dB threshold shift in the left ear at 3000 Hz (Fig. 3). In subject 8, tinnitus was associated with a 10 dB threshold shift in the left ear at 8000 Hz (Fig. 3). In addition, subject 2, whose prestimulation audiogram was abnormal, showed 5–10 dB threshold shifts in both ears at several frequencies, in the absence of any complaints (Fig. 3). Repeat audiograms showed reversal of all these changes within 4 h.

In all subjects stimulated at frequencies of 5 Hz or higher, the movements evoked by rTMS applied over the motor cortex seemed to increase in amplitude and complexity with each train. For example, contralateral movements of the thumb progressed, within a few pulses, to twitching of the entire hand with each stimulus, followed by extension or flexion of the wrist and then the elbow, and occasionally even shoulder abduction or adduction. This apparent spread of the TMS-induced cortical excitation seemed to be related to the stimulus frequency and intensity. It was very prominent in subject 5 (20 Hz, 167% of threshold intensity) but barely noticeable in subject 3 (10 Hz, 154% of threshold intensity), and absent in subjects 1 and 6 (1 Hz).

Subject 8 had the impression that, after the last train of rTMS at 25 Hz was applied to the left motor cortex, his right arm had continued jerking for a few seconds. The video recording confirmed that, indeed, after the end of the train, marked by the end of the clicking noise associated with the discharge of the coil, the subject’s right arm did jerk 3 or 4 times. The jerks were of decreasing amplitude and consisted of hand fisting and elbow flexion. The jerks may have been caused by afterdischarges induced by rTMS. However, this could not be demonstrated due to contamination of the EEG by rTMS-induced artifacts. The EEG was normal by the time it became readable after the rTMS train.

The most serious complication occurred in subject 9, who had a seizure after the third train of stimuli was
delivered to the left motor cortex (the first position stimulated). During the preceding trains, we had observed the same progressive increase in movement amplitude mentioned earlier, but no afterdischarges were recorded on the EEG and no poststimulation jerks, as in subject 8, had occurred. The seizure started as a simple partial motor seizure characterized by tonic arm abduction at the shoulder. At that point, the subject exclaimed, “Wait, wait, my hand.” Thereafter, clonic flexion and extension of the elbow started and was associated with speech arrest (the subject said later that she was “just unable to speak”). Clonic jerking of the arm spread to the hand and ipsilateral face, for which the subject was later amnestic, and then to the leg, and finally became generalized. The secondarily generalized convulsion lasted for 57 sec, as timed on the video recording, and was characterized by an early clonic phase, a subsequent tonic phase, and a final clonic phase with much slower and infrequent jerks. During the seizure, the subject was given oxygen (4 l/min) by mask.

Immediately after the seizure, the blood pressure was 150/80, the pulse was regular at 96 beats/min, and the arterial blood gases, glucose and electrolytes were normal. Postictal confusion lasted approximately 20 min. She had flaccid paralysis of the right side of the body, which resolved over a period of 35 min, with the arm recovering last. No postictal aphasia was noted.

The prolactin level was elevated 30 min after the seizure (Table II). Postictally, the EEG showed generalized slowing, initially of very low amplitude, but the record returned to normal within 45 min. The subject was admitted to the Clinical Center at the National Institutes of Health for overnight observation, and approximately 1 h after the seizure, the vital signs were stable, she had no fever, no clinical or laboratory evidence of infection, and a negative toxicology screen. The results of repeated neurological examinations during the night were normal. The results of neuropsychological tests the next morning, 17 h after the seizure, were unchanged from the results of the prestimulation tests. One week later, the neurological examination findings, neuropsychological test results and EEG were normal.

Subject 9 was a 35-year-old right-handed woman who had an unremarkable medical history, with no history of seizures or syncopal episodes. She was taking no medications and denied substance abuse. She had slept well the night before the study, and her last menstrual period had occurred 1 week before the testing. Her only potential risk factors for seizures were a positive family history of uncomplicated febrile convulsions in a sister and a daughter, and of a drug-induced convulsion in another sister. The results of the prestudy neurological examination were normal. A month earlier, she had volunteered for another study.

