

Effects of repetitive transcranial magnetic stimulation on visual evoked potentials in migraine

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Summary

Between attacks, migraine patients are characterized by potentiation instead of habituation of stimulation-evoked cortical responses. It is debated whether this is due to increased or decreased cortical excitability. We have studied the changes in visual cortex excitability by recording pattern-reversal visual evoked potentials (PR-VEP) after low- and high-frequency repetitive transcranial magnetic stimulation (rTMS), known respectively for their inhibitory and excitatory effect on the cortex. In 30 patients (20 migraine without, 10 with aura) and 24 healthy volunteers, rTMS of the occipital cortex was performed with a focal figure-of-eight magnetic coil (Magstim®). Nine hundred pulses were delivered randomly at 1 or 10 Hz in two separate sessions. Stimulus intensity was set to the phosphene threshold or to 110% of the motor threshold if no phosphenes were elicited. Before and after rTMS, PR-VEP were averaged sequentially in six blocks of 100 responses during uninterrupted 3.1 Hz stimulation. In healthy volunteers, PR-VEP amplitude was

significantly decreased in the first block after 1 Hz rTMS and the habituation normally found in successive blocks after sustained stimulation was significantly attenuated. In migraine patients, 10 Hz rTMS was followed by a significant increase of first block PR-VEP amplitude and by a reversal to normal habituation of the potentiation (or dishabituation) characteristic of the disorder. This effect was similar in both forms of migraine and lasted for at least 9 min. There were no significant changes of PR-VEP amplitudes after 1 Hz rTMS in migraineurs and after 10 Hz rTMS in healthy volunteers, nor after sham stimulation. The recovery of a normal PR-VEP habituation pattern after high-frequency rTMS is probably due to activation of the visual cortex and the dishabituation in healthy volunteers to cortical inhibition. We conclude, therefore, that the deficient interictal PR-VEP habituation in migraine is due to a reduced, and not to an increased, pre-activation excitability level of the visual cortex.

Keywords: migraine; transcranial magnetic stimulation; visual evoked potentials

Abbreviations: HV = healthy volunteer control subjects; MA = migraine with typical aura; MO = migraine without aura; PR-VEP = pattern-reversal visual evoked potential; rTMS = repetitive transcranial magnetic stimulation

Introduction

The pathogenesis of the common forms of migraine, migraine without and migraine with aura, is probably heterogeneous because the underlying genetic predisposition depends on various combinations of different susceptibility genes (Montagna, 2000; Sándor *et al.*, 2000). Pathophysiological studies in migraine patients and in animal models of migraine headache have identified the trigeminovascular system (reviewed by Reuter *et al.*, 2000), brainstem (Weiller *et al.*, 1995; Bahra *et al.*, 2001) and the cerebral cortex (Schoenen *et al.*, 1987; Welch *et al.*, 1989; Olesen *et al.*, 1990) as structures which may have primary causative roles. Modern

neuroimaging studies (Cutrer *et al.*, 1998; Cao *et al.*, 1999; Hadjikhani *et al.*, 2001) have confirmed that migraine aura symptoms are due to a cortical phenomenon similar to spreading depression (Leão, 1944).

In addition, even between attacks, some aspects of cortical functioning are peculiar in migraineurs. The strongest evidence for this comes from studies of stimulation-induced changes in visual cortex activities. Following the seminal observation by Golla and Winter (1959) of increased photic driving in the EEG of patients with migraine, the reactivity of electrocortical activity to visual stimuli has been assessed

with a number of different methods (reviewed by Schoenen, 1998). An increased amplitude of visual evoked potentials obtained by flash or pattern-reversal stimulation (PR-VEP) was found interictally in several studies (Kennard *et al.*, 1978; Gawel *et al.*, 1983). When the amplitude change of the PR-VEP was measured sequentially during sustained stimulation, we found that migraineurs were characterized by a deficit in the physiological habituation, i.e. amplitude reduction of the cortical response, which was replaced in most of them by a potentiation or dishabituation, i.e. an amplitude increase (Schoenen *et al.*, 1995). This potentiation may, in part, explain why in some studies in which global averagings of a number of responses were used, PR-VEP amplitude was found to be increased. Lack of habituation was also one of the abnormalities of contingent negative variation recorded in migraineurs (Maertens de Noordhout *et al.*, 1986; Kropp and Gerber, 1993; Schoenen *et al.*, 1993) and, except in two PR-VEP studies where it was found only for certain spatial frequencies of the stimulation pattern (Oelkers *et al.*, 1999; Sand and Vingen, 2000), it could be demonstrated in all interictal studies of cortical evoked or event-related potentials (Áfra *et al.*, 1998a; Evers *et al.*, 1999; Siniatchkin *et al.*, 1999).

Habituation in the nervous system is a ubiquitous phenomenon with complex, region- and function-dependent mechanisms. In the cerebral cortex, it is likely to be modulated by excitatory neurones receiving thalamocortical input, intracortical inhibitory interneurons and subcortical state-setting, e.g. serotonergic, afferents; one of its roles could be the protection against cortical overstimulation (Megela and Teyler, 1979; Sappey-Marinié *et al.*, 1992; Schoenen, 1996).

