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Characteristics of very high frequency oscillations of somatosensory evoked potentials in humans with epilepsy

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Abstract

We previously firstly reported very high frequency oscillations (VHFOs, over 1,000 Hz) in somatosensory evoked potentials (SEP) recorded by subdural electrodes following median nerve stimulation on 6 patients. In this study, we fatherly studied the characteristics and the clinical significance of VHFOs) in SEP elicited by stimulating not only the median, but also the ulnar nerves. Conventional somatosensory evoked potentials, including higher frequency components, were recorded by subdural electrodes in 25 patients with intractable epilepsy who underwent intracranial electroencephalographic monitoring for epilepsy surgery. The location, latency, frequency, amplitude and duration of very high frequency components were analyzed. The location of VHFOs was compared with N20 for median and ulnar nerves in each patient. VHFOs were recorded in a very limited region around the central sulcus, mainly on the postcentral gyrus. All VHFOs preceded the earliest peaks of conventional SEP, with the following characteristics: frequencies ranging from 1,000 to 5,000 Hz (mostly from 1,000 to 2,500 Hz), mean amplitude 1.5 μV, and mean duration 1.67 ms. There were no significant differences in amplitude and frequency of VHFOs among median and ulnar nerve stimulations. We hypothesize that VHFOs may be generated in the representative zone for each nerve within the primary somatosensory cortex, and hence can be utilized for more precise localization of the central sulcus.

INTRODUCTION

Confirmation of the primary somatosensory area (SI) and the primary motor area (MI) is clinically important in epilepsy surgery. Currently, cortical stimulation is generally used as the golden standard, and somatosensory evoked potentials (SEP) are recorded in the clinical situation. However, cortical stimulation is well known to give false negative and false positive results.[1] Furthermore, although SEP in response to median nerve stimulation (Med-SEP) can be used for this purpose by analyzing N20/P22, the specificity is also limited. Therefore, it is clinically important to develop a new technique to identify these eloquent areas more precisely.

The first cortical component of Med-SEP is termed N20, and has been reported to be generated from area 3b in SI.[2-5] Recent studies on human SEP have identified the existence of a high frequency component around 600 Hz, which can be isolated from the underlying parietal N20 component by expanding the high-pass filter (to above 300 Hz). This component is termed high frequency oscillations (HFOs).[6-10] HFOs reportedly show phase reversal across the central sulcus, and are therefore speculated to be generated within SI, probably in area 3b.[11,12] Magnetoencephalographic studies also suggest that HFOs are generated in SI.[13-15] In contrast, dipole source analysis of multichannel scalp SEP recordings showed that the early oscillations originate from the subcortical structures near the thalamus, whereas the subsequent components originate from SI.[16] Our previous study also demonstrated that HFOs do not show clear phase reversal between MI and SI in some patients, which indicates that the generator is not likely to be on the bank of the central sulcus.[17] Furthermore, the amplitude of

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HFOs decreases in sleep and the waves gradually disappear, which suggests that HFOs may be generated by mechanisms different from that of N20.[9,18]

Only a few studies have reported SEP (Uln-SEP) and HFOs in response to ulnar nerve stimulation.[19,20] On scalp EEG, Med-SEP and Uln-SEP show no significant difference. To the best of our knowledge, the present study is the first to record and characterize HFOs in response to ulnar nerve stimulation, recorded directly from the surface of human cortex by subdural electrodes.

In a previous animal study, very high frequency components of SEP (greater than 1,000 Hz) were reported in pigs.[21] We also recorded high frequency SEP components greater than 1,000 Hz from the human brain[17], and named these components "very high frequency oscillations (VHFOs)". Compared with N20/P22 and HFOs, VHFOs were recorded in a more restricted area around SI. Therefore, we speculated that VHFOs might be clinically useful to delineate the eloquent areas. However, in the previous study, we studied only four patients showing VHFOs in response to median nerve stimulation. In the present study, we increased the number of patients, and studied VHFOs not only from the median nerve but also from the ulnar and tibial nerves. Furthermore, we investigated the characteristics of VHFOs more precisely, and examined their clinical significance.

METHODS

Subjects

We studied 25 epilepsy patients (13 males and 12 females) who underwent continuous intracranial EEG recording for the clinical purpose of determining the epileptogenic zones and the eloquent areas. This study was approved by the institutional review board, and written informed consent was obtained from all subjects before conducting the study. No abnormal focal neurological findings such as sensory impairment were observed in all subjects. Table 1 summarizes the clinical data of all the subjects. The subdural electrodes (Ad-Tech Medical Instrument Corporation, WI) were made of platinum. Each electrode was 2.3 mm in diameter and the center-to-center inter-electrode distance was 10 mm. The placement sites varied depending on the estimated epileptogenic zone and clinical necessity for individual patients.

Electrical stimulation of cortex

Electrical stimulation of the cortex with subdural electrodes was conducted according to the standard procedures.[22] Each electrode was stimulated with square-wave electric pulse of 0.3 msec duration and 50 Hz frequency for 1 to 5 sec, generated from a constant current electrical stimulator (SEN-3301/ SSI04J; Nihon Kohden Corporation, Tokyo). The positive/negative motor, sensory, and verbal responses elicited were analyzed systematically by the same investigators.

SEP, HFOs, and VHFOs recordings

The patient was placed supine on a bed and instructed to relax during recording. Both SEP and HFOs were recorded using an evoked potential analyzer system (Neuropack Sigma; Nihon Kohden Corporation, Tokyo). Stimulation was delivered to the median or ulnar nerve at the wrist contralateral to the recording subdural electrodes. Square-wave electrical pulse of 0.2 msec duration and 3Hz frequency was used for stimulation. The intensity of stimulation was adjusted to be above the motor threshold without causing pain. Because HFOs waves are reduced during sleep, the recordings were conducted in an awaken state.[9,14,18] Selection of the recording electrodes was based on the results of cortical electrical stimulation. The numbers of subdural electrodes (from 8 to 46) used for recording SEP and HFOs varied depending on the location of electrodes in each individual patient. Subdural electrodes placed on non-active and non-eloquent areas were used as reference electrodes.