![Hearing sensitivity in subjects 2, 5 and 8 before (open circles) and after (filled circles) rTMS showing the rTMS-induced temporary threshold shifts (see text for details). Subject 2 had no complaints, subject 5 had fullness of the right ear, and subject 8 complained of tinnitus in the left ear. All symptoms resolved within 3 h and follow-up audiograms showed the resolution of all changes.](image-url)
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rTMS train (20 Hz, 210% of threshold) Control after 5 min

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Fig. 4. Representative example of the spread of cortical excitability induced by rTMS of a single scalp position (optimal position for activation of the abductor pollicis brevis, APB). The numbers are the number of stimuli in the train, with each stimulus separated by 40 msec (20 Hz rTMS). Note the initial increase in the amplitude and duration of the motor evoked potential (MEP) in the APB, the subsequent appearance of progressively larger MEPs in the extensor carpi radialis (ECR), and the final spread of excitability to the biceps brachii (BB) and the deltoid (DEL). The increase in cortical excitability resolved 5 min after the end of rTMS (control).

at the National Institutes of Health, and a cranial MRI and a resting PET scan of the brain obtained at that time were negative. She had the lowest motor threshold intensity (48% of the stimulator’s maximal output) of any of the subjects. Therefore, the stimulus intensity, relative to the threshold intensity, was higher than in the other subjects (Table 1). In addition, she was the only subject who had a positive family history of seizures.

Experiment 2

Even though the coil was centered over a single scalp position, each train of rTMS caused the spread of cortical excitation in all subjects. The spread of excitation was characterized by the appearance of, or an increase in the amplitude of, MEPs in the extensor carpi radialis, the biceps brachii, and the deltoid muscles, which were not specifically targeted (Fig. 4). The spread of excitation was preceded by an increase in the amplitude and duration of the MEP in the abductor pollicis brevis. Evidence of the excitatory spread disappeared within 5 min of the end of the train (Fig. 4).

The number of pulses required to induce the excitatory spread decreased as the frequency and intensity of the stimulus increased. The number varied slightly among the different subjects, but never by more than 5 pulses. Fig. 5 shows the number of pulses for each intensity and frequency of rTMS that resulted in the spread of cortical excitation.

Discussion

Neurological and neuropsychological effects

The neurological and neuropsychological changes observed in subject 9 were presumably due to the seizure, and they resolved within the expected time-course of the postictal confusional state. The neurological and neuropsychological status of the other subjects was unchanged. As in single-pulse TMS (Bridgers and Delaney 1989; Ferbert et al. 1991), cognitive performance was unaffected by rTMS. This finding is in agreement with the results of an rTMS study in patients with epilepsy (Dhuna et al. 1991). Contrary to the report by Saltuari et al. (1990), we found no evidence of slowing in reaction time after rTMS. In fact, reaction time and memory appeared to improve as the frequency and number of stimuli increased. However, this effect may be an artifact of the small number of subjects studied.

Effects on the EEG

The EEG was unchanged after rTMS in all subjects, except subject 9, who had a seizure. This finding is in agreement with the results of single-pulse magnetic stimulation (Bridgers and Delaney 1989; Levy et al. 1989) and of rTMS in patients with epilepsy (Dhuna et al. 1991).
Although the generalization of the seizure in subject 9 and the presumed afterdischarges in subject 8 could not be recorded on the EEG because of amplifier blocking, their clinical correlates were unequivocally demonstrated on the video recording, which emphasizes the importance of concurrent video monitoring during rTMS.

Effects on hormone levels

The increase of prolactin in the subject who had a seizure is not unexpected, as an increase in prolactin after a generalized tonic-clonic convulsion is well documented (Pritchard 1991). The absence of any hormonal effects of uncomplicated rTMS is in agreement with the findings of single-pulse magnetic stimulation (Bridgers and Delaney 1989; Levy et al. 1989) and TMS in trains (Hufnagel et al. 1990b). We conclude that rTMS does not affect the hypothalamus, a finding predicted by the results of modeling of the electrical fields induced in the brain by TMS (Cohen et al. 1990; Roth et al. 1991).

Effects on hearing

In several of our subjects, rTMS led to temporary threshold shifts, as evidenced by the audiometric findings. In a previous study, we found no hearing loss in subjects exposed to multiple sessions of single-pulse TMS (Pascual-Leone et al. 1992b). The noise associated with the discharge of the CRRMS coil is not markedly different from that associated with the discharge of standard single-pulse magnetic stimulators (Shortland et al., unpublished observations). However, the stimulus frequency may be an important variable (Pascual-Leone et al. 1992b) because of several factors, including the relative timing of the protective middle ear acoustic reflex (Wilson et al. 1984; Danielson et al. 1991), and the transient period of increased susceptibility to noise-induced hearing loss (Price 1976), which follows exposure to high-amplitude noise.

Spread of cortical excitation

The spread of cortical excitation with rTMS was similar to that observed in anesthetized animals following focal repetitive electrical stimulation (Erickson 1940; Rosenblueth and Cannon 1942). A similar spread of cerebral cortical myoclonic activity occurs in humans, and presumably is related to the increased risk of seizures in patients with cortical myoclonus (Brown et al. 1991). The spread of movements from the hand to the forearm, then to the arm, and finally the shoulder suggests a somatotopic pattern reminiscent of the body representation in the sensorimotor cortex (Penfield and Boldrey 1937).