The visual cortex is thought to be hyperexcitable in migraineurs between attacks because of circumstantial evidence coming from functional MRI (Cao *et al.*, 1999), psycho-physical studies of visual functions (Mulleners *et al.*, 2001b) and transcranial magnetic stimulation (TMS) of the occipital cortex (Aurora *et al.*, 1998; Mulleners *et al.*, 2001a). Assessing excitability of the visual cortex via TMS may not be reliable, because the measured variable, occurrence of phosphenes, is highly subjective. For instance, using a similar method, we have found in migraine with aura indications for decreased excitability of the visual cortex (Áfra *et al.*, 1998b). This has also been reported for the motor cortex where the tested variable, the peripheral EMG response, is more objective (Bettucci *et al.*, 1992; Maertens de Noordhout *et al.*, 1992; van der Kamp *et al.*, 1997). Moreover, in our studies of cortical evoked potentials in migraine, the response obtained after a small number of averagings, i.e. the first block, had normal or decreased amplitudes (Schoenen, 1998), which is not compatible with a net increase in cortical excitability. We have therefore hypothesized that the habituation deficit or response potentiation in migraineurs could be due to a decreased pre-activation level of excitability of sensory cortices (Wang *et al.*, 1996; Schoenen, 1998) and explained by the so-called 'ceiling effect' (Knott and Irwin,

1973). In this model, habituation during repeated stimulation occurs when the 'ceiling' of maximal cortical activation is reached, i.e. more rapidly if the cortical pre-activation level is high.

Repetitive TMS (rTMS) offers a unique opportunity to test this hypothesis. It is able to modify cortical excitability in opposite ways depending on the stimulation frequency (Hallett, 2000; Fierro *et al.*, 2001). Low-frequency rTMS (<1 Hz) decreases (Chen *et al.*, 1997b; Wassermann *et al.*, 1998; Boroojerdi *et al.*, 2000a), whereas high-frequency rTMS (5–20 Hz) enhances cortical excitability (Pascual-Leone *et al.*, 1994). In the present study, we have therefore used rTMS to change the excitability of the visual cortex and monitored these changes by measuring PR-VEP amplitudes in sequential blocks during continuous stimulation in migraine patients between attacks and, for comparison, healthy volunteers.

Methods

Subjects

Fifty-four subjects took part in the study: 24 healthy volunteer control subjects (HV) without personal or family history of primary headache recruited among medical students (14 women and 10 men; mean age 23.5 ± 2.5 years) and 30 outpatients with migraine recruited from a specialized headache clinic (25 females and five males, mean age 33.5 ± 10.8 years). According to International Headache Society criteria (1988), 20 patients had migraine without aura (MO, IHS code 1.1) and 10 migraine with typical aura (MA, IHS code 1.2.1). Only patients suffering exclusively from one form of migraine were enrolled. All subjects were devoid of any other medical condition and had no personal, or family history of epilepsy, which is recommended for rTMS studies (Chen *et al.*, 1997a). They had between one and eight attacks per month (mean 2.31 ± 2.14) and a history of migraine ranging from 1 to 30 years (mean 13.71 ± 11.29). None of them received prophylactic anti-migraine treatment for at least 3 months before the study, nor used ergotamine as acute treatment. All the recordings were made in the headache-free interval, at least 3 days before and after an attack. The date of the last attack was verified by history, and absence of an attack within the next 3 days by a telephone call made 4 days after the recordings. All subjects were naive to rTMS. To avoid interference with changes of cortical excitability due to hormonal variations (Smith *et al.*, 1999), females were recorded at mid-cycle, i.e. 12–16 days after the first day of menses. Written informed consent was obtained from all subjects. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Liège, Belgium.

Pattern-reversal visual evoked potentials

We recorded PR-VEP before and immediately after the rTMS. Subjects were seated in an armchair, in a quiet room

with dimmed light, 1 m in front of a television monitor (24 cm × 18 cm, mean luminance 240 cd/m², colour temperature 9500 K). Stimuli were presented as a chequer-board pattern of black and white squares (8 min of arc), at a reversal frequency of 3.1 Hz. Subjects were instructed to fixate on a red dot in the middle of the screen with the left eye covered by a patch. We used two-pin electrodes inserted into the scalp on the midline: the first 2.5 cm above the inion (Oz—active electrode) and the second over the frontal region (Fz—reference). The ground electrode was placed on the forearm. During uninterrupted stimulation, six sequential blocks of 100 responses were averaged for a total duration of 194 s using a CED 1401 averager (Cambridge Electronic Design®, Cambridge, UK) (analysis time 300 ms, 100 Hz high-cut and 1 Hz low-cut filters). To evaluate the duration of the rTMS effect beyond 3 min, we performed long-term PR-VEP recordings in six migraineurs and eight controls, alternating 3 min of recording with 3 min of rest for up to 30 min after rTMS.

TMS

We used a Magstim Rapid® magnetic stimulator (Magstim Co. Ltd, Whitland, Dyfed, UK), connected to a double 7.0 cm figure-of-eight-shaped coil, with a maximal stimulator output of 1.2 T.

We first identified the phosphene and motor thresholds, using single TMS pulses of 100 µs duration. The phosphene threshold was defined as the lowest stimulation intensity (expressed as a percentage of the maximal stimulator output) able to evoke phosphenes in at least three out of five trials. The coil was placed in a vertical position (its handle pointing upward) on the inion–nasion line, with its inferior limit 1 cm above the inion. The patients were blindfolded in a dark room. As this may change visual cortex excitability after 40–45 min (Borojerdj *et al.*, 2000b), the total duration of blindfolding was limited to 10–15 min. Stimulation was applied initially at 40% of stimulator output. The intensity of the stimulation was increased by 5% steps until the subject reported phosphenes. The threshold was then determined finely, by increasing and decreasing the intensity by 1% steps. In patients who did not report phosphenes at the 100% intensity level, the procedure was repeated with the coil placed 1 or 2 cm higher or lower and, if necessary, to the right or to the left, before accepting the absence of phosphenes. With the coil placed at the optimal position over the left motor area, the motor threshold was defined as the lowest intensity able to produce at rest an EMG response in the first dorsal interosseus muscle of the right hand, of at least 50 µV peak-to-peak amplitude, in at least five of 10 trials. Stimulation intensity was 40% of stimulator output initially and increased by 1% steps.

