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Transcranial magnetic stimulation in migraine : a review of facts and controversies

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Abstract

There is compelling evidence that cortical excitability is modified in migraine patients between attacks. Transcranial magnetic stimulation (TMS) is a non-invasive tool to investigate this abnormality. Repetitive transcranial magnetic stimulation (rTMS) activates the underlying cortex at high, but inhibits it at low stimulation frequencies. This is a review of published results obtained in migraineurs with TMS and rTMS over motor or visual cortices. Prevalence and/or threshold data of phosphenes induced by single pulse TMS of the visual cortex are contradictory, some favouring increased, others decreased interictal excitability. The discrepancies may be due to differences in methodology and poor reliability of phosphene reporting. In a recent rTMS study of the occipital cortex we have found evidence in favour of an interictal decrease of the preactivation excitability level by using amplitude of visual evoked potentials and its habituation during sustained stimulation as indices of cortical excitability. The hypothesis of increased cortical excitability, taken in its strict physiological sense of a decreased response threshold and/or an increased response to a single suprathreshold stimulus, may thus not be any longer tenable. The long lasting effects of rTMS allow in future studies to assess metabolic changes of the cortex and subcortical structures with functional imaging methods and to explore novel therapeutic strategies for migraine.

Key words : Migraine ; transcranial magnetic stimulation ; TMS ; rTMS ; review ; cortical excitability ; habituation.

Introduction

The pathophysiology of migraine is only partly understood. None of the proposed hypotheses for migraine pathogenesis comprehensively encompasses all available clinical and pathophysiological features of this disorder. Nevertheless, the present consensus is that both neuronal and vascular components are relevant in migraine and most probably interrelated (Ferrari 1998). The neuronal structures involved are the cerebral cortex, the brain stem (periaqueductal gray matter, aminergic nuclei) and the peripheral as well as the central components of the trigeminovascular system. The sequence of activation and the relative role of these structures are still controversial (Sándor *et al.* 2001).

Functional magnetic resonance imaging (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). A recent magnetoencephalographic study in migraine with aura confirmed that the aura is a spreading depression-like neuro-electric event that can arise spontaneously or be visually triggered in widespread regions of the occipital cortex (Bowyer *et al.* 2001). A link between the migraine aura and the headache is suggested by the experimental finding that cortical spreading depression is able to activate trigeminovascular afferents and to evoke a series of cortical, meningeal and brainstem events consistent with the development of headache (Bolay *et al.* 2002). It is generally thought that the aura, and thus spreading depression, is favoured by an increase in cortical excitability (Aurora *et al.* 2000). Indeed environmental studies suggest that migraineurs are more sensitive to light and sound also outside of an attack (Hay *et al.* 1994).

Between attacks, a functional pecularity of cerebral cortex can be demonstrated in most migraine patients by evoked potential studies. Cortical information processing of repetitive stimulations is characterized in migraineurs by a deficient habituation of the evoked response (Schoenen 1998). This has been demonstrated for event-related (Schoenen *et al.* 1985, Maertens de Noordhout *et al.* 1986, Kropp *et al.* 1993, Wang *et al.* 1998, Evers *et al.* 1997) and visual evoked potentials (VEPs) (Schoenen *et al.* 1995, Áfra *et al.* 1998a). Moreover, intensity dependence of auditory evoked cortical potentials (IDAP) is increased in migraine

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patients compared to normal controls (Wang *et al.* 1996) which is also mostly due to lack of habituation (Ambrosini *et al.* 2001). Is the habituation deficit due to increased cortical excitability ? Probably not, since the initial amplitude of evoked potentials is normal or low. The habituation deficit has on the contrary been attributed to a reduced preactivation level of sensory cortices (Schoenen 1998) applying the model of the "ceiling effect" (Knott and Irwin 1973). In this model the habituation depends closely on the preactivation level which determines the range of cortical activation before the 'ceiling' is reached and the protective mechanism of habituation engaged. To test this hypothesis, transcranial magnetic stimulation (TMS) appears to be of interest.

Transcranial magnetic stimulation is an interesting tool, as it can non-invasively alter the excitability of the cerebral cortex, as well as of intracortical inhibitory circuits (Hallet 2000). Since its first application in humans (Barker *et al.* 1985), TMS of the motor cortex has been extensively studied, because the peripheral electromyographic response offers an objective measure of cortical activation and allows to determine motor thresholds accurately. TMS studies of the visual cortex, by contrast, have to rely on subjective assessments of phosphenes (Barker *et al.* 1985, Meyer *et al.* 1991) or visual imagery tasks (Kosslyn *et al.* 1999), which probably explains why they are less abundant and less reproducible. In migraine, in particular, single TMS studies of the visual cortex have produced contradictory results which we will review in detail.

