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Central sensitization mechanisms in chronic migraine with medication overuse headache: a study of thalamocortical activation and lateral cortical inhibition

Gabriele Sebastianelli[1], Francesco Casillo[1], Chiara Abagnale[1], Antonio Di Renzo[2], Ettore Cioffi[1], Vincenzo Parisi[2], Cherubino Di Lorenzo[1], Federica Fazio[3], Fausto Petricola[3], Consalvo Mattia[3], Mariano Serrao[1], Jean Schoenen[4] and Gianluca Coppola[1,3]

Abstract

Background: It is unclear whether cortical hyperexcitability in chronic migraine with medication overuse headache (CM-MOH) is due to increased thalamocortical drive or aberrant cortical inhibitory mechanisms.

Methods: Somatosensory evoked potentials (SSEP) were performed by electrical stimulation of the median nerve (M), ulnar nerve (U) and simultaneous stimulation of both nerves (MU) in 27 patients with CM-MOH and, for comparison, in 23 healthy volunteers (HVs) of a comparable age distribution. We calculated the degree of cortical lateral inhibition using the formula: $100 - [MU/(M + U) \times 100]$ and the level of thalamocortical activation by analyzing the high frequency oscillations (HFOs) embedded in parietal N20 median SSEPs.

Results: Compared to HV, CM-MOH patients showed higher lateral inhibition (CM-MOH $52.2\% \pm 15.4$ vs. HV $40.4\% \pm 13.3$; $p = 0.005$), which positively correlated with monthly headache days, and greater amplitude of pre-synaptic HFOs ($p = 0.010$) but normal post-synaptic HFOs ($p = 0.122$).

Conclusion: Our findings suggest that central neuronal circuits are highly sensitized in CM-MOH patients, at both thalamocortical and cortical levels. The observed changes could be due to the combination of dysfunctional central pain control mechanisms, hypersensitivity and hyperresponsiveness directly linked to the chronic intake of acute migraine drugs.

Keywords

Thalamocortical activation, high-frequency oscillations, somatosensory evoked potentials, habituation, pain control mechanisms, lateral inhibition

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[1]Sapienza University of Rome Polo Pontino ICOT, Department of Medico-Surgical Sciences and Biotechnologies, Latina, Italy
[2]IRCCS – Fondazione Bietti, Rome, Italy
[3]Specialization School in Medicine and Palliative Care, Sapienza University of Rome Polo Pontino ICOT, Latina, Italy
[4]CHU de Liège, Neurology, Headache Research Unit, Citadelle Hospital, Liège, Belgium

Corresponding author:
Gabriele Sebastianelli, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino ICOT, Via Franco Faggiana 1668, 04100, Latina, Italy.
Email: gabriele.sebastianelli@uniroma1.it

Introduction

Medication-overuse headache (MOH) is a secondary headache attributed to chronic overuse of analgesics or specific antimigraine drugs (1). According to the diagnostic criteria in the *International Classification of Headache Disorders*, 3rd edition (ICHD-3) (1), to diagnose MOH, patients must have a pre-existing primary headache, headache on $\geq$15 days per month and regular overuse of one or more acute medications for $\geq$3 months (1). Thresholds for overuse vary with medication classes: $\geq$10 days per month for triptans, ergots, opioids, combination analgesics or combinations of multiple drug classes; $\geq$15 days per month for simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) (1). It has been estimated that medication overuse headache accounts for up to 50% of the chronic headaches and is most prevalent in chronic migraine (CM) (2).

Despite the clear association between headache chronification and overuse of symptomatic drugs, the pathophysiology of medication overuse headache is still poorly understood (3). According to studies conducted on rodents, persistent administration of sumatriptan or analgesics enhances susceptibility to evoked cortical spreading depression (4–7) and causes central sensitization (8) with increased activation of the trigeminal nucleus caudalis as a consequence (6). Evidence from clinical studies also supports cortical hyperexcitability in MOH. CM patients with MOH (CM-MOH) have increased sensitization of somatosensory cortical evoked responses and potentiation to repetitive non-painful stimuli (9). Compared to CM-MOH patients, CM patients without medication overuse display an initial sensitization but no response potentiation when the stimulation is repeated (10,11). Analyzing somatosensory evoked potentials (SSEP), we observed that the initial sensitization in CM patients is not accompanied by altered levels of thalamocortical activation (12) or cortical lateral inhibition (13).

It would thus be of interest to know whether the peculiar electrophysiological pattern of CM-MOH patients is due to increased thalamocortical drive or to aberrant cortical lateral inhibition. In humans, thalamocortical drive can be easily evaluated by analyzing the high-frequency oscillations (HFOs) (around 600 Hz) embedded in the broad-band SSEPs elicited by median nerve stimulation at the wrist (14). Furthermore, studies in humans and animal have indicated that the amplitude of the cortical component of the SSEPs obtained during simultaneous stimulation of two adjacent nerves is smaller than the sum of the amplitudes of the SSEPs elicited by separate stimulation of each nerve, which is explained by lateral inhibition mechanisms at the cortical level (15,16).