For SEP recording, a bandpass filter of 10 Hz to 10,000 Hz was used for Med- and Uln-SEP. N20 and P22 were analyzed for Med- and Uln-SEP.[5,17,23]

For HFOs recording, a bandpass filter of 500 Hz to 10,000 Hz was used for Med- and Uln-SEP. The filtered signals were averaged on-line, and no off-line filtering program was used. The analogue filter used had a low-frequency cutoff of 6 dB/oct, and a high-frequency cutoff of 12 dB/oct. The time window of analysis was 40 msec for Med- and Uln-SEP. The sampling frequency ranged from 10,000 to 25,000 Hz, depending on the time window. The cortical responses of 100 to 500 epochs were averaged. To test for reproducibility, each set of stimulation was conducted at least twice. According to previous study, HFOs were defined as high frequency components over 300 Hz. HFOs were divided into two subtypes: early high frequency oscillations (EHFOs) that occur

Table 1: Clinical data of patients

Patient	Sex/Age	MRI finding	Ictal EEG onset (scalp)	Stimulation nerve
1	M/26	No definite abnormality	Rt. occipital	Lt. median N.
2	M/22	No definite abnormality	Lt. temporal	Rt. median/oral N.
3	M/27	Cortical dysplasia in Rt. frontal lobe	Bi. frontal	Lt. median N.
4	F/16	No definite abnormality	Lt. temporal	Rt. median/oral N; Lt. oral N.
5	M/35	No definite abnormality	Bi. temporal	Bi. median/oral N.
6	M/32	Diffuse cortical atrophy	Rt. frontal	Lt. median/tibial/oral N.
7	M/13	Cortical dysplasia in Rt. temporal lobe	Rt. temporal	Lt. median N.
8	F/30	Abnormality in Lt. frontal lobe	Rt. frontal	Lt. median/tibial N.
9	M/26	Cortical dysplasia in Lt. parietal lobe	Rt. parietal	Rt. median/ulnar/tibial N.
10	F/20	Cortical dysplasia in Rt. frontal lobe	Rt. frontal	Lt. median N.
11	F/43	No definite abnormality	Rt. frontal	Lt. median/ulnar/tibial N.
12	M/23	Cortical dysplasia in Rt. frontal lobe	Non-localizable	Lt. median/tibial N.
13	M/15	Cortical dysplasia in Lt. frontal lobe	Lt. frontal	Rt. median/tibial N.
14	F/14	Cortical dysplasia in Rt. frontal/parietal lobes	Rt. parietal and temporal	Lt. median/tibial N.
15	F/22	Cortical dysplasia in Lt. frontal lobe	Lt. frontal	Rt. median/tibial N.
16	M/14	Cortical dysplasia in Lt. frontal lobe	Lt. frontal	Rt. median N.
17	F/25	Cortical dysplasia in Rt. parietal lobe	Rt. parietal	Lt. median N.
18	M/18	Benign tumor in Rt. frontal lobe	Rt. frontal	Lt. median/tibial/ulnar N.
19	F/44	Cortical dysplasia in Rt. insular lobe	Rt. temporal	Lt. median/tibial/ulnar/oral N.
20	M/19	Cortical dysplasia in Rt. occipital lobe	Rt. occipital	Lt. median/tibial/ulnar N.
21	M/40	Cortical dysplasia in Lt. frontal lobe	Lt. frontal	Rt. median N
22	F/43	Slight atrophy in Lt. hemisphere	Non-localizable	Rt. median N
23	F/30	Right hippocampus sclerosis	Lt. temporal	Rt. median N
24	F/10	Polymicrogyria in Lt. frontal lobe	Lt. frontal	Rt. median N
25	M/11	Atrophy in Rt. occipital/ temporal lobes	Rt. occipital and temporal	Lt. median N

M, male; F, female; Bi, bilateral; Rt, right; Lt, left; N, nerve

before the N20 peak and late high frequency oscillations (LHFOs) that occur after the N20 peak.[24,25] VHFOs was defined as a distinct component superimposed on the conventional SEP with high frequency (>1000Hz) and at least two cycles of wave. Because the background activities differed among patients, we could not make a good criteria for the amplitude. VHFOs would be identified if the waves are outstanding from the background. The location, latency, frequency, duration, and amplitude of each component were evaluated visually on a computer monitor. We analyzed the peak by visual inspection.

3D-MRI

Three-dimensional reconstructed magnetic resonance imaging (3D-MRI) data (Spoiled gradient echo: SPGR, 1.5T, 2mm slice thickness) were acquired before and after implanting subdural electrodes in patients with VHFOs except patient 3, 16 and 24. We identified the location of subdural electrodes by using automated methods based on coregistration, normalization and volume rendering of 3D-MRI imaging data of them.[26] In patient 3 and 16, we only performed the post- operative 3D-MRI because of some nonmedical factors.

Statistics analysis

Data is presented as mean ± standard deviation (SD). Intergroup differences were analyzed using Student's t-test, and were considered statistically significant if p was less than 0.05.

RESULTS

Median nerve SEP, HFOs, and VHFOs

Recordings of conventional SEP and HFOs from the median nerve were performed in all 25 patients. The sensitivity and specificity of Med-SEP, -HFOs and -VHFOs were shown in Table 2. Among these 35 Med-VHFOs waveforms, 6 appeared independent of N20/P22, 26 were superimposed on the first half of N20, and 7 were superimposed on the first half of P22. Typical waveforms of Med-SEP and the magnified waves of Med-VHFOs are shown in Figure 1.