The TMS modality which is of most interest to cognitive neuroscientists is application of multiple pulses, i.e. repetitive transcranial magnetic stimulation (rTMS). rTMS is nowadays tested to treat various brain disorders, especially depression, but also obsessive-compulsive disorder, schizophrenia, motor disorders like Parkinson's disease, task-related dystonia (writer's cramp) or tics, and epilepsy (for a review, see Wassermann *et al.* 2001). rTMS is able to modify cortical excitability in opposite ways depending on the stimulation frequency (Hallet 2000). Low-frequency rTMS (£ 1 Hz) decreases (Chen *et al.*1997), whereas high-frequency rTMS (5-20 Hz) enhances cortical excitability (Pascual-Leone *et al.* 1994).

We were first to study the effects of single pulse TMS and rTMS on cortical excitability in migraine and will review here published literature data as well as our most recent results.

Single pulse Transcranial Magnetic Stimulation

Motor cortex

TMS of the motor cortex in migraine mainly assessed cortical excitability by determining motor thresholds (conventionally of the EMG response elicited in hand muscles). This measure reflects, however, neuronal membrane excitability (Chen 2000) rather than cortical excitability. The latter is better assessed by the paired-pulse paradigm (Kujirai *et al.* 1993) in which, with short interstimulus interval, the response of a suprathreshold stimulus is inhibited by a subthreshold conditioning stimulus, an effect attributed to local circuit inhibitory interneurons and inhibitory collaterals from excited corticospinal fibers. Another way to study the motor cortex with TMS is to measure the silent-period (SP) which refers to the duration of interruption of voluntary motor activity after a TMS pulse and is thought to reflect cortical as well as spinal mechanisms (Fuhr *et al.* 1991).

The first TMS study of motor thresholds (MT) in migraineurs was performed in our laboratory (Maertens de Noordhout *et al.* 1992). To overcome the problem of large interindividual MT variability, we decided to investigate migraine patients with symptoms always located on the same side which allowed us to use the other side as intraindividual control. We observed that interictally MT was significantly increased on the affected side of patients suffering from migraine with aura (MA) compared to normal subjects or to the unaffected side. No MT differences were observed between normal subjects and patients with unilateral migraine without aura (MO) or between the normal and affected side of MO patients. Moreover, the maximal amplitude of motor evoked potentials (MEP) expressed as the ratio over the maximal motor response (M) to peripheral nerve stimulation (MEPmax/Mmax) was found to be significantly reduced on the body side of the auras in MA patients. Anamnestic information and telephone calls after the recordings ensured that patients did not have migraine attacks in the week preceding or following electrophysiological testing.

Abnormally high MT were also reported in menstrual migraine without aura (Bettuci *et al.* 1992). All participants were right-handed and most patients experienced menstrual migraine on either side of the head. MT were increased bilaterally and no clear difference was found between those obtained interictally and during attacks.

These results were not confirmed in a study by van der Kamp *et al.* (1996) who found increased MEP amplitudes and reduced MT between attacks of MA as well as MO patients. They also reported a positive correlation between MEP amplitudes and attack frequency but did not mention whether migraine patients suffered from attacks in the days following the study. In a subsequent paper (1997), the same authors reported on the contrary increased interictal MT and reduced MEP amplitudes in patients with familial hemiplegic migraine (FMH) on the side on which of the motor deficit occurred. These results were very similar to those obtained in

our first study of patients with unilateral MA.

In a subsequent study (Áfra *et al.* 1998b), we investigated a larger group of MA and MO patients with attacks occurring on either side, ensuring that TMS was done in a temporal distance of at least 3 days from the attack. We found significantly higher mean MT, but only during contraction, in MA patients than in controls. Maximal MEP/Max values were normal in MA as well as in MO patients, whose attacks were not always located on the same side. Other parameters were also considered : EMG silent period (SP) elicited by motor cortex stimulation and paired TMS showed no significant abnormalities of cortical SP or intracortical inhibition in any group of migraineurs.

By contrast, Aurora *et al.* (1999a) found that the cortical silent period was significantly shorter in MA patients than in controls. A possible occurrence of a migraine attack within 24 hours after the recordings was, however, not controlled for.

Werhahn *et al.* (2000) found no significant changes of MT, silent periods or responses to paired stimulation in 12 patients with MA and 9 patients with FHM, while Brighina *et al.* (2002) reported a slightly, but non significantly, higher MT in MA. Finally, in a recent study where we reassessed motor and phosphene thresholds in migraineurs with a more focal figure-of-eight coil, MT tended to be higher in MA (63%) and MO patients (60%) than in healthy volunteers (58%), but these differences were not significant (Bohotin *et al.* 2003).

