Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Research 57 (2007) 140–142
Neuroscience Research
www.elsevier.com/locate/neures

Effects of repetitive transcranial magnetic stimulation on spike-and-wave discharges

Antonella Conte [a,b], Francesca Gilio [a,b], Elisa Iacovelli [a], Chiara Marini Bettolo [a], Carlo Di Bonaventura [a], Vittorio Frasca [a], Antonio Carbone [a], Massimiliano Prencipe [a], Alfredo Berardelli [a,b], Maurizio Inghilleri [a,c,*]

[a] *Department of Neurological Sciences, University of Rome "La Sapienza", Rome, Italy*
[b] *Institute Neuromed, University of Rome "La Sapienza", Pozzilli, IS, Italy*
[c] *IRCCS San Raffaele, University of Rome "La Sapienza", Rome, Italy*

Received 26 June 2006; accepted 26 September 2006
Available online 7 November 2006

Abstract

Aim of this study was to evaluate the effect of 5 Hz-suprathreshold repetitive transcranial magnetic stimulation (rTMS) on the duration of the spike-and-wave discharges (SWDs) in a patient presenting idiopathic absence seizures.

At the moment of the study the patient presented a mild blunting of consciousness due to the high frequency of absences and EEG recordings showed sub-continuous, generalized, symmetrical and synchronous 3c/s SWDs, petit mal status. Trains of 10 stimuli (120% resting motor threshold) were delivered at 5 Hz frequency at the beginning of the SWDs.

5 Hz-rTMS trains significantly changed the EEG activity by reducing the duration of SWDs without changing the intervals between two consecutive discharges. rTMS had not significant after-effects on the epileptic activity and patient's clinical status.

Despite the limitations of a single case report, our neurophysiological findings suggest that 5 Hz-suprathreshold rTMS delivered in short trains induces a transitory interference of the ongoing epileptic activity.

Keywords: Repetitive transcranial magnetic stimulation; Spike-and-wave discharges; Absence seizures

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a technique able to modulate the excitability of cortical circuits. Low frequency-rTMS produces inhibitory effects on cortical circuits, while high frequency-rTMS produces excitatory effects (Pascual-Leone et al., 1994; Berardelli et al., 1998; Romeo et al., 2000). Although, high frequency-rTMS could be considered inappropriate in patients suffering from epilepsy, it has already been applied by many authors in order to modulate the excitability of cortical networks (Jennum et al., 1994a,b; Tassinari et al., 2003; Graff-Guerrero et al., 2004).

We had the opportunity to evaluate the possibility to induce a transitory decrease of epileptic activity applying short duration trains of rTMS in a patient with absence seizures who presented at the moment of the study an high frequency of absences and sub-continuous, generalized, symmetrical and synchronous 3c/s spike-and-wave discharges (SWDs) at the EEG recordings, petit mal status. Ten stimuli-trains were applied at 5 Hz frequency and suprathreshold intensity at the beginning of the SWDs in order to study the effects on the SWDs duration. Previous studies (Pascual-Leone et al., 1994; Berardelli et al., 1998; Inghilleri et al., 2004, 2005) in healthy subjects have shown that 5 Hz-suprathreshold rTMS produces changes in the cortical excitability through intracortical mechanisms mainly acting on the strength of synaptic connections.

2. Material and methods

A 25-year-old patient presenting idiopathic absence seizures was treated since the age of 11 years in our outpatient clinic and received a diagnosis of childhood absence epilepsy. The patient also had tonic–clonic seizures

* Corresponding author at: University of Rome "La Sapienza", Viale dell'Università, 30, 00185 Rome, Italy. Fax: +39 0649914576.
E-mail address: maurizio.inghilleri@uniroma1.it (M. Inghilleri).

0168-0102/$ – see front matter
doi:10.1016/j.neures.2006.09.015

which appeared at the age of 15 occurring at a frequency of two to three times per year. Magnetic resonance imaging scans gave normal findings. In the last 2 years the patient presented five episodes of generalized nonconvulsive status epilepticus. The patient has been treated with valproate and blood samples showed plasma level of drug in the therapeutic ranges.

At the time of the study the patient was taking valproate 1000 mg/day. Although neurological examination showed a mild blunting of consciousness due to the high frequency of absences, the patient was able to cooperate to the study. EEG recordings showed sub-continuous, generalized, symmetrical and synchronous 3c/s SWD particularly evident over the frontal regions, petit mal status.