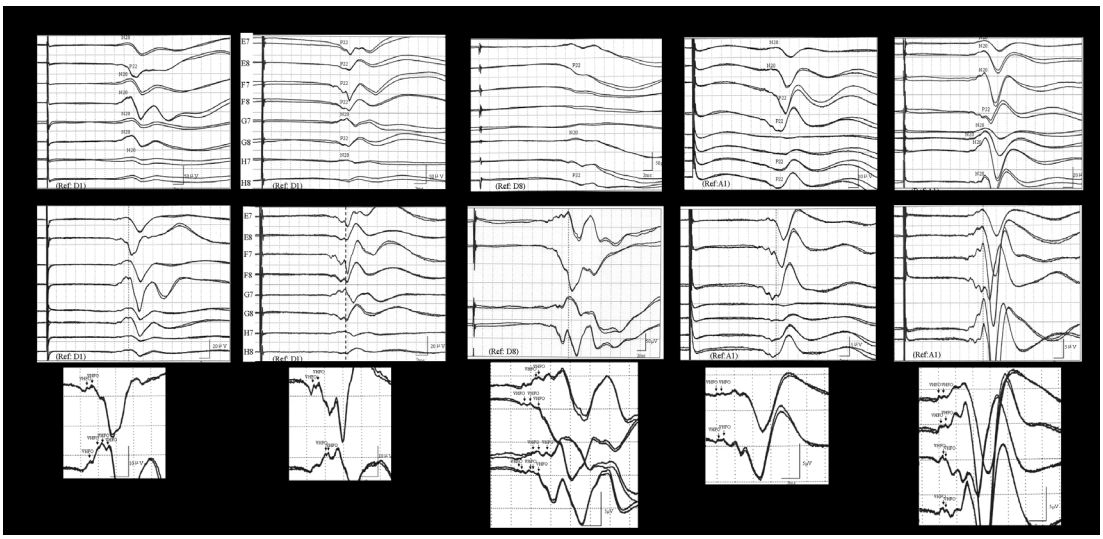

Figure 1. Typical waveforms of conventional SEP, HFOs and VHFOs (magnified) in response to median nerve stimulation in 3 patients who demonstrated Med-VHFOs.
A: Conventional SEP recording following median nerve stimulation. In patient 10, N20 was recorded at E5, F5-6, G5-7, H5-7 and G7, with the maximum response at F6, while P22 was recorded at E6-8, F7-8 and G8. In patient 13, N20 was recorded at C3 and D3, while P22 was recorded at C4 and D5. In patient 15, N20 was recorded at B2-3,C2-4 and D2-5, while P22 was recorded at A4-5, B4-5 and C5. **B**: HFOs recording following median nerve stimulation. N20 peak latencies are marked by dash lines on the figures. All VHFOs preceded the N20 peak. In patient 10, EHFOs were recorded at E5-8, F5-8 and G5-8, and VHFOs were recorded at E6, F6-7 and G7. In patient 13, VHFOs were recorded at C3-4 and D3-4, although no HFOs were observed. In patient 15, EHFOs were recorded at B3-5 and D4, and VHFOs were recorded at B3-4, C3-5 and D5. **C**: The channels showing VHFOs are magnified.

Table 2: Characteristics of SEP, HFOs and VHFOs elicited by median, tibial and ulnar nerve stimulation

		Number of electrodes					Latency (msec)			Dur-VHFOs*	Amp-VHFOs*	Frequency of VHFOs(Hz)	
	Patient	**N20**	**P22**	**EHFOs**	**LHFOs**	**VHFOs**	**N20**	**P22**	**VHFOs**	**(msec)**	**(μV)**	**Minimum**	**Maximum**
Median Nerve	3	17	4	18	5	3	17.60	18.20	15.19	1.28	2.31	1250	2500
	4	3	0	2	0	2	16.50	18.60	13.45	2.15	1.31	1000	5000
	6	2	12	9	12	3	18.40	19.20	14.80	2.13	2.13	1136	2500
	10	7	5	12	1	4	17.40	17.90	14.94	1.16	1.91	1042	2500
	13	2	2	10	10	6	19.28	21.00	15.65	1.09	0.68	1087	2500
	15	9	5	5	0	6	17.24	19.30	14.17	0.58	0.78	1351	2083
	16	6	6	11	1	3	18.04	19.16	14.92	2.61	1.80	1020	3125
	18	2	4	4	4	1	17.60	18.60	14.72	0.72	2.50	1389	1389
	20	1	2	4	11	2	19.60	20.16	16.46	0.98	1.63	1190	1923
	24	8	4	12	11	4	16.90	19.60	12.80	3.60	0.60	1408	2174
	25	7	1	5	3	1	16.50	17.60	14.50	4.00	1.20	1667	2326
	Average	5.82	4.09	8.36	5.27	3.18	17.73	19.03	14.69	1.85	1.53	1231	2663
	Patient	**N20**	**P22**	**EHFOs**	**LHFOs**	**VHFOs**	**N20**	**P22**	**VHFOs**	**Dur-VHFOs**	**Amp-VHFOs**	**Minimum**	**Maximum**
Ulnar Nerve	18	2	2	1	0	1	17.76	18.6	14.24	2.20	2.00	1389	2273
	20	1	3	8	7	2	20.00	21.3	17.04	0.76	0.94	1786	2500
	Average	1.50	2.50	4.50	3.50	1.50	18.88	19.95	15.64	1.48	1.47	1588	2387

*Dur-VHFOs: Duration of VHFOs; Amp-VHFOs: Amplitude of VHFOs.

Locations of Med-SEP, -HFOs and –VHFOs

N20 components were recorded from an average of 5.82 ± 4.67 electrodes, and Med-VHFOs from an average of 3.18 ± 1.72 electrodes. The number of electrodes recording Med-VHFOs tended to be less than that recording N20, although the difference was not statistically significant by paired t-test analysis (t = 1.87, p = 0.09). Med-EHFOs were recorded from an average of 8.36 ± 4.80 electrodes. The number of electrodes recording Med-EHFOs was significantly greater from that recording Med-VHFOs by paired t-test analysis (t = 3.81, p = 0.003). These data suggest that Med-VHFOs are recorded in more restricted regions than N20 and EHFOs.

