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Short-term cortical synaptic depression/potentiation mechanisms in chronic migraine patients with or without medication overuse

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Abstract

Objective: To study the effects of trains of repetitive transcranial magnetic stimulation (rTMS) over the motor cortex in patients with chronic migraine (CM) with or without medication overuse (MOH).

Subjects and methods: Thirty-two patients (CM [n = 16]; MOH [n = 16]) and 16 healthy volunteers (HVs) underwent rTMS recording. Ten trains of 10 stimuli each (120% resting motor threshold) were applied over the left motor cortex at 1 Hz or 5 Hz in random order. The amplitude of motor evoked potential (MEP) was evaluated from electromyographic recording in the first dorsal interosseous muscle. The slope of the linear regression line for the 10 stimuli for each participant was calculated using normalized data.

Results: rTMS-1 Hz had a normal depressive effect on MEP amplitude in all groups. rTMS-5 Hz depressed instead of potentiating MEP amplitudes in MOH patients, with a significantly different response from that in HVs and CM patients. The slope of the linear regression of MEP amplitudes was negatively correlated with pain intensity in CM patients, and with the duration of overuse headache in MOH patients.

Conclusions: This different plastic behaviour suggests that MOH and CM, despite exhibiting a similar clinical phenotype, have different neurophysiological learning processes, probably related to different pathophysiological mechanisms of migraine chronification.

Keywords

Synaptic plasticity, repetitive transcranial magnetic stimulation, chronic migraine, depression, potentiation

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Introduction

Chronic migraine (CM) is characterized by headaches occurring ≥ 15 days per month, with ≥ 8 headache days fulfilling the criteria for migraine headaches, for at least 3 months (1). Every year, approximately 3% of migraineurs progress to CM (2). Different factors may favour migraine chronification, including overuse of analgesics, ineffective acute treatment(s), obesity, and psychological factors such as depression, stressful life events, and specific personality traits (3). Medication overuse headache (MOH) is very prevalent among patients attending specialized headache clinics and is associated with excessive use of acute medication

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drugs, defined as intake of analgesics or triptans on more than 15 and 10 days per month, respectively (1).

According to the current diagnostic criteria from the International Classification of Headache Disorders (ICHD-3 beta), analgesic abuse is no longer an exclusion criterion for the diagnosis of CM. However, morphofunctional studies have shown that MOH patients exhibit peculiar cerebral morphological (4–6) and electrophysiological patterns when compared with pure CM patients (i.e. without medication overuse). In particular, while evidence for cortical sensitization (calculated as the initial amplitude increase of evoked potentials) has been observed in both pure CM and MOH patients in response to different sensorial stimulations (4–6), deficient habituation – or persistent sensitization – to repetitive somatosensorial stimulation is exhibited by patients with MOH (4,7,8), but not those with CM (6). Because habituation can be considered a basic form of learning and memory (9), these findings suggest that the mechanisms underlying sensorimotor plasticity and learning processes could be dysfunctional in CM patients and depend on the co-occurrence of medication overuse.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive tool used to modulate cortical excitability. When applied over the motor cortex, this neuromodulatory technique has been shown to induce pain relief in different types of chronic pain (10), mainly by effecting plastic changes in the motor area, whose extension is positively associated with pain intensity (11).

In normal subjects, rTMS is able to induce functional plastic changes depending on the number, intensity, and frequency of the stimulation pulses. In particular, high-frequency trains (5 Hz) of rTMS have been reported to increase cortical excitability in the short term, while low-frequency stimulations (0.1–1 Hz) have been reported to decrease it (12,13). Because chronic pain is characterized by maladaptive plasticity in the motor system, studying the relationship between CM and motor cortex excitability could be interesting, not only to reveal the mechanisms related to headache chronification, but also for future therapeutic targets and interventions.