Data of these published studies are summarised in Table 1 (asterisk = statistically significant at $p < 0.05$).

Visual cortex

TMS over the occipital pole has been shown to interfere with visual perception (Amassian *et al.* 1989) and to induce visual sensations such as phosphenes (Barker *et al.* 1985, Meyer *et al.* 1991). Aurora *et al.* (1998), using TMS over the occipital lobe, reported an abnormally high interictal prevalence of TMS-induced phosphenes in MA patients, which could favour the hypothesis of visual cortex hyperexcitability. Again there was no information on the possible occurrence of an attack within 24 hours after the recordings and most patients were selected on the basis that their attacks could be triggered by visual stimuli. The threshold (PT) at which phosphenes were reported was lower in MA patients than in controls.

Aguggia *et al.* (1999) found a significant decrease of PT in MA patients compared to controls and also compared to a group of patients suffering from tension-type headache.

Mulleners *et al.* (2001a) found a reduced PT in MA and also in MO and interpreted their findings as hyperexcitability of the occipital cortex in migraine, but in their study, the proportion of patients who experienced TMS-induced phosphenes was not different from controls. In another study, the same authors (Mulleners *et al.* 2002) found a significant effect of sodium valproate on mean PT values in MA. After one month of valproate treatment MA, but not MO, patients had increased PT. The same research group (Mulleners *et al.* 2001b) found the ability of TMS to suppress visual perception to be reduced in MA patients, suggesting reduced activity of inhibitory circuits in the occipital cortex.

Battelli *et al.* (2002) studied phosphene production after TMS over extrastriate cortex (V5). They found significantly lower PT in both MO and MA compared to healthy subjects. There was no difference between left and right V5. The phosphene prevalence was higher in migraineurs for both sides of stimulation. A study published in abstract form by Young *et al.* (2001) also concluded that PT for occipital TMS were lower in migraine with aura (36 ± 3%) or without aura (40 ± 6%) than in healthy subjects (55 ± 9%).

By contrast, Áfra *et al.* (1998b), obtained rather opposite results : the prevalence of phosphenes was significantly lower in MA patients than in controls while no differences were found between controls and MO patients. Among subjects reporting phosphenes, mean thresholds of phosphene induction were similar in all groups. For all patients there was at least a 3 day-interval free of headache before and after the study, which excludes the cortical changes of the peri-attack period (Judit *et al.* 2000) as a confounding factor.

Brighina *et al.* (2002) found no differences in PT between migraineurs and healthy volunteers, but the former had a higher prevalence of phosphenes. In a recent study published as an abstract (Valli *et al.* 2002) prevalence of magnetophosphenes was similar in migraineurs and controls, but interestingly phosphene thresholds tended also to be higher in MA (71.04%) and MO (74.21%) than in controls (62.51%). In our laboratory, Bohotin *et al.* 2003 found no phosphene prevalence difference, but also a higher PT in both patients with or without aura relative to normal subjects.

Data of these published studies on visual cortex TMS are summarised in Table 2 (asterisk = statistically significant at $p < 0.05$).

Repetitive Transcranial Magnetic Stimulation

To the best of our knowledge, we were first to use repetitive transcranial magnetic stimulation (rTMS) to study migraine pathophysiology (Bohotin *et al.* 2002). The rationale was that rTMS would allow to increase or decrease cortical excitability by using high (5-20 Hz) or low frequency rTMS (≤ 1 Hz) (Hallet 2000). For this purpose, we decided to use pattern-reversal visual

