High-frequency Somatosensory Evoked Potentials of Normal Subjects

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Abstract-

Background: We investigated the characteristics and correlates of high-frequency oscillations (HFOs) of somatosensory evoked potentials (SEPs).

Methods: Subjects were 26 healthy volunteers. SEP was recorded from the hand sensory area contralateral to the median nerve stimulated at the wrist. HFOs were obtained by digitally filtering raw SEPs from 500 to 1000 Hz, and their amplitudes and area-under-curve, duration, and number of negative peaks were measured. We also measured amplitudes of the N20 onset-peak (N20o-p), and N20 peak-P25 peak (N20p-P25p).

Results: In normal subjects, several oscillation potentials were observed at the latency of 0 to 10 ms after the onset of N20. The mean number of negative peaks of total HFOs was 6.96 ± 1.20 (early phase 3.36 ± 0.62; late phase 3.60 ± 1.14). The mean maximal amplitude of total HFOs was 0.16 ± 0.07 μV (early phase 0.14 ± 0.05 μV; late phase 0.15 ± 0.07 μV). The mean duration of total HFOs was 10.19 ± 1.98 ms (early phase 4.89 ± 1.04 ms; late phase 5.31 ± 1.95 ms). The mean area of total HFOs was 567.54 ± 227.86 μV·ms (early phase 268.46 ± 98.40 μV·ms; late phase 299.08 ± 183.44 μV·ms). The amplitude ratio was 7.30 ± 3.32% of HFO_{early}/$N20_{o-p}$, 3.19 ± 1.55% of HFO_{late}/N20-P25, and 3.54 ± 1.84% of HFO_{total}/N20p-P25. During the test, the amplitude of HFO was significantly reduced by drowsiness.

Conclusions: In waking subjects, a burst of low-amplitude HFO can be extracted from the N20.

Key Words: Somatosensory evoked potential, High-frequency oscillation, Median nerve

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INTRODUCTION

Somatosensory evoked potentials (SEP) study provides important information of sensory cortical processing. It has been demonstrated that the N20 component of median nerve SEP reflects initial excitation of neurons in Brodmann area 3b[1,2]. Using digital high-pass filtering (> 400 Hz), a burst of low-amplitude (< 500 μV)

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high-frequency (300-900 Hz) oscillations can be extracted[3]. Such high-frequency oscillations (HFOs) could be recorded not only from the cortex but also from the thalamus, the thalamocortical radiation, and the thalamocortical terminals[4-9]. In the study of median nerve SEPs, HFOs are superimposed in time onto the primary cortical response (N20), but are functionally independent SEP components[6,10].

The generator of HFOs is still uncertain and has been proposed as the thalamus, the thalamocortical fibers or the postsynaptic activities in the primary sensory cortex[5,6,8,11,12]. The studies on the median nerve-stimulated HFOs in humans suggest that HFOs reflect presynaptic activities in the thalamocortical projection fibers and activities in inhibitory interneurons of the 3b cortex[3,4,6]. It is also speculated that the oscillations represent localized burst activities of GABAergic inhibitory interneurons in the sensory cortex[8]. More recently, based upon the magoencephalography (MEG) and electroencephalogaphy (EEG) experiments, the HFO was regarded as being composed of two different parts, one peaking during the ascending slope of the N20 and the second during the descending slope[13-15]. The early one (early-phase HFO) is thought to be of pre-cortical origin in the terminals of thalamocortical radiation fibers, the late one (late-phase HFO) seems to be intrinsically generated by postsynaptic contributions from intracortical S-I or by inhibitory interneurons[7,9,15,16].

HFOs have been studied in several ways: their modulations by arousal changes[17], movements[18], drugs[10,19-21], their recovery function[22,23], effects of transcranial magnetic stimulation on them[24] and also their changes in patients with various neurological diseases[15,16,25-27]. HFO provides an opportunity to monitor the timing of highly synchronized and rapidly repeating neurons generated in the human somatosensory system. Here, the purpose of the study was to set up the HFO parameters of our laboratory.

MATERIALS AND METHODS

Subjects

We recruited twenty-six healthy individuals (9 men, 17 women, mean age: 31.2 ± 6.5). They were all free from neurological diseases or any known systemic diseases. The purpose of the study was explained to every subject, and the informed consent was obtained before recruitment. This study protocol was approved by the Institutional Review Board of the hospital.

SEP and HFO recording

For SEP recording, subjects were asked to lay supine on a bed, and were instructed to keep alert through the test. The amplitude of HFO was monitored as the index of alertness. A warning was given when the amplitude of HFO decreased up to 20%. 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 region served as a reference. Electrode impedances were less than 5 kΩ. A trial of 1000 stimuli was collected for average each SEP, and two successive SEPs were obtained under the same conditions to ascertain the reproducibility of SEPs.

For separation and isolation of the HFOs from the underlying N20 primary cortical responses, the wide-band (0.5-2000 Hz) recorded responses were analyzed offline. A fast Fourier transformation (FFT) for frequency of the wide-band SEP was performed, and it showed two energy loci. The main signal energy was distributed broadly between 20 and 300 Hz with a peak around 40-60 Hz, and a weaker signal energy was found between 600-900 Hz with a peak around 680 Hz (Fig. 1). Via invert FFT, we could digitally filter the original SEP into low-pass (0.5-500 Hz), and high-pass (500-1000 Hz) trains.

For identification of the HFOs, the wavelets after the onset of primary cortical response with an amplitude of twice or more than that of the background noise level were considered as the signal.

Data analysis

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

HFOs were divided into early phase and late phase base on N20p. The HFOs from N20o to N20p were regarded as early HFOs, and the late HFOs were those later than the N20p. We then measured the maximal peak-to-baseline amplitude, the area-under-curve, which was measured as the total area of positive and negative deflections from the baseline, duration, and the number of wavelets of both components.