Using SSEPs, we compared therefore cortical lateral inhibition and HFOs in CM-MOH patients and in healthy volunteers. To calculate the percentage of lateral inhibition, we stimulated the median (M) and ulnar (U) nerves and recorded low-frequency (LF) SSEPs from the parietal cortex, after which we compared the amplitude of LF-SSEPs M and U components stimulated simultaneously with the arithmetic sum of the amplitude of corresponding SSEPs elicited by stimulating each nerve separately. In addition, we assessed somatosensory thalamocortical drive by measuring the early HFOs embedded in the broad-band median nerve SSEPs.

Methods

Participants

Twenty-seven patients (mean $\pm$ SD, 38.1 $\pm$ 14.4 years; 23 women) who received a diagnosis of chronic migraine with medication overuse headache, according to the ICHD-3 diagnostic criteria (1), were recruited among consecutive patients attending the Headache clinic of Sapienza University of Rome Polo Pontino (ICOT, Latina). All patients had migraine without aura as the primary headache. None of them were under prophylactic therapy or had taken one in the last 3 months before the study. We collected the patients' clinical characteristics: duration of the migraine disease (years), days with headache (n per month), days of tablet intake (days per month), monthly number of days with tablet intake (n per month), type and number of acute medications and headache severity (visual analogue scale 0–10) (Table 1). All patients had filled in a headache diary mailed when they took an appointment at the consultation enclosed for at least 1 month before the first visit.

For comparison, we recorded a cohort of 23 healthy volunteers (HVs) of comparable age and gender distribution (35.1 $\pm$ 9.0 years; 18 women). Inclusion criteria for the control group were no personal or familial history (first- and second-degree relatives) of migraine, no regular medication intake except for the contraceptive pill, no neurological or psychiatric illness and no other overt medical condition. Each participant in the study went through a thorough neuro-ophthalmological evaluation that included measuring intraocular pressure, best-corrected visual acuity, slit-lamp biomicroscopy and binocular indirect ophthalmoscopy. To minimize variability due to hormonal changes, women were recorded outside their premenstrual or menstrual periods.

Both patients and controls were recorded in the same laboratory and period of the day. They all gave their written informed consent to participate in

Table 1. Demographics and clinical features.

	HV (n = 23)	MOH (n = 27)
Women (n)	18	23
Age (years)	35.1 ± 9.0	38.1 ± 14.4
Duration of the migraine disease (years)		22.7 ± 12.8
Days with headache/month (n)		24.3 ± 5.2
Days with tablet intake/month (n)		20.8 ± 6.9
Total tablet intake/month (n)		27.8 ± 7.0
Headache severity (0–10)		7.9 ± 1.6
Median nerve motor threshold (mA)	8.1 ± 2.4	10.3 ± 5.6
Ulnar nerve motor threshold (mA)	8.3 ± 2.8	9.5 ± 5.41
Triptan overusers		N = 8
NSAID overusers		N = 14
Combination medication overusers		N = 5

Data are expressed as the mean ± SD. HV, healthy volunteers; CM-MOH, chronic migraine patients with medication overuse; N, number of subjects; NSAID, non-steroidal anti-inflammatory drug.

the study. The study was approved by the local ethics committee and conducted in adherence with the Declaration of Helsinki.

Data acquisition

Three sessions of SSEPs recordings, separated by a 5-min rest period, were performed by two investigators (FC and CA): M nerve stimulation, U nerve stimulation and simultaneous stimulation of both nerves (MU). SSEPs were obtained using the same procedure as in our previous studies (13,17). Constant current square wave pulses (0.2 ms width, cathode positioned proximally) were used as a stimulus, with intensity set at 1.2 times the motor threshold and a repetition rate of 2.2 Hz. Three active electrodes were positioned: the first over Erb's point ipsilateral to the stimulus and referenced to the contralateral side; the second over the fifth cervical spinous process (Cv5) and the third over the contralateral parietal area (C30, 2 cm posterior to C3 in the International 10–20 system), both referenced to Fz; a ground electrode was placed on the right wrist. Digitimer (Digitimer Ltd, Welwyn Garden City, UK) (band-pass 0.05–2500 Hz, gain 1000) was used to amplify SSEPs signals, which were recorded with a CED power 1401 device (Cambridge Electronic Design Ltd, Cambridge, UK). Recordings were carried out in the afternoon (between 2 PM and 6 PM) with the participants sitting relaxed in a comfortable chair in a well-lit room with eyes open. They were instructed to concentrate on the stimulus-induced thumb movement. Next, 300 consecutive sweeps of 50 ms, sampled at 5000 Hz, were collected for each session. Two investigators (GC and GS) analyzed all the recordings offline using Signal, version 4.11 (Cambridge Electronic Design Ltd). The investigators were blinded to the participants' diagnoses. The Signal artifact rejection tool automatically rejected artifacts with an amplitude exceeding 90% of the analog-to-digital converter range. All rejected artifacts were verified by visual inspection.

