Subcortical Hyperexcitability in Migraineurs: A High-Frequency Oscillation Study

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ABSTRACT: ***Objective:*** An abnormal central nervous system excitability level was found in patients with migraine. Whether it is hyper- or hypo-excitable is still debated. This study aimed to compare the somatosensory high-frequency oscillations (HFOs), which reflected subcortical excitability (early phase) and intracortical inhibition (late phase), between patients with migraine and control subjects. ***Methods:*** HFOs were recorded from C3'-Fz, using a 500-1000 Hz frequency filter after stimulation at right median nerves at the wrists, and divided into early and late phases based on the N20 peak. Fifty-nine untreated patients (n=24 during ictal period; n=35, interictal) and 22 controls finished the study. ***Results:*** In early HFOs, patients both during ictal and interictal periods had higher maximal amplitudes (p =0.039) and area-under-curve (p =0.029) than those of the controls. Regarding the late HFOs, there were no significant differences among these groups. ***Conclusion:*** Our study suggests a hyper-excitable state in the subcortical regions in patients with migraine both during interictal and ictal periods.

RÉSUMÉ: Hyperexcitabilité sous-corticale chez les migraineux : une étude d'oscillations à haute fréquence. *Objectif :* Un niveau anormal d'excitabilité du système nerveux central a été observé chez les patients atteints de migraine. Que ce soit de l'hyper ou de l'hypo excitabilité demeure un sujet de controverse. Le but de cette étude était de comparer les oscillations somatosensives à haute fréquence (OHF), reflétant l'excitabilité sous-corticale (phase précoce) et l'inhibition intra corticale (phase tardive), entre des patients atteints de migraine et des sujets témoins. ***Méthode :*** Les OHF ont été enregistrées de C3'-FZ, avec un filtre de fréquence 500-1000 Hz après stimulation du nerf médian droit au poignet, et séparées en phase précoce et tardive selon le pic N20. Cinquante-neuf patients non traités (n = 24 pendant une crise ; n = 35 entre les crises) et 22 sujets témoins ont complété l'étude. ***Résultats :*** En phase précoce d'OHF, les patients, qu'ils soient ou non en période de crise, avaient des amplitudes maximales (p = 0,039) et une aire sous la courbe (p = 0,029) plus élevées que celles des sujets témoins. Quant à la phase tardive d'OHF, il n'y avait pas de différence entre les groupes. ***Conclusion :*** Notre étude suggère qu'il existe un état d'hyperexcitabilité dans les régions sous-corticales chez les patients atteints de migraine, tant en période de crise qu'entre les crises.

The pathophysiology of migraine remains largely undetermined. Current evidence suggests that activation of the trigeminovascular system (TGVS) is responsible for the generation of pain, and cortical spreading depression is the most probable primary event that triggers the activation of TGVS[1]. Since cortical spreading depression is preceded by transient synchronized neuronal excitation[2], an altered state of brain excitability may be one of the fundamental pathophysiological mechanisms of migraine[3]. Thus, during the past decade, many electro-physiological studies have addressed the issue on interictal and ictal brain excitability in patients with migraine including somatosensory, visual and motor cortices by somatosensory evoked potential (SEP)[4,5], visual evoked potential (VEP)[6,7] and transcranial magnetic stimulation (TMS)[8,9]. However the results are conflicting and whether the brain is in a hyper- or hypo-excitable state in patients with migraine has been inconclusive.

Migraine is considered a disorder of sensory processing disturbance with altered perception of normality[10]. The pain process is likely to be a combination of activation of the nociceptors of the TGVS, and the facilitation or lack of inhibition of these signals in their pathway to the cortex[11]. Along the pain-transmission pathway, both the brainstem and the thalamus can exert their modulatory effects. The crucial role of the brainstem in the modulation of pain transmission in migraine pathophysiology is well documented[12,13]; whereas the role of the thalamus in migraine pathogenesis is less studied.