For rTMS of the visual cortex, the coil was positioned as for the phosphene detection. Stimulus intensity was set to the phosphene threshold or, in accordance with published guidelines (Chen *et al.*, 1997a), to 110% of the motor

threshold, if the patient reported no phosphenes, or if the phosphene threshold was >75%.

We used two different stimulation frequencies in a randomized order: 1 Hz (low-frequency rTMS) and 10 Hz (high-frequency rTMS) with at least a 24 h interval between the two sessions, as recommended by others (Wu *et al.*, 2000). A 1 Hz rTMS was applied without interruption for 15 min. The 10 Hz rTMS was applied in 18 trains of 5 s with inter-train intervals of 10 s. For both frequencies, the same number of 900 pulses was thus delivered. In six migraine patients, we performed a 10 Hz rTMS sham stimulation during which the coil was placed at a 90° angle to the occiput, with its anterior border pressed against the scalp. To keep these patients blinded, the stimulator output was set to 65%, the highest intensity used in the other patients, without performing a threshold search. Six HV chosen at random underwent a 1 Hz rTMS sham stimulation session in the same conditions. In the sham situation, there is a subjective sensation and noise similar to that achieved with effective rTMS, but no brain activation occurs (Klein *et al.*, 1999a), which was not known to the subjects.

Data analysis

We analysed the 12 blocks of 100 PR-VEP responses (six before, six after rTMS) in terms of latencies and peak-to-peak amplitudes of the N1–P1 and P1–N2 components. The N1 peak was defined as the most negative point between 60 and 90 ms after the stimulus, P1 as the most positive point following N1 between 80 and 120 ms and N2 as the most negative point following P1 between 90 and 200 ms. PR-VEP potentiation or habituation were defined as percentage amplitude increase or decrease between the first and the sixth block of 100 averaged responses. These amplitude changes were calculated separately for N1–P1 and P1–N2. To visualize better the slope of N1–P1 and P1–N2 amplitude changes over the total duration of visual stimulation, a linear regression analysis of the mean amplitudes in the six blocks of 100 averaged responses was performed.

Statistical analysis

Means ± standard deviations were calculated for amplitude (µV), potentiation and slope before and after rTMS, for each PR-VEP component (N1–P1 and P1–N2), for each rTMS frequency (1 and 10 Hz) and for each group of migraine (MO and MA). Paired Student's *t*-tests were used to compare the variables before and after rTMS at 1 or 10 Hz, for each component and for each group. Student's *t*-tests were used to compare the effects of rTMS between the two groups of migraineurs. Generalized linear models were used to compare the variables in relation to rTMS (before and after 1 or 10 Hz rTMS), to diagnosis (migraine with or without aura) and the interaction between them.

All results were considered significant at the 5% level ($P < 0.05$). Statistical calculations were carried out with SAS

(Version 6.12 for Windows; SAS Institute, Cary, North Carolina, USA).

Results

Phosphene and motor thresholds

Single transcranial magnetic stimulation over the occipital cortex elicited phosphenes in 15 (nine MO and six MA) out of 24 patients (62.5%) and in 14 out of 24 HV (58%), a non-significant difference. Phosphenes were reported as short-lasting flashes or lines. The mean threshold for phosphene production was $86.75 \pm 12.31\%$ (range 65–100%) of the maximal stimulator output for MO patients, 82.80 ± 13.39 (range 59–95%) for MA patients and $66.85 \pm 11.93\%$ (range 40–87%) for HV. The difference between both migraine groups and HV was significant ($P = 0.001$).

The mean motor threshold to activate the first dorsal interosseus muscle at rest was not significantly different between subject groups: $59.21 \pm 9.31\%$ (range 45–81%) for MO patients, 62.83 ± 7.49 (range 50–70%) for MA and $57.67 \pm 8.35\%$ (range 30–74%) for HV.

Latencies

In all PR-VEP recordings, the N1, P1 and N2 peaks were clearly identified. No significant latency differences were detected after rTMS.

Amplitudes in the first block of averaged responses

In the first block of 100 averaged responses, amplitude decreased after 1 Hz rTMS (Table 1) in 20 out of 24 HV (83%) for N1–P1 and in 19 out of 24 HV (79%) for P1–N2. N1–P1 amplitude decreased on average for all 24 HV by $1.06 \pm 1.24 \mu\text{V}$ ($P = 0.0002$), and P1–N2 amplitude by $0.62 \pm 1.28 \mu\text{V}$ ($P = 0.017$). The 1 Hz rTMS sham stimulation produced no significant amplitude changes.

Similarly, first block amplitudes decreased after 1 Hz rTMS in 11 MO (68.76%) for N1–P1 (mean $0.53 \pm 1.14 \mu\text{V}$) and P1–N2 ($0.16 \pm 1.32 \mu\text{V}$) and in five MA patients (62.5%) for N1–P1 (mean $0.22 \pm 1.23 \mu\text{V}$), but none of these changes was significant.

After 10 Hz rTMS (Table 2), there was a slight non-significant reduction of first block amplitudes in fewer than half of the HV. In contrast, in migraineurs, 10 Hz rTMS induced a significant amplitude increase in the first block in 14 MO (87.65%) and in all eight MA patients. The mean amplitude rise was $0.81 \pm 0.85 \mu\text{V}$ ($P = 0.003$) for N1–P1 and $0.74 \pm 1.39 \mu\text{V}$ ($P = 0.05$) for P1–N2 in the MO and 2.1 ± 1.79 for N1–P1 ($P = 0.02$) and 1.94 ± 2.01 for P1–N2 ($P = 0.04$) in the MA group. When the combined data from both migraine groups were analysed, N1–P1 ($P = 0.0007$) and P1–N2 ($P = 0.0072$) first block amplitudes were significantly increased after 10 Hz TMS. After 10 Hz sham stimulation in

six migraine patients, there were no significant amplitude changes.