Activation of descending corticospinal pathways by TMS is associated with activation of excitatory intracortical axon collaterals to neighboring pyramidal cells (DeFelipe et al. 1986) and to inhibitory interneurons, which in turn project to the same neighboring pyramidal cells (Stefanis and Jasper 1964). In normal circumstances, these monosynaptic excitatory and disynaptic inhibitory connections of the pyramidal axon collaterals balance each other so that no horizontal spread of the excitation occurs. However, at higher frequencies of rTMS, temporal summation of excitatory postsynaptic potentials may occur without compensatory inhibitory postsynaptic potentials because of the different number of synapses and the faster conduction along the myelinated monosynaptic excitatory collaterals (Waxman and Bennett 1972; DeFelipe et al. 1986). This would lead to a net excitation of neighboring pyramidal cells and the horizontal spread of excitation. The resulting imbalance in excitatory and inhibitory cortico-cortical connections is similar to the mechanisms advocated for the interictal-ictal transition in patients with focal epilepsy (Ebersole and Chatt 1986; Roberts 1986; Magnac-Amitai and Connors 1989; Wong and Price 1990). Prolonged trains of rTMS of appropriate frequency may result in such widespread horizontal excitation that re-entering, self-regenerating activity could develop and lead to a focal seizure, even in subjects without predisposing factors.

The induction of seizures is very rare with single-pulse TMS, even in patients with epilepsy (Claus 1989; Michelucci et al. 1989; Kandler 1990; Tassinari et al. 1990). However, Hufnagel et al. (1990a) reported that trains of TMS activated the seizure focus and induced a single complex partial seizure in patients with focal epilepsy, and Dhuna et al. (1991) reported that a focal, secondarily generalized seizure was induced in an epileptic patient exposed to high-intensity (25 Hz) rTMS. In the present study, high-intensity (10 Hz) rTMS induced a seizure in a subject whose only possible risk factor was a family history of epilepsy. It is clear that rTMS can lead to seizures, and caution is warranted.

The spread of excitation induced by rTMS raises the concern that magnetic stimulation might induce "kindling." In kindling, the repeated administration of a subconvulsive stimulus results in the progressive intensification of the induced electrical activity (Goddard et al. 1969). An animal is kindled when the subconvulsive stimulus induces seizures, and in some cases, the seizures will occur without the stimulus. The basic mechanisms thought to underlie kindling are similar to those related to the spread of cortical excitability induced by rTMS (Sato et al. 1990). Nevertheless, the relevance of kindling in human epilepsy remains controversial (Goldenson 1984), and it may be significant only in the generation of mirror foci, or secondary epileptogenesis, in patients with focal epilepsy (Morrill 1991). Kindling has never been documented in the large number of patients who have had electrical corti-
cal stimulation over the years (Goldenson, 1984; Sato et al. 1990), even though afterdischarges, which can be considered an early marker for kindling in animals, are not uncommonly induced during electrical cortical stimulation, and most laboratories use stimulation parameters that would lead to kindling in animals (Engel 1987; Lesser et al. 1987). In any case, rTMS should not lead to afterdischarges and, thus, should pose no danger of kindling when the stimulus intensities and frequencies are lower than those required to produce the spread of cortical excitation.

Safety guidelines

rTMS is likely to expand the applications of single-pulse TMS in the study of the human cortex. However, it can have potentially serious side effects. The following guidelines are offered for the safe use of rTMS.

(1) All subjects and investigators exposed to rTMS at frequencies greater than 1 Hz should wear earplugs because of the potential induction of temporary threshold shifts. Earplugs should also be worn when using single-pulse stimulation of 1 Hz (Counter et al. 1990; Pascual-Leone et al. 1992b).

(2) High-frequency rTMS may induce seizures. All subjects, but especially those with a family history of seizures, should be made aware of this risk, and rTMS should be performed in settings equipped for the management of convulsions.

(3) In the presence of electrodes, rTMS may cause scalp burns, and the special precautions described by Roth et al. (1992) should be followed.

(4) The presence of afterdischarges on the EEG is not reliable enough to predict a risk of seizure induction with rTMS (Dhuna et al. 1991). Clinical evidence of the spread of excitability should be considered the earliest sign of the epileptogenic effects of rTMS. Obviously, this does not apply when areas other than the motor cortex are stimulated. In such instances, the parameters summarized in Fig. 5 may be used as a guide. For example, rTMS at 25 Hz and 200% of threshold intensity can only be applied safely for a total of 4 pulses. The safety of these parameters is supported by the fact that the threshold for the induction of afterdischarges with electrical cortical stimulation is lowest in the motor cortex (Penfield and Jasper 1954).

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References