Somatosensory evoked potential is a method used to evaluate the function and integrity of the somatosensory pathway. Recent studies on SEP have disclosed several brief wavelets

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superimposed on the N20 and P40 primary cortical response, following stimulation of the median nerve or the tibial nerve[14-16]. Because these inflections are of much higher frequencies (about 500 – 1000 Hz) and smaller amplitudes than the N20 (about 20-50 Hz), they are designated as "high-frequency oscillations" (HFOs). More recently, the generators of HFOs have been found to be of two origins. Using dipole source analysis in multichannel electroencephalogram (EEG) study, Gobbelé et al[17-19] demonstrated that the early phase of the HFOs originated from the deep thalamocortical fibers close to the thalamus. The late phase of the HFOs probably originated from intra-cortical GABAergic (gamma aminobutyric acid) inhibitory interneurons[20,21], although some other generators have also been suggested, e.g., terminal thalamocortical fibers[17,18], or pyramidal chattering cells[22].

Since HFOs explore both the excitatory thalamocortical pathway from the thalamic relay nucleus, and probably an inhibitory intracortical activity, they can be used to study the pathophysiology of migraine. Two recent studies have addressed the issue on HFOs in patients with migraine and normal subjects[23,24]. However, the results of the two studies were not completely the same. Sakuma et al[23] demonstrated that the amplitudes of HFOs were significantly diminished in migraineurs at the interictal period compared to controls. Coppola et al[24] found that the amplitudes and area-under-curve (AUC) of early HFOs in patients with migraine were decreased at their interictal period, but normalized at the ictal period. Regarding the late HFOs, there was no significant difference between patients and controls. In this study, we aim to examine both the conventional broad-band SEPs and HFOs in patients with migraine at ictal and interictal periods.

MATERIALS AND METHODS

Subjects

This study recruited both patients with migraine from the Headache Clinic of Taipei Veterans General Hospital and sex- and age-matched control subjects. The diagnoses of migraine without aura (MO) and migraine with aura (MA) were based on the criteria proposed by the International Classification of Headache Disorders, 2nd edition (ICHD-2) (code 1.1 and 1.2)[25]. This study recruited only patients with episodic migraine; therefore, patients with more than 15 headache days per month were excluded. In addition, subjects on migraine prophylactic agents or hormone therapy, which might alter the brain excitability, were excluded. Post recruitment, all study subjects were required to keep a headache diary. Every subject completed a semi-structured questionnaire on demographics, medical history, medication behavior, and headache and aura profile during their first visit. Acute treatment was not allowed within three days prior to the examinations. The control subjects were colleagues, their relatives, or friends who did not have past or family histories of migraine and denied any headache attack in the past year. All of the subjects included in this study were naive to the SEP examination.

Both patients and control subjects received a face-to-face interview and physical and neurological examinations. The hospital's Institutional Review Board approved the study protocol and each participant provided written informed consent. The time interval (number of days) between HFO recordings (denoted as Day 0) and the most recent migraine attack prior to or after the measurement was determined in all patients based on their headache diaries. Patients who did not have migraine attack within a period of three days before (Days -1 to -3) and after (Days 1 to 3) the HFO recordings (Day 0) were classified as interictal, while those with migraine attacks within 24-hours (Day -1 to 1) were classified as ictal. Selection of the time window for the interictal and ictal periods was based on earlier studies[9,23,24].

SEP and HFO recordings

For SEP recording (Neuropack M1, Nihon Kohden, Tokyo, Japan), subjects were asked to lay supine on a bed, and were instructed to keep alert with their eyes closed. Since HFOs are influenced by sleep and arousal changes[16,26,27], we simul-taneously recorded EEG by means of two recording electrodes located in the occipital and right parietal regions, referred to left mastoid[22,28]. In all subjects, EEG did not show any change related to drowsiness or sleep during the experiment. Electrical stimuli of 0.2 ms duration were delivered to the right median nerve at the wrist, at a regular interval with a repetition rate of 3.8 Hz. The anode was placed over the median nerve at the wrist, and the cathode 3 cm proximal to the anode. The stimulus intensity was set just above the motor threshold. The original broad-band SEPs were obtained using a band-pass filter of 0.5-2000 Hz. Recording electrodes were placed on C3' (2 cm posterior to C3), and Fz of the International 10-20 System. The frontal scalp region served as a ground. Electrode impedances were less than 5 kΩ. A trial of 1000 stimuli was collected for averaging each SEP, and two successive SEPs were obtained under the same conditions to ascertain the reproducibility of SEPs[15,20,23,27,29,30], and only the first recordings were used for analysis.