Amplitude changes over six blocks of averaged responses

Confirming our previous findings, before rTMS, N1–P1 and P1–N2 amplitudes decreased, i.e. habituated, between the first and subsequent blocks of averagings in all control subjects, while they increased in all migraine patients, indicating potentiation or dishabituation (see Tables 1 and 2). These patterns were changed profoundly by rTMS.

After 1 Hz rTMS (Table 1), habituation disappeared in HV both for the N1–P1 ($25.23 \pm 17.33 \mu\text{V}$ before, -2.89 ± 18.83 after) and the P1–N2 component (16.82 ± 14.19 before, -7.80 ± 31.29 after). The mean absolute habituation decrease after 1 Hz rTMS was $28.12 \pm 21.18\%$ ($P < 0.0001$) for N1–P1 and $24.62 \pm 29.19\%$ ($P = 0.0004$) for P1–N2. This contrasted with the 1 Hz rTMS sham stimulation which was delivered in six HV without changing the normal habituation of their PR-VEP. In both migraine groups, 1 Hz rTMS further enhanced the pre-stimulation potentiation in 62.5% of patients by 15.41 to 27.41% in absolute values, but no change was significant.

After 10 Hz rTMS (Table 2 and Fig. 1), N1–P1 and P1–N2 pre-rTMS habituation was not significantly modified in HV, whereas in migraineurs the pre-rTMS potentiation was reduced or replaced by a habituation. All MO patients, except one, had a reduction of PR-VEP potentiation which averaged for the whole group in absolute values $-28.57 \pm 24.22\%$ for N1–P1 ($P = 0.001$) and $-35.48 \pm 43.47\%$ for P1–N2 ($P = 0.01$). High-frequency rTMS attenuated potentiation in all MA patients, on average by -37.58 ± 13.54 ($P = 0.0003$) for N1–P1 and -24.36 ± 23.41 ($P = 0.02$) for P1–N2. This effect was also significant for the combined MO and MA data ($P < 0.0001$ for N1–P1; $P = 0.005$ for P1–N2). Sham stimulation at 10 Hz rTMS in six migraineurs had no significant influence on their N1–P1 and P1–N2 potentiation.

Slope

After 1 Hz rTMS (Table 1), in HV, the mean PR-VEP slope increased by 0.34 ± 0.28 for N1–P1 ($P < 0.0001$) and by 0.23 ± 0.28 for P1–N2 ($P = 0.0005$) (Fig. 2), while in MO these slopes remained unchanged (Fig. 3) and in MA there was only a non-significant enhancement of potentiation (Fig. 4). Sham rTMS at 1 Hz had no effect on slopes in HV.

After 10 Hz rTMS (Table 2), there were no significant slope differences in the control group (Fig. 2). By contrast, mean slopes were significantly different in migraineurs. In MO patients, this reduction was on average -0.25 ± 0.21 ($P = 0.001$) for N1–P1 and -0.19 ± 0.26 ($P = 0.01$) for P1–N2 (Fig. 3). In MA patients, the mean N1–P1 slope dropped on average by -0.47 ± 0.26 ($P = 0.003$) and the P1–N2 slope by -0.23 ± 0.22 ($P = 0.04$) (Fig. 4). The 10 Hz rTMS-induced

Table 1 PR-VEP initial amplitude, potentiation and slope before and after 1 Hz rTMS (means \pm standard deviation)

Groups and VEP comparison	Amplitude (μ V) (first block)		Potentiation (%) (sixth block – first block/first block)		Slope (over the six blocks)	
	Before	After	Before	After	Before	After
MA ($n = 8$)						
N1–P1	5.57 \pm 1.42	5.17 \pm 1.23	9.74 \pm 16.66	32.98 \pm 39.12	0.09 \pm 0.17	0.18 \pm 0.31
P1–N2	4.86 \pm 2.31	5.08 \pm 2.72	1.82 \pm 32.54	10.98 \pm 35.43	0.05 \pm 0.21	0.10 \pm 0.15
MO ($n = 16$)						
N1–P1	6.38 \pm 3.10	5.85 \pm 2.90	17.78 \pm 21.96	24.94 \pm 34.70	0.06 \pm 0.18	0.06 \pm 0.17
P1–N2	5.29 \pm 2.11	5.13 \pm 2.18	30.95 \pm 39.16	30.14 \pm 34.45	0.20 \pm 0.26	0.17 \pm 0.24
Mig ($n = 24$)						
N1–P1	6.14 \pm 2.71	5.64 \pm 2.48	15.41 \pm 20.39	27.41 \pm 35.22	0.07 \pm 0.18	0.33 \pm 1.64
P1–N2	5.16 \pm 2.10	5.12 \pm 2.28	22.20 \pm 38.91	24.40 \pm 35.00	0.15 \pm 0.23	0.15 \pm 0.21
HV ($n = 24$)						
N1–P1	6.58 \pm 2.39	5.52 \pm 2.11*	–25.32 \pm 17.33	2.89 \pm 18.83*	–0.36 \pm 0.23	–0.02 \pm 0.23*
P1–N2	6.11 \pm 2.41	5.49 \pm 2.22*	–16.82 \pm 14.19	7.80 \pm 31.29*	–0.18 \pm 0.20	0.05 \pm 0.25*
Sham in six HV						
N1–P1	5.04 \pm 0.36	5.20 \pm 1.69	–32.77 \pm 12.99	–36.09 \pm 23.43	–0.23 \pm 0.15	–0.20 \pm 0.13
P1–N2	5.12 \pm 1.53	5.36 \pm 2.02	–37.73 \pm 10.41	–26.50 \pm 19.87	–0.23 \pm 0.13	–0.18 \pm 0.15

