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Time–frequency analysis reveals decreased high-frequency oscillations in writer's cramp

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High-frequency oscillations (HFO) have been suggested to reflect the activity of thalamocortical and/or intracortical neurons bursting at high frequencies. These circuits seem to be involved in pathophysiological mechanisms of focal dystonia. In healthy subjects, we characterized the spectrotemporal properties of HFO patterns evoked by dominant-hand median-nerve stimulation, using magnetoencephalography coupled with time–frequency analysis. Then, we investigated HFO in patients with writer's cramp and found that HFO patterns are strongly decreased in power and disorganized in time. This supports the assumption that abnormal HFOs reflect pathophysiological mechanisms occurring in focal dystonia, possibly resulting from a dysfunction of somatosensory processing.

Keywords: high-frequency oscillations; dystonia; time–frequency analysis; MEG; somatosensory evoked fields

Abbreviations: HFO = high-frequency oscillations; HFOh = HFO high; HFOl = HFO low; MN = median nerve

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Introduction

High-frequency oscillations (HFO) have been identified as a burst of low amplitude with frequencies higher than 400 Hz, in both EEG and MEG. They are superimposed in time on N20 waves, corresponding to the first cortical somatosensory evoked potential (SEP). Moreover, when evoked by stimulation of different nerves, HFO exhibit a somatotopic source organization within S1, as does the first cortical somatosensory potential (Curio *et al.*, 1997; Maegaki *et al.*, 2000). Several studies have shown that HFO are functionally dissociated from N20, and that they represent independent SEP components (Hashimoto *et al.*, 1996, 1999; Gobbele *et al.*, 1999, 2000; Klostermann *et al.*, 1999; Halboni *et al.*, 2000).

At the cortical level, HFO are thought to be generated by two sources, both located in the S1 area (Haueisen *et al.*, 2001). As high timing precision leading to precise phase locking is required for HFO to be detectable, only fast-spiking neurons, able to burst with high synchronicity, can be potentially considered as HFO generators. Two temporally separated HFO subcomponents have been identified (Klostermann *et al.*, 1999; Mochizuki *et al.*, 1999*a*; Halboni *et al.*, 2000; Haueisen *et al.*, 2001; Kojima *et al.*, 2001; Barba *et al.*, 2004). Early HFO are thought to reflect pre-synaptic repetitive discharges conducted in the terminal segments of thalamocortical axons, while late HFO would be generated by post-synaptic contributions from intracortical S1 neurons, including bursting pyramidal cells and fast-spiking inhibitory GABAergic interneurons [reviewed in Curio (2000)]. However, the nature of HFO generators remains controversial.

Although the functional significance of HFO is unknown, they might play a role in the processing of somatosensory inputs. In line with this hypothesis we studied HFO in dystonia, a disorder in which somatosensory processing is disrupted.

Dystonic patients experience involuntary movements and postures during the execution of motor tasks, owing to abnormal co-contraction of antagonist muscles and motor overflow to remote muscles. In writer's cramp, a focal hand dystonia, dystonic spasms are triggered only during a specific context, namely writing. The pathophysiology of dystonia is unclear, but a somatosensory dysfunction is well documented.

Various defects of somatosensory functions have been reported in dystonic patients, including (i) abnormal processing of the spatiotemporal characteristics of somatosensory stimuli (Bara-Jimenez *et al.*, 2000; Sanger *et al.*, 2002), (ii) abnormal somatosensory integration (including proprioceptive feedback), as illustrated by abnormal gating of simultaneous somatosensory stimuli (Tinazzi *et al.*, 2000) and (iii) abnormal sensorimotor coupling, as illustrated by impaired force scaling (Odergren *et al.*, 1996), or defective suppression of motor evoked potentials elicited by transcranial magnetic stimulation following peripheral stimulation (Abbruzzese *et al.*, 2001; Bertolasi *et al.*, 2003).

A deficit of cortical inhibitory mechanisms (GABA-mediated) has also been extensively described in dystonia (Ridding *et al.*, 1995; Stinear and Byblow, 2004), and decreased cortical GABA levels (Levy and Hallett, 2002) were recently demonstrated. A link between abnormal somatosensory processing and deficient GABA inhibition is currently under investigation in dystonia (Simonetta-Moreau *et al.*, 2006). Cutaneous and muscular afferent inputs reduce the excitability of GABAergic interneurons in M1 in healthy subjects but not in dystonic patients.