In patients affected by episodic migraine with aura, low-frequency rTMS has been shown to produce a paradoxical increase of intracortical facilitation in the motor cortex (14). Studies investigating effects of high-frequency rTMS in patients affected by migraine with aura yielded different results depending on the TMS variables and experimental protocols. In patients, 5 Hz-rTMS on the motor cortex induced motor evoked potential (MEP) facilitation when the stimulation was delivered at an intensity of 110% resting motor threshold (RMT) and paradoxical MEP inhibition when delivered at 130% RMT (15). In patients with episodic migraine without aura, Conte and co-workers (16) found that 5 Hz-rTMS, delivered at 120% RMT, induced abnormally high MEP facilitation. Moreover, in patients affected by migraine without aura, MEP response to trains of high-frequency rTMS yielded different effects depending on the phase within the migraine cycle, and on the frequency of migraine, with a physiological increasing response in the interictal phase and paradoxical decremental response in both episodic migraineurs recorded ictally and in CM patients (17).

To the best of our knowledge, no studies to date have performed a detailed examination of short-term plasticity mechanisms of the primary motor cortex individually in CM and MOH patients. The goal of the current study, therefore, was to use both low- and high- frequency rTMS over the motor cortex to identify distinctive neurophysiological mechanisms underpinning learning and plasticity in individuals with CM or MOH compared with normal subjects.

Material and methods

Subjects

Among consecutive patients attending the authors' headache clinic, 40 provided informed consent to participate in the study, of whom eight were excluded because they did not fulfil the inclusion criteria. Participants were included if they were between 18 and 65 years of age and had at least a 1-year clinical history of migraine. Participants were excluded from the study if they were regularly taking medication (e.g. antibiotics, corticosteroids, antidepressants, benzodiazepines, or prophylactic migraine medication) during the 3 months preceding the study, except for contraceptive pills (taken by three HV, two CM, and two MOH). Individuals with a history of other neurological disorder(s), systemic hypertension, diabetes or other metabolic or autoimmune disease, or any other type of primary or secondary headache, were also excluded. Patients did not always experience the headaches on the same side. All participants received a complete description of the study and provided written informed consent. The study was approved by the local ethics review board and was conducted in accordance with the Helsinki Declaration.

According to the inclusion/exclusion criteria, the final dataset comprised 32 patients (Table 1), of whom 16 were diagnosed with *de novo* CM (IHCD-IIIb code 1.3), with no history of medication overuse, and 16 with *de novo* MOH (ICHD-IIIb code 8.2), who had never undergone a detoxification program during their first screening visit. The inclusion criteria were

Table 1. Demographic characteristics of study participants and headache profiles of patients. Data expressed as mean ± SD. HV: healthy volunteers; CM: chronic migraneurs; MOH: medication overuse headache patients; n: number of subjects.

	HV (n = 16)	CM (n = 16)	MOH (n = 16)
Women (n)	12	12	13
Age (years)	32.1 ± 10.2	32.1 ± 10.2	34.4 ± 11.6
Duration of history of migraine (years)		13.5 ± 10.3	16.5 ± 9.2
Days with headache/month (n)		22.6 ± 6.4	20.4 ± 6.9
Severity of headache attacks (0–10)		6.9 ± 2.2	8.1 ± 1.6
Nausea/vomiting (n)		13	16
Photophobia (n)		15	14
Phonophobia (n)		13	14
Pulsating (n)		13	14
Duration of chronic headache (years)		22.7 ± 24.6	18.1 ± 14.9
NSAID tablet intake/month (n)		3.2 ± 3.8	27.8 ± 13.7*

*$p < 0.001$ vs. CM.