* $P < 0.01$.**Table 2** PR-VEP initial amplitude, potentiation and slope before and after 10 Hz rTMS (means \pm standard deviation)

Groups and VEP comparison	Amplitude (μ V) (first block)		Potentiation (%) (sixth block – first block/first block)		Slope (over the six blocks)	
	Before	After	Before	After	Before	After
MA ($n = 8$)						
N1–P1	5.03 \pm 1.42	7.13 \pm 1.68*	11.50 \pm 18.62	–26.10 \pm 19.21*	0.12 \pm 0.13	–0.35 \pm 0.24*
P1–N2	5.13 \pm 2.31	7.07 \pm 2.58*	12.90 \pm 18.81	–11.40 \pm 26.48*	0.01 \pm 0.17	–0.22 \pm 0.21*
MO ($n = 16$)						
N1–P1	5.59 \pm 2.46	6.40 \pm 2.06*	22.50 \pm 21.89	–6.09 \pm 16.31*	0.16 \pm 0.14	–0.09 \pm 0.14*
P1–N2	5.37 \pm 1.98	6.11 \pm 1.74*	37.70 \pm 35.80	2.23 \pm 20.00*	0.24 \pm 0.23	0.04 \pm 0.19*
Mig ($n = 24$)						
N1–P1	5.38 \pm 2.30	6.67 \pm 1.91*	18.40 \pm 20.89	–13.54 \pm 35.22*	0.15 \pm 0.11	–0.18 \pm 0.21*
P1–N2	5.28 \pm 2.11	6.46 \pm 2.14*	28.60 \pm 32.45	–2.80 \pm 22.92*	0.15 \pm 0.19	–0.05 \pm 0.24*
HV ($n = 24$)						
N1–P1	6.56 \pm 2.03	5.97 \pm 1.59	–17.80 \pm 20.01	–15.54 \pm 17.71	–0.27 \pm 0.23	–0.22 \pm 0.29
P1–N2	5.83 \pm 2.19	5.71 \pm 1.93	–9.52 \pm 20.68	–8.69 \pm 22.36	–0.16 \pm 0.16	–0.09 \pm 0.25
Sham in six Mig						
N1–P1	5.87 \pm 0.29	5.86 \pm 0.62	26.71 \pm 26.37	31.08 \pm 29.74	0.20 \pm 0.10	0.16 \pm 0.24
P1–N2	6.03 \pm 1.70	6.26 \pm 1.66	36.02 \pm 28.73	27.82 \pm 28.56	0.29 \pm 0.22	0.18 \pm 0.12

* $P < 0.01$.

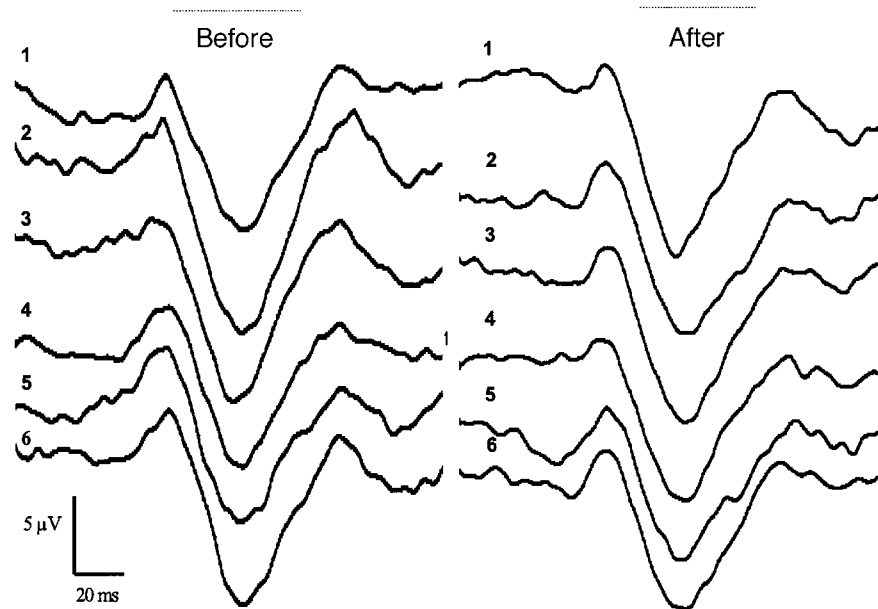
slope decrease was also significant for the total group of patients ($P < 0.0001$ for N1–P1; $P = 0.011$ for P1–N2). The 10 Hz rTMS sham stimulation in six migraineurs had no significant effect on slopes in either group of migraineurs.

Global GLM effect of rTMS frequency, PR-VEP component and diagnostic group

In controls, there was a significant difference between rTMS frequencies ($P = 0.0006$) and between the two components ($P = 0.0032$) for amplitude measures. For habituation and for the calculated slope, there was an interaction between rTMS frequency ($P < 0.0001$ and $P = 0.0002$) and an effect of the VEP component ($P = 0.0067$ and $P < 0.0001$).