Protocol of study was approved by the Ethical Committee Neurophysiological Research, Department of Neurological Sciences and the patient had previously signed his written consent.

rTMS was delivered through a Magstim Super-rapid stimulator (Magstim Company Ltd., UK) connected to a round coil placed over the vertex with an orientation optimal for eliciting motor evoked potentials (MEPs) in the right first dorsal interosseous muscle (FDI). The first phase of current in the coil flowed with a clockwise direction. Motor threshold was calculated at rest (RMT) as the lowest intensity able to evoke a MEP of more than 50 μV in at least 5 out of 10 trials. rTMS was delivered at suprathreshold intensity (120% RMT) in trains of 10 stimuli at 5 Hz frequency. Trains started within 4 s after the beginning of the SWD bursts defined at visual inspection during the continuous EEG recordings.

5 Hz-rTMS was also delivered in trains of 10 stimuli over the cervical region in order to activate cervical roots. Intensity of stimulation was set to obtain a MEP amplitude similar to that recorded after cortical stimulation. The inter-train interval was 1 min. Immediately after the end of the rTMS-study the patient was treated with i.v. Lorazepam.

2.1. Recordings and measurements

The EMG activity was recorded through surface electrodes from the right FDI muscle. EMG signals were recorded and filtered with a Digitimer D360 (20 Hz–1 kHz) and stored in a personal computer through a 1401 plus A/D laboratory interface (Cambridge Electronic Design, UK). The size of MEPs evoked by rTMS was measured peak-to-peak and expressed as a percentage of the first MEP in the train. The MEP latency was also measured.

EEG activity was recorded through surface electrodes placed over the scalp (according to the 10/20 conventional EEG system), visually inspected, and analyzed off-line (Digitimer D360, 0.05–50 Hz). In order to evaluate the SWDs during the experimental session we monitored the EEG activity. We collected randomly, firstly 50 SWDs and measured their mean duration and the mean interval elapsing between SWD complexes. Then, we delivered rTMS during a further 50 complexes. The duration of the SWDs (with or without cortical or cervical rTMS) was measured from the first to the last spike and then averaged. Because stimuli artefacts precluded EEG recording, in the trials with rTMS, the measurements were performed from the first spike to the last stimulus of the train if the discharges did not outlast the end of rTMS. We also measured the intervals elapsing between consecutive rTMS-SWDs and SWDs.

2.2. Statistical analysis

Paired *t*-test was used to compare the duration of SWDs recorded before and during rTMS and the intervals elapsing between consecutive rTMS-SWDs and SWDs.

All values were expressed as mean ± S.E. p-Values < 0.05 were considered to indicate statistical significance.

3. Results

EEG recordings before the experimental procedures showed continuous, generalized, symmetrical and synchronous 2.9 ± 0.1c/s SWDs.

3.1. Effects of rTMS delivered over the vertex

RMT was 65% of the maximal output. The MEP amplitude and latency were 0.8 ± 0.1 mV and 19.2 ± 0.1 ms, respectively. During the train the MEP increased in size (last MEP: 152 ± 2% of the first MEP).

rTMS significantly shortened the SWDs duration (SWDs without rTMS lasted 15.4 ± 0.93 s; with rTMS 6.43 ± 0.19 s; $p < 0.0001$) (Fig. 1) without affecting the intervals elapsing between consecutive SDWs (without rTMS 6.29 ± 0.73 s; with rTMS 6.54 ± 0.54 s; $p = 0.79$). None SWD outlasted the duration of the rTMS burst.

rTMS left the patient's consciousness and EEG recordings unchanged. Moreover, the EEG findings during SWDs intervals with and without rTMS were similar.

3.2. Effects of rTMS delivered over the cervical region

Cervical region stimulation evoked MEPs with 1.02 ± 0.02 mV amplitude and 14.1 ± 0.1 ms latency.

rTMS altered neither the SWDs duration (SWDs duration with rTMS 15.1 ± 0.76 s; $p = 0.78$) nor the intervals between the SWD complexes (6.54 ± 0.54 s; $p = 0.94$).