For separation and isolation of the HFOs from the underlying N20 primary cortical responses, the wide-band (0.5-2000 Hz) recorded responses were digitally filtered using fast reversed Fourier transformation through a band-pass of 500-1000 Hz. To determine the onset and offset of the HFO burst, we used the same method as described by Hashimoto et al: the oscillations after the onset of primary cortical response (N20) with an amplitude of twice or more than that of the background noise level were considered as the signal[15,30]. The noise level was measured between 9 and 15 ms after the stimulus[15,30]. The signal to noise ratio of HFO recordings is within the range of 20 - 25 dB.

Data analysis

Broad-band SEPs

For broad-band SEPs (0.5-2000 Hz), we measured the latencies of N20o (N20 onset), N20p (N20 peak), P25, N33, and the peak-to-peak amplitudes of the N20o-N20p, N20p-P25, and P25-N33.

HFOs

HFOs were divided into early phase and late phase based on N20p. The HFOs from N20o to N20p were regarded as early HFOs, and the late HFOs were those later than the N20p (Figure). We then measured the maximal peak-to-baseline amplitude, the AUC (total area of positive and negative
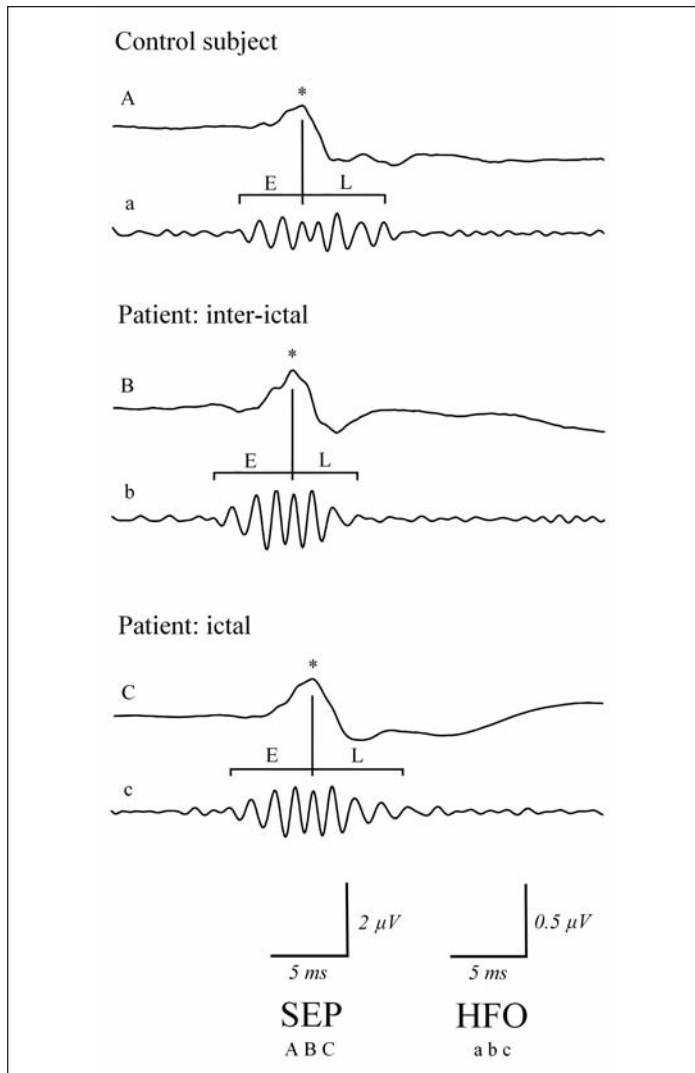
Figure: Typical somatosensory evoked potentials (SEPs) and high-frequency oscillations (HFOs) pattern in control subjects and patients with migraine. High-frequency oscillations are divided into early phase and late phase based on the peak of N20 (N20p) of the somatosensory evoked potential (SEP). The HFOs from onset of N20 (N20o) to N20p are regarded as early HFOs, and the late HFOs are those after the N20p. There was no difference among these three individuals regarding the latencies and amplitudes of SEPs. For early HFOs, most patients with migraine whether in the interictal (b) or ictal (c) state, had significantly higher maximal amplitudes and area-under-curve (AUC) than those of the control subjects (a). However, the interictal and ictal groups did not differ in these two parameters. Besides, there was no significant difference among the three groups in duration and the number of wavelets. Regarding the late HFOs, there were no differences among the three groups across all the parameters, including the maximal amplitude, AUC, duration, and number of wavelets. Upper panel: SEP (A) and HFO (a) from a control subject. Middle panel: SEP (B) and HFO (b) from a patient during interictal period. Lower panel: SEP (C) and HFO (c) from a patient during ictal period. *=Peak of N20 (N20p); E: early HFOs; L: late HFOs; SEP: somatosensory evoked potential; HFO: high-frequency oscillation.

deflections from the baseline), duration, and number of wavelets of both components.