When comparing the N1–P1 first block amplitude between rTMS and rTMS frequency in migraineurs, there was a significant amplitude increase for 10 Hz ($P = 0.0015$). Similarly, for the P1–N2 amplitude, there was a significant increase in the 10 Hz group ($P = 0.015$). There was no effect of the migraine groups. The N1–P1 potentiation change was significantly different between 1 and 10 Hz rTMS ($P = 0.0004$) without effect of the migraine group. For the P1–N2 component, there was an effect of the migraine group ($P = 0.023$), the pre-rTMS potentiation being lower in MA than in MO ($P = 0.012$). This agrees with the finding of an effect of the diagnostic group for the P1–N2 slope, which was lower in MA ($P = 0.012$). The change of slopes was significantly more pronounced for the 10 Hz than for the 1 Hz rTMS ($P = 0.031$).

Migraine patient: 10 Hz rTMS



Healthy volunteer: 1 Hz rTMS

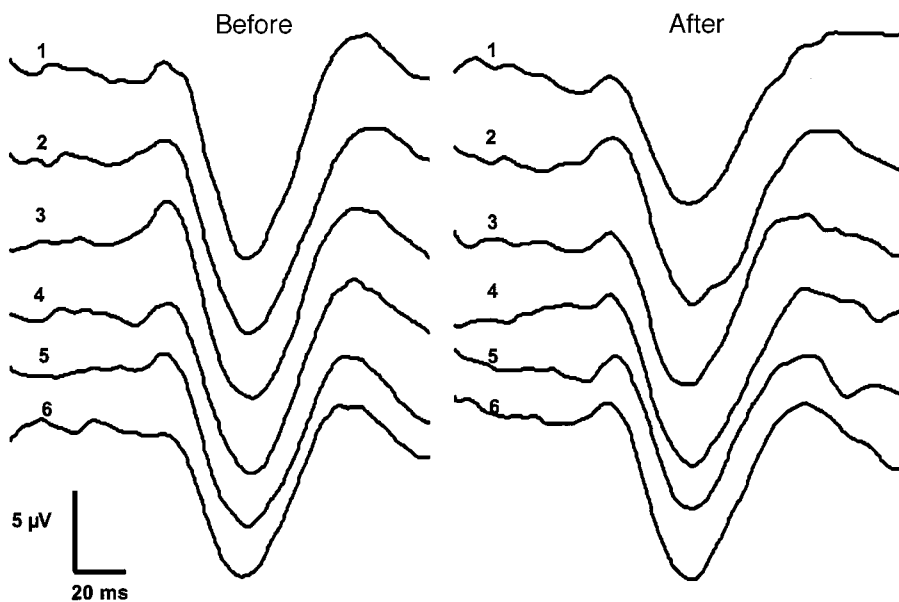


Fig. 1 Illustrative example of six sequential blocks of 100 averaged pattern-reversal visual evoked potentials in a healthy volunteer and a migraine patient before and after 10 Hz rTMS.

Duration of rTMS effects

The effects of rTMS were followed for 30 min in eight controls and in six patients (four MO and two MA). The changes of PR-VEP induced in HV by 1 Hz rTMS remained significant for at least 15 min (range 15–30 min) and those produced in migraineurs by 10 Hz rTMS for at least 9 min (range 9–30 min). Similarly, there was no significant effect of 1 Hz rTMS in migraine patients and of 10 Hz rTMS in controls at any time during the 30 min time period.

Discussion

The most striking finding in our study is that the consequences of rTMS on visual evoked potentials in migraineurs contrast with those observed in HV. In the latter, only the low-frequency 1 Hz stimulation has significant effects: it decreases the first block amplitude and habituation. Conversely, PR-VEP of migraineurs are significantly modified by the high-frequency 10 Hz rTMS, which increases first block amplitude and habituation, but not by the low-

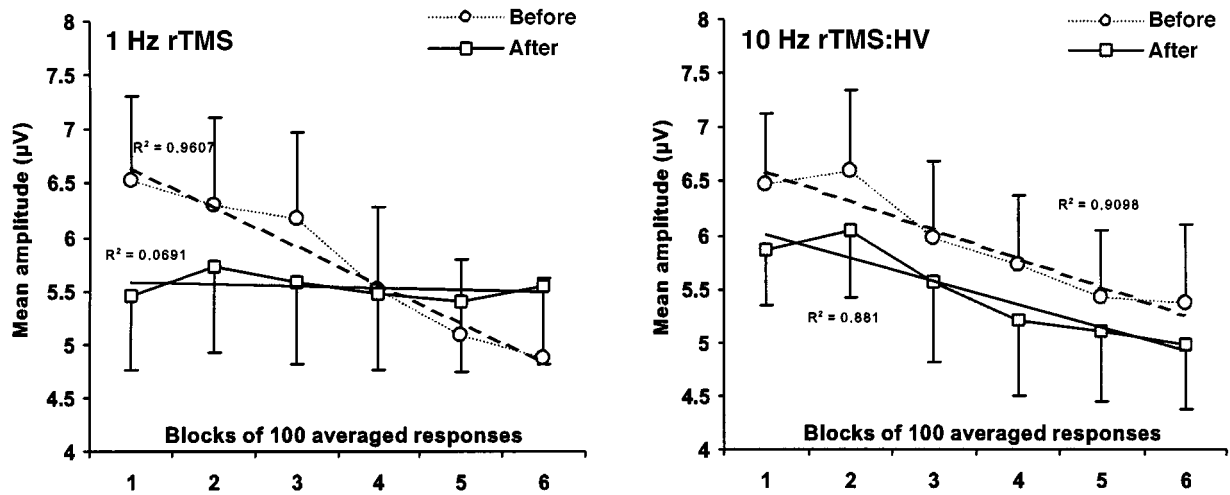


Fig. 2 The mean PR-VEP N1-P1 amplitudes and the linear regression slopes for healthy volunteers in six successive blocks of 100 averaged responses before and after rTMS ($n = 24$).