restricted to MOH patients overusing non-steroidal anti-inflammatory drugs (NSAIDs) only (IHCD-IIIb code 8.2.3), because it has been demonstrated in a previous study that these patients exhibit the most pronounced abnormalities at the sensorimotor system level compared with MOH patients overusing anti-migraine-specific (triptan) acute medication (4,18). Before progressing to MOH, all patients had a clear-cut history of episodic migraine without aura (ICHD-IIIb code 1.1). Except for four patients who had mild headache (mean visual analogue scale score 4/10), all patients underwent the MEP recordings in a pain-free state. Because MOH patients tend to take acute medications compulsively and frequently during the day, it was impossible to prevent them from taking medication on the day of recordings. It was managed, however, to perform the recordings at least 3 h after the last medication intake. For comparison, MEP trains were recorded in 16 healthy volunteers (HVs) with comparable age and sex distribution (Table 1), and no personal or familial history (first- or second-degree relatives) of migraine and no detectable medical condition. To avoid variability due to hormonal changes, female participants were examined outside their pre-menstrual or menstrual cycles.

TMS procedures. During TMS, patients were seated in a comfortable armchair and asked to remain fully relaxed with their eyes closed to ensure similar attention levels. TMS was delivered through a high-frequency biphasic magnetic stimulator (MagstimRapid, The Magstim Company Ltd., Whitland, Carmarthenshire, Wales, UK), which was connected to a figure-of-eight coil with a maximal output of 1.2 T. First, the optimal orientation and position of the coil (i.e. "hot spot") over the left motor area for stimulating the first dorsal interosseous muscle were determined. Thereafter, the RMT was identified using single TMS pulses; complete relaxation of the first dorsal interosseous (FDI) muscle was verified by the absence of electromyographic (EMG) signals, both visually (on a monitor) and by acoustic feedback. The RMT was defined as the minimal intensity required to elicit an EMG response of at least 50 μV with 50% probability in a fully relaxed muscle. Because all of the enrolled participants were right-handed, and because patients did not always experience the headaches on the same side, rTMS trains were only delivered over the left motor cortex. EMG activity in the right FDI muscle was recorded through surface electrodes placed over the right FDI muscle. Thereafter, 10 consecutive trains of 10 single pulses of TMS (stimulus intensity, 120% of the RMT; inter-train interval, 1 min) were delivered at a frequency of 1 or 5 Hz in two separate sessions (intersession interval of at least 1 week) performed in random order. The resulting EMG activity was filtered (bandwidth 20 Hz–1 kHz). All recordings were collected in a 3 h period between 09.00 am and 12.00 pm by two investigators (CL, CC). The 10 trains of 10 stimuli were averaged, then numbered anonymously and analysed off-line in a blind manner by one investigator (FC). The peak-to-peak MEP amplitudes (μV) of each of the 10 responses were measured within the train of 10 stimuli.

Statistical analysis. Data were statistically analysed in a blinded manner by a single investigator (GC) using Statistica version 8.0 (StatSoft Inc., Tulsa, OK, USA) for Windows (Microsoft Corporation, Redmond, WA, USA).

Data were first analysed using the Kolmogorov-Smirnov to test for normal distribution. Preliminary descriptive analysis revealed that some of the 10 MEP peak-to-peak amplitudes within the rTMS trains had a non-normal distribution. After log transformation (log10[x]), all data achieved normal distribution (Kolmogorov-Smirnov test, $p > 0.05$).

A repeated measures analysis of variance (rm-ANOVA) was performed using the between-subject factor "group" (HV, CM, MOH) and the within-subject factor was "stimuli". To investigate the interaction effect, the two models of rm-ANOVA were followed by univariate ANOVA. Moreover, to quickly evaluate MEP amplitude trends within trains of rTMS stimuli, the slope of the linear regression line was calculated for the 10 stimuli for each participant on the normalized data. To analyse the slope of the linear regression, an ANOVA model with the between-subject factor "group" (HV, CM, MOH) was used; post hoc Tukey honest significant difference tests were also performed.

A one-way ANOVA test was used to compare the clinical and neurophysiological (RMT, first amplitude MEP) variables at baseline. Pearson's coefficient was used to test for correlations between neurophysiological (first MEP amplitude, MEP amplitude slope) and clinical variables (disease duration, days with headache, visual analogue scale score, monthly tablet intake, duration of the chronic phase, duration of the overuse phase). p values < 0.05 were considered statistically significant.