LF-SSEPs and lateral inhibition

Three hundred artifact-free evoked responses were averaged in each subject for each of the three sessions. The SSEP components N9, N13, N20, P25 and N33 were identified according to their latencies and after digital filtering of the signal between 0 and 450 Hz. We measured the peak-to-peak amplitude of all the SSEP components and calculated the degree of lateral inhibition using the formula $100-[MU/(M+U) \times 100]$, where MU is the amplitude of the SSEP component obtained after simultaneous stimulation of M and U nerves and M + U is the arithmetic sum obtained by stimulating separately these nerves.

SSEP high-frequency oscillations (HFOs)

Digital zero-phase shift band-pass filtering between 450 and 750 Hz (Barlett-Hanning window, 51 filter coefficients) was applied off-line on SSEPs elicited by the M nerve alone to obtain the HFOs embedded in parietal N20 SSEP component. The method utilized is described widely in our previous study (12). Two separate bursts of HFOs were identified in most recordings: an early pre-synaptic burst within the latency range of the ascending slope of the conventional N20 SSEP component and a late post-synaptic burst within the latency of the descending slope of N20, sometimes extending into the ascending portion of the N33 component. The decrease of amplitude and frequency between the pre-and post-synaptic bursts generally allows for their visual separation. When a clear distinction between the two components was not possible, we considered the bursts before the N20 peak as pre-synaptic and those after this peak as post-synaptic. Thereafter, we eliminated the stimulus artifact and measured the latency of the negative oscillatory maximum and the maximum peak-to-peak amplitude for pre-and post-synaptic bursts.

Statistical analysis

We applied the SPSS, version 25.0 (IBM Corp., Armonk, NY, USA) for all analyses. Anderson–Darling or Kolmogorov–Smirnov tests were used on each electrophysiological parameter to assess the normal distribution of data. A two sample *t*-test was used for data that were normally distributed; otherwise,

a non-parametric Mann–Whitney test was employed. Pearson's correlation coefficient was used to search for correlations between clinical variables (duration of chronic and of overuse phase in months, days with and total acute medication intake per month, days with headache per month, history of primary headache, days since the last headache, and mean severity of headache per month) and electrophysiological data that were significant different between groups.

General linear models were developed to evaluate the age and sex effects, they included significant electrophysiological parameters and age as covariates and sex and group as factors.

$P < 0.05$ was considered statistically significant.

Results

Demographics and clinical features are shown in Table 1. Assessable SSEPs recordings were obtained from all participants. No statistical differences in the motor threshold, for both nerves (M and U), were observed between HV and MOH patients.

LF and HFOs of SSEPs

Grand-average N9, N13, N20, P25 and N33 latencies and peak-to-peak amplitudes of N9 and N13 did not differ between groups following stimulation of M or U nerves (Table 2).

However, peak-to-peak amplitudes of N20-P25 and P25-N33 were significantly greater in the CM-MOH group (N20-P25 M: $t = -2.08$, $p = 0.007$; P25-N33 M: $t = -4.12$, $p < 0.001$; N20-P25 U: $t = -2.09$, $p = 0.007$; P25-N33 U: $t = -3.36$, $p = 0.002$). Similarly, after M stimulation the amplitude of each of the first three blocks of averaged responses was significantly larger in CM-MOH patients than in HV (1st block: $t = -2.04$, $p = 0.047$; 2nd block: $t = -3.69$, $p = 0.001$; 3rd block: $t = -4.57$, $p = 0.001$) (Table 2). Regarding the change of SSEPs amplitude over the three blocks of 100 response (i.e. habituation), after M nerve stimulation, CM-MOH patients showed a progressive increase of the N20-P25 amplitude slope (i.e. deficient habituation), between block 1 and block 2 (slope $= 0.17 \pm 0.7$, $t = -2.51$, $p = 0.017$) and between block 1 and block 3 (slope $= 0.19 \pm 0.4$, $t = -3.68$, $p = 0.001$) (Table 2).

Latencies of the negative oscillatory maximum peak for pre-and post-synaptic bursts of somatosensory HFOs were not different between the two groups. However, CM-MOH had a greater peak-to-peak amplitude for the pre-synaptic component but not for the post-synaptic component compared to HV (pre-HFO $t = -2.71$, $p = 0.010$; post-HFO $U = 572$, $p = 0.79$) (Figure 1a and Table 3).

Lateral inhibition of SSEPs

We found no difference between the two groups in the amplitudes of N9, N13 and N20-P25 SSEP components obtained after simultaneous stimulation of M and U nerves, nor for the arithmetic sum of separate M and U nerve stimulation (M + U) of the N9 and N13 components (Table 4). However, CM-MOH patients had a greater peak-to-peak amplitude than HV for the arithmetic sum of the N20-P25 ($t = -2.57$, $p = 0.014$)

Table 2. Latencies and amplitudes of the various somatosensory evoked potential components after median or ulnar stimulation (mean ± SD; 300 averaged responses).