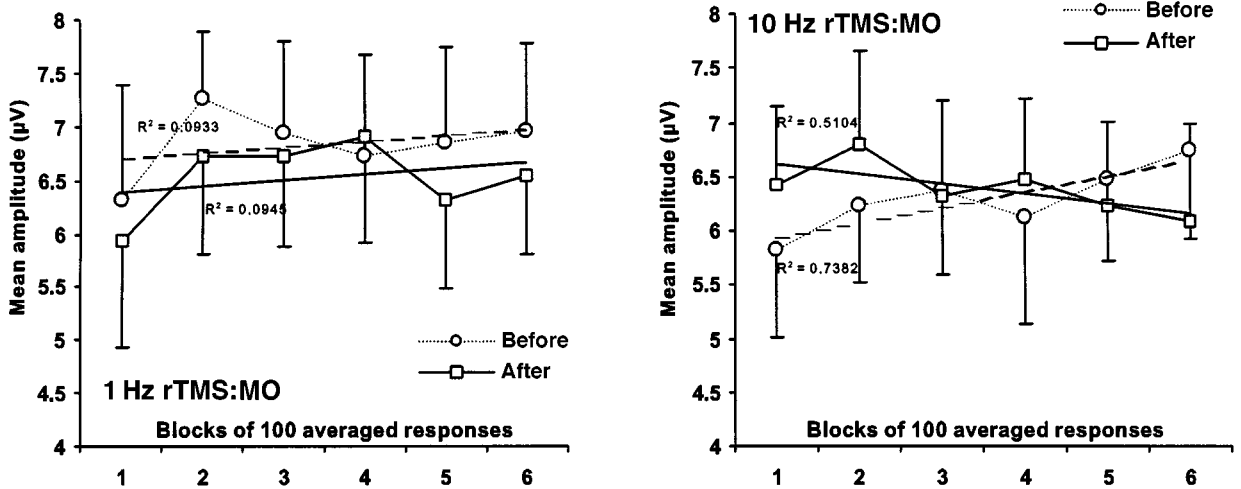


Fig. 3 The mean PR-VEP N1-P1 amplitudes and the linear regression slopes for migraine without aura patients in six successive blocks of 100 averaged responses before and after rTMS ($n = 16$).

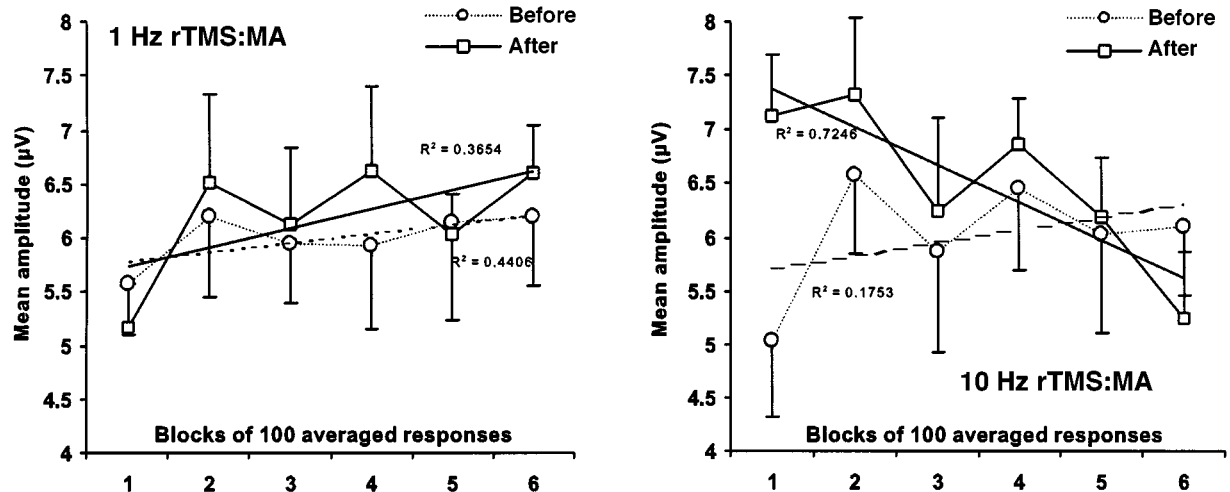


Fig. 4 The mean PR-VEP N1-P1 amplitudes and the linear regression slopes for migraine with aura patients in six successive blocks of 100 averaged responses before and after rTMS ($n = 8$).

frequency stimulation. This difference must be interpreted in the light of the presumed differential effects of rTMS on cortical excitability and may contribute to a better definition of the interictal changes of cortical excitability in migraine.

In the last decade, numerous studies on the effects of rTMS on cortical excitability have been performed (Berardelli *et al.*, 1999; Klein *et al.*, 1999b; Hallett, 2000; Maeda *et al.*, 2000). They demonstrate that low-frequency (<1 Hz) rTMS inhibits (Chen *et al.*, 1997a; Bohning *et al.*, 1999; Boroojerdi *et al.*, 2000a; Muellbacher *et al.*, 2000) while high-frequency (>5 Hz) rTMS excites the cortex (Pascual-Leone *et al.*, 1994; Fierro *et al.*, 2001; Boroojerdi *et al.*, 2001). A recent study of motor cortex excitability following short trains of rTMS (Modugno *et al.*, 2001) shows that for moderate intensities, inhibition is predominant after short trains, whereas facilitation dominates after long trains, suggesting that variables other than stimulation frequency have to be taken into account.