The results of cortical stimulation and locations of Med-SEP, -HFOs and -VHFOs in the 11 patients who demonstrated VHFOs are shown at Figure 2. The location of central sulcus estimated from N20/P22 was not consistent with that estimated from cortical stimulation except in 3 patients (Patients 6, 18, and 25). On the other hand, all Med-VHFOs were recorded at the postcentral gyrus as determined by cortical stimulation in Patients 3, 6, 8, 10, 18, 20, and 25. In Patients 13, 15, 16, and 24, one to three Med-VHFO responses (D4 in patient 13; B3 and C3 in patient 15; D2, E2, and F2 in patient 16, and I2 in patient 24) were recorded at the precentral gyrus as determined by cortical stimulation. In patient 18, the location of Med-VHFOs (F5) could not be determined by cortical stimulation because neither motor nor sensory response was elicited by cortical stimulation. In patient 4, the location of Med-VHFOs (LTC1 and LTC2) could not be determined by cortical stimulation due to the limited number of electrodes. But all these electrodes in which Med-VHFOs were recorded were identified on postcentral gyrus by 3D-MRI or high resolution CT.

No apparent relationship could be demonstrated between the locations of Med-EHFOs/LHFOs and the central sulcus because Med-EHFOs/LHFOs were distributed in wider areas and did not demonstrate phase reversal.

Latencies of Med -SEP, -HFOs and -VHFOs

The average peak latencies of N20 and P22 were 17.7 and 19.0 msec, respectively, and the average onset latency of Med-VHFOs was 14.7 msec. These data suggest that VHFOs precede the peaks of N20 or P22. The average onset latency of Med-EHFOs was 14.1 msec. There was no significant difference between the latencies of Med-EHFOs and Med-VHFOs (p >0.05).

Frequencies of Med-HFOs and -VHFOs

The frequencies of Med-HFOs ranged from 407 to 909 Hz. The frequencies of Med-VHFOs ranged from 1,000 to 5,000 Hz, with the majority from 1,000 to 2,500 Hz, except for Patient 16 who

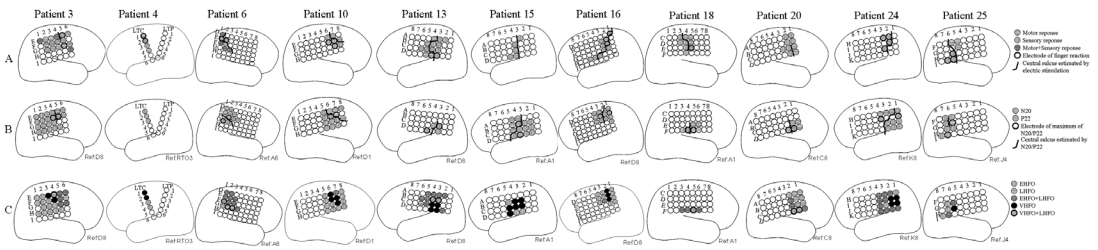

Figure 2. Schematic diagrams showing the results of cortical stimulation and locations of the conventional SEP components, HFOs and VHFOs following median nerve stimulation in 11 patients who demonstrated Med-VHFOs.

A: Schematic diagram showing the localization of cortical functional response from electrical stimulation studies in individual patients. The electrodes in which motor and/or sensory responses were elicited are marked by circles filled with horizontal and vertical lines, respectively. Electrodes from which finger reaction was recorded are denoted by bold circles. The bold lines indicate the location of the central sulcus estimated by electric stimulation. **B**: Results of the conventional SEP. The electrodes from which N20 and P22 were recorded are marked by circles filled with vertical and horizontal lines, respectively. Electrodes from which maximum N20 or P22 were recorded are denoted by bold circles. The bold lines indicate the location of the central sulcus estimated by N20/P22. **C**: Result of HFOs. Electrodes from which EHFOs and LHFOs were recorded are marked by circles filled with vertical and horizontal lines, respectively. Electrodes from which EHFOs and LHFOs were recorded simultaneously are marked by circles filled with gird lines. Electrodes from which VHFOs were recorded are marked by solid circles. Electrodes from which VHFOs and LHFOs were recorded simultaneously are marked by bold circles filled with horizontal lines.

showed a maximum frequency of 3,125 Hz and patient 4 a maximum of 5,000 Hz.

Amplitudes of Med -SEP, -HFOs and -VHFOs

The average amplitudes of N20/P22, Med -HFOs and -VHFOs were 19.8, 6.24 and 1.53 μV, respectively. The amplitude of Med-VHFOs was significantly lower than those of N20/P22 and Med-HFOs ($p<0.01$).

Durations of Med -HFOs and -VHFOs

The average durations of Med-HFOs and -VHFOs were 4.22 and 1.85 msec, respectively. The duration of Med-VHFOs was significantly shorter than that of HFOs ($p <0.01$).

Ulnar nerve SEP, HFOs, and VHFOs

Recordings of conventional SEP and HFOs in response to ulnar nerve stimulation were performed in 5 patients. The sensitivity and specificity of Uln-SEP, -HFOs and -VHFOs were shown in Table 2. Among the three Uln-VHFOs waveforms, one appeared independent of N20/P22, one was superimposed on the first half of N20, and another was superimposed on the first half of P22. Typical waveforms of Uln-SEP and the magnified waves of Uln-VHFOs are shown in Figure 3.

