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ORIGINAL COMMUNICATION

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Safety of single and repetitive focal transcranial magnetic stimuli as assessed by intracranial EEG recordings in patients with partial epilepsy

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Abstract The safety of single and repetitive (paired and quadruple) focal transcranial magnetic stimuli as possible inducers of epileptic discharges or clinically manifest seizures was investigated in 21 patients with intractable epilepsy during invasive presurgical monitoring. Subdural and/or intracerebral depth electrodes had been implanted in close proximity to the suspected epileptogenic zone, and the anticonvulsant medication had been reduced. Focal transcranial magnetic stimuli were applied by a Magstim QuadroPulse magnetic stimulator over the hand area of the motor cortex ipsilateral to the epileptogenic focus at intensities of 120% and 150% of motor threshold and additionally as close as possible to the suspected epileptogenic zone at 40–100% of maximal stimulator output. Stimulation did not induce any complex partial or secondary generalized tonic-clonic seizures. One patient with hippocampal sclerosis experienced an aura associated with rhythmic electroencephalographic discharges restricted to the ipsilateral intrahippocampal depth electrode after stimulation over his left temporal lobe. This patient, however, also had frequent spontaneously occurring auras with focal ictal discharges originating from this hippocampus. Interictal discharges were not influenced significantly by single or repetitive magnetic stimuli. In conclusion, from this study there is no evidence that single or serial focal transcranial magnetic stimuli activate epileptogenic foci. At least four high-frequency repetitive stimuli of high intensity may thus be applied with a low risk of seizure induction even in patients with low seizure threshold.

Key words Transcranial magnetic stimulation · Repetitive · Safety · Intracranial EEG recording · Epilepsy

Introduction

Transcranial magnetic stimulation has become an important tool in the electrophysiological investigation of descending motor pathways. The value of motor evoked potentials (MEP) has been demonstrated in the clinical evaluation, for example, of demyelinating diseases, and also provides important information in various other neurological disorders. Several uses require the application of repetitive stimuli, such as MEP monitoring during orthopedic and neurosurgical operations [38]. Single transcranial magnetic stimuli during surgery are not sufficient for eliciting suprathreshold motor responses because anesthetic agents substantially suppress I waves induced by transcranial stimuli [20, 24, 33, 36, 38–41]. Therefore repetitive stimulation at high frequencies and intensities is used to obtain temporal summation of descending pyramidal tract volleys at spinal α-motoneurons and to achieve reliable MEP monitoring [18, 35]. Repetitive transcranial magnetic stimulation has also proved to be of use for speech lateralization [16, 22, 26] and in treating major de-

pressive episodes; in the latter, magnetic stimuli are used to replace electroconvulsive therapy and avoid the side effects associated with seizure induction [8, 25].

Whereas the safety of single electric and magnetic stimuli regarding possible damage to the stimulated tissue has been well established [2, 3], a potential of transcranial magnetic stimuli to induce epileptic seizures has been reported by several authors at least in patients with epilepsy [6, 11, 14]. Investigations carried out on patients evaluated for epilepsy surgery have not provided consistent findings regarding the potential of magnetic stimuli to induce seizures [21, 30, 34]. In recent years stimulators have been constructed capable of discharging repetitively at short interstimulus intervals. Especially stimulators producing repetitive stimuli at higher frequencies (as used for electrostimulation in functional mapping of cortical areas) have been reported to induce seizures even in healthy subjects with a presumably normal threshold for seizure induction [27]. This study examined whether repetitive stimulation with stimulus parameters as used for MEP monitoring performed peri- and intraoperatively in cases of spinal surgery entails a major risk of inducing seizures.

This study was designed to assess the safety of single to quadruple magnetic stimuli regarding changes in interictal epileptiform discharges, induction of electroencephalographic (EEG) afterdischarges, ictal activity, and clinically manifest epileptic seizures in epilepsy patients undergoing presurgical evaluation with implanted subdural and/or intrahippocampal depth electrodes. In these patients the recording of seizures is necessary to identify the epileptogenic zone. The anticonvulsant medication is reduced during the monitoring period; this lowers the threshold for activation and increases excitability of the motor cortex compared to healthy subjects [15, 19, 28, 29, 31, 32]. A lower threshold for induction of epileptic activity may be assumed in these patients [12], and – unlike in most healthy individuals – seizures can often be induced by other activation methods such as hyperventilation [23].

Intracranial electrodes as used for presurgical evaluation of epileptic patients are the most reliable means for evaluating the effects of activation methods as they are placed close to the area of lowest seizure threshold and also detect ictal activity when it is restricted to regions not accessible by surface EEG recordings. These patients were thus chosen for evaluation of the risk of repetitive transcranial magnetic stimulation to trigger focal epileptic discharges.