Table 1

Single pulse Transcranial Magnetic Stimulation of motor cortex

Motor cortex TMS												
Authors	**Diagnosis (N° subjects**	**Mean age**	**Attack control**		**Methods**		**Results**					
			before	after	coil shape	Max. output	Motor threshold %		MEP amplitude	Central motor conduction time (ms)	Cortical silent period (ms)	Intracortical inhibition
							rest	active				
Maertens de Noordhout et al.(1992)	MA (10)	36 ± 14	1 week	1week	circular 130 mm	1.5 Tesla	55 ± 9* (↑)	41 ± 8* (↑)	↓	6.6 ± 0.7		
	MO (10)	39 ± 11					45 ± 6	33 ± 5	normal	6.5 ± 0.7		
	HV (20)	40 ± 14					48 ± 6	33 ± 3	normal	6.5 ± 0.6		
Bettucci et al. (1992) °	MO (10)	33	no	no	circular 130 mm	1.9 Tesla	58 ± 5* (↑)			5.7 ± 0.3		
	HV (10)	31					48 ± 7			5.7 ± 1.3		
Van der Kamp et al. (1996)	MA (10)	35	3 days	no	circular 130 mm	?	37 ± 4		↑	5.7 ± 1.2		
	MO (10)	50					38 ± 9		↑	6.6 ± 1.9		
	HV (10)	30					36 ± 5			5.7 ± 1.3		
Van der Kamp et al. (1997)	MA (10)	35	3 days	no	circular 130 mm	?	37 ± 6		↑	5.7 ± 1.2		
	FHM (10)	30					44 ± 6* (↑)		normal	6.8 ± 1.3		
	HV (6)	30					36 ± 7		normal	5.7 ± 1.3		
Afra et al. (1998)	MA (25)	36 ± 15	3 days	3 days	circular 130 mm	2.5 Tesla	54 ± 8	43 ± 8* (↑)	normal		101 ± 49	normal
	MO (33)	36 ± 15					52 ± 12	41 ± 10			100 ± 49	normal
	HV (27)	33 ± 10					47 ± 7	36 ± 6			101 ± 23	normal
Aurora et al. (1999)	MA (10)	36 ± 7	1 week	none	circular 95 mm	2 Tesla	63 ± 14				63 ± 27*	
	HV (10)	38 ± 6					58 ± 9				107 ± 20	
Werhahn et al. (2000)	MA (12)	38 ± 14	2 days	none	8-coil 90 mm	2.2 Tesla	61 ± 12				183 ± 30	normal
	FHM (9)	37 ± 13					60 ± 10				178 ± 5	normal
	HV (17)	29 ± 6					55 ± 12				179 ± 30	normal
Brighina et al. (2002)	MA (13)	39 ±12	2 days	2 days	8-coil 45 mm	?	58 ± 5					
	HV (15)	32 ±10					55±7					
Bohotin et al. (2003)	MA (13)	30.3± 10.1	3 days	3 days	8-coil 70 mm	1.2 Tesla	62 ± 6		normal			
	MO (24)	30.3± 10.1					59 ± 9					
	HV (33)	25.5 ± 6.6					57 ± 7					

evoked potentials (PR-VEP) amplitude and its modification during sustained stimulation as indices of visual cortex excitability changes.

In 30 patients (20 MO, 10 MA) and 24 healthy volunteers, rTMS of the occipital cortex was performed with a focal figure-of-eight magnetic coil (Rapid Magstim®). Nine hundred pulses were delivered randomly at 1 Hz or at 10 Hz in two separate sessions. Stimulus intensity was set to the phosphene threshold or to 110% of the motor

Table 2

Single pulse Transcranial Magnetic Stimulation of visual cortex

Visual cortex TMS									
Authors	**Diagnosis (N° subjects)**	**Mean age**	**Attack control**		**Methods**		**Results**		
			before	after	coil shape	Max. output	Phosphene prevalence	Phosphene threshold	Others
Aurora et al. (1998)	MA (11)	37 ± 7	1 week	no	circular coil 95 mm	2 Tesla	100* (↑)	44.2 ± 8.6* (↓)	
	HV (11)	36 ± 7					27	68.7 ± 3.1	
Afra et al. (1998)	MA (25)	36 ± 15	3 days	3 days	circular 130 mm	2.5 Tesla	56* (↓)	46	
	MO (33)	36 ± 15					82	50	
	HV (27)	33 ± 10					89	48	
Aurora et al. (1999)	MA (14) +MO (1)	40 ± 8	1 week	no	circular coil 95 mm	2 Tesla	86.7* (↑)	45* (↓)	
	HV (8)	37 ± 6					25	81	
Mulleners et al. (2001a)	MA (16)	43	1 day	no	circular coil 130 mm	2 Tesla	75	47 ± 4.7* (↓)	
	MO (12)	46					83	46 ± 3.6* (↓)	
	HV (16)	43					94	66 ± 10.1	
Mulleners et al. (2001b)	MA (7)	34 ± 12	no	no	circular coil 130 mm	2 Tesla	no	no	↓ visual extinction
	HV (7)	36 ± 13							
Battelli et al. (2002)	MA (16)	42 ± 14	2 weeks	no	8-coil 70 mm	2 Tesla	Left side: 65 Right side: 59	80 ± 24* (↓) 82 ± 26* (↓)	
	MO (9)	35 ± 15					Left side: 67 Right side: 78	88 ± 22* (↓) 80 ± 18* (↓)	
	HV (16)	40 ± 14					Left side: 6 Right side: 19	108 ± 9.9 104 ± 11.8	
Brighina et al. (2002)	MA (13)	39 ± 12	2 days	2 days	8-coil 45 mm	?	100	56 ± 7	↓ by 1Hz rTMS
	HV (15)	32 ±10					47	57 ± 13	↑ by 1Hz rTMS
Bohotin et al. (2003)	MA (13)	30.3± 10.1	3 days	3 days	8-coil 70 mm	1.2 Tesla	69	84 ± 12 * (↑)	
	MO (24)	30.3± 10.1					62	84 ± 12 * (↑)	
	HV (33)	25.5 ± 6.6					63	68 ± 12	