The exact mechanism by which rTMS modifies cortical excitability remains to be determined. It is thought, however, that the rTMS-induced changes might be explained by the phenomena of long-term potentiation (LTP) and long-term depression (LTD) which can be induced in hippocampus, visual and motor cortices in animal models by high- and low-frequency electrical stimulations, respectively (Dudek and Bear, 1992; Hess and Donoghue, 1996; Kimbrell *et al.*, 1999). In concordance with the above-mentioned study of the human motor cortex (Modugno *et al.*, 2001), low numbers of stimuli favour LTD while high numbers produce LTP in hippocampal slices (Mizuno *et al.*, 2001). High-frequency rTMS increases regional cerebral blood flow; in contrast, low-frequency rTMS is able to inhibit regional cerebral glucose metabolism (Speer *et al.*, 2000). Changes of neurotransmitters and receptors were found after chronic rTMS in rats: decreased sensitivity of cerebral 5-HT_{1A} and 5-HT_{1B} autoreceptors (Gur *et al.*, 2000) and an increase of dopamine and serotonin and their turnover rates after 15 Hz rTMS (Ji *et al.*, 1998; Ben-Shachar *et al.*, 1999).

The effect of rTMS may differ with the level of activation of the underlying cortex. Low-frequency rTMS has, for instance, a greater depressing effect on an area with a prior hypermetabolism, while the activation produced by high-frequency rTMS is higher when there is a local hypometabolism (Eschweiler *et al.*, 2000).

In both types of migraine, the 10 Hz rTMS increases the amplitude in the first block of 100 averaged PR-VEP, which suggests that the visual cortex was facilitated. Facilitation was indeed expected after the high number of stimuli ($n = 900$) applied at 10 Hz, based on available data in humans (Modugno *et al.*, 2001) and in animals (Mizuno *et al.*, 2001). Before rTMS, migraineurs were characterized by a potentiation of PR-VEP amplitude during subsequent stimulation and averaging, confirming our previous findings (Schoenen *et al.*, 1995; Áfra *et al.*, 1998a). The potentiation of the P1–N2 component was significantly less pronounced in MA patients, which agrees with results from a previous study

of long-lasting checkerboard stimulation (Áfra *et al.*, 1998a) and remains unexplained. After the 10 Hz rTMS, PR-VEP potentiation is replaced by habituation, with the exception of P1–N2 in MA where it is only attenuated (see Table 2 and Figs 3 and 4). Since it is reversed, i.e. normalized, by an excitatory stimulation, PR-VEP potentiation is thus a consequence of a low cortical activation level, a hypothesis previously made on the basis of low first block amplitudes of PR-VEP and other evoked potentials in migraineurs between attacks (Schoenen, 1998). One possible explanation for a causal relationship between decreased cortical excitability and lack of habituation or potentiation of evoked responses could be the 'ceiling effect' model (Knott and Irwin, 1973; Schoenen, 1996). In this model, the habituation depends closely on the pre-activation level of cortical excitability, which determines, for sensory cortices, the range of activation before the 'ceiling' is reached and the protective mechanism of habituation engaged. The cortical pre-activation level is set by the so-called 'state-setting' brainstem projections on the cortex, among which serotonergic and noradrenergic neurones play a central role (Mesulam, 1990). In migraine, the cortical pre-activation level appears to be low, i.e. near to the 'floor', which probably explains why the 1 Hz rTMS, although producing a trend for a reduction in first PR-VEP amplitude and an increase in potentiation (see Table 1 and Figs 3 and 4), was unable to induce a further significant decrease in cortical excitability. The cortical pre-activation level of healthy subjects is close to the 'ceiling', which correlates with a rapid habituation of evoked potentials and allows for a robust depressing effect of 1 Hz rTMS (Table 1 and Fig. 2), but not for a supplementary significant increase of excitability after the 10 Hz rTMS (Table 2 and Fig. 2).

The concept of an interictal decrease of cortical pre-activation excitability in migraineurs has been challenged on the basis of metabolic studies performed during visual stimulation (Cao *et al.*, 1999) and of single occipital TMS-produced phosphenes (Aurora *et al.*, 1998; Mulleners *et al.*, 2001b). While the former do not record cortical excitability but metabolic changes induced by repetitive visual stimuli, the latter have shown normal or decreased excitability in other centres (reviewed by Maertens de Noordhout and Schoenen, 1999), a variability which is due partly to the subjective nature of phosphenes. In the present study, we found, nonetheless, an increased phosphene threshold in both groups of migraineurs and a normal prevalence, which confirms our previous results in a larger cohort of patients (Áfra *et al.*, 1998b) and is yet another argument in favour of a cortical hypoexcitability.

Interestingly, evoked potentials recover a normal habituation pattern just before and during the migraine attack, suggesting that cortical excitability increases at that time (Kropp and Gerber, 1995; Evers *et al.*, 1999; Áfra *et al.*, 2000). If this increase plays a pathogenic role in the initiation of the migraine attack, for instance by abruptly increasing metabolic demands (Schoenen, 1996), one may speculate that

pre-emptive application of 1 Hz rTMS may prevent the attack.

In summary, we have shown that 10 Hz rTMS facilitates the visual cortex in migraineurs for up to 9 min, which changes the interictal potentiation of PR-VEP into quasi-normal habituation. The inhibitory 1 Hz rTMS has little effect on PR-VEP in migraine patients, although it significantly decreases cortical excitability and habituation in healthy subjects. Taken together, these results confirm that the evoked potential changes, in particular the habituation deficit found in migraineurs between attacks, are due to a decreased pre-activation level of sensory cortices and that the hypothesis of an interictal cortical hyperexcitability, taken in its strict physiological sense of a decreased response threshold and an increased response to a single stimulus, is no longer tenable.

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