Given the possibility that HFO reflect a part of somatosensory processing and involve the GABAergic inhibitory system, we used magnetoencephalography (MEG) recording coupled to time–frequency analysis to investigate HFO patterns in patients with writer's cramp. As somatosensory disorders and defective GABA inhibition are probably involved in the pathophysiological mechanisms of dystonia, such patients would be expected to have abnormal HFO.

Subjects and methods

Subjects

We studied 13 right-handed females with pure writer's cramp (Burke–Fahn–Marsden scale score: 1–3; upper limb dystonic movement only), with a mean age of 39 years (range: 20–63). We tested the dominant hand, which was also the symptomatic hand in all the patients.

As a control group we studied 10 age-matched, right-handed healthy females with a mean age of 32 years (range: 23–63).

This study was approved by the local ethics committee, and all the participants gave their informed consent to MEG investigation and anatomical MRI.

Peripheral nerve stimulation

The median nerve was electrostimulated transcutaneously on the right wrist by using a bipolar electrode (Medtronic) connected directly to the stimulator (S88 stimulator, Astro-Med Inc. GRASS, W. Warwick, RI, USA).

The motor threshold (MT, the minimal stimulus intensity required to produce thumb movement) was determined for each subject, and the experimental stimulus intensity was set at MT + 10% (Curio *et al.*, 1997).

Eight hundred stimulations (0.5 ms shocks) were delivered, with a randomized inter-stimulus interval varying from 350 to 450 ms.

Magnetoencephalography

Recordings were made in a magnetically shielded room with a 151-channel MEG system (CTF Systems Inc., Port Coquitlam, Canada). The subjects were comfortably seated with the head immobilized by a cushion. The left side of the head was pressed against the MEG helmet, and only signals coming from the left hemisphere were recorded (80 channels). The subjects were asked to keep their attention focused on the stimuli, with their eyes open.

The MEG signal was digitized at 4 kHz. Ocular and stimulus artefacts were eliminated offline, and then somatosensory evoked fields (N20m, HFO) were computed by averaging all trials.

Evoked field analysis

N20 parameters were evaluated using both filtered data and time–frequency analysis. The N20m peak latency was determined on filtered data, by low-pass filtering (<100 Hz). The N20m peak amplitude was measured both on filtered data and time–frequency maps.

For HFO, we used only the time–frequency analysis. Two parameters were assessed first in the healthy subjects, namely latency and energy. Frequency subcomponents were defined in the HFO signal. Then, these parameters were evaluated and compared with patient data by using the Mann–Whitney test.

The time–frequency analysis was applied on the evoked averaged signal. It was based on a Morlet wavelet transformation (Norra *et al.*, 2004; Waberski *et al.*, 2004). For the low-frequency SEP, time resolution was 16 ms, and 1.2 ms for HFO. Baseline was measured between 100 and 1 ms before stimulation.

For the N20m, the time–frequency included frequency bands ranging from 5 to 100 Hz, with a frequency step of 1 Hz.

For HFO, the frequency bands ranged from 450 to 1000 Hz, with a frequency step of 15 Hz. Time–frequency power maps were finally computed after baseline correction (averaged mean baseline power subtracted from the data).

For N20m and HFO, respectively, maps from the five sensors with the largest signal amplitude were selected and averaged. The average across all frequencies (5–100 Hz for N20m, 450–1000 Hz for HFO) was then computed to obtain a global energy time course. This was done for each subject.

Latency measures

The latency of the HFO peak was determined on global HFO energy time courses.

To find out whether the N20m wave and HFO were time-synchronized, the time correlation between latencies of N20m and the global HFO peak was computed in the control and patient groups.

Energy measures

For the N20m, we computed an integrated power value on global energy time courses, in a time window ranging from 15 to 25 ms post-stimulation. For each subject, the maximum amplitude of HFO energy was measured on the global energy time courses.