Statistics

SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Student-t and chi-square tests were used for comparisons when appropriate. One-way analysis of variance (ANOVA) followed by post-hoc least significant difference (LSD) test was used to examine the difference among the three groups: interictal, ictal, and control subjects. Statistical significance was defined as a *p*-value of <0.05. All tests were two-tailed.

RESULTS

We initially recruited 75 patients with migraine. Of them, 16 patients with migraine attacks one to three days prior to or post HFO recordings were excluded from analyses. The remaining 59 patients were divided into interictal (n = 35) and ictal (n = 24)

groups. In the analysis sample, 39 patients had MO, and the other 20 had MA. In addition, 22 healthy, sex- and age-matched control subjects were also studied. Both patients and control subjects denied any history of systemic or other neurologic disease (except for migraine in the patient group), and their physical and neurological examinations were normal. The demographics and headache profile are shown in Table 1. In patients with migraine, the headache characteristics were similar between the ictal and interictal groups except for headache frequency (days/month) being higher in the ictal group.

Broad-band SEPs

There was no difference among the three groups (interictal, ictal, and control groups), regarding the stimulation intensity, and the latencies of N20o, N20p, P25, N33, and the peak-to-peak amplitudes of the N20o-N20p, N20p-P25, and P25-N33 (Table 2 and Figure).

Table 1: Demographics and headache profiles of control subjects and patients with migraine

	Control	Migraine		p value
		Interictal	Ictal	
	(n=22)	(n=35)	(n=24)	
Age	31.6 ± 6.8	33.3 ± 7.6	33.8 ± 9.7	0.616
Female (%)	15 (68.2)	24 (68.6)	16 (66.7)	0.988
MO : MA	N/A	22 : 13	17 : 7	0.525
Disease duration (year)	N/A	10.6 ±6.7	13.2 ± 9.7	0.260
Headache frequency (d/m)	N/A	2.0 ± 1.2	4.2 ± 3.5	0.007
Pulsating headache	N/A	60%	79%	0.122
Headache intensity (% of severe intensity)	N/A	60%	67%	0.320

MO: migraine without aura; MA: migraine with aura; N/A: not applicable; d/m: days/month; % of severe intensity: the percentage of which each migraine group (ictal and interictal) suffered from severe headache in most of their attacks

HFOs

We calculated both the maximal amplitudes and AUC of the HFOs in order to avoid the overestimation or underestimation by either means. We found the maximal amplitude and AUC were highly correlated ($r = 0.915$ for early HFO, and $r = 0.859$ for late HFO, $p < 0.001$, Pearson's correlation), and both calculations were good representatives of the HFO.

Early HFOs

The early HFOs results showed patients with migraine, whether in the interictal or ictal groups had significantly higher maximal amplitudes (interictal 0.190 ± 0.091 µV, ictal 0.186 ± 0.084 µV, control 0.136 ± 0.057 µV, one-way ANOVA, $p = 0.039$; post-hoc LSD: interictal vs. control, $p = 0.016$; ictal vs. control, $p = 0.039$) and AUC (interictal 293.1 ± 124.7 nv·ms, ictal 304.3 ± 147.6 nv·ms, control 214.6 ± 84.2 nv·ms, one-way ANOVA, $p = 0.029$; post-hoc LSD: interictal vs. control, $p = 0.022$; ictal vs. control, $p = 0.016$) than control subjects. However, the interictal and ictal groups did not differ in these two parameters. There was no difference among the three groups in duration and the number of wavelets of the early HFOs (Table 3, Figure).

