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Letter to the Editor

Seizure produced by 20 Hz transcranial magnetic stimulation during isometric muscle contraction in a healthy subject

Epileptic seizure is a rare side effect of repetitive transcranial magnetic stimulation (rTMS) in healthy subjects (Pascual-Leone et al., 1993). Safety guidelines for safe stimulus parameters were first published in 1998 (Wassermann, 1998) and updated in 2009 (Rossi et al., 2009). Since 1998, only two cases of seizure have been reported in subjects with no predisposing conditions when rTMS is performed within safe stimulus parameters (Nowak et al., 2006; Oberman and Pascual-Leone, 2009). The safety parameters were determined in subjects at rest. It remains unclear whether contracting a muscle sufficient to generate motor evoked potentials (MEPs) during stimulus trains may affect the risk for seizure.

This is a case of a healthy 22-year-old right-handed male who suffered a partial, secondarily generalized seizure with 20 Hz rTMS to the right motor cortex during muscle contraction. Prior to enrollment, careful screening indicated that neither he nor anyone in his family had a history of seizures. He had no history of neurologic or psychiatric disease and was not taking any prescription or over-the-counter medication. He denied any sleep deprivation in the days leading up to the study session, did not use drugs, and rarely drank alcohol.

The subject was enrolled in a study designed to induce plastic changes in motor cortex by using EMG activity from a muscle to trigger magnetic stimulation of the same muscle's area of motor cortex. We used a Dantec MagPro TMS device with a 70-mm figure-eight coil delivering biphasic pulses. EMG was recorded from abductor pollicis brevis (APB), extensor carpi radialis longus (ECR), flexor carpi radialis (FCR), and lateral triceps during all sessions. Subjects served as their own controls, with experimental sessions and control sessions occurring on alternating weeks. The experimental TMS sessions consisted of 40 min of 0.5–20 Hz (average 8.7 Hz) variable frequency TMS in which single TMS pulses were triggered immediately when the EMG amplitude exceeded a threshold of 30% of maximum voluntary contraction, but were rate limited to no more than 20 pulses per second. Stimulus train durations varied according to an algorithm based on established safety guidelines with short durations (as short as 1.5 s) for high-frequency stimulation and long durations (as long as 270 s) for low-frequency stimulation. Control sessions consisted of 20 Hz rTMS delivered in 1.5 s trains. The inter-train interval (ITI) for both the experimental and control sessions was 30 s. During all sessions, the subject was asked to contract the muscle of study (either APB or ECR) isometrically at 30% of maximum amplitude during the stimulus trains and to rest during the ITIs. After approximately 40 min of stimulation, plasticity was assessed by a change in resting MEP amplitude induced by single-pulse TMS. Subjects underwent 5 sessions (including a mapping session) that were each separated by a week. In week 1 output effects were mapped using 3 single TMS pulses delivered to 80 spots over the right motor cortex along a 1 cm grid at 50% of maximum stimulator output. In week 2 the subject received 40 min of TMS triggered off of APB activity (2781 stimuli) to the cortical site of APB at 70% APB resting motor threshold (RMT). Week 3 he received 20 Hz rTMS (2781 stimuli) to the APB hotspot of right motor cortex at 70% of APB RMT while contracting the left APB muscle. Week 4 he received 40 min of TMS triggered off of ECR activity (2554 stimuli) to the ECR hotspot of right motor cortex at 90% of APB RMT while contracting his left ECR. During his final session, a control session, this subject received 20 Hz rTMS in 1.5 s trains to the ECR hotspot of right motor cortex at 90% of APB RMT (34% of maximum stimulator output) while contracting the left ECR muscle and developed seizure activity after 8 min.

During the first few minutes of the last session, rTMS evoked motor potentials in the left ECR and in some intrinsic hand muscles during the stimulus trains. Five minutes into the session the subject began to experience MEPs in more proximal muscles, including the left biceps and deltoid. Eight minutes into the session he started to develop flexor posturing of the left upper extremity during a stimulus train. The experimenter (M.E.) asked, "Are you OK?". He replied, "No". His head turned to the left, eyes deviated to the left and he became unresponsive. His body became rigid and he had a tonic seizure lasting for 60 s. After this activity ceased he snored loudly, and after another 30 s he responded to questions. Immediately after the seizure he was hypertensive with a blood pressure of 176/97 mmHg and tachycardic with a heart rate of 136 beats per min. He remained disoriented to place and time for 30 min before completely regaining his faculties. His vital signs had returned to normal by that time. There was a large tongue laceration on the left side. He did not experience bowel or bladder incontinence. A chemistry panel did not reveal any metabolic derangements. Subsequently, he has not experienced any recurrent seizures and denies any cognitive or other side effects. A sleep/wake EEG and MRI of the brain with and without contrast were performed 2 weeks after the seizure. Both were within normal limits. The differential diagnosis for this spell includes seizure, convulsive syncope, and psychogenic nonepileptic seizure. There is a suggestion that some previously reported TMS induced seizures may actually represent convulsive syncope (Epstein, 2006). Our subject's unilateral flexion of the upper extremity, eye deviation, head turn, and significant post-ictal state all argue in favor of a partial, secondarily generalized seizure as opposed to convulsive syncope (Zaidi et al., 2000). Moreover, the tongue laceration argues against psychogenic nonepileptic seizure (Oliva et al., 2008).