Frequency subcomponents

Two frequency subcomponents were defined in the HFO signal according to their time courses. A frequency subcomponent was defined as a concatenation of several consecutive frequency bands, for which time-course correlation was higher than 0.9. The energy of each frequency subcomponent was assessed in two different ways. First, the power of the maximum peak was determined on the

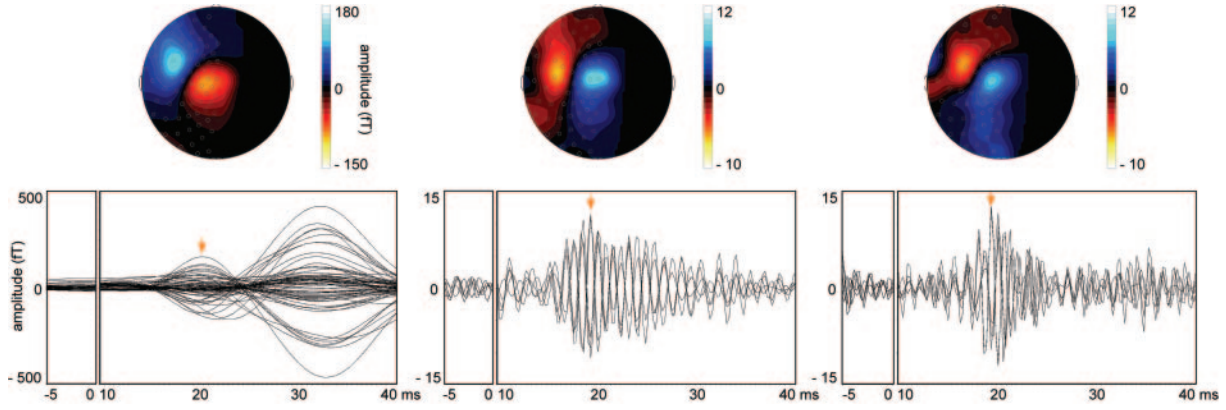

Fig. 1 N20m and HFO components in a healthy subject. N20m, HFOl and HFOh waves (left to right), with the corresponding topographical maps for the maximum (orange arrow). For HFO, the five sensors with the largest amplitude are represented. All figures: *x*-axis is time in milliseconds. The part between −5 and 0 ms illustrates part of the baseline.

Table 1 Ranges of the HFO frequency components in healthy subjects

Frequency range	Mean ± SD (Hz)				*P*
Low-range HFO					
Inferior bound	519 ± 21	]	0.011	]	0.02
Superior bound	645 ± 39				
High range HFO					
Inferior bound	697 ± 55	]	0.011		
Superior bound	1008 ± 81				

energy time courses. Secondly, an integration of power in a given time window (±5 ms around the corresponding N20m maximum peak latency) was computed to obtain an integrated power value.

Results

Median-nerve stimulation elicited HFO in all the patients and controls. No differences were found in baseline values and baseline standard deviation (SD) between the two groups (Mann–Whitney test).

HFO characterization in healthy subjects

The correlation between the latencies of N20m and the global (450–1000 Hz) HFO peak was very strong in the control group (correlation coefficient = 0.86; $P < 0.05$). HFO latency was thus normalized to the conduction time of sensory incoming information by adjusting each subject's HFO to their N20m timing.

There were two main frequency subcomponents in the HFO signal, with non-contiguous ranges of frequency: the first one, HFO low (HFOl), ranged from 519 ± 21 Hz to 645 ± 39 Hz, and the second, HFO high (HFOh), ranged from 697 ± 55 to 1008 ± 81 Hz (*see* Fig. 1). These two subcomponents were statistically different (Wilcoxon test, *see* Table 1). In healthy subjects these two bands correlated in terms of their amplitude over time (median correlation coefficient = 0.77).

Comparison between the patients and controls

Latency measures

The time analysis showed that, contrary to the healthy subjects, the global HFO was not time-correlated with the N20m wave in the patients (correlation coefficient = 0.77). However, there was no significant difference in the HFOl and HFOh peak latencies between the two groups.

Energy measures

As regards the N20m energy, both measures on filtered data and time–frequency analysis showed no differences between the two groups (Fig. 2).

For the global HFO (illustrated in Fig. 3A–D), HFO energy was reduced in the patients ($P = 0.014$, *see* Fig. 4A).

