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Altered recovery from inhibitory repetitive transcranial magnetic stimulation (rTMS) in subjects with photosensitive epilepsy

Tommaso Bocci [a], Matteo Caleo [b], Laura Restani [b], Davide Barloscio [b,d], Simone Rossi [c,e], Ferdinando Sartucci [a,b,d,*,1]

[a] Department of Clinical and Experimental Medicine, Unit of Neurology, Pisa University, Pisa, Italy
[b] CNR Institute of Neuroscience, Pisa, Italy
[c] Department of Medical and Surgical Science and Neuroscience, Unit of Neurology and Clinical Neurophysiology Brain Investigation & Neuromodulation Lab., Azienda Ospedaliera Universitaria Senese, Siena, Italy
[d] DAI of Neuroscience, Cisanello Neurology Unit, AOUP, Pisa, Italy
[e] Human Physiology Section, Department of Medical and Surgical Science and Neuroscience, University of Siena, Italy

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HIGHLIGHTS

- We studied visual evoked potentials (VEPs) after inhibitory rTMS of visual cortex in photosensitive epilepsy (PSE).
- VEPs recovered faster in the stimulated hemisphere and disinhibition persisted in the contralateral one in PSE compared to controls.
- Persistent interhemispheric disinhibition in PSE may underlie the occurrence of photoparoxysmal responses.

ABSTRACT

Objective: To investigate functional changes underlying photosensitivity, we studied the response of the visual cortex to low-frequency, inhibitory repetitive transcranial magnetic stimulation (rTMS) in drug-free patients with photosensitive seizures and healthy volunteers.
Methods: Visual evoked potentials (VEPs) triggered by grating stimuli of different contrasts were recorded in both hemispheres before and after transient functional inactivation of the occipital cortex of one side via low-frequency rTMS (0.5 Hz for 20′). VEPs were recorded before (T0), immediately after (T1) and 45′ following the completion of rTMS (T2).
Results: Baseline amplitudes of the early VEP components (N1 and P1) were enhanced in photosensitive patients. At T1, rTMS produced an inhibitory effect on VEPs amplitudes at all contrasts in the targeted side and a concurrent facilitation of responses in the contralateral hemisphere. Compared with PSE subjects, VEP amplitudes remained persistently dampened in the stimulated hemisphere of controls (Holm–Sidak post-hoc method, $p < 0.05$). In the contralateral hemisphere, we found a clear enhancement of VEP amplitude in photosensitive subjects but not controls at T2 (Holm–Sidak test, $p < 0.001$).
Conclusions: Visual responses recovered more quickly in the stimulated hemisphere, and disinhibition persisted in the contralateral side of photosensitive subjects.
Significance: The rapid recovery of excitability and the persistent transcallosal disinhibition following perturbation of cortical activity may play a role in the pathophysiology of photosensitive epilepsy.

* Corresponding author at: Pisa University, Clinical and Experimental Medicine Department, Via Roma, n. 67, I 56126 Pisa, Italy. Tel.: +39 050 996760; fax: +39 050 550563.
E-mail addresses: ferdinando.sartucci@med.unipi.it, f.sartucci@ao-pisa.toscana.it (F. Sartucci).
URL: http://www.unipi.it (F. Sartucci).
[1] Current address: Unit of Neurology, Cisanello Hospital, SD Unit of Neurology, Via Paradisa, n. 2, I 56124 Pisa, Italy. Fax: +39 050 995731.

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1. Introduction

Photosensitive epilepsy (PSE) is the most common reflex epilepsy characterized by seizures induced by intermittent photic stimulation, with a high tendency towards generalization from occipital cortex (Harding et al., 2005). Only few studies have explored the pathophysiology of PSE; some Authors have suggested a defective visual inhibition as a contributing factor to photoparoxysmal response (Strigaro et al., 2012), pointing to an overactive visuomotor connectivity thus inducing abnormal motor responses (Strigaro et al., 2015).

Previous studies have investigated the characteristics of the visual stimuli triggering the hypersynchronous neuronal response (Porciatti et al., 2000; Strigaro et al., 2012). Contrast values above 40%, a spatial frequency of 2–4 cycles per degree and 10–20 Hz reversal frequency are the most effective stimulus characteristics for inducing seizures (Porciatti et al., 2000; Kasteleijn-Nolst Trenite et al., 2012). Moreover, both achromatic and chromatic sensitivities are higher in PSE compared with healthy subjects. In animals, the hypothesis of a defective cortical inhibition is supported by the low levels of inhibitory aminoacids found in the cerebrospinal fluid of photosensitive baboons (Lloyd et al., 1986). Porciatti and colleagues (Porciatti et al., 2000) showed that the VEPs amplitude saturation with increasing contrasts was dramatically altered in PSE, likely suggesting that the mechanism responsible for contrast gain control is suppressed. Indeed, Tsai demonstrated that patients suffering from idiopathic generalized epilepsy (IGE), with or without photo-paroxysmal responses, have impaired contrast gain modulation (Tsai et al., 2011).