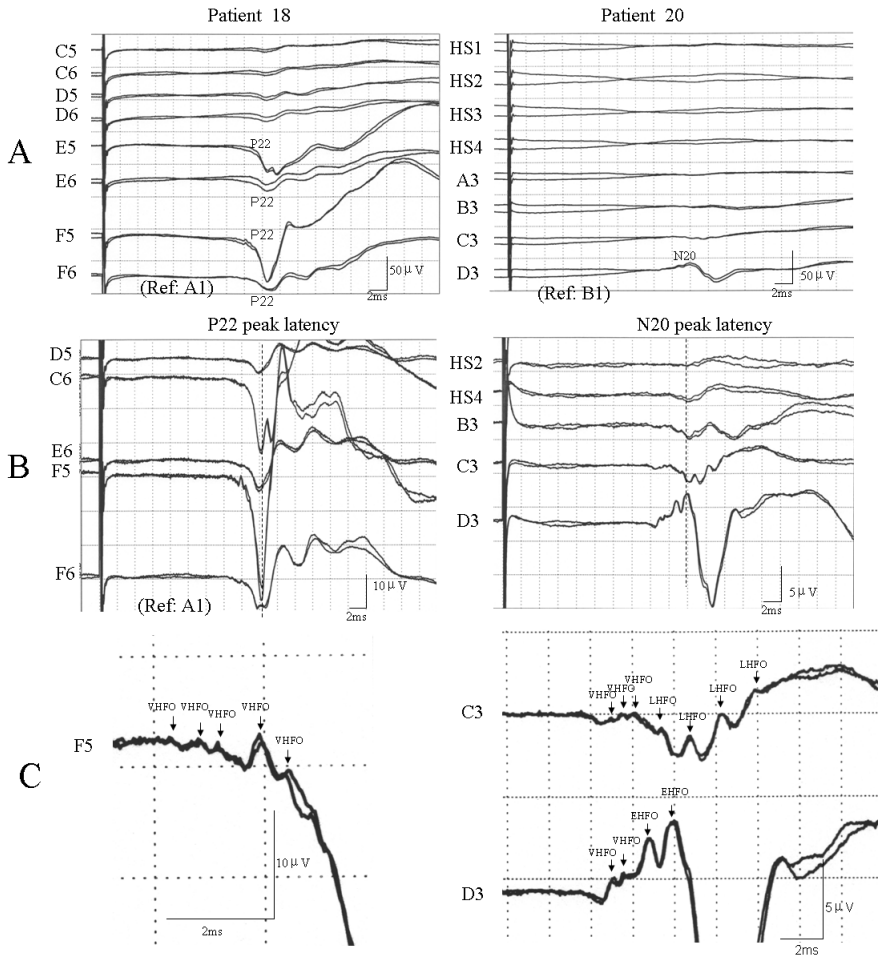

Figure 3. Typical waveforms of conventional SEP, HFOs and VHFOs (magnified) in response to ulnar nerve stimulation in 2 patients who demonstrated Uln-VHFOs.
A: Conventional SEP recording following ulnar nerve stimulation. In patient 18, P22 was recorded at E5-6 and F5-6, with the maximum at F5. In patient 20, N20 was recorded at D3. **B**: HFOs recording following ulnar nerve stimulation. N20 and P22 peak latencies are marked by dash lines on the figures. All VHFOs preceded the N20/P22 peak. In patient 18, EHFOs were recorded at F6 and VHFOs were recorded at electrode F5. In patient 20, EHFOs were recorded at B3 and D3, LHFOs were recorded at C3, and VHFOs were recorded at C3 and D3. **C**; The channels showing VHFOs are magnified.

Locations of Uln -SEP, -HFOs and -VHFOs

Uln-VHFOs were recorded from an average of 1.5 electrodes in two patients (F5 in Patient 18; and C3 and D3 in Patient 20). N20 was also recorded from an average of 1.5 electrodes, and Uln-EHFOs from an average of 4.5 electrodes in the two patients. These results suggest that Uln-VHFOs are recorded in a narrower region than Uln-EHFOs. However, there was no difference in the number of electrodes from which N20 and Uln-VHFOs were identified, possibly due to the small number of patients. Med-VHFOs were also recorded from an average of 1.5 electrodes in these two patients (F5 in Patient 18; D2 and D3 in Patient 20), with no difference in number of electrodes compared to Uln-VHFOs.

The results of cortical stimulation and locations of Uln-SEP, -HFOs and -VHFOs in the two patients who demonstrated VHFOs are shown at Figure 4. Among three Uln-VHFOs responses, two of them were recorded at the postcentral gyrus as determined by cortical stimulation (C3 and D3 in patient 20). The location of the third of them (F5 in patient 18) could not be determined because neither motor nor sensory response was elicited by cortical stimulation. Otherwise, it could be identified to be on postcentral gyrus by 3D-MRI. In Patient 18, all N20 were recorded from the postcentral gyrus, but in Patient 20, two P22 were recorded from the postcentral gyrus. The location of central sulcus estimated by cortical stimulation was inconsistent with that estimated by N20/P22 in Patient 20, but was consistent in Patient 18. No apparent relationship between the location of conventional Uln-HFOs and the central sulcus can be identified, as was also observed on Med-HFOs.

Latencies of Uln -SEP, -HFOs and -VHFOs

The average peak latencies of N20/P22 were 18.9 and 20.0 msec, respectively, and the average onset latency of Uln-VHFOs was 15.6 msec. Uln-VHFOs preceded the peak of N20 or P22. The average onset latency of Uln-EHFOs was 14.3 msec. There was no significant difference between the onset latencies of Uln-EHFOs and Uln-VHFOs. In addition, there was also no significant difference between the onset latency of Med-VHFOs and that of Uln-VHFOs.