Patients and methods

We examined 21 patients with epilepsy of focal origin (8 men, 13 women; aged 18–62 years, mean 35). Of these, 12 suffered from simple partial seizures, 20 from complex partial seizures, and 12 from secondarily generalized tonic-clonic seizures. As judged by magnetic resonance imaging, the underlying lesions were hippocampal sclerosis and/or atrophy (n = 9), hamartomas (n = 3), gliomas (n = 2), and in one patient each a cyst, cavernoma, cerebral infarction, contusional lesion, and lesion due to prior bleeding; in two patients no underlying lesion could be identified by imaging techniques (magnetic resonance imaging and positron-emission tomography). As seizures had been refractory to any medical anticonvulsant treatment, patients underwent invasive presurgical evaluation with implanted subdural strip electrodes (n = 12), subdural grids (n = 5), and/or intrahippocampal depth electrodes (n = 20). According to invasive recordings, seizure origin was allocortical (hippocampal) in 11 patients and neocortical in 10 patients. Neocortical epileptogenic zones were temporolateral (n = 7), frontal (n = 2), and occipital (n = 1).

For presurgical video-EEG monitoring anticonvulsant medication was reduced partially (n = 17) or completely (n = 3) to record spontaneously occurring seizures. In addition, in some patients activation of the epileptigenic zone was induced by drugs [1, 13], and/or by intracranial electrostimulation using the implanted electrodes [4].

Magnetic stimulation was performed using a Magstim QuadroPulse stimulator. This stimulator consists of four independent capacitators and two charger systems that provide between one and four stimuli of a maximal magnetic field of 2 T each at a minimum interstimulus interval of 1 ms. Stimuli were applied via a figure-of-8-shaped angulated or flat coil with outer diameters of 12 or 7 cm over the hand area of the motor cortex ipsilateral to the epileptogenic focus. Stimuli were applied singly, paired, and in series of four stimuli at interstimulus intervals of 50, 20, 10, and 2 ms (corresponding to frequencies of 20, 50, 100, and 500 Hz, respectively).

In the first series the coil position was adjusted to obtain maximal amplitudes of compound motor evoked potentials using surface electromyographic recordings from contralateral abductor pollicis brevis and abductor digiti minimi muscles (using tendon-belly arrangements of cup electrodes and conventional recording techniques; filter settings were 30–10,000 Hz). Motor thresholds for evoking compound muscle action potentials by single stimuli were determined for each muscle. Then stimuli of 120% and 150% of the higher motor threshold were applied; in a few patients with high motor threshold the maximal stimulator output had to be used instead of 150% motor threshold.

In the second series stimuli were applied with the coil positioned as close as possible to the epileptogenic focus (i.e., in most cases over the temporal lobe). The exact relationship is unknown between excitability of the epileptigenic focus and the motor cortex with regard to transcranial magnetic stimuli, and therefore stimulus intensities were used independently of the motor threshold at 40%, 60%, 80%, and 100% of maximal stimulator output. Several patients, however, did not tolerate repetitive stimulation at 100% stimulator output as temporal or facial muscle contractions became painful at this intensity. The total number of stimulations after assessment of motor threshold was 54 per patient.

EEG and simultaneous video-image were recorded continuously during stimulation using implanted subdural and/or intrahippocampal electrodes. EEG recordings were analyzed with regard to the occurrence of afterdischarges immediately after stimulus application, ictal activity, and changes in the pattern of interictal discharges compared to the period before stimulation and to other recording sessions of spontaneous activity. All patients gave their consent to magnetic stimulation having been informed about the possible risk of seizure induction. They were asked to report any abnormal sensations such as those typically experienced during auras or complex partial seizures.

Approval of the local ethics committee was obtained for transcranial magnetic stimulation during presurgical evaluation of epilepsy patients.

Results

No complex partial seizures or secondarily generalized seizures occurred within 1 h following stimulation. Only one patient reported any subjective feeling other than the click

noise of the coil and the muscle contractions evoked in facial or temporal muscles. Stimulation was tolerated without any sequelae except in one patient, in whom stimulation-induced contraction of the temporal muscle caused a tongue bite.