Frequency subcomponents

The two subcomponents isolated in the patients group (*see* Table 2) were not different from those obtained in the control group (Mann–Whitney test). Energy measures were done on the frequency bands 510–645 Hz for HFOl and 720–1008 Hz for HFOh. The energy analysis of both subcomponents revealed that HFO maximum and integrated power were strongly reduced in the patients with writer's cramp, even if the difference in HFOl integrated power failed to reach significance (maximum power: HFOl $P = 0.021$, HFOh $P = 0.018$; integrated power: HFOl $P = 0.054$, HFOh $P = 0.015$) (Fig. 4B and C). Moreover, these two frequency subcomponents were significantly less strongly correlated over time than in the control group (median correlation coefficient = 0.48; $P = 0.0023$), as illustrated in Fig. 3E and F.

Discussion

We applied neuromagnetic imaging with time–frequency analysis to compare HFO in healthy subjects and in patients

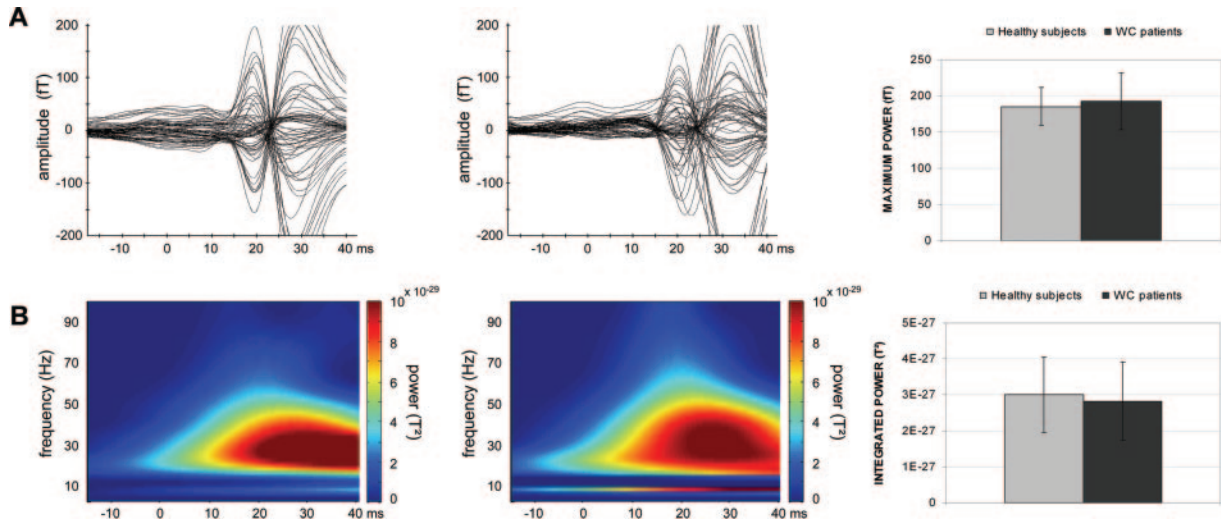

Fig. 2 N20m (**A**) filtered data (<100 Hz) for a healthy subject (left) and a patient with writer's cramp (middle). There is no difference in N20m amplitude between the two groups (right). (**B**) Time–frequency maps for a healthy subject (left) and a patient with writer's cramp (middle). There is no difference in N20m energy (<100 Hz) between the two groups (right).

with writer's cramp. The resolution of MEG allowed us to characterize the cortical sources of HFO, while time–frequency analysis offered access to the oscillatory activity of underlying neuronal assemblies, representing a window on cortical network activities.

This study provides (i) spatiotemporal characterization of high-frequency oscillatory activity in healthy subjects; and (ii) an analysis of HFO activities in a focal dystonia (writer's cramp).

Time–frequency analysis has already been used to describe the HFO signal (Halboni *et al.*, 2000; Haueisen *et al.*, 2001; Barba *et al.*, 2004), but this is the first such study characterizing HFO frequency subcomponents in patients with writer's cramp.

HFO characterization in healthy subjects

The main result obtained in healthy subjects was that the HFO activity measured after median-nerve stimulation was distributed into two frequency bands, namely HFOl (519–645 Hz) and HFOh (697–1008 Hz). These two bands had strongly correlated energy time courses.