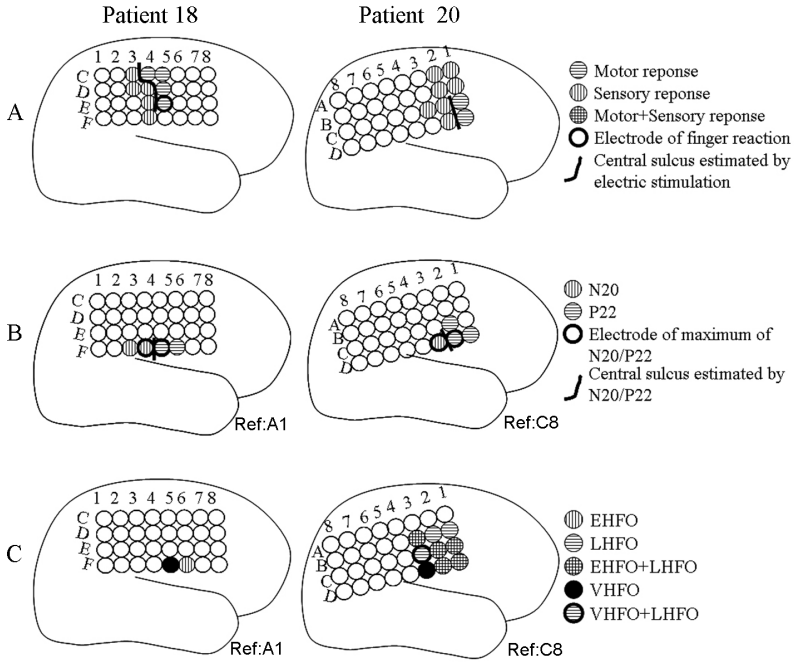

Figure 4. Schematic diagrams showing the results of cortical stimulation and locations of conventional SEP, HFOs and VHFOs following ulnar nerve stimulation in 2 patients who demonstrated Uln-VHFOs. The methods of marking are the same as those of median nerve stimulation.
A: Schematic diagram showing the localization of cortical functional response from electrical stimulation studies in individual patients. **B**: Results of conventional SEP. **C**: Results of HFOs.

Frequencies of Uln-HFOs and -VHFOs

The frequencies of Uln-HFOs ranged from 380 to 988 Hz, and those of Uln-VHFOs from 1,389 to 2,500 Hz. The minimum and maximum frequencies of Uln-VHFOs were not significantly different from those of Med-VHFOs.

Amplitudes of Uln -SEP, -HFOs and -VHFOs

The average amplitudes of Uln -SEP, -HFOs and -VHFOs were 25.3, 5.40 and 1.47 μV, respectively. The amplitude of Uln-VHFOs was significantly lower than those of Uln -SEP and -HFOs ($p < 0.01$). No significant difference in amplitude was detected between Uln-VHFOs and Med-VHFOs.

Durations of Uln -HFOs and -VHFOs

The average durations of Uln-HFOs and -VHFOs were 5.2 and 1.5 msec, respectively. The duration of Uln-VHFOs was significantly shorter than that of Uln-HFOs. No significant difference in duration was found between Uln-VHFOs and Med-VHFOs.

The location of electrodes with VHFOs identified by imaging results

We identified all electrodes in which VHFOs were recorded on postcentral gyrus in patient 4, 6, 10, 13, 15, 18, 20 and 25 by using automated methods based on coregistration, normalization and volume rendering of 3D-MRI imaging data of them. In addition we confirmed the location of postcentral gyrus at electrodes by using the post-operative 3D-MRI imaging data in patient 3 and 16, and high resolution CT (2mm slice thickness) showing the signal voids of electrodes in patient 24.

DISCUSSION

In this study, we recorded SEP, HFOs and VHFOs in response to median and ulnar nerve stimulations from subdural electrodes in patients evaluated for epilepsy surgery. Most of the previous HFOs studies obtained HFOs by applying a digital filter after conventional SEP determinations. In this study, we obtained HFOs by applying an analogue filter to the raw data before averaging during the HFOs and VHFOs recording. We used a higher sampling frequency and recorded directly from subdural electrodes, which allowed us to record waves with high frequency up to 5,000 Hz. In this study, we investigated the characteristics of VHFOs, and attempted to examine their clinical significance.

Location of VHFOs

We recorded VHFOs of three nerves from 1-6 electrodes in different patients. Based on the results of cortical electrical stimulation, VHFOs are generated from a narrow region surrounding the central sulcus althoughnot all Uln- and Med-VHFOs, were recorded in the postcentral gyrus. In Patient 18, Uln- and Med-VHFOs were recorded from F5 at which neither motor nor sensory response was elicited by cortical stimulation. In Patients 15 and 16, several Med-VHFOs were recorded from electrodes at which motor response was elicited by cortical stimulation. As is well known, cortical stimulation may yield false negative result, and both motor and sensory responses may be elicited in the primary somatosensory area.[1] Therefore we cannot exclude the possibility that these electrodes were located on the postcentral gyrus. Interestingly, the location of Med-VHFOs was consistent with that of N20 in these patients except for one electrode (C3 in Patient 15). Therefore, we may also hypothesize that the lesion of cortical dysplasia located around the central sulcus in Patients 15 and 16 might have distorted the distribution of motor or sensory cortex. On the other hand, based on the result of 3D-MRI, almost all electrodes in which VHFOs were recorded located on the postcentral gyrus. Further studies are needed to confirm the precise relationship between the central sulcus and VHFOs.

Latency, frequency, amplitude, and duration of VHFOs

All VHFOs preceded the peaks of the conventional SEP, but there was no significant difference between the latencies of HFOs and VHFOs. The frequencies of VHFOs ranged from 1,000 to 5,000 Hz, with the majority from 1,000 to 2,500 Hz, and were significantly higher than those of HFOs. The average amplitude of VHFOs (1.39 μV) was significantly lower than those of conventional SEP and HFOs, while the average duration of VHFOs (2.06 ms) was significantly shorter than that of HFOs. The characteristics of high frequency, low amplitude and short duration of VHFOs make them outstanding and easily distinguished.

When comparing Med-VHFOs with Uln-VHFOs, most of the characteristics were identical. It should be noted that although the average number of electrodes recording Uln-VHFOs was

apparently smaller than that of Med-VHFOs, the numbers of electrodes recording Uln-VHFOs and Med-VHFOs were the same in two patients who exhibited both Uln- and Med-VHFOs (Patients 18 and 20).

Generators of conventional SEP

For median nerve stimulation, N20 and P22 were regarded as the initial negative and positive cortical components, respectively, of Med-SEP. Some studies identified N20 as generated from SI, and P22 from MI. Therefore, N20 and P22 show phase reversal on the central sulcus.[5,27] Because of this phase reversal, N20/P22 has been suggested to be clinically useful to identify the central sulcus. However, in the present study, the results of cortical stimulation showed that not all N20 were localized at the postcentral gyrus, and not all P22 at the precentral gyrus. A possible reason is that both N20 and P22 generate electrical field over wide regions, and therefore can be recorded in areas at a distance from the generators. In addition, identification of the central sulcus by N20/P22 alone is difficult in some patients probably because of the following reason: (1) The peaks may be distorted by the subsequent components, and the waveform can become very complex. For example, at electrode D4 of patient 13, identification of these components is difficult possibly due to the influence by both N20 and P22; (2) The peaks of N20 and P22 cannot be determined if they appear at the edge of the subdural plate.