One patient with left hippocampal sclerosis reported a feeling of coldness and warmth as typically experienced during epileptic auras after left temporal stimulation using four repetitive stimuli of 80% stimulator output at 50 Hz. EEG recordings showed transition from rhythmic sharp wave activity to high-frequency low-amplitude discharges restricted to the anterior four contacts of the left intrahippocampal depth electrode; these discharges lasted for a period of 22 s and were simultaneous with the subjectively reported aura (Fig. 1). In this patient, however, sim-

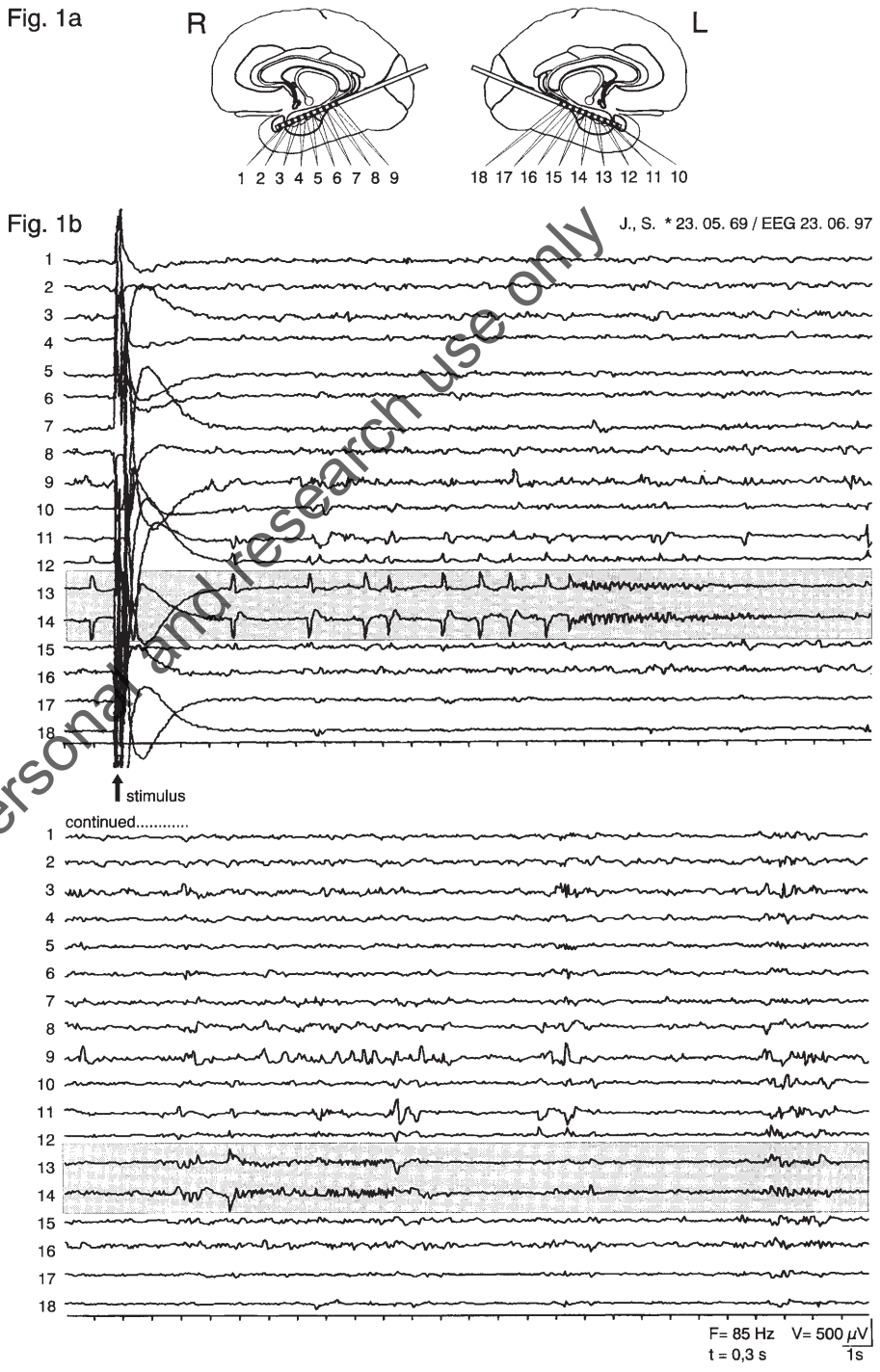

Fig. 1 **a** Positions of intrahippocampal depth electrodes with ten contacts each. **b** EEG recordings from intrahippocampal depth electrodes. Four transcranial magnetic stimuli of 80% of maximal stimulator output were applied at 50 Hz via a plane figure-of-8-shaped coil positioned over the left temporal lobe. Note the transition from rhythmic sharp waves to ictal high frequency low amplitude discharges 16 s after the stimulus artifact accompanied by the subjective experience of a typical aura

ilar auras occurred also spontaneously several times a day; these auras were accompanied by the same ictal EEG pattern in the left intrahippocampal depth electrode. To confirm a causal relationship between stimulation and aura induction, attempts to were made to reproduce the induction of an aura; the aura and EEG changes could not be reproduced by repeated stimulation with identical stimulus parameters over the same site.

In no case did EEG recordings show afterdischarges following transcranial magnetic stimulation. However, stimulus artifacts after high-intensity repetitive stimulation may have obscured short-lasting afterdischarges especially if restricted to electrodes close to the coil position.