	HV (n = 23)		CM-MOH (n = 27)	
	Median	Ulnar	Median	Ulnar
N9 (ms)	10.0 ± 0.8	10.6 ± 1.1	9.7± 0.8	10.4 ± 0.9
N13 (ms)	13.3 ± 1.2	14.0 ± 1.4	13.2 ± 0.7	13.9 ± 0.9
N20 (ms)	19.0 ± 1.1	19.4 ± 1.3	19.1 ± 1.0	20.0 ± 1.1
P25 (ms)	24.0 ± 2.3	24.7 ± 2.3	22.8 ± 2.2	24.0 ± 2.1
N33 (ms)	30.8 ± 2.7	31.1 ± 2.6	30.6 ± 2.3	31.9 ± 2.0
N9-peak (μV)	2.4 ± 1.1	1.3 ± 0.5	2.7 ± 1.1	1.6 ± 1.2
N13-peak (μV)	1.7 ± 0.8	1.0 ± 0.6	1.8 ± 0.7	1.2 ± 0.8
N20-P25 (μV)	1.9 ± 0.7	1.5 ± 0.7	2.5 ± 0.9*	2.2 ± 1.5*
P25-N33 (μV)	0.8 ± 0.3	0.8 ± 0.4	1.5 ± 0.6*	1.3 ± 0.5*
1st N20-P25 (μV)	2.4 ± 0.7		2.8 ± 0.7*	
2nd N20-P25 (μV)	2.2 ± 0.7		3.1 ± 0.9*	
3rd N20-P25 (μV)	2.1 ± 0.7		3.1 ± 0.8*	
Slope (block 1–2)	–0.22 ± 0.3		0.17 ± 0.7*	
Slope (block 1–3)	–0.6 ± 0.2		0.19 ± 0.4*	
ICLI	40.4 ± 13.3		52.5 ± 15.4*	

HV, healthy volunteers; CM-MOH, chronic migraine patients with medication overuse. *$p < 0.05$ vs. HV.

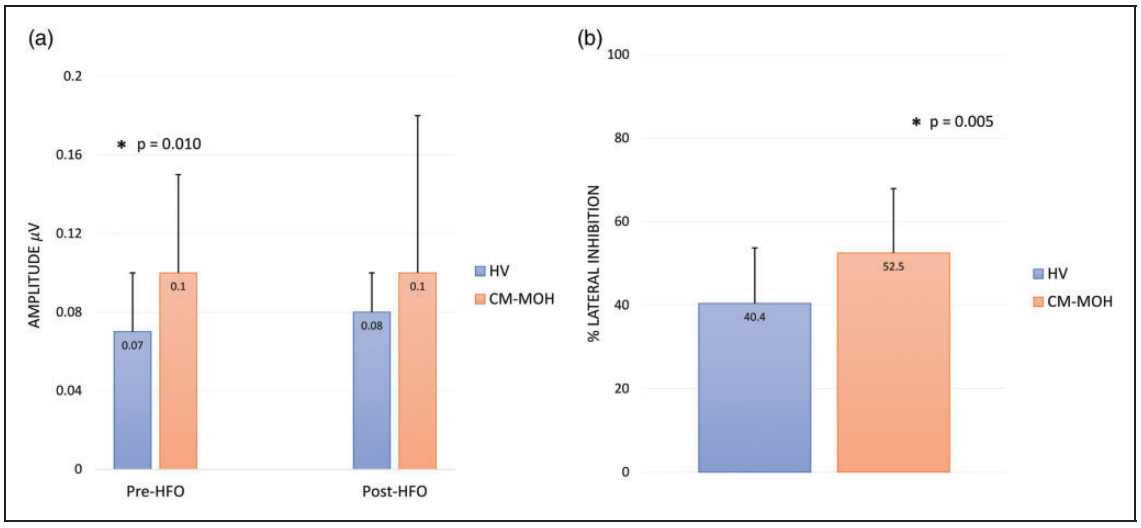

Figure 1. (a) Maximal amplitude (mean ± SD) of pre-synaptic (Pre-HFO) and post-synaptic (Post-HFO) components of somatosensory evoked potential (SSEP) high-frequency oscillations (HFOs) in healthy volunteers (HV) and in chronic migraine patients with medication overuse headache (CM-MOH). (b) Histogram showing the mean percentage of lateral inhibition 100 – [(MU/M + U) × 100 for the SSEP N20–P25 component in healthy volunteers (HV) and in chronic migraine patients with medication overuse headache (CM-MOH). M, median nerve; U, ulnar nerve.

Table 3. Latencies of maximum negative peak and maximum peak-to-peak amplitudes (mean ± SD) of the pre-synaptic and post-synaptic high-frequency oscillations embedded in median nerve somatosensory evoked potentials.