Table 2: Latencies and amplitudes (mean ± SD) of broad-band somatosensory evoked potential

	Control	Migraine		p values*
		Interictal	Ictal	
Stimulation intensity (mV)	7.7 ± 1.6	7.7 ± 1.5	8.4 ± 2.1	0.317
N20o latency (ms)	16.32 ± 0.84	15.95 ± 0.93	16.01 ± 0.90	0.314
N20p latency (ms)	18.94 ± 1.03	18.64 ± 0.81	18.94 ± 1.02	0.362
P25 latency (ms)	24.25 ± 2.52	23.90 ± 3.03	23.67 ± 2.29	0.767
N33 latency (ms)	32.43 ± 5.24	30.36 ± 6.46	30.97 ± 5.20	0.422
N20o-N20p (µV)	2.10 ± 0.75	2.34 ± 1.13	2.70 ± 1.29	0.179
N20p-P25 (µV)	5.36 ± 2.60	5.31 ± 3.12	5.66 ± 3.78	0.911
P25-N33 (µV)	2.89 ± 2.26	2.68 ± 2.32	3.06 ± 3.53	0.866

* One-way analysis of variance (ANOVA) test; N20o: onset of N20; N20p: peak of N20

Table 3: All electrophysiological parameters (mean ± SD) of HFOs

	Early phase				Late phase			
	Control	Migraine		p value*	Control	Migraine		p value*
		Interictal	Ictal			Interictal	Ictal	
Max peak-to-baseline amplitude (μV)	$0.136 \pm 0.057^{a,b}$	0.190 ± 0.091^{a}	0.186 ± 0.084^{b}	0.039	0.151 ± 0.069	0.180 ± 0.084	0.164 ± 0.096	0.421
Area-under-curve (nv·ms)	$214.6 \pm 84.2^{a,b}$	293.1 ± 124.7^{a}	304.3 ± 147.6^{b}	0.029	295.7 ± 175.9	313.6 ± 154.5	321.8 ± 229.6	0.887
Duration of HFO (ms)	3.26 ± 0.48	3.52 ± 0.66	3.42 ± 0.54	0.265	4.69 ± 1.19	4.73 ± 1.03	4.97 ± 1.12	0.638
Number of wavelets of HFO	2.34 ± 0.32	2.43 ± 0.46	2.38 ± 0.40	0.717	3.23 ± 0.67	3.26 ± 0.59	3.40 ± 0.66	0.612

* One-way analysis of variance (ANOVA) test ; $_{a,b}$: $p<0.05$, Post-hoc least significant difference (LSD) paired comparisons; HFO: high-frequency oscillation, nv: nano-volt

Late HFOs

Regarding the late phase of the HFOs, there were no differences among the three groups in the maximal amplitude, AUC, duration, and number of wavelets (Table 3, Figure).

Migraine without aura vs. migraine with aura

Within both the ictal and interictal groups, there were no differences in all recorded parameters of both SEPs and HFOs between MA and MO patients.

DISCUSSION

In this study, patients with migraine had higher amplitudes and AUC of early HFOs than controls. This may imply a hyperexcitability state in the subcortical regions because prior studies suggest that early HFO originates from excitatory thalamocortical fibers[17-19,31]. In addition, we found this hyperexcitable state may exist in both ictal and interictal periods.

It has been found during the ictal period, there is an increase in the sensitivity in the second-order (trigeminal nucleus) and third-order (thalamic relay nucleus, i.e. the ventroposterior complex, VPC) central neurons that receive convergent inputs from intracranial structures, as well as from extracranial and extracephalic structures[32]. Since early HFO represents the activity of deep thalamocortical fibers that originate from the VPC, an enlarged early HFO in patients with migraine during ictal period probably were derived from a sensitized hyperexcitable thalamic VPC nucleus. On the other hand, such a phenomenon has been found in both the ictal and interictal periods[33,34]. Zohsel et al showed that an enhanced sensitivity to painful stimuli could be observed in patients suffering from migraine during an interictal period, even in patients with an average disease duration of 4.4 years[34]. It is likely that the result of sensitization in nociceptive pain pathways can be caused by frequent pain experiences.

Studies on the subcortical regions in patients with migraine are rare. One study, by using diffusion tensor imaging, showed that patients with migraine had a lower fractional anisotropy along the thalamocortical tract[35]. This study may imply hyper-functioning of the thalamocortical projections during the interictal period, in accordance with our findings.