In previous studies, HFO were subdivided into two temporally distinct subcomponents designated p1 (early part) and p2 (latter part), with the division boundary coinciding with the N20(m) peak latency (Klostermann *et al.*, 1999; Haueisen *et al.*, 2001). These two subcomponents display different intraburst frequencies, of 700 and 494 Hz, respectively (Klostermann *et al.*, 1999). A gradual increase in the stimulus rate from 0.5 to 2 Hz dissociated the two burst subcomponents, with the late burst showing a steeper decline than the early burst. From 2 to 25 Hz, the two subcomponents decreased in parallel. Given their differential responses to stimulus rate variations, early and late bursts are likely to be functionally segregated (Klostermann *et al.*, 1999). At the cortical level, HFO are thought to be generated by at least two sources (Gobbele *et al.*, 2004), both located in the same part of the somatosensory cortex (Barba *et al.*, 2004), and more precisely in the 3b Brodmann area, when evoked by median-nerve stimulation.

Our findings are consistent with these data. Indeed, using a precise time–frequency analysis, the spectral pattern of cortical HFO can be subdivided into two distinct frequency subcomponents, which could be likened to the above-mentioned subcomponents p1 (HFOh) and p2 (HFOl). The subcomponent frequencies described here are slightly different from those reported elsewhere, but this can easily be explained by differences in the frequency computation methods. Klostermann *et al.* (1999) determined HFO frequencies by computing the mean inverse of the burst interpeak intervals, while the time–frequency analysis used here provided higher frequency resolution. Neither subcomponent occurred systematically before or after the N20m peak, that is, the two subcomponents had no fixed order of appearance. However, the time courses of HFOl and HFOh correlated strongly, possibly indicating that the neuronal population generating the two subcomponents burst almost simultaneously.

Comparison between patients and controls

The major result of this study was that patients with writer's cramp had decreased HFO energy compared with healthy subjects. Moreover, the HFO patterns observed in the patients were very different from those of the healthy subjects. First, HFO energy was strongly reduced for both HFOl and HFOh. Secondly, the correlation between the HFOl and HFOh energy time courses was weaker.

Two studies have explored HFO elicited by MN stimulation in dystonic patients so far. The first one by