Generators of conventional HFOs

According to previous reports, EHFOs are generated by the activity of the terminal segments of thalamocortical fibers reaching area 3b.[13,14,24,28-33] LHFOs have been reported to originate from the intracortical network in area 3b and/or area 4, and reflect the activity of the intracortical inhibitory network.[16,24,25,28-37] Our previous study has demonstrated that the distribution of HFOs is not narrow, and indicated that the HFOs might not show clear phase reversal on the central sulcus (Sakura *et al.,* 2009). Therefore, it could also be assumed that both EHFOs and LHFOs are not limited to area 3b, but may be generated in other areas such as the association cortices surrounding SI, suggesting limited clinical usefulness of HFOs. In the present study, we also identified both HFOs from median, ulnar and tibial nerves, and all were recorded in wide areas surrounding MI and SI. Therefore, we confirm that HFOs has limited clinical utility in identification of the central sulcus.

Generators of VHFOs

Fedele T *et al* detected 1 kHz human SEP (VHFOs) non-invasively and mapped their scalp distribution using a dedicated low-noise set-up. They speculated that their topographies indicate a set of subcortical/cortical generators, at least partially distinct from the topography of the 600 Hz sigma-bursts (HFOs) described previously.[38] In this study, all VHFOs were recorded within a limited area surrounding the SI corresponding to the stimulated sites. Compared to EHFOs and LHFOs, the distribution of VHFOs is significantly narrower, the duration is significantly shorter, and the amplitude is significantly smaller. Hence, we speculate that VHFOs are not only the faster components of EHFOs/LHFOs, but may have different generators from EHFOs/LHFOs. The generators of VHFOs could not be concluded in this study. However, judging from their characteristics, especially the distribution, we assume that the generators might be around SI, most likely within or very close to the somatotopically equivalent area of SI. The frequency of VHFOs can be over 2,000 Hz. Very high frequency activities similar to VHFOs have been recorded in the epileptogenic zones using subdural electrodes in epilepsy patients.[39] In neuronal cells, an absolute inactive phase is about 2 msec, and the upper limit of the neuronal discharges is about 500 Hz. Therefore, it is impossible that these very fast activities are generated by a single synchronized neuronal group. Explanation of these very high frequency components should assume multiple neuronal units consisting of at least four to five groups. These groups should be time-locked to the peripheral electrical stimulation, but should be firing independent of each other. Further studies are needed to identify the generators and the mechanisms of VHFOs.

The clinical significance of VHFOs

In epilepsy surgery, it is very important to identify the location of central sulcus because destroying or resection of primary motor and somatosensory area could cause the loss of moving and sense function irreversibly. However, it is difficult to identify the location of central sulcus by the naked eye during operation because of the limitation of operation area and the variability of some patients. Cortical stimulation was considered as the gold standard previously, but the limitation of age and false negative rate are the unavoidable problem. 3D-MRI was a new method but it is infeasible

as routine examination due to the complicate technique and expensive electrodes which is acceptable in MRI room. As described above, VHFOs are supposed to be localized within or very close to SI, which are more specific than SEP or HFO, and are more specific than cortical stimulation for the identification of SI. The location of the central sulcus can be identified easily by the edge of SI. So, VHFOs would be clinically useful to identify location of the central sulcus in epilepsy surgery.

CONCLUSION

In this study, we directly recorded VHFOs using subdural electrodes, which allowed us to further study Med-VHFOs and report for the first time Uln-VHFOs. VHFOs were recorded within a very narrow region around the central sulcus, and most of them were localized at the postcentral gyrus. We hypothesize that VHFOs may be generated only from the primary somatosensory cortex, and can be utilized to localize the central sulcus.