Ictal activity was not induced in any other than in the above patient. Interictal activity occurred in 18 of 21 patients during the recording session before, during, and after the application of magnetic stimuli. The frequency of interictal spikes during and after stimulation did not change significantly in any patient compared to prestimulation time or recordings of spontaneous activity during other sessions. Magnetic stimulation did not elicit the appearance of interictal discharges or change the pattern of interictal discharges (e.g., from single spikes to bursts) in any case, and there was no spread of interictal activity to recording positions not involved in the spontaneous generation of epileptic discharges.

Discussion

Safety aspects of transcranial magnetic stimulation have become a major issue since cases have been reported in which repetitive stimuli applied over the motor cortex induced focal motor seizures with secondary generalization in healthy subjects [9, 27]. In epilepsy patients, auras and complex partial seizures have been reported to occur during or after single transcranial magnetic stimuli or with repeated low-frequency single stimuli [13, 14]. Other authors, however, have reported repetitive transcranial magnetic stimuli to be safe even in patients with temporal lobe epilepsy [17]. Only surface EEG recordings have been used so far during repetitive transcranial magnetic stimulation to assess the induction of epileptic discharges. Patients with implanted subdural and/or intracerebral depth electrodes for evaluation of the epileptogenic zone offer a unique possibility of investigating the safety of repetitive transcranial magnetic stimuli regarding their potential risk of inducing seizures or subclinical epileptic discharges.

In this study, focal ictal epileptic discharges occurring in close temporal relation with the application of repetitive transcranial stimuli were recorded only in one out of 21 patients. At the time of ictal discharges, the patient experienced a typical aura. The localization of these epileptic discharges were identical to discharges recorded during spontaneously occurring isolated auras. Continuous EEG monitoring in this patient showed her to have similar ictal EEG discharges spontaneously several times a day, and attempts to reproduce the induction of ictal discharges by applying identical series of transcranial magnetic stimuli failed. There is thus no convincing evidence that transcranial magnetic stimuli applied singly and in series of two and four were causal in the induction of ictal EEG discharges in the patients investigated in this study.

Hufnagel and Elger [12] investigated the possibility of inducing epileptic activity of the presumed epileptic zone in patients undergoing presurgical evaluation by single or low frequency (≤ 0.3 Hz) repetitive transcranial magnetic stimuli. Although 3 of 48 patients in their study developed simple or complex partial seizures during stimulation, they concluded that the low rate of seizure induction limits the value of transcranial magnetic stimulation in presurgical assessment of the epileptogenic zone. Their study used circular coils with a less focal magnetic field which may be more efficacious in synchronization of neuronal activity than the focal magnetic fields applied in this study using figure-of-8-shaped coils [7]. Focal high-frequency repetitive stimulation in the setting used in our study appears not to contribute to the localization of the epileptogenic zone value during presurgical evaluation.

The question arises whether the results obtained in this study can be extended to healthy subjects and patients with diseases other than epilepsy.

In general, the clinical manifestation of epilepsy indicates a lower threshold for the occurrence of epileptic seizures than in normal healthy subjects. Intracortical inhibition has been shown to be decreased in focal epilepsy and juvenile myoclonus epilepsy [5, 10], and the threshold for motor evoked potentials is lower in idiopathic generalized epilepsy [28]. The patients investigated in this series had seizures resistant to all previous anticonvulsant treatment. Transcranial magnetic stimulation was carried out after anticonculsive medication had been withdrawn completely or reduced to a degree sufficient to record spontaneously occurring seizures during the implantation period. These patients can thus be presumed to have a low seizure threshold at the time of stimulation. The fact that even under these conditions no clinically manifest seizure occurred after repetitive stimulation with up to four stimuli and at frequencies ranging from 20–500 Hz suggests that high-intensity single to quadruple magnetic stimuli can be applied safely also in nonepileptic patients, healthy subjects, and epileptic patients with effective anticonvulsant medication. The focal ictal activity recorded during stimulation in one of our patients cannot be causally attributed to the preceding magnetic stimuli. Thus this study found no evidence of an epileptogenic effect of single, double, or quadruple focal high-intensity transcranial magnetic stimuli. This is in accordance with the findings of Jennum et al. [17], who failed to record interictal or ictal epileptic discharges using scalp electrodes and did not induce epileptic seizures using 30 Hz and 50 Hz stimulation of

low intensity in patients with mesial temporal lobe epilepsy. Stimulation using the Quadropulse stimulator and 8-shaped coils is thus safe, for example, for perioperative MEP monitoring. Longer trains of repetitive stimuli, as used for treatment of depression and for lateralization of speech, may entail a higher risk for seizure induction, and further investigations are necessary to establish the safest parameters in their use [8, 16, 27, 37].

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