Results

Basic clinical and neurophysiological parameters

Assessable rTMS trains of MEPs were acquired from all study participants. The patient groups exhibited similar clinical features except for the mean monthly tablet intake (Table 1), which was clearly higher in MOH than in CM patients ($p < 0.001$). The RMT and the first MEP amplitude were not significantly different between groups at both 1 and 5 Hz rTMS (Table 2).

Effects of rTMS on neurophysiological parameters

In the rm-ANOVA model, using the rTMS 1 Hz MEP peak-to-peak amplitude as the dependent variable, the multivariate test was significant for the factor "stimuli" ($F_{9,405} = 5.220$, $p < 0.001$), but not for the factor "group" ($F_{2,45} = 0.892$, $p = 0.417$) and for the "group" × "stimuli" interaction effect ($F_{18,405} = 0.589$, $p = 0.907$) (Figure 1 [left panel). As confirmation, the slope of the linear regression of MEP amplitudes over all stimuli was not significantly different between groups ($F_{2,45} = 0.726$, $p = 0.489$) (Figure 2 [left panel]).

In the rm-ANOVA model using the rTMS 5 Hz MEP peak-to-peak amplitude as the dependent variable, the multivariate test was not significant for the factors "stimuli" ($F_{9,405} = 1.535$, $p = 0.133$) and "group" ($F_{2,45} = 0.085$, $p = 0.918$), but it reached statistical significance for the "group" × "stimuli" interaction effect ($F_{18,405} = 2.846$, $p < 0.001$) (Figure 1 [right panel]). The slope of the linear regression of MEP amplitudes over all stimuli was significantly different between groups ($F_{2,45} = 6.11$, $p = 0.004$) (Figure 2 [right panel]). A post-hoc analysis revealed that the slope of MEP amplitudes from stimulus 1 to 10 calculated in the MOH patient group (−0.021) was significantly different from that calculated in HVs (+ 0.010, $p = 0.001$) and in CM patients (−0.003, $p = 0.047$) (Table 2 and Figure 2 [right panel]).

In CM patients, the mean severity of migraine assessed according to visual analogue scale correlated negatively with the slope of the linear regression of MEP amplitudes recorded in response both to 1 Hz

Table 2. Transcranial magnetic stimulation (TMS) resting motor thresholds (RMT) and motor evoked potential (MEP) first amplitude (Log transformed) and slope of the linear regression line from the first to the 10th stimulus of the train. Data expressed as mean ± SD. HV: healthy volunteers; CM: chronic migraine patients; MOH: medication overuse headache patients; n: number of subjects.

	HV (n = 16)	CM (n = 16)	MOH (n = 16)
1 Hz repetitive TMS train			
RMT (%)	54.9 ± 11.3	55.0 ± 12.6	53.6 ± 6.4
First MEP amplitude	2.2 ± 0.3	2.3 ± 0.5	2.5 ± 0.4
MEP slope	−0.002 ± 0.015	−0.005 ± 0.017	−0.009 ± 0.017
5 Hz repetitive TMS train			
RMT (%)	54.6 ± 11.4	54.0 ± 11.5	54.2 ± 6.4
First MEP amplitude	2.3 ± 0.3	2.3 ± 0.5	2.4 ± 0.4
MEP slope	0.010 ± 0.031	−0.003 ± 0.027	−0.021 ± 0.016*

*$p < 0.05$ vs. CM and HV.