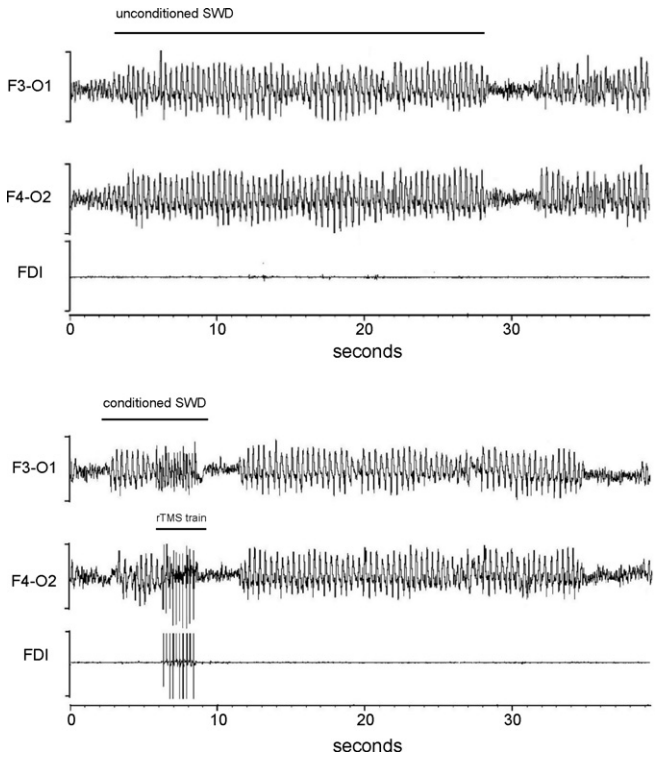

Fig. 1. The EEG (top traces), using two representatives bipolar leads, one for each hemisphere (F3-O1, F4-O2) and the first dorsal interosseous (FDI) EMG recordings (bottom trace) of the patient is shown. In the upper panel the EEG recording shows a symmetrical and synchronous 3c/s SWD. In the lower panel the figure shows the effect of 5 Hz-rTMS on the SWD and the EMG recordings. Note that rTMS delivered at the beginning of the SWD significantly reduced the duration of the epileptic discharge. Vertical calibration is 50 μV for the EEG traces, and 1 mV for the EMG trace.

4. Discussion

Our findings showed that in a patient with absence seizures 5 Hz-rTMS delivered in short trains significantly changed the EEG activity by reducing the duration of SWDs without changing the intervals between two consecutive discharges.

5 Hz-rTMS produced an increase in the MEP size during the train of stimuli according to previous findings obtained with suprathreshold high frequency-rTMS (Pascual-Leone et al., 1994; Berardelli et al., 1998; Inghilleri et al., 2004, 2005), suggesting a recruitment of cortical excitatory circuits during rTMS.

In the present study the simultaneous observation of the MEP size facilitation and transient inhibition of SWDs during rTMS seems in contrast with previous reports demonstrating that high frequency and suprathreshold rTMS increases the cortical excitability (Berardelli et al., 1998), whilst rTMS at low frequency produces inhibitory effects (Tergau et al., 1999).

The observed phenomena seem to be a temporary effect, present only during the stimulation and produce no after-effects. Indeed, the interval between two consecutive discharges remains unchanged.

The shortening of SWDs induced by cortical rTMS could be explained with various mechanisms. An electronic interdiction of the EEG-amplifiers is unlikely because cervical magnetic stimulation, that induced the same stimuli artefacts, failed to produce similar changes in the SWDs-pattern. Another hypothesis could be that epileptic discharges can be altered by sensory afferent inflow set up by muscle twitches induced by transcranial stimulation. Indeed, previous studies in animals showed that proprioceptive afferents can modulate seizures (Gioanni et al., 1982; Rajna and Lona, 1989). If this had happened in our patient, the muscle twitches evoked by cervical stimulation should have altered the SWDs duration; conversely cervical magnetic stimulation left the epileptic discharges unchanged. Finally we propose that the SWD duration could have been reduced by a transient unresponsiveness of the cortical neurons involved in generating the SWD.

SWDs are generated through corticothalamic and thalamocortical connections (Crunelli and Leresche, 2002). SWDs evolve from a transformation of slow sleep spindles, arising from summated intracortical excitatory postsynaptic potentials, and the slow waves from summated intracortical inhibitory postsynaptic potentials (Gloor et al., 1990). The thalamus is quickly recruited into an oscillation pattern that involves specific thalamic nuclei. Maintaining this oscillatory pattern requires the integrity of both the cortex and the thalamus (Crunelli and Leresche, 2002).

