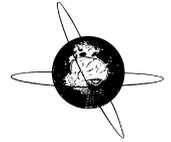




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Letter to the Editor

Report of a delayed seizure after low frequency repetitive Transcranial Magnetic Stimulation in a chronic stroke patient

We report a seizure in a stroke patient 24 h after exposure to 1 Hz repetitive Transcranial Magnetic Stimulation (rTMS).

This 56-year-old man (initials: BS) had suffered a right parietal stroke 8 months prior. MRI scan showed an ischemic lesion in the region of the right middle cerebral artery mainly involving the parieto-temporal areas. The neuropsychological evaluation three months after the stroke showed evidence of visual hemispatial neglect and extinction and he was enrolled in a research study where rTMS was used to relieve the symptoms of visual extinction. He met all inclusion criteria, had no risk factor for TMS, was not taking antiepileptic or epileptogenic drugs, and had never had a seizure. At the time of the enrolment in the study he was suffering from essential hypertension for which he was taking nebivolol and irbesartan; he was also treated with statins and acetylsalicylic acid.

The study was three weeks long. During the first week we completed baseline behavioral testing, which consisted of computerized tasks and a complete neuropsychological evaluation that confirmed the presence of visual extinction deficits. In addition, we determined resting motor threshold (RMT) to set the intensity of TMS for the subsequent intervention sessions. RMT was defined as the minimum TMS intensity necessary to elicit a motor response on 5 out of 10 consecutive trials. Stimulation was performed using a 70 mm figure-8-coil connected to a Magstim Rapid² (Magstim Co., UK), and his RMT was 74% of machine output intensity. During the second week he underwent 5 days of sham stimulation sessions followed, during the third week, by 5 days of daily active stimulation sessions. Stimulation was applied as 1-Hz rTMS and 90% RMT intensity over the intact left parietal cortex for 20 min (with the coil centered over the electrode location P3 identified using the 10/20 EEG measurement system). For the active stimulation condition, the coil was held with the handle pointing toward the back of the head and positioned perpendicularly to the stimulated region, while for the sham stimulation the coil was tilted at 90 deg, oriented perpendicular to the scalp, with the border of one wing placed against the subject's scalp.

On day 5 of each week he was re-tested on the computerized tests as well as on the neuropsychological tests battery. Moreover, he was screened for possible side effects and asked if he had headache, neck pain, scalp pain, hearing difficulties, trouble concentrating or mood changes. He reported none.

On Saturday, 24 h after he completed the third week of the experimental protocol, thus following the week of active rTMS

sessions, he experienced tonic and then clonic movements of the left part of the body lasting about 4–5 min. There were no preceding symptoms, no nausea and no postictal confusion; he only reported to be exhausted. He was rapidly assisted by the doctor in charge and laid down. The episode ended spontaneously. There was no loss or alteration of consciousness. Postictally, detailed physical examination did not reveal any neurological or cardiovascular abnormal findings or symptoms. BS was started on the antiepileptic drug (levetiracetam) the same day. This was a non-standard clinical decision of the neurologist on call. Four days after the seizure he underwent electroencephalographic recording (EEG) that showed moderate voltage relative focal theta and delta slowing in the right hemisphere, with some low voltage sharply contoured waveforms consistent with probable spike waves noted maximally in the right posterior quadrant and centro-parietal regions. These EEG findings are consistent with likely focal dysfunction in those regions with underlying cortical irritability.

To our knowledge this is the first report of a delayed seizure (24 h from the end of the treatment) following consecutive rTMS therapeutic sessions in a chronic stroke patient. Delayed seizures following single pulse TMS three and four weeks after stimulation were described by [Kandler \(1990\)](#) in two multiple sclerosis (MS) patients over a total of 108 patients. Given the prevalence of epileptic seizures in MS patients (1.1–4.5%) these cases were considered in the normal range. [Figiel et al. \(1998\)](#) also reported a major depression patient who developed a left motor seizure 6 h after 10 Hz rTMS stimulation. In this case the use of antidepressant might have increased the risk of seizures. In addition, one case has been reported of a subject suffering from chronic tinnitus who developed a seizure after one 580-pulses session of 1 Hz rTMS ([Nowak et al., 2006](#)), however the seizure in this latter case developed immediately after stimulation. Our patient experienced a focal, simple seizure, arising from the damaged right hemisphere, following a course of 1 Hz rTMS to the left, undamaged hemisphere.

Following the stroke, our patient had an increased risk of seizures arising from the right hemisphere. The course of rTMS might have contributed to the seizure by suppressing activity in the intact hemisphere and interhemispherically promoting an increase in excitability in the damaged, right hemisphere ([Agosta et al., 2014](#); [Oliveri et al., 1999](#)).

Since the time interval between the end of the stimulation session and the seizure was about 24 h, we cannot completely rule out other causes for the ictal episode. It is however unlikely because, according to his medical record and from the patient's report and he never had seizures before the study. In conclusion, we believe precautions should be taken even when unilateral stroke patients are enrolled in studies where low frequency

stimulation is delivered over the undamaged hemisphere. We recommend that patients undergoing multiple rTMS sessions should be monitored up to 24 h after the end of the clinical/experimental trial.

It is also worth to point out that notwithstanding the present report, the risk of low-frequency rTMS-induced seizures remains very low at the current state of knowledge.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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