This case raises some key issues concerning the safety of rTMS. The first is proper recognition of cortical spread. In TMS studies where no motor activity is expected, any MEPs induced by TMS are likely to represent cortical spread. In studies where MEPs are expected the guidelines recommend recording EMG from a muscle just proximal to the muscle of study. If MEPs spread to involve the

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more proximal muscles, as evidenced by EMG or visual observation, TMS should be stopped (Rossi et al., 2009). Unfortunately, the investigator (M.E.) did not realize that the MEPs witnessed visually in the biceps and deltoid represented cortical spread and rTMS was continued for an additional three minutes. It seems likely that this seizure could have been avoided if rTMS had been stopped at that point. It should be stressed that the MEPs witnessed by visual observation of proximal muscles representing this potentially dangerous cortical spread appeared no different than the expected MEPs in the more distal muscles of study; both were time-locked to the stimuli. No clonic activity was ever witnessed at the end of stimulus trains or at any time during the seizure.

The second important safety issue raised by this case is whether background muscle activity during stimulus trains might increase the possibility of cortical spread, thereby lowering the seizure threshold. Muscle contraction is associated with increased activation and excitability of the motor cortex (Hess et al., 1987; Baker et al., 1995) which would increase the size and spread of MEPs. There is some evidence from single pulse TMS studies that such motor activity may increase the possibility of cortical spread (Izumi et al., 2000). To our knowledge, no one else has performed high-frequency rTMS (>1 Hz) while the subject was actively contracting a muscle. The guidelines for safe stimulus parameters with rTMS were determined for subjects at rest. When subjects actively contract a contralateral muscle, it may be necessary to use shorter stimulus trains for a given frequency and lower intensity of stimulation to prevent cortical spread. The intensity of stimulation during the session in question was 90% of APB RMT. This corresponds to approximately 110% of the active motor threshold (AMT) for the ECR muscle. For similar studies undertaken in the future, the stimulation intensity should be based on AMT instead of RMT, as AMT is a more accurate gauge of the level of cortical excitability in the contracted state. We would caution against using stimulation intensities >100% AMT. The focus should be on distal muscles, where AMT can be reached at lower stimulation intensities, thereby decreasing the likelihood of cortical spread. This case also illustrates the need for close supervision in such studies by a physician properly trained in the recognition of cortical spread. As with all rTMS studies, emergency medical access should be available in case an adverse event occurs.

References

Baker SN, Olivier E, Lemon RN. Task-related variation in corticospinal output evoked by transcranial magnetic stimulation in the macaque monkey. Physiology 1995;488:795–801.

Epstein CM. Seizure or convulsive syncope during 1-Hz rTMS? Clin Neurophysiol 2006;117:2566–77.

Hess CW, Mills KR, Murray NM. Responses in small hand muscles from magnetic stimulation of the human brain. J Physiol 1987;388:397–419.

Izumi S, Koyama Y, Furukawa T, Ishida A. Effect of antagonistic voluntary contraction on motor responses in the forearm. Clin Neurophysiol 2000;111:1008–114.

Nowak DA, Hoffmann U, Connemann BJ, Schonfeldt-Lecuona C. Epileptic seizure following 1 Hz repetitive transcranial magnetic stimulation. Clin Neurophysiol 2006;117:1631–3.

Oberman LM, Pascual-Leone A. Report of seizure induced by continuous theta burst stimulation. Brain Stimul 2009;2:246–7.

Oliva M, Pattison C, Carino J, Roten A, Matkovic Z, O'Brien TJ. The diagnostic value of oral lacerations and incontinence during convulsive "seizures". Epilepsia 2008;49:962–7.

Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, et al. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol 1993;89:120–30.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39.

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;1:1–16.

Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. J Am Coll Cardiol 2000;36:181–4.

M. Edwardson
Department of Neurology, University of Washington, Seattle, WA 98195, United States
Tel.: +1 206 719 7187; fax: +1 206 685 8100.
E-mail address: edwardso@u.washington.edu

E.E. Fetz
Department of Physiology and Biophysics, University of Washington, Seattle, WA 98195, United States

D.H. Avery
Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195, United States