threshold, if no phosphenes were elicited. Before and after rTMS, PR-VEPs were sequentially averaged in 6 blocks of 100 responses during uninterrupted 3.1 Hz stimulation and analysed in term of N1-P1 and P1-N2 components. The most striking finding was that the effects of rTMS on PR-VEP in migraineurs contrast with those observed in healthy volunteers. In the latter, only the low frequency 1 Hz stimulation has significant effects : it decreases 1st block amplitude and habituation. To the opposite, PR-VEP of migraineurs are significantly modified by the high frequency 10 Hz rTMS, which increases 1st block amplitude and habituation, but not by the low frequency stimulation (Fig. 1). There were no differences between MO and MA. The effects of one rTMS train at 1 Hz on N1-P1 habituation remained significant during 33 min in the 10 normal subjects recorded for long durations

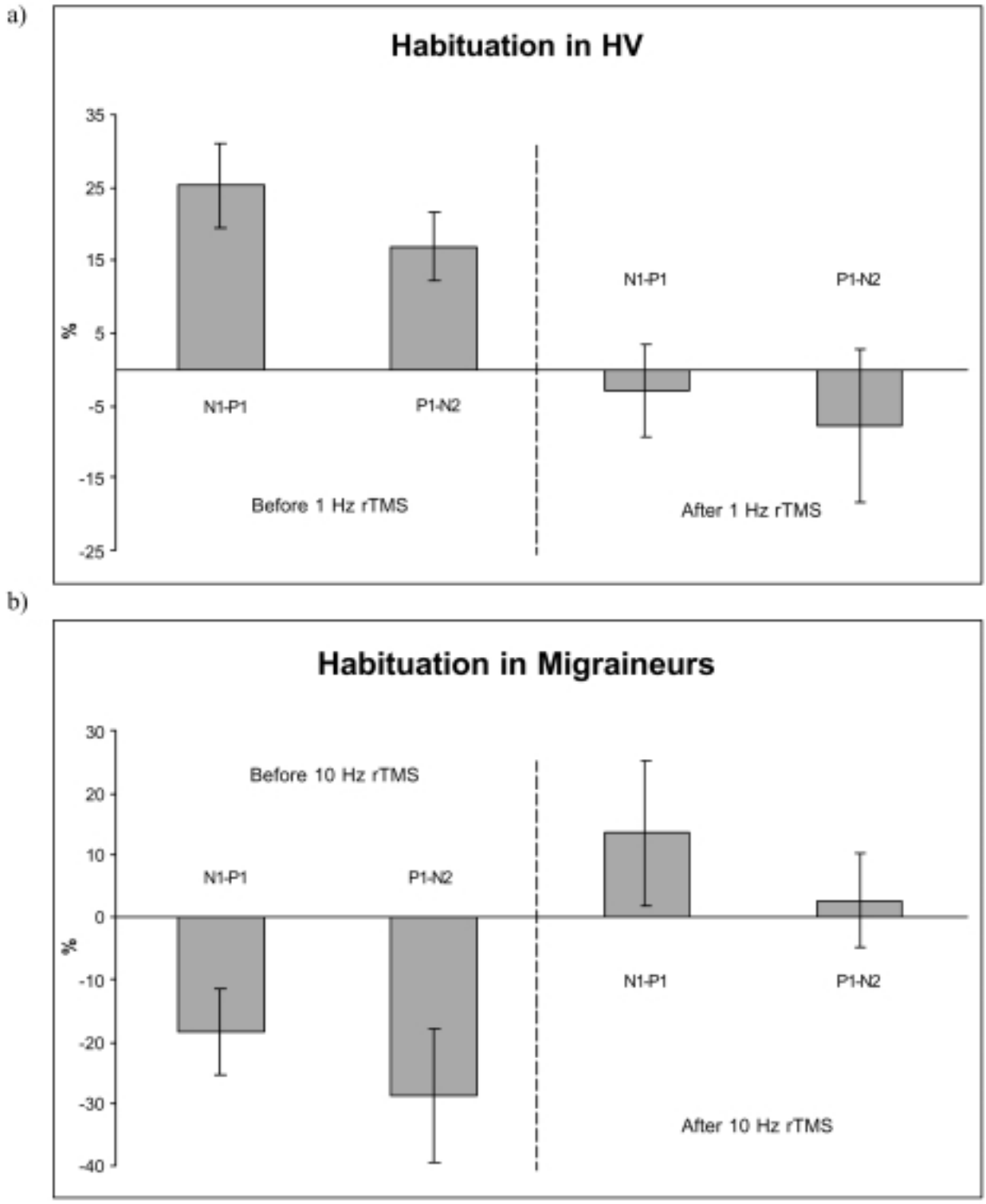

FIG. 1. — Habituation of N1-P1 and P1-N2 components of PR-visual evoked potentials (mean ± SE) before and after rTMS at 1 Hz in 24 healthy volunteers (HV) (a), at 10 Hz in 24 migraineurs (b). Habituation is expressed as the percentage reduction of 6th block amplitude relative to 1st block amplitude.

(Fig. 2). The effect was more pronounced at 9 minutes and at 15 min than immediately after the stimulation. The lack of effect after 10 Hz rTMS persisted for the total 43 min-recording period (Fumal *et al.* 2003). On the contrary, in the 6 migraineurs tested for duration of effect, 10 Hz rTMS increased significantly N1-P1 habituation for only 9 min after the stimulation (Bohotin *et al.* 2002).

In a pilot study of 5 HV and 4 migraineurs (Fumal *et al.* 2002) we searched whether daily rTMS sessions respectively at 1 Hz or 10 Hz could produce long lasting effects on PR-VEP. In all 5 HV, mean duration of the 1 Hz rTMS-induced dishabituation increased on consecutive sessions. In 2 of them, dishabituation after the last session lasted for more than 2 but less than 24 hours. In the