5 Hz-rTMS could put cortical neurons into a functionally blocked state by inducing a transitory interference of neuronal population activity as previously demonstrated in animal and human experiments (Ebert and Ziemann, 1999; Lesser et al., 1999). Alternatively, as recently proposed by Oliviero et al. (2003), 5 Hz-rTMS could modulate indirectly cortical circuits acting on subcortical structures.

In conclusion, our neurophysiological findings suggest that 5 Hz-rTMS interferes with epileptic activity acting – directly or indirectly – at cortical level and that the 5 Hz-rTMS induced effects do not outlast the end of the trains. Further studies in a large number of patients are warranted to assess the effects of rTMS delivered at different frequencies on the ongoing spike-and-wave activities.

References

Berardelli, A., Inghilleri, M., Rothwell, J.C., Romeo, S., Curra, A., Gilio, F., Modugno, N., Manfredi, M., 1998. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp. Brain Res. 122, 79–84.

Crunelli, V., Leresche, N., 2002. Childhood absence epilepsy: genes, channels, neurons and networks. Nat. Rev. Neurosci. 3, 371–382.

Ebert, U., Ziemann, U., 1999. Altered seizure susceptibility after high-frequency transcranial magnetic stimulation in rats. Neurosci. Lett. 273, 155–158.

Gioanni, Y., Ballet, C., Lamarche, M., 1982. Proprioceptive afferents of the transcortical reflex in motor epilepsy: localisation of their thalamic relay in the cat. C.R. Seances. Acad. Sci. III 294, 37–40.

Gloor, P., Avoli, M., Kostopoulos, G., 1990. Thalamocortical relationships in generalized epilepsy with bilaterally synchronous spike-and-wave discharges. In: Avoli, M., Gloor, P., Kostopoulos, G., Naquet, R. (Eds.), Generalized Epilepsy. Birkhäuser, Boston, MA, pp. 190–212.

Graff-Guerrero, A., Gonzales-Olvera, J., Ruiz-Garcia, M., Avila-Ordonez, U., Vaugier, V., Garcia-Reyna, J.C., 2004. rTMS reduces focal brain hyperperfusion in two patients with EPC. Acta Neurol. Scand. 109, 290–296.

Inghilleri, M., Conte, A., Frasca, V., Curra', A., Gilio, F., Manfredi, M., Berardelli, A., 2004. Antiepileptic drugs and cortical excitability: a study with repetitive transcranial stimulation. Exp. Brain Res. 154, 488–493.

Inghilleri, M., Conte, A., Frasca, V., Gilio, F., Lorenzano, C., Berardelli, A., 2005. Synaptic potentiation induced by rTMS: effect of lidocaine infusion. Exp. Brain Res. 163, 114–117.

Jennum, P., Friberg, L., Fuglsang-Frederiksen, A., Dam, M., 1994a. Speech localization using repetitive transcranial magnetic stimulation. Neurology 44, 269–273.

Jennum, P., Winkel, H., Fuglsang-Frederiksen, A., Dam, M., 1994b. EEG changes following repetitive transcranial magnetic stimulation in patients with temporal lobe epilepsy. Epilepsy Res. 18, 167–173.

Lesser, R.P., Kim, S.H., Beyderman, L., Miglioretti, D.L., Webber, W.R., Bare, M., Cysyk, B., Krauss, G., Gordon, B., 1999. Brief bursts of pulse stimulation terminate after discharges caused by cortical stimulation. Neurology 53, 2073–2081.

Oliviero, A., Strens, L.H., Di Lazzaro, V., Tonali, P.A., Brown, P., 2003. Persistent effects of high frequency repetitive TMS on the coupling between motor areas in the human. Exp. Brain Res. 149, 107–113.

Pascual-Leone, A., Valls-Sole, J., Wassermann, E.M., Hallett, M., 1994. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117, 847–858.

Rajna, P., Lona, C., 1989. Sensory stimulation for inhibition of epileptic seizures. Epilepsia 30, 168–174.

Romeo, S., Gilio, F., Pedace, F., Ozkaynak, S., Inghilleri, M., Manfredi, M., Berardelli, A., 2000. Changes in the cortical silent period after repetitive magnetic stimulation of cortical motor areas. Exp. Brain Res. 135, 504–510.

Tassinari, C.A., Cincotta, M., Zaccara, G., Michelacci, R., 2003. Transcranial magnetic stimulation and epilepsy. Clin. Neurophysiol. 114, 777–798.

Tergau, F., Naumann, U., Paulus, W., Steinhoff, B.J., 1999. Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. Lancet 353, 2209.