Recently, our group has shown that in healthy subjects, inter-hemispheric connections regulate cortical gain by dampening neural responses to high-contrast stimuli in the target hemisphere (Bocci et al., 2011). Thus, we hypothesized that alterations in transcallosal inhibition may explain the impaired mechanisms of contrast gain control in photosensitive subjects. To address this issue, we enrolled twelve drug-free patients with PSE and we compared changes in VEP amplitudes induced by off-line low-frequency inhibitory rTMS applied to one occipital lobe.

2. Materials and methods

2.1. Subjects

Twelve patients (mean age: 16.4 ± 7.3; range 10–34 years) with photosensitive seizures (7 males) were enrolled (Table 1). None of the patients had been previously diagnosed as having epilepsy and they were all drug-free at the time of experimental procedure; in the follow-up period, ten were diagnosed as having juvenile myoclonic epilepsy and in remaining cases, both coming from the same pedigree, a rare epileptic syndrome, called familial cortical myoclonic tremor with epilepsy (FCMTE), was identified.

Twelve age- and sex-matched healthy volunteers (mean age 17.3 ± 7.6; range 11–33; 8 males) served as controls: all had normal or corrected-to-normal vision, no history of neurologic or psychiatric disorders and no photosensitivity to EEG. We also discarded migraineurs, who might have lower excitability thresholds than healthy subjects (Schoenen, 1996) and might react paradoxically to low-frequency rTMS (Brighina et al., 2002). None of the healthy subjects was intaking medications at the time of inclusion in the study or at least one month before and they all had suspended alcohol consumption at least 48 h before.

Written informed consent was obtained from all subjects prior to participation in the study that had been approved by the local ethical Committee and followed the tenets of Helsinki. Both patients and healthy volunteers were screened before rTMS with a standard questionnaire (Rossi et al., 2009, 2011). For under age patients, both parents signed the consent form.

2.2. Transcranial magnetic stimulation (TMS)

Subjects sat in a comfortable chair in a dimly lit room and visual stimuli were presented at a viewing distance of 100 cm. TMS pulses were applied unilaterally to the occipital pole, at about 2 cm from the midsagittal plane. This site likely lies on the portion of V1 mapping the central part of the visual field, where interhemispheric projections terminate densely (Clarke and Miklossy, 1990; Houzel and Milleret, 1999; Putnam et al., 2010; Saenz and Fine, 2010). Anatomical correspondence was confirmed by a navigated stimulation system (SofTaxic optically-tracked by EMS, Italy). The software uses passive spherical markers applied both on the coil and on the subjects' head. Tridimensional space positions of the head and coil are reproduced on the computer screen and superimposed to an average brain anatomy based on a 3D realistic MR-constructed brain model.

A Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Dyfed, UK, 2.2 T maximum field output) connected to a standard eight-shaped focal coil with wings diameter of 70 mm was used. The coil was placed with its handle pointing upward, so as to induce a current flowing in a craniocaudal direction and kept in a constant position (Fierro et al., 2005). The magnetic stimuli induced biphasic pulses with a mean duration of 200 μs and a rise-time of 100 μs. For each subject we performed one session of low-frequency rTMS (0.5 Hz) over a period of 20′ (600 pulses), by using supra-threshold intensities (120% of resting

Table 1
Clinical and electrophysiological features.

Patient	Sex	Age	Age at onset	Reported seizure frequency	Syndromic diagnosis	Therapy	PPR type at 20 Hz	Effective ILS frequencies (range, Hz)
1	F	10	9	1–2/week	JME	None	IV	8–30
2	M	13	12	1/month	JME	None	II	14–30
3	M	12	11	1/week	JME	None	IV	14–25
4	M	10	10	1/week	JME	None	IV	10–30
5	F	14	14	2/month	JME	None	II	14–25
6	M	17	15	1/month	JME	None	IV	10–30
7	F	34	31	2–3/week	FCMTE	None	III	5–35
8	M	28	25	1/month	FCMTE	None	III	5–35
9	M	18	16	1/week	JME	None	IV	14–25
10	F	14	14	2–3/month	JME	None	IV	14–25
11	M	15	14	2–3/week	JME	None	IV	14–25
12	F	12	11	2–3/week	JME	None	II	5–30

JME, juvenile myoclonic epilepsy; FCMTE, familial cortical myoclonus tremor with epilepsy.
According to Waltz et al. (1992): (I) spikes within the occipital rhythm; (II) parieto-occipital spikes with a biphasic slow; (III) parieto-occipital spikes with a biphasic slow wave and frontal involvement; (IV) generalized spikes and wave or polyspikes and wave.