REFERENCES

1. Penfield W, Jasper H. Epilepsy and the Functional anatomy of the human brain. Boston: Little, Brown and Company Publishing, 1954.
2. Allison T, McCarthy G, Wood CC, *et al.* Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. *J Neurophysiol* 1989; 62:694-710.
3. Balzamo E, Marquis P, Chauvel P, *et al.* Short-latency components of evoked potentials to median nerve stimulation recorded by intracerebral electrodes in the human pre- and postcentral areas. *Clin Neurophysiol* 2004; 115:1616-23.
4. Desmedt JE, Nguyen TH, Bourguet M. Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses. *Electroencephalogr Clin Neurophysiol* 1987; 68:1-19.
5. Lüders H, Lesser RP, Hahn J, *et al*. Cortical somatosensory evoked potentials in response to hand stimulation. *J Neurosurg* 1983; 58:885-94.
6. Maccabee PJ, Pinkhasov EI, Cracco RQ. Short latency somatosensory evoked potentials to median nerve stimulation: effect of low frequency filter. *Electroencephalogr Clin Neurophysiol* 1983; 55:34-44.
7. Eisen A, Roberts K, Low M, *et al*. Questions regarding the sequential neural generator theory of the somatosensory evoked potential raised by digital filtering. *Electroencephalogr Clin Neurophysiol* 1984; 59: 388-95.
8. Emerson RG, Sgro JA, Pedley TA, *et al*. State-dependent changes in the N20 component of the median nerve somatosensory evoked potential. *Neurology* 1988; 38:64-8.
9. Yamada T, Kameyama S, Fuchigami Y, *et al*. Changes of short latency somatosensory evoked potential in sleep. *Electroencephalogr Clin Neurophysiol* 1988; 70:126-36.
10. Emori T, Yamada T, Seki Y, *et al*. Recovery functions of fast frequency potentials in the initial negative wave of median SEP. *Electroencephalogr Clin Neurophysiol* 1991; 78:116-23.
11. Maegaki Y, Najm I, Terada K, *et al*. Somatosensory evoked high-frequency oscillations recorded directly from the human cerebral cortex. *Clin Neurophysiol* 2000; 111:1916-26.
12. Sonoo M, Genba-Shimizu K, Mannen T, *et al*. Detailed analysis of the latency of subcomponents of the P13/P14 and N20 potentials. *Electroencephalogr Clin Neurophysiol* 1997; 104:296-311.
13. Curio G1, Mackert BM, Burghoff M, *et al*. Somatotopic source arrangement of 600 Hz oscillatory magnetic fields at the human primary somatosensory hand cortex. *Neurosci Lett* 1997; 234:131-4.
14. Hashimoto I, Mashiko T, Imada T. Somatic evoked high-frequency magnetic oscillations reflect activity of inhibitory interneurons in the human somatosensory cortex. *Electroencephalogr Clin Neurophysiol* 1996; 100:189-203.
15. Ozaki I, Suzuki C, Yaegashi Y, *et al*. High frequency oscillations in early cortical somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1998; 108:536-42.
16. Gobbelé R, Buchner H, Curio G.. High-frequency (600) Hz SEP activities originating in the subcortical and cortical human somatosensory system. *Electroencephalogr Clin Neurophysiol* 1998; 108:182-9.
17. Sakura Y, Terada K, Usui K, *et al*. Very high-frequency oscillations (over 1000 Hz) of somatosensory-evoked potentials directly recorded from the human brain. *J Clin Neurophysiol* 2009; 26:414-21.
18. Emerson RG1, Sgro JA, Pedley TA, *et al*. State-dependent changes in the N20 component of the median nerve somatosensory evoked potential. *Neurology* 1988; 38:64-8.
19. Fujii M, Yamada T, Aihara M, *et al*. The effects of stimulus rates upon median, ulnar and radial nerve somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1994; 92:518-26.
20. Grisolia JS, Wiederholt WC. Short latency somatosensory evoked potentials from radial, median and ulnar nerve stimulation in man. *Electroencephalogr Clin Neurophysiol* 1980; 50:375-81.
21. Ikeda H, Leyba L, Bartolo A, *et al.* Synchronized spikes of thalamocortical axonal terminals and cortical neurons are detectable outside the pig brain with MEG. *J Neurophysiol* 2002; 87:626-30.
22. Lesser RP, Gordon B. Methodologic considerations in cortical electrical stimulation in adults. In: Lüders HO, Noachtar S, eds: Epileptic seizures: Pathophysiology and clinical semiology. Philadelphia, PA: Churchill Livingstone Publishing 2000:153-65.
23. Allison T, McCarthy G, Wood CC, *et al*. Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve: are view of scalp and intracortical recordings. *Brain* 1991; 114:2465-503.

24. Haueisen J, Schack B, Meier T, *et al*. Multiplicity in the high-frequency signals during the short-latency somatosensory evoked cortical activity in humans. *Clin Neurophysiol* 2001; 112:1316-25.
25. Klostermann F, Nolte G, Losch F, *et al*. Differential recruitment of high frequency wavelets (600 Hz) and primary cortical response (N20) in human median nerve somatosensory evoked potentials. *Neurosci Lett* 1998; 256:101-4.
26. Kovalev D, Spree J, Honeqqer J, *et al*. Rapid and fully automated visualization of subdural electrodes in the presurgical evaluation of epilepsy patients. *Am J Neuroradiol* 2005; 26:1078-83.
27. Allison T1, McCarthy G, Wood CC, *et al*. Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. *J Neurophysiol* 1989; 62:694-710.
28. Baker SN, Curio G, Lemon RN. EEG oscillations at 600 Hz are macroscopic markers for cortical spike bursts. *J Physiol* 2003; 550:529-34.
29. Halbonia P, Kaminski R, Gobbele R, *et al*. Sleep stage dependent changes of the high-frequency part of the somatosensory evoked potentials at the thalamus and cortex. *Clin Neurophysiol* 2000; 111:2277–84.
30. Ikeda H, Wang Y, Okada YC. Origins of the somatic N20 and high-frequency oscillations evoked by trigeminal stimulation in the piglets. *Clin Neurophysiol* 2005; 116: 827-41.
31. Klostermann F, Funk T, Vesper J, Curio G. Spatiotemporal characteristics of human intrathalamic high-frequency (400 Hz) SEP components. *Neuroreport* 1999*;* 10:3627-31.
32. Klostermann F, Nolte G, Curio G.. Multiple generators of 600 Hz wavelets in human SEP unmasked by varying stimulus rates. *Neuroreport* 1999; 10:1625-29.
33. Restuccia D, Ulivelli M, De Capua A, *et al*. Modulation of high-frequency (600 Hz) somatosensory-evoked potentials after rTMS of the primary sensory cortex. *Eur J Neurosci* 2007; 26:2349-58.
34. Curio G, Mackert BM, Burghoff M, *et al*. Localization of evoked neuromagnetic 600 Hz activity in the cerebral somatosensory system. *Electroencephalogr Clin Neurophysiol* 1994; 91:483-7.
35. Gobbelé R, Buchner H, Scherg M, *et al*. Stability of high-frequency (600 Hz)components under variation of stimulus rate--evidence for a thalamic origin. *Clin Neurophysiol* 1999; 110:1659-63.
36. Gobbelé R, Waberski TD, Thyerlei D, *et al*. Functional dissociation of a subcortical and cortical component of high-frequency oscillations in human somatosensory evoked potentials by motor interference. *Neurosci Lett* 2003; 350:97-100.
37. Hashimoto I, Kimura T, Fukushima T, *et al*. Reciprocal modulation of somatosensory evoked N20m primary response and high-frequency oscillations by interference stimulation. *Clin Neurophysiol* 1999; 110:1445-51.
38. Fedele T, Scheer HJ, Waterstraat G, *et al*. Towards non-invasive multi-unit spike recordings: Mapping 1kHz EEG signals over human somatosensory cortex. *Clin Neurophysiol* 2012; 123:2370-76.
39. Usui N, Terada K, Baba K, *et al*. Very high frequency oscillations (over 1000Hz) in human epilepsy. *Clin Neurophysiol* 2010; 121:1825-31.