	HV (n = 23)		CM-MOH (n = 27)	
	Pre-synaptic	Post-synaptic	Pre-synaptic	Post-synaptic
Latency of maximum negative peak (ms)	15.9 ± 1.5	23.0 ± 2.7	16.7 ± 1.3	23.07 ± 2.3
Maximum peak-to-peak amplitude (μV)	0.07 ± 0.03	0.08 ± 0.02	0.10 ± 0.05*	0.10 ± 0.08

HV, healthy volunteers; CM-MOH, chronic migraine patients with medication overuse. *$p < 0.05$ vs. HV.

Table 4. Amplitudes of the various somatosensory evoked potential components (mean ± SD) after simultaneous median and ulnar nerve stimulation (MU) or summed stimulation of these nerves (M + U) (300 averaged responses).

	HV (n = 23)		CM-MOH (n = 27)	
	MU	M + U	MU	M + U
N9-peak (μV)	1.9 ± 1.0	3.6 ± 1.7	1.9 ± 1.4	3.5 ± 1.5
N13-peak (μV)	1.5 ± 0.7	2.8 ± 1.2	1.8 ± 0.8	2.5 ± 0.8
N20-P25 (μV)	1.9 ± 0.9	3.4 ± 1.1	2.3 ± 1.1	4.6 ± 2.1*
P25-N33 (μV)	0.8 ± 0.5	1.4 ± 0.4	1.6 ± 0.8*	2.4 ± 0.8*

HV, healthy volunteers; CM-MOH, chronic migraine patients with medication overuse. *$p < 0.05$ vs. HV.

and P25-N33 ($t = -5.43$, $p = 0.001$) components after separate stimulation (M + U) and for the P25-N33 component ($t = -4.47$, $p < 0.001$) obtained after simultaneous stimulation of both nerves (MU) (Figure 2 and Table 4).

The degree of lateral inhibition was significantly higher in CM-MOH patients (52.2 ± 15.4%, $t = -3.97$, $p = 0.005$) than in HVs (40.4 ± 13.3%) (Figure 1b and Table 2).

Correlation analyses

In patients with CM-MOH, Pearson's correlation tests revealed that the percentage of lateral inhibition was positively correlated with monthly headache days ($r = 0.54$, $p = 0.003$) (Figure 3). The total monthly number of tablets taken and the number of monthly days with tablet intake were negatively correlated with amplitude of pre-synaptic HFO ($r = -0.41$, $p = 0.04$;

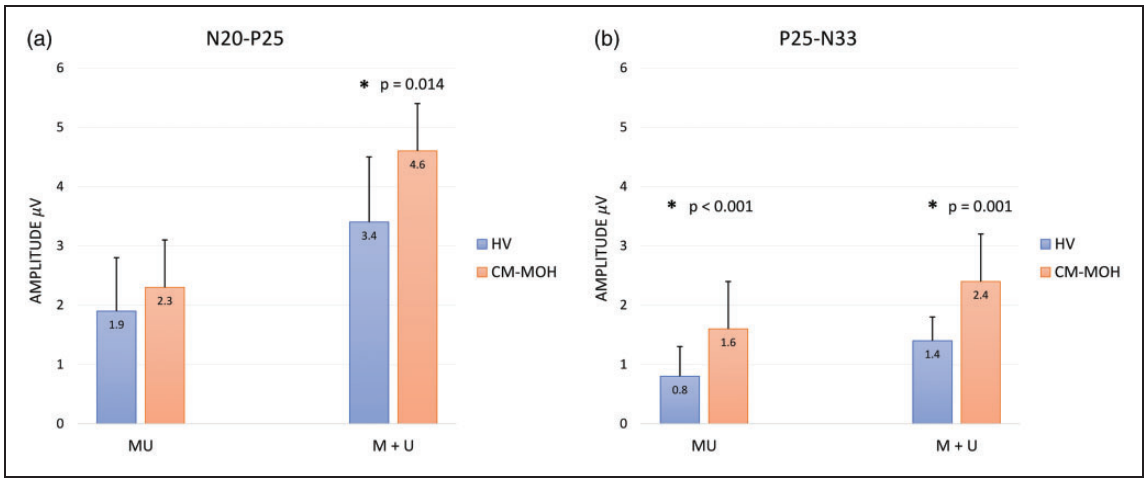

Figure 2. Amplitudes (mean ± SD) of (a) N20-P25 and (b) P25-N33 components of low-frequency somatosensory evoked potentials in healthy volunteers (HV) and in chronic migraine patients with medication overuse headache (CM-MOH). M, median nerve; U, ulnar nerve. MU, simultaneous median and ulnar nerve stimulation; M + U, arithmetic sum of the amplitude elicited by stimulating median and ulnar nerve separately.