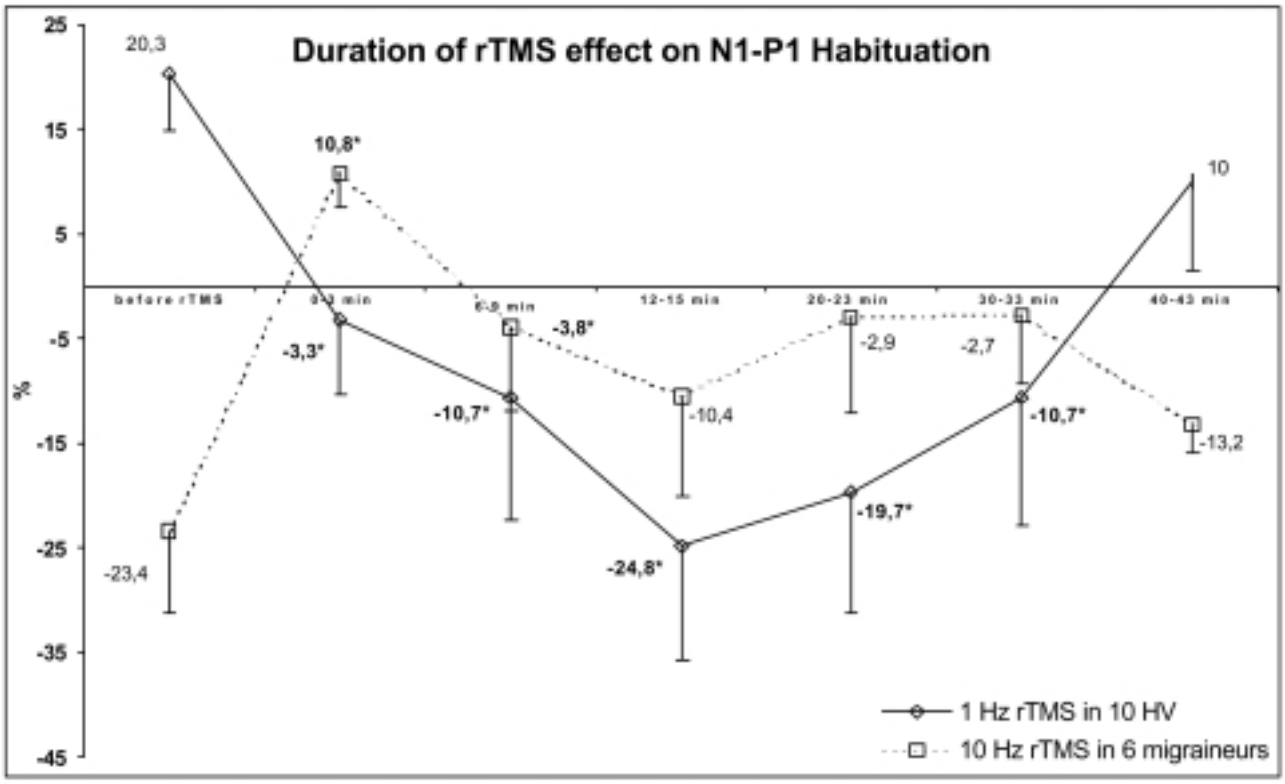

FIG. 2. — Duration of the 1 Hz rTMS effect on habituation of the PR-VEP N1-P1 component in 10 healthy volunteers (HV) and of the 10 Hz rTMS effect in 6 migraineurs (mean ± SE, asterisk : $p < 0.05$).

remaining 3 HV, the cumulative effect of rTMS was more pronounced : it lasted 4 weeks in 2 subjects and 11 weeks in the last one. In migraineurs, daily 10 Hz rTMS induced long lasting effects but, contrary to those found in HV, their total duration did not exceed 2 hrs, except in one subject where it lasted 1 week. Daily rTMS may thus induce long-lasting changes in cortical excitability and habituation pattern of VEP, which might open therapeutic perspectives.

In a recent study of low frequency (1 Hz) rTMS of the visual cortex, Brighina *et al.* (2002) found after the 15-min rTMS session a significant decrease of PT in MA patients whereas in normal subjects PT increased, as also previously shown (Boroojerdi *et al.* 2000).

Discussion

On the basis of the above mentioned studies, the use of single pulse TMS to assess excitability of motor and visual cortices seems to have yielded conflicting results.

Some discrepancies could be due to methodological differences which may be device- and patient dependent. The first difference is the type of coil used. There are two main coil types of different sizes : circular and figure-of-eight coils. The two types of coils differ substantially, since a figure-8 coil produces a focal stimulation under the centre of the coil while a circular coil causes more diffuse stimulation of the underlying cortex (Hallet 2000). It is thus likely that a larger cortical area was stimulated when circular coils were used. In addition, the human cortex is sensitive to the direction of current flow in the coil – with the circular coil this effect is more pronounced. Other technical differences between the set-ups used for TMS, such as for example shape magnetic pulse wave (biphasic or monophasic), maximum stimulator output, must also be taken into account.