High-frequency oscillation is a relatively new method to study the sensory pathway. However, since it explore simultaneously both the excitatory and inhibitory mechanisms of the central nervous system, it has been widely used to explore various neurological disorders, including Parkinson's disease and myoclonus epilepsy[28], multiple system atrophy[36], amyotrophic lateral sclerosis[29], and cervical dystonia[37]. There are two previous studies addressing the issue on HFOs in patients with migraine. Sakuma et al[23] demonstrated that the amplitudes of HFOs were significantly diminished in migraineurs at the interictal period compared to controls. Coppola et al[24] found that the amplitudes and AUC of early HFOs in patients with migraine were decreased at their interictal period, but normalized at the ictal period. Regarding the late HFOs, there was no significant difference between patients and controls. They referred to these findings as a reduced pre-activation excitability in migraineurs. The reasons for the discrepancies among these studies including ours are not clear. Some possible explanations are described as follows. First, the HFO settings are not completely the same among these studies (Table 4). There is an important difference between Sakuma et al's and our settings (as well as Coppola et al's), that is, the number of stimulation for average. Sakuma et al used 5000 response to generate and to average the HFOs.[23] Given the stimulation rate of 4 Hz in their study, it would take more than 20 minutes to complete the recording. In contrast, it took four minutes in our study, and about two minutes in Coppola et al's.[24] HFOs are dependent on the vigilance state[38,39], and a change in the arousal state, such as eye opening or eye closing, can modify the strength of the thalamic source activity (i.e. eye opening increases and eye closing decreases thalamic activity). Prolonged recording time may cause arousal changes, which may in turn result in decreased HFO responses. However, this may not explain the discrepancy between the results from Coppola et al's and our studies. The conflicting results could be

Table 4: Comparison of the settings and results of HFO studies on migraine patients

		Sakuma (23) (2004)	Coppola (24) (2005)	Lai, current study
Stimulus Settings	Intensity	3x ST (~ 1x MT)	2x MT	1x MT
	Frequency	3.8 - 4.7 Hz	4.4 Hz	3.8 Hz
	Montage	C3'-Fz	C3'-Fz	C3'-Fz
	Response	5000	500	1000
	HFO filter	400 - 800 Hz	450 - 750 Hz	500 - 1000 Hz
	early/late discrimination	N20 peak	N20 peak	N20 peak
Characteristics of patients	Total patients, N	19	42	59
	Female, N(%)	14 (73.7%)	28 (66.7%)	40 (67.8%)
	Age (Mean ± SD)	38.5 ± 17.6	30.5 ± 10.5	33.5 ± 8.4
	MO:MA, N	13:6	23:19	39:20
	Headache frequency (attacks/month)			
	0-2	N=8 (42%)	N/A	N=36 (61%)
	3-4	N=4 (21%)		N=16 (27%)
	>4	N=7 (37%)		N=7 (12%)
	Disease duration (years)	N/A	N/A	11.7±8.1
Results — Interictal	Early HFO	↓ amplitude	↓ in both amplitude and AUC	↑ in both amplitude and AUC
	Late HFO	↓ amplitude	no significance	no significance
Results — Ictal	Early HFO	N/A	no significance	↑ in both amplitude and AUC
	Late HFO	N/A	no significance	no significance

HFO: high-frequency oscillation, ST: sensory threshold, MT: motor threshold, MO: migraine without aura, MA: migraine with aura, N: number

due, not only completely to the different technical parameters, but also to the high variability of the subcortical and/or cortical excitability change in patients in migraine, which was also seen in the study of phosphene threshold using TMS[40].

Regarding the late HFOs, there was no difference between our patient (both ictal and interictal) and control groups. Our late HFOs results are consistent with those done by Coppola et al[24] although the findings of early HFOs were different. Since the late HFOs probably represent the intracortical GABAergic inhibitory activity[20,21], this indicates that the inhibitory mechanism over the somatosensory cortex in patients with migraine did not differ from normal subjects.

A recent study done by Restuccia et al showed that in normal subjects, enlarged early HFOs with decreased late HFOs can be induced after slow frequency repetitive TMS (rTMS) over the primary sensory cortex[41]. They concluded that the inhibition of cortical excitability by slow frequency rTMS triggered an opposite, compensatory effect at the subcortical level, i.e. the increased activity of thalamocortical tract. Thus, another explanation to our finding, enlarged early HFOs in patients with migraine, might be a compensatory hyperactivity of the thalamocortical tract due to a reduced cortical excitability.