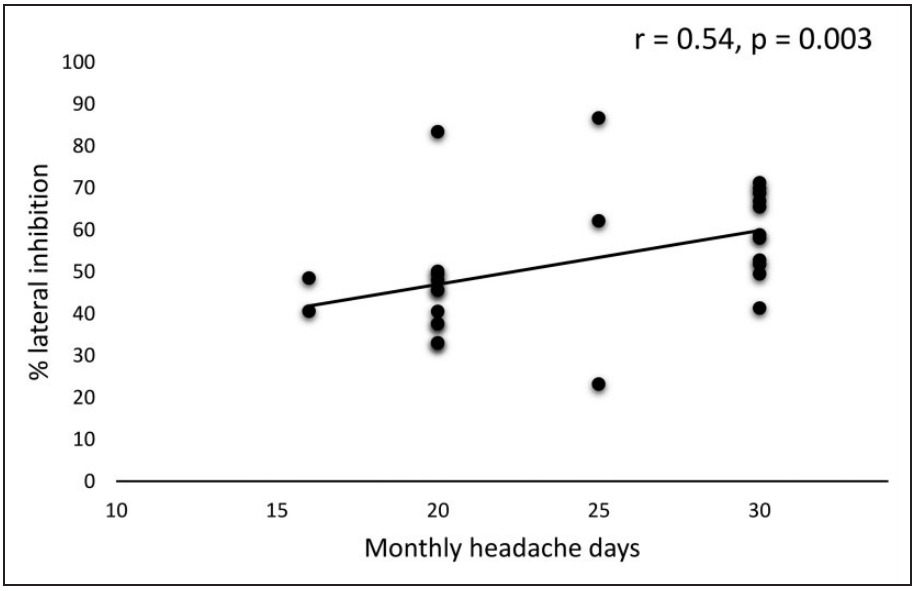

Figure 3. Correlation between the monthly headache days and the mean percentage of lateral inhibition 100 – [(MU/M + U] × 100 in chronic migraine patients with medication overuse headache (CM-MOH).

$r = -0.44$, $p = 0.02$, respectively) (Figure 4). No other correlation emerged between neurophysiological parameters and the other clinical features.

Discussion

The present study aimed to investigate subcortico-cortical excitability in patients with CM and medication overuse (CM-MO) through the analysis of different neural circuits along the somatosensory pathway.

It was previously observed that the level of excitation of the somato-sensory cortex in CM-MOH does not fluctuate between the ictal initial sensitization and the interictal lack of habituation as occurs during episodic migraine cycles, but is locked in a pre-ictal state, where hypersensitivity (due to sensitization) and hyperresponsiveness (due to deficient habituation) coexist (9). We confirmed this here, showing that CM-MO patients have a higher cortical activation than healthy controls, as reflected by a greater amplitude of the grand-average N20-P25 cortical component and of each of the three sequential blocks of averaging, together with a steeper amplitude slope (i.e. deficient habituation).

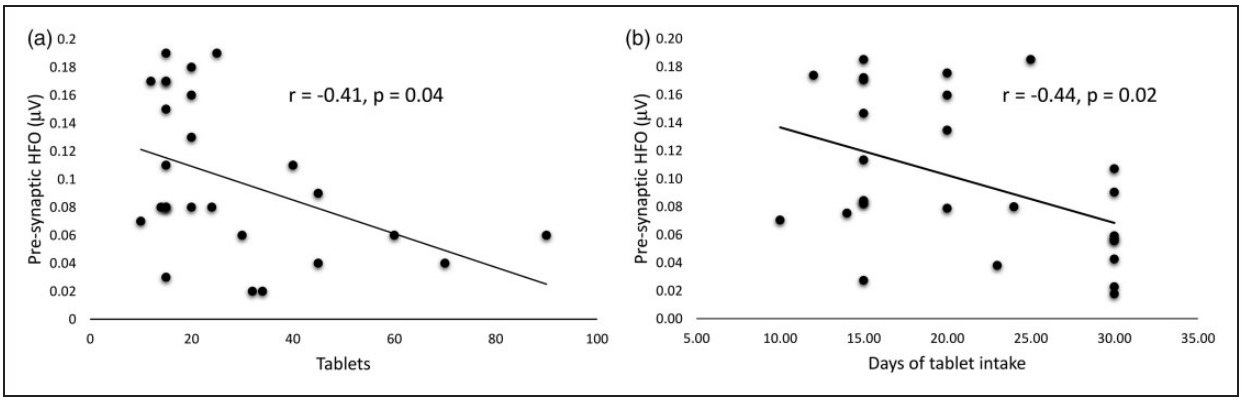

Figure 4. Correlation between the mean amplitude of pre-synaptic high-frequency oscillations (HFOs) and total monthly (a) and days with (b) tablet intake in chronic migraine patients with medication overuse headache (CM-MOH).

The present study adds the following novel findings:

(i) Compared to HV, CM-MOH patients have a higher amplitude for the arithmetic sum of the N20-P25 and P25-N33 components after separate median (M) or ulnar (U) stimulation (M + U) and a greater P25-N33 amplitude after simultaneous stimulation of both nerves (MU).
(ii) The degree of cortical lateral inhibition, evaluated as the ratio between MU and M + U amplitudes, is significantly higher in CM-MOH patients than in HVs and the percentage of lateral inhibition positively correlates with monthly headache days.
(iii) CM-MOH patients have larger pre-synaptic HFOs than HVs, indicating a higher thalamocortical drive, but normal post-synaptic, primarily cortical, HFOs.