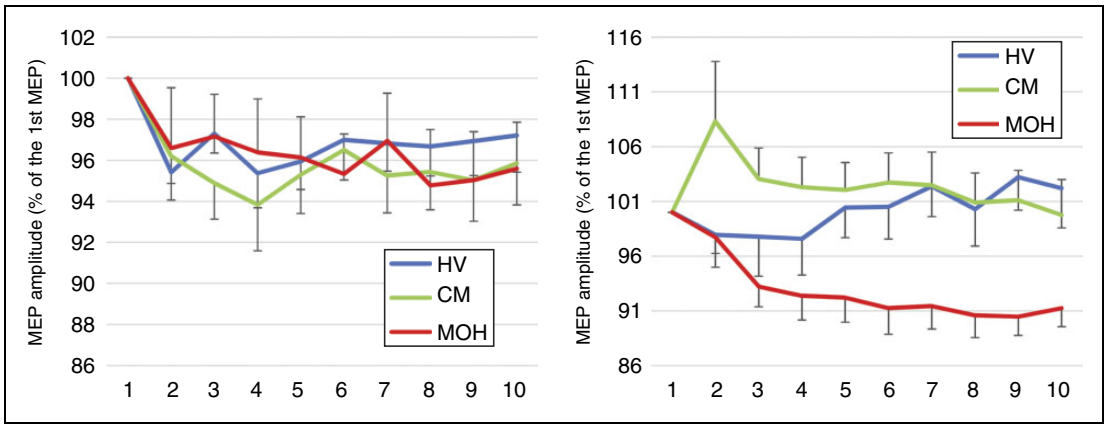

Figure 1. Motor evoked potentials (MEP) elicited by repetitive transcranial magnetic stimulation trains delivered at 1 Hz (left panel) and 5 Hz (right panel) at 120% resting motor threshold in healthy volunteers (HV), chronic migraine (CM), and medication overuse headache (MOH) patients.

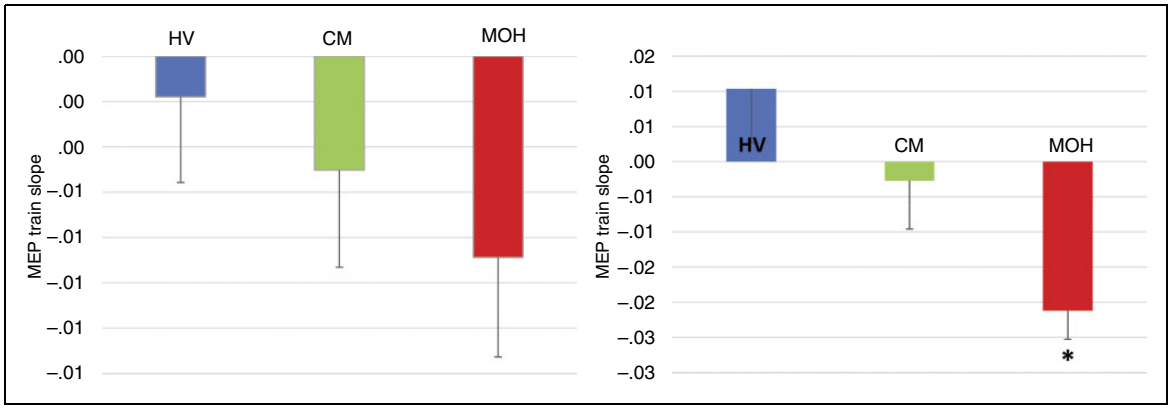

Figure 2. Bar charts representing the motor evoked potential (MEP) amplitude slope of the linear regression line from the first to the 10th stimulus of the 1 Hz (left panel) and 5 Hz (right panel) train of stimuli in healthy volunteers (HV), chronic migraine (CM), and medication overuse headache (MOH) patients (*$p < 0.05$ MOH vs. HV and CM).

($r = -0.507$, $p = 0.045$) and to 5 Hz ($r = -0.637$, $p = 0.008$) rTMS trains. Whereas, in MOH patients, the duration of the overuse phase correlated negatively with the slope of the linear regression of MEP amplitudes recorded in response to 5 Hz rTMS trains ($r = -0.506$, $p = 0.045$). No other significant correlation between neurophysiological and clinical variables was observed in either group.