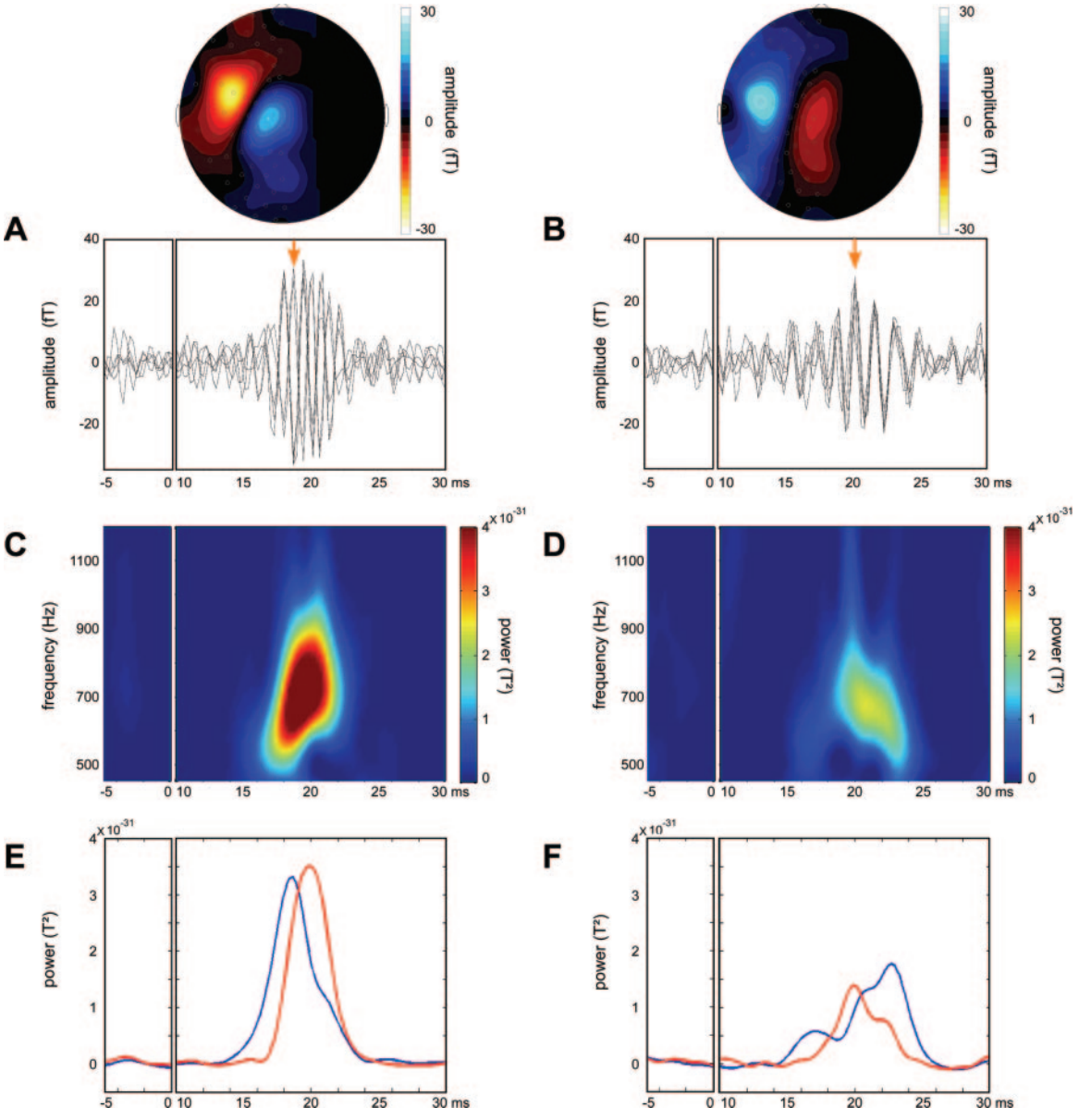

Fig. 3 HFO filtered data, time–frequency maps and HFO components time courses. All figures: *x*-axis is time in milliseconds. The part between −5 and 0 ms illustrates part of the baseline. (**A** and **B**) Filtered data representing the five sensors with the largest HFO amplitude in a healthy subject (**A**) and in a patient (**B**), with the topographical maps corresponding to the HFO maximum (orange arrow). Please note the synchronicity of the sensors during the HFO burst. (**C** and **D**) Average of the time–frequency maps in high-frequency bands corresponding to the sensors in **A** and **B**. (**E** and **F**) Corresponding time courses of low HFO (blue) and high HFO (red) bands.

Mochizuki *et al.* (1999*b*) showed similar HFO patterns in patients with hand dystonia and control subjects. In this earlier study, only four patients with hand dystonia (type not specified) were investigated, a too small number to provide statistical reliability; furthermore, HFO amplitude was assessed directly on filtered data, a technique far less precise than time–frequency analysis. On the contrary, Inoue *et al.* (2004) found reduced HFO amplitude in patients with cervical dystonia. Our findings are in line with Inoue *et al.* (2004), and lead to the conclusion that stimulation of a dystonic as well as a non-dystonic part of the body evokes reduced HFO in dystonic patients.

Our data suggest that the network involved in HFO generation is abnormal in patients with writer's cramp. Reduced global HFO power could come from different mechanisms: (i) the bursting neurons (one or more populations) were less activated by the somatosensory inputs than they were in healthy subjects; or (ii) the bursting neurons were activated at the same level, but their bursts were not well synchronized, leading to a reduced burst of HFO.