SSEPs recorded from the scalp reflect the glutamate-mediated depolarization of neurons in layers 3 and 2 of the somatosensory cortex (18). These neurons receive at their initial axon segment input from cortical axo-axonic cells, a subtype of GABAergic interneurons that control the range of their activation (19,20). Axo-axonic cells with the largest lateral axonal field (>700 mm) mediate the short-range lateral inhibition between cortical columns (21). Lateral inhibition is one of the mechanisms playing a pivotal role in the processing of incoming sensory stimuli (22).

From an electrophysiological point of view, lateral inhibition fails when the response from converging inputs is larger than the sum of the responses to each input separately (15,16,23–25). We have previously investigated lateral inhibition in episodic migraine and CM patients without a history of medication overuse. While in CM the degree of lateral inhibition was normal (13), it was reduced in episodic migraine between attacks, but improved with the proximity of an attack (17,26), and was proportional to somatosensory thalamocortical activity (17). Here, we show that, compared to HVs, CM-MOH patients have a larger degree of lateral inhibition combined with a greater somatosensory thalamocortical drive. They also have larger amplitudes of the cortical responses both for the arithmetic sum after separate stimulations (M + U) (N20-P25 and P25-N33) and the simultaneous peripheral nerve stimulations (MU) (P25-N33). Such a response pattern suggests that central neuronal circuits of the somatosensory system are highly sensitized in CM-MOH patients, especially at the cortical level. Central sensitization occurs via adaptive changes in circuits that regulate ascending sensory transmission and results in a net amplification of nociceptive and innocuous afferent inputs (8,27).

Several studies have suggested that central sensitization in CM-MOH chiefly involves structures outside the trigeminal system, probably at the supraspinal level (28,29). For instance, CM-MOH patients had enhanced cephalic and extracephalic nociceptive responses, while they had no modification of nociceptive blink reflexes (28). Moreover, they had sensitized spinal noxious flexion reflexes (29) and pain-related cortical potentials (30), which were both normalized after withdrawal from the overused drugs (29,30). Insufficient descending inhibition and thus decreased antinociceptive activity from supraspinal structures were hypothesized to participate in the sensitization of spinal cord pain processing (29). In CM-MOH, supraspinal pain control centers, such as the periaqueductal grey (31) and thalamic nuclei (32), were found to have adaptive grey matter changes and abnormal connectivity with other pain-modulatory (frontal) regions (33,34).

Grey matter volume was increased in the thalamus as a whole and in all thalamic subnuclei, including the ventroposterior-lateral/medial and intralaminar nuclei

relaying non-painful somatosensory information, in CM-MOH patients compared to chronic myofascial pain and healthy controls (32). In a fluorodeoxyglucose-positron emission tomography study of CM-MOH, the bilateral thalamus was described as hypometabolic, which reversed to almost normal glucose uptake after analgesic withdrawal (34).

Grey matter volume in the periaqueductal grey was also greater in CM-MOH patients than in healthy controls (31). Nevertheless, when comparing CM-MOH patients to CM patients without medication overuse, no significant differences in neurotransmitters level (GABA and glutamate) were observed in the periaqueductal grey, while a significant difference emerged for both neurotransmitters when CM patients (both with and without medication overuse) were compared with episodic migraine patients and healthy controls (35).

Furthermore, compared to CM patients without medication overuse, CM-MOH patients had increased grey matter volume in left temporal pole/parahippocampus and decreased volume in orbitofrontal cortex and left middle occipital gyrus (36), while no differences emerged in the functional connectivity between the right caudate nucleus and other brain regions involved in pain perception (37). Finally, in comparison with other chronic pain disorders, MOH patients were characterized by hyperconnectivity of the saliency network (33). This network has been found to exhibit alterations in functional connectivity with reward-related circuits; specifically, the nucleus accumbens and rostral dorsal putamen (38), and hyperconnectivity with habenula (involved in anti-reward circuit) (39).

Taken together, these results reflect functional and morphological reorganization of subcortical and cortical structures due to central sensitization and dysfunctioning central pain control mechanisms in CM-MOH patients (32,40,41).

Pre-synaptic somato-sensory HFOs and SSEP habituation clearly distinguish CM-MOH patients from CM patients without medication overuse: while the former have increased HFOs and deficient habituation, these electrophysiological markers were shown to be normal in the latter (12).

In previous studies, we have shown that 5Hz repetitive transcranial magnetic stimulation over the motor cortex had a paradoxical increased inhibitory effect on motor evoked potentials in patients with CM-MOH (42), which was restored to physiological potentiation effect after drug withdrawal and in proportion with the percentage reduction in monthly headache days (43). The different neurophysiological patterns between CM-MOH and CM and the reversal of the neurophysiological dysfunction after medication withdrawal indicates that the two patient groups, despite a similar clinical phenotype, have different learning and memory processes with different short-term synaptic plasticity probably related to the different mechanisms underlying migraine chronification, which in CM-MOH patients is closely related to medication overuse (42,43).