Discussion

The main finding of this study was that the mechanisms of short-term synaptic potentiation – but not depression – in the primary motor cortex of patients affected by MOH are different from those in HVs and pure CM patients. In fact, whereas 1 Hz-rTMS induced similar effects in the three groups, causing a decrease in M1 excitability, 5 Hz-rTMS led to MEP facilitation in normal subjects while having a paradoxical inhibitory effect in MOH patients (with a significantly different slope of MEP amplitudes from that calculated in HVs and pure CM patients). We discuss the possible neurobiological underpinnings of these data on motor cortex excitability in CM and MOH and their relevance to their pathophysiology.

In healthy subjects, rTMS at a frequency of 5 Hz with an intensity above RMT was shown to increase MEP magnitude and to induce a post-train facilitation up to 4 min (19). This facilitation occurs at the cortical level and the mechanism involved is not completely clear because the output from corticospinal cells depends on the sum of all inhibitory and excitatory inputs to the pyramidal cells. Using 5 Hz-frequency rTMS at different stimulation intensities,

several studies have reported an increase in cortical silent period duration within the stimulation train (20) and a decrease in intracortical inhibition both within train and post-train (21). The latter finding is consistent with the reported effects of high-frequency rTMS in increasing MEP magnitude, because the down-regulation of inhibitory inputs is expected to result in increased excitability. Pharmacological studies performed to characterise the plasticity underlying this process reported that rTMS-induced facilitation is distinguished by a specific pharmacological profile, suggesting a short-term potentiation mechanism and particularly a post-tetanic potentiation (PTP) (22). PTP, which is a N-methyl-D-aspartate-receptor independent mechanism, was shown to be sustained by presynaptic processes including an increased spontaneous release of neurotransmitters and increased calcium influx (23). This is consistent with studies reporting that short-lasting MEP facilitation, induced by 5 Hz rTMS, mainly depends on presynaptic mechanisms of glutamatergic neurotransmission (15,16,20).

In our MOH patients, we found a paradoxical decrease – instead of a normal increase – in MEP amplitude during 5 Hz rTMS trains despite a physiological decrease in response during 1 Hz rTMS trains. This paradoxical pattern may reflect either an increase in GABAergic or a reduction in presynaptic glutamatergic excitatory neurotransmissions. One possible explanation for this phenomenon could be the homeostatic plasticity of the human motor cortex. In a hyper-excited cortex, high-frequency rTMS could facilitate the activation of homeostatic inhibitory mechanisms aimed to maintain the cortical level of excitability within a physiological range and stabilize the properties of neural networks (24). However, this homeostatic mechanism would be engaged only in the presence of a hyper-excitable motor cortex. The first MEP amplitude block in our MOH patients did not differ from that of HV and CM patients. Therefore, this mechanism cannot explain our results.

Interestingly, the MEP amplitude slope of the linear regression line in MOH patients was not only significantly different from that of healthy subjects, but also from that of pure CM patients, indicating that the mechanisms of short-term synaptic plasticity are different in the two groups of patients. We noticed a trend toward a decrease in cortical excitability during 5 Hz rTMS in CM patients, but we failed to show a significant difference in MEP amplitude slope between CM and HVs. In contrast to the present results, the results of the study by Cosentino et al. (17) showed that MEP amplitudes significantly decreased during high-frequency trains in patients affected by CM when compared to those in healthy subjects. The difference in the reported results could be explained by the different experimental protocol and TMS apparatus we used and the clinical differences in the patients between the two studies. In fact, we used 10 trains of 10 stimuli with a 1 min inter-train interval, instead of six trains of 10 stimuli with a 2 min inter-train interval used in the study by Cosentino et al. (20), and we considered CM patients with a shorter mean duration of history with the disease (13.5 years versus 21.7 years). Moreover, the different magnetic stimulator and coil used by Cosentino et al. (Cadwell High Speed Magnetic Stimulator) could account for different effective stimulation intensities. Furthermore, our criteria for MEP behavioural assessment differed because we considered the slope of the linear regression of MEP amplitudes over all stimuli, while Cosentino et al. (17) classified responses as "facilitatory" or "inhibitory", in which at least six of the MEPs were larger or smaller in amplitude than the first MEP, respectively.