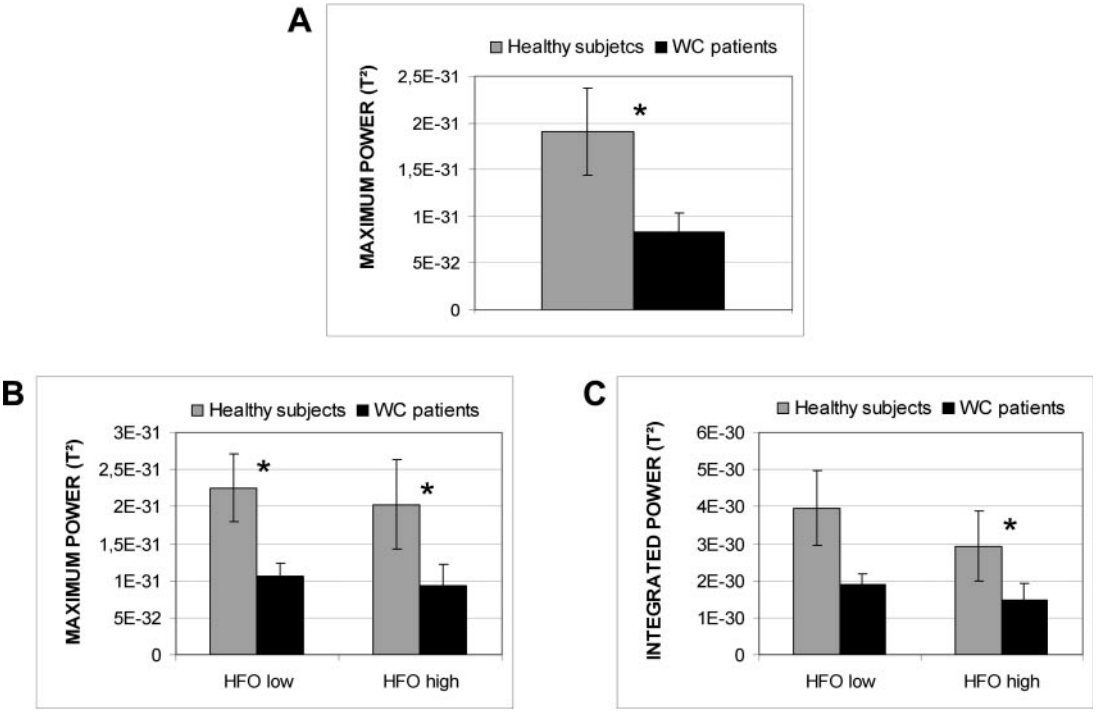

Fig. 4 Comparison of HFO energy between patients and healthy subjects groups. (**A**) Global HFO (450–1000 Hz) power in patients and healthy subject groups (difference: $P = 0.014$, Mann–Whitney test). (**B** and **C**) Power of HFOl and HFOh components, (**B**) at the maximum peak, and (**C**) integrated power for a time window corresponding to ±5 ms around time 0. Differences between groups: (**B**) HFOl $P = 0.021$, HFOh $P = 0.018$; (**C**) HFOl $P = 0.054$, HFOh $P = 0.015$, Mann–Whitney test.

Table 2 Ranges of the HFO frequency components in WC patients

Frequency range	Mean ± SD(Hz)			*P*
Low range HFO				
Inferior bound	510 ± 27.6	]	<0.01	0.045
Superior bound	642 ± 52.7			
High range HFO				
Inferior bound	725 ± 56.2	]	<0.01	
Superior bound	985 ± 73.2			

Interestingly, as regards our HFO subcomponents, both maximum and integrated HFO power were decreased in the patients. This indicated impaired bursting synchronization. In addition, the weaker correlation of the subcomponents energy time courses showed defective temporal coordination within the HFO-generating structures. Taken together, these results suggest that the functional relationships between the neural sources responsible for HFO are disturbed in patients with writer's cramp, probably owing to alterations of the temporal coupling characteristics of the generating network.

Functional implications

In healthy subjects, it seems now clear that two distinct cortical generators are involved in HFO production, reflected in the two HFO subcomponents. Each subcomponent described here had, most of the time, a monophasic time course (as they present only one peak), and the two subcomponents were highly correlated along time. It indicates that the generating neurons react to the somatosensory input in a coordinated manner, and that activities of the neuronal assemblies responsible for the two HFO subcomponents are connected. In healthy subjects at least two neuronal assemblies strongly connected are probably involved in synchronized bursting, to produce sharp, strong, monophasic HFO waves.

In patients with writer's cramp, we wondered what kind of abnormalities occurred in the HFO-generating network.

It is worth noting that no N20m differences, neither in energy nor in timing, were found between patients and control subjects. It suggests that the somatosensory signal is normally conducted along the somatosensory pathways up to the S1 cortex. However, in patients, decreased HFO energy was associated with multi-phasic time courses. HFO subcomponents displayed more than one peak, with a decreased correlation between the two main subcomponents. This clearly signs for a spatiotemporal desynchronization taking place in the generating networks responsible for HFO. Indeed, in order to avoid phase cancellation, a strong timing precision (inferior to 1 ms) is necessary for HFO bursting. A slight jitter in the bursting dynamic might lead to a variable expression of HFO, depending on the precision

of synchronization between neuronal sources. This could in turn prevent the spatial and temporal summation of oscillatory activities and produce HFO of reduced amplitude, with multi-phasic patterns. On the other hand, a slight synchronization jitter might be not sufficient to modify the N20m.