Although both cortical areas show considerable variation in their location, the motor hand area is likely to vary more in the medio-lateral and anterior-posterior directions between individuals while the primary visual cortex will tend to vary more in depth. Movement of the coil can compensate to some extent for variability in location over the surface of the skull but not in depth. The more so that the magnitude of the electric field induced y TMS drops to about 75% of the peak field within a radius of 10 mm (Cohen *et al.* 1990, Roth *et al.* 1991).

Thus the threshold for primary visual cortex will vary more between subjects than for the motor hand area (Stewart *et al.* 2001). It should be noted that primary visual cortex is not the sole candidate site for the generation of phosphenes ; the optic tract or extrastriate areas abutting V1 have also been suggested (Kammer *et al.* 2001) however, regardless of the exact location from which phosphenes are elicited, the same arguments about anatomical variability would still apply.

With regard to patient selection, one must keep in mind that dramatic changes of evoked cortical responses, and thus of cortical excitability, occur at least 24 hours before and during the attack and may outlast it for 24-72 hours (Judit *et al.* 2000). While the occurrence of the last attack before the recording can be checked by anamnestic information, attacks after the recording have to be controlled for, e.g. by means of telephone calls. The latter was done only in a few studies.

Despite the discrepancies highlighted above, most TMS studies of the motor cortex seem to indicate reduced interictal membrane excitability of large pyramidal neurons in various forms of migraine with aura. Changes of spinal motoneuron excitability are indeed unlikely in migraine. Excitability changes of the motor cortex do not seem to result from a dysfunction of cortical inhibitory interneurons, found to be normal in MA and MO patients (Áfra *et al.* 1998b, Werhahn *et al.* 2000). Moreover, TMS-induced silent periods which were normal in all migraine studies except one, do not favour an abnormality of inhibitory output pathways in the motor cortex, although the precise mechanisms of this silent period remains debated (Chen 2000). These findings do not support therefore the hypothesis (Welch *et al.* 1990) of a permanent cortical hyperexcitability in migraine.