One possible explanation for the different outcomes in response to high-frequency rTMS trains between CM and MOH patients may be that they exhibit different habituation responses to repetitive stimulations. In fact, previous studies have shown that pure CM patients exhibit a normal habituation pattern to sensorimotor stimulations (6) (which is similar to healthy subjects), while MOH patients exhibit a habituation deficit (4,25), although both groups of patients exhibit an initial response sensitization (4,6,25). The latter evidence implies that the neurobiological mechanisms that may differentiate the brain response in CM and MOH patients are not related to a central sensitization process because it is a general mechanism of pain chronification, but to a factor able to set delayed behavioural response plasticity. Habituation represents a basic form of learning and plasticity; therefore, it is not surprising that mechanisms underlying neural plasticity and learning processes could be differentially modulated depending on the co-occurrence of external neurobiological factors such as the clinical features and behaviour of patients.

This interpretation is supported by the correlation analysis. In CM patients, the mean severity of migraine was negatively correlated with the slope of the linear regression of MEP amplitudes recorded in response both to 1 Hz and to 5 Hz rTMS trains. This supports our argument that short-term plasticity of the motor cortex is positively influenced by the severity of chronic head pain, as already observed in other chronic painful conditions (11).

The same correlation was not observed in MOH patients. They showed a peculiar neurophysiological pattern that was proportional to the duration of the overuse phase, such that the greater the decreasing response during 5 Hz rTMS trains, the higher the

duration of the overuse headache. Interestingly, previous studies have shown that the association between the duration of medication overuse and neurophysiological properties in the brain of MOH patients is influenced by genetic factors (25,26). Overall, these data reinforce the concept of MOH as a bio-behavioural disorder in which chronic headache is the result of a co-occurrence of biologically inherited, behavioural and environmental (i.e. medication overuse) factors.

A limitation of the present study was the lack of a detailed examination of short-term plasticity mechanisms in the primary motor cortex in CM and MOH patients. Furthermore, it would be interesting to compare motor cortex plasticity in chronic versus episodic migraine patients; however, this study focused on chronic migraine. This is because our objective was to provide insights about modifications in motor cortex plasticity in relation to different chronification mechanisms. Another, methodological, limitation of the present study was that we only stimulated the right hemisphere in all subjects, as we assumed that, in patients with non-fixed side of headache, the mechanisms of short term plasticity are shared between the right and left motor cortices. Finally, we did not administer a specific questionnaire relating to depression, even though there is evidence that depression may affect neuroplasticity (27).

Conclusions

Our study demonstrates that the mechanisms of short-term plasticity induced by high-frequency rTMS are dysfunctional in MOH patients when compared with pure CM patients and HVs. The evidence of different plastic behaviour in the two groups of patients may indicate that MOH and CM – despite exhibiting a similar phenotype – exhibit different neurophysiological learning processes, probably related to different pathophysiological mechanisms of migraine chronification and that chronic exposure to non-steroidal anti-inflammatory drug use could cause modifications in short-term plasticity mechanisms.

Further studies are needed to understand whether pharmacological interventions or medication withdrawal are able to reverse the dysfunctional plasticity to a normal state and to reveal whether modifications of cortical excitability using non-invasive stimulation techniques are able to promote this process and induce clinical benefit. Finally, assessing brain excitability in migraine is limited by exploring only one of the aspects of a more complex picture of abnormal cortical excitability; therefore, future studies should combine different neurophysiological techniques to explore different pathophysiological aspects of migraine chronification.

Article highlights

- Detailed examination of short-term plasticity mechanisms of the primary motor cortex individually in chronic migraine (CM) and medication overuse headache (MOH) patients is lacking.
- We found that MOH patients exhibited paradoxical decreased short-term potentiation mechanisms compared with pure CM patients and healthy subjects.
- In MOH patients, the peculiar neurophysiological pattern was proportional to the duration of the overuse headache.

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