Chronic exposure to acute anti-migraine medication in rodents modifies peripheral nociceptors, amplifies central circuits, increases susceptibility to cortical spreading depression (6) and suppresses descending antinociceptive system (3,44–46), which results in facilitation of trigeminal nociceptive transmission via up-regulation of the CGRP system (4,47–51) and upstream in central sensitization of third-order neurons in the thalamus (52). In clinical studies, CM-MOH patients overusing NSAIDs had greater cortical inhibition than episodic migraineurs, contrary to triptans overusers (53), but larger pain-related cortical potentials (28). Of note, long-term use of acute headache medication may disrupt the function of central serotonin (4,45) and the mesolimbic dopamine pathway (54), which respectively may favour cortical sensitization and overuse behaviour.

Whether the increased lateral inhibition in CM-MOH is a brain state (i.e. secondary effects to the medication overuse and/or to central sensitization) or a brain trait that predisposes a person to enter the vicious circle of medication overuse remains to be determined. The fact that, in the present study lateral inhibition was positively correlated with monthly headache days rather favours the hypothesis of a modified brain state where lateral inhibition would increase as an attempt to counteract the persistent sensitization and hyper-responsiveness of the CM-MOH brain. Admittedly, this hypothesis is not supported by the lack of correlation between the degree of lateral inhibition and monthly days and number of tablets taken or headache severity. Studying lateral inhibition before and after withdrawal of medication overuse might help to better understand its role in CM-MOH and to determine whether its augmentation is permanent or reversible.

An intriguing finding in the present study is the inverse relationship between thalamocortical activity (pre-synaptic HFOs) and acute medication consumption. Given that thalamocortical drive seems normal in CM without medication overuse, one might expect a pathogenic effect of the overconsumed drugs and thus a positive correlation with thalamo-cortical activity in CM-MOH. The apparent paradox could, however, be explained in part by the differential physiological effect that some drugs can have on thalamic and thalamocortical terminal activity (55). For instance, psilocybin, a 5-hydroxytryptamine 2A receptor agonist, was found to decrease thalamic blood flow (56), contrasting

with an increase of functional thalamocortical connectivity (57). Whatever the explanation might be, despite the negative correlation in individual CM-MOH patients, medication overuse seems unable to genuinely decrease average thalamo-cortical drive at the group level, probably because of the brain's pervasive and persistent state of central sensitization.

We acknowledge that the present study has some limitations. First, we did not screen patients for allodynia, and we cannot exclude that this might have influenced our neurophysiological results. Another potential weakness of the study is that we did not record patients after drug withdrawal or analyze patients with MOH and other primary headaches. As a result, we cannot completely rule out the possibility that our findings may be influenced not only by medication-induced effects, but also by the pathophysiological factors related to the underlying primary headache. However, the fact that, in our previous study with the same paradigm (13), we observed a different behaviour in CM patients without medication overuse is against this and supports a primarily medication-induced effect. To gain further clarity on this matter, future studies should focus on analyzing MOH patients both before and after withdrawal from medication.

Finally, our relatively small sample size precluded a subanalysis of patients according to the type of overused medication.

Conclusions

In conclusion, we show that central neuronal circuits are highly sensitized in CM-MOH patients, at the thalamocortical and, even more so, at the cortical level. The observed changes can be explained by dysfunctional central pain control mechanisms, hyper-sensitivity (due to sensitization) and hyper-responsiveness (due to deficient habituation) probably linked to the chronic administration of acute migraine drugs. To shed light on the unique aspects of MOH-CM and gain a clearer understanding of its characteristics and differences compared to episodic and CM without history of medication overuse, it would be highly interesting to design a study that directly compares these three groups and/or follows the patient's progression from episodic to chronic migraine.

Finally, comparative recordings in other primary headaches, such as tension-type headaches, and in other brain disorders where the level of consciousness is diminished, such as areas of supportive and palliative care, would be useful to verify the specificity and sensitivity of these electrophysiological techniques.

Clinical implications

- The levels of thalamocortical activation and lateral cortical inhibition are increased in patients with medication overuse headache.
- These results suggest that subcortico-cortical circuits are highly sensitized in medication overusers.

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Declaration of conflicting interests

The authors declare that there are no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical statement

The study was approved by the local ethics committee and conducted in adherence with the Declaration of Helsinki. All volunteers gave their written informed consent to participate in the study.

ORCID iDs

Gabriele Sebastianelli https://orcid.org/0000-0002-4231-4417
Francesco Casillo https://orcid.org/0000-0003-4642-950X
Jean Schoenen https://orcid.org/0000-0002-6506-6460
Gianluca Coppola https://orcid.org/0000-0002-8510-6925

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