In visual cortex studies, one puzzling result in Aurora *et al.*'s studies (1998,1999b) is the very low prevalence of phosphenes elicited in the control group while all previous studies conducted in normal subjects report a very high prevalence of phosphenes (Meyer *et al.* 1991, Kammer *et al.* 2001, Stewart *et al.* 2001). Methodological considerations or subject selection may in part be responsible these contradictory results, but further studies of visual areas with TMS are needed to clarify this point. Preponderance of patients who had visually-triggered attacks might also explain why Aurora *et al.* found such an extreme phosphene prevalence (100%) in their migraine population. On the other hand, several studies suggest that the threshold to induce phosphenes with TMS is reduced in migraine with aura as well as without aura. Moreover, Mulleners *et al.* (2001b) also observed that visual perception was less suppressed by TMS in migraineurs than in controls. These arguments might be in favour of either some degree of visual cortex hyperexcitability in migraineurs, or maybe some deficient function of intracortical inhibitory pathways, as previously suggested (Chronicle *et al.* 1994). One major problem with PT is that subjects who experience no phosphenes are not included in the measurement. In case of a difference in phosphene prevalence between controls and patients, this may distort the results in favour of one or the other group. Absence of magnetophosphenes indeed would indicate decreased rather than increased cortical excitability. Several studies showing normal or increased PT favour normal or decreased visual cortex excitability in migraine.

As mentioned in the introduction, phosphenes are a highly subjective experience which lacks reliability. The results obtained with PR-VEP which is an objective measure may be more reliable.

The modifications induced by rTMS in PR-VEP are in keeping with the hypothesis that the interictal habituation deficit in migraineurs is due to a decreased preactivation excitability level of sensory cortices. High frequency rTMS, which is supposed to activate the underlying cortex, indeed increased amplitude in the first block of averagings and normalized habituation in migraineurs. It probably had no effect in healthy volunteers because they have an optimal level of cortical preactivation. Such an effect can be interpreted within the frame of Knott and Irwin's ceiling model, as long as one accepts that the interictal preactivation excitability level of the visual cortex is lowered in migraineurs. The rTMS results do not support 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 suprathreshold stimulus. The finding by Brighina *et al.*(2002) that 1 Hz rTMS has opposite effects in migraineurs compared to healthy volunteers suggests that the effect of low frequency rTMS effects could depend on the pre-existing imbalance between excitatory and inhibitory circuits in visual cortex. However, if 1 Hz rTMS would increase cortical excitability in migraineurs, we would have expected an amplitude increase in 1st block averages in our study (Bohotin *et al.* 2002), which was clearly not the case.

The exact mechanisms by which rTMS modifies cortical excitability remain, however, to be determined. It is thought that the rTMS-induced changes might be explained by the phenomena of long-term potentiation and long-term depression (Bohotin *et al.* 2002). Cortical, but also subcortical neurones may be involved. We hypothesize that diffusion of the rTMS effect to subcortical pathways could explain the lasting effect found after 1 Hz rTMS in HV (see figure 2). Such a response pattern has already been found by others with rTMS of motor cortex (Romero *et al.* 2002).

Further investigations are needed to test the possible cumulative effect of rTMS on VEP habituation. Daily rTMS is currently used in psychiatry to treat depression and subsequent functional imaging has shown long-term metabolic effect (Speer *et al.* 2000, Kimbrell *et al.* 1999). Furthermore, a recent study using daily rTMS of motor cortex showed persistent changes for at least 2 days after the last stimulation session (McKay *et al.* 2002). It will be of interest to monitor the persistence of the VEP

habituation increase in migraineurs with daily 10 Hz rTMS and to compare the electrophysiological effect to the metabolic changes occurring in the visual cortex. Finally, if one assumes that the habituation deficit has a pathogenic role in migraine (Schoenen 1996), it seems worthwhile to explore the possible influence of daily rTMS on the clinical course of the disorder.

Conclusions

Studies of magnetophosphenes induced by single pulse transcranial magnetic stimulation of the visual cortex have disclosed contradictory results in migraineurs between attacks, some favouring hyperexcitability, others hypoexcitability. The latter was suggested by most TMS studies of the motor cortex in migraine. The discrepancies between data for TMS of the visual cortex are likely to be method- and patient-related, but their major cause is probably the lack of reliability of subjective phosphene reporting. We have therefore used pattern-reversal visual evoked potentials as an index of visual cortex excitability and its changes induced by repetitive transcranial magnetic stimulation. Our results clearly favour the hypothesis put forward to explain the habituation deficit found interictally in migraineurs on evoked potentials, i.e. that the preactivation excitability level of the visual cortex is reduced. If the habituation deficit in cortical information processing plays as suggested (Schoenen 1996) a pathogenic role in migraine, rTMS may open novel therapeutic perspectives, as it is able to modify durably excitability of the visual cortex.

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