However, a major difference existed between our study and Restuccia et al's. The late HFOs (as well as SEP, discussed below) in our study showed no difference between our patient and control groups, indicating no abnormal cortical inhibition. Thus, we presumed that the enlarged early HFOs in our patient group was a primary event, instead of a compensatory phenomenon.

Regarding SEP recordings, our results were similar to those reported by these two studies, i.e. normal N20 amplitude and latency in patient and control groups[23,24]. Since the N20 in SEP recordings is generated by postsynaptic potentials of the pyramidal neurons in the area 3b of the somatosensory cortex[42], normal SEP and late HFOs in patients with migraine indicates that the somatosensory area is functionally intact.

A dissociation behavior between early HFO and SEP was observed in our findings (i.e. enlarged early HFO and normal SEP). This dissociation behavior was also found in Coppola et al's study (normal N20 despite decreased or normal early HFO, in interictal and ictal period, respectively[24]). Moreover, in previous studies[16,21], the dissociation phenomenon was observed in physiologic conditions (i.e. sleep-awake cycle, interference tasks, etc.), and it was speculated accordingly that the late HFO

was derived from discharges of intracortical GABAergic inhibitory neurons, which received thalamocortical input and exerted a feed-forward inhibition to pyramidal cells. Since the inhibitory mechanism over sensory cortex is intact as demonstrated in our and Coppola et al's studies, an enlarged ascending thalamocortical input message to pyramidal cells probably is counterbalanced by a normal-functioning inhibitory mechanism, which also received enhanced thalamocortical input. This speculation also fits well with the findings of Coppola et al's study[24]. In their study, normal N20 was noted despite a reduced thalamocortical input during interictal period, or a normal thalamocortical activity during ictal period. A reduced thalamocortical input may lead to a hypo-activation of both post-synaptic pyramidal cells and intracortical inhibitory neurons, resulting in a normal N20.

Another finding of our study is that in normal subjects, the early HFOs are lower in amplitude and smaller in AUC than the late HFOs. In the literature, some studies showed the same pattern as ours[29,37], although some are not, i.e. larger early HFOs then the late HFOs. Interestingly, in the study conducted by Sakuma et al[23], it was shown that both patterns exist in normal subjects by stimulation over right or left hands. Restuccia et al also demonstrated both patterns in their recordings[41]. We concluded that two patterns regarding the amplitude and AUC of early and late HFOs in normal subjects may exist, even in the same laboratory. Thus, the interpretation and comparison of HFOs across different laboratories should be careful, especially for individual data.

The study has some limitations in methodology. First, interictal and ictal recordings in the same subject were not obtained. Theoretically, a longitudinal study using paired design (interictal vs. ictal) would be more sensitive in determining the excitability changes since within-subject comparison reduces inter-subject variation. Second, one may ask if the time interval considered as the ictal period (Day 0 ± 1) in this study is optimum because excitability may vary during this period. However, if we limited our ictal group as "within 12 hours of migraine attack" as used in Coppola et al's study[24], the results of early HFOs did not differ from the current results (n=12, data not shown). Third, based on patient's recall, there was a 2.2-day difference in the monthly headache frequency between interictal and ictal groups, which may cause bias. However, the comparisons did not show any difference in the parameters of HFOs and SEP in both groups. Fourth, since migraine is a painful disorder involving cranial region, exploring the trigeminal SEP and its high-frequency components may provide more information about the pathophysiology of migraine. However, there is no well-established model of HFO in trigeminal SEP settings yet. Fifth, we did not simultaneously record the clinical correlate of a hyperexcitable thalamocortical pathway, i.e. the allodynic symptoms, which should be further evaluated in subsequent studies.

Conclusions

Our study showed that patients with migraine had higher amplitudes and AUC of the early-phase HFOs during interictal and ictal periods. This finding implicates subcortical hyper-excitability in patients with migraine. The N20 results did not differ between patients and controls, indicating that the

ascending sensory pathway is intact. We hypothesize that the effect of enlarged early HFO might result from a sensitized ascending pathway after repeated migraine attacks. Further large-scale studies on HFOs in different headache centers may be warranted to solve the discrepancies among current studies.

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