It remains to be determined which cortical neurons are involved in generating HFO. Our results must be interpreted with care, owing to the incomplete knowledge of HFO generators. As both subcomponents were abnormal in our patients with writer's cramp, we can suppose that bursting desynchronization takes place in both pre-synaptic and post-synaptic HFO-generating networks. As regards the post-synaptic intracortical generators, bursting pyramidal neurons and fast-spiking interneurons are strongly connected, and both may contribute to HFO. This is consistent with our finding of reduced and disorganized HFO activity in patients with writer's cramp, as abnormalities of sensory processing have been demonstrated (reviewed in Abbruzzese and Berardelli, 2003; Tinazzi *et al.*, 2003; Kaji *et al.*, 2004), and linked to deficits of cortical inhibition. Moreover, in human motor pathways, very high frequency waves can be elicited by brief electrical or magnetic stimulation of the motor cortex. It has been suggested that these activities imply a neuronal network involving both interneurons and pyramidal neurons (reviewed in Amassian and Stewart, 2003) highly connected within both deep and superficial layers of the motor cortex. Bad coupling between deep and superficial layers, particularly in the S1 cortex, may be involved in dystonia. It was recently suggested that HFO alteration could be due to changes in the dendritic spine density of cortical inhibitory interneurons (Hashimoto *et al.*, 2004). Poor synchronization between different populations of neurons could lead to changes in burst coupling, resulting in modified frequency patterns, as shown here in patients with writer's cramp.

As suggested by rodent studies, HFO could be involved in spatiotemporal integration of incoming sensory information (Jones and Barth, 1999; Barth, 2003). In dystonic patients, even a slight lack of synchronization of HFO neuronal networks might disrupt the processing of the incoming sensory information. This fits with the view that an initial dysfunction of the somatosensory system could represent an endophenotype in dystonia (Meunier *et al.*, 2001; Inoue *et al.*, 2004; O'Dwyer *et al.*, 2005). Indeed, several studies have shown altered organization of the somatosensory cortex in both hemispheres of patients with unilateral focal dystonia (Tempel and Perlmutter, 1993; Rome and Grunewald, 1999; Butterworth *et al.*, 2003), as in other forms of focal hand dystonia (Elbert *et al.*, 1998), and in the cortical somatosensory representation of a non-dystonic body part (hand representation in cervical dystonia, for example). How this initial dysfunction leads to the motor abnormalities observed in dystonic patients is unclear. Aberrant spatiotemporal sensory processing during motor task execution may trigger a vicious circle, modelled by Sanger and Merzenich (2000) as unstable control of the sensorimotor loop. As a consequence of abnormal somatosensory processing, wrong or even aberrant information reaches the motor cortex, leading to the programming of mismatched motor outputs. Abnormal movements generate abnormal contraction-induced somatosensory feedback, thereby reinforcing the abnormal activation pattern of the somatosensory cortex.

However, it cannot be excluded that the sensory abnormality stressed by abnormal HFO is a secondary phenomenon following a primary motor dysfunction. To investigate this hypothesis, motor interference effects on HFO have to be explored. It has been done in healthy subjects, but the results are controversial, mainly because of the different properties of the motor interferences tasks applied. Motor interference effects of isometric motor activation of forearm and hand muscles resulted in an attenuation of the N20 but stable HFO (Klostermann *et al.*, 2001). Otherwise, three studies investigated the motor interference induced by finger movements. During a task implying opposing movements between the thumb and the other fingers, the N20m and HFO were decreased (Tanosaki *et al.*, 2002). In addition, pressing a button with the index in response to a visual target (Gobbele *et al.*, 2003), or voluntary free finger movements (Inoue *et al.*, 2002) resulted in decreased N20(m) and late HFO component. To test the hypothesis of a primary motor dysfunction leading to a sensory abnormality in dystonia, motor interference tasks have to be applied in both healthy subjects and dystonic patients.

In conclusion, using MEG and time–frequency analysis, we confirm and extend previous studies showing that HFO activity is distributed into two functionally separate subcomponents. The literature indicates that they are probably generated by two distinct cortical sources. In patients with writer's cramp, HFO activities are reduced and disorganized, most probably owing to desynchronized bursting of cortical neuron assemblies. This could reflect an abnormality of sensory processing taking place in the somatosensory cortex, namely unfocused spatiotemporal distribution of the somatosensory afferent inputs at the cortical level.

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