RESULTS

Following stimulations of the median nerve, the original wide-band (0.5-2000 Hz) SEP recordings showed some small inflections superimposed on the N20 response (Fig. 2A). After band-pass of 0.5 - 500 Hz (Fig. 2B), and band-pass of 500 - 1000 Hz (Fig. 2C) filtering, the HFOs were isolated and could be easily recognized in all subjects. The HFOs started approximately at or after the onset of the primary cortical responses (N20o) and ended between the middle and the end of the second slope, showing several peaks. The parameters of HFOs are shown in Table.

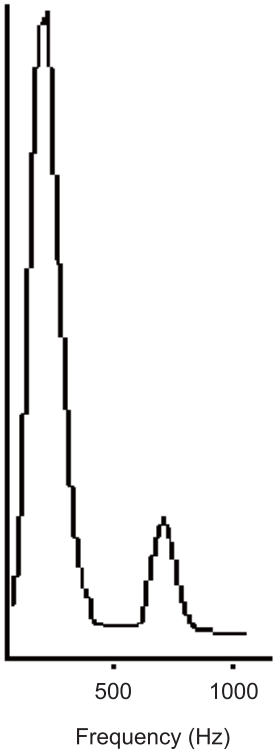

Figure 1. The power spectrum is illustrated on a linear scale in which the abscissa is frequency of the signals and the ordinate indicates the signal energy in an arbitrary unit.

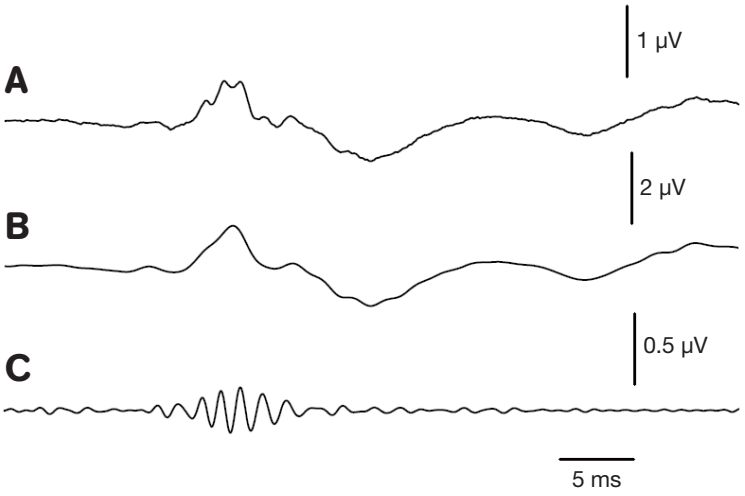

Figure 2. Low- and high-frequency somatosensory evoked potentials of a 36 year-old healthy man.

Table. *Parameters of high-frequency oscillations (HFOs) and the primary cortical response following median nerve stimulation*

HFO number of negative peaks	
Early	3.36 ± 0.62
Late	3.60 ± 1.14
Total	6.96 ± 1.20
HFO amplitude (μV)	
Early	0.14 ± 0.05
Late	0.15 ± 0.07
Total	0.16 ± 0.07
HFO duration (ms)	
Early	4.89 ± 1.04
Late	5.31 ± 1.95
Total	10.19 ± 1.98
HFO area (μV·ms)	
Early	268.46 ± 98.40
Late	299.08 ± 183.44
Total	567.54 ± 227.86
$N20_{o-p}$ amplitude (μV)	2.03 ± 0.75
$N20_p$-P25 amplitude (μV)	5.29 ± 2.49
$HFO_{early}/N20_{o-p}$ amplitude ratio (%)	7.31 ± 3.32
$HFO_{late}/N20_p$-P25 amplitude ratio (%)	3.19 ± 1.55
$HFO_{total}/N20_p$-P25 amplitude ratio (%)	3.54 ± 1.84

HFO: high frequency oscillations.

In one subject, it was noted that the N20 and HFO changed in the condition of vigilance (Fig. 3). In the state of drowsiness, the peak amplitudes were decreased and their onset latencies were prolonged, especially in the HFO. In addition, the phase number of HFO also decreased.

Fig. 4 shows that the difference between two healthy men could be due to aging. The amplitude of the primary cortical response and the HFOs/N20 amplitude ratio were smaller for the young than those of the aged man (Fig. 4). The duration of N20 was longer in the aged man. The number of negative peaks, amplitudes, duration, and area of the late HFO were larger in the aged man.

DISCUSSION

Our results showed that the late HFOs tended to have more negative peak waves, higher amplitudes, longer durations and larger areas as compared to the early HFOs. These findings are consistent with the routine SEP findings that the amplitude of N20o-P25 is usually higher than that of P15-N20o in normal subjects. Higher amplitude is usually associated with a longer duration[12].

Early HFOs are originated from presynaptic thalamocortical projections, and late HFOs arise from the intracortical inhibitory GABAergic interneurons located within the parietal cortex[8]. HFO exerts inhibition to the pyramidal neurons, the early HFO through feed forward mechanism and the late HFO through feed back mechanism[8,28,29]. Because of different mechanisms, they do not always behave a same response in an event, such as in the sleep[3,8,30].

In our study, we observed the effect of vigilance on HFOs in some subjects (Fig. 3). In the literatures, HFOs were usually diminished during sleep whereas the N20 persisted[3,8,30]. Similar findings were noted in the study of drug usage. Propofol is an anesthetic agent. Its administration slows the scalp HFO from 640 Hz to 480 Hz and reduced its amplitude up to 28%[10]. However, the underlying low-frequency SEP components (N20) did not change significantly. In contrast, the HFOs are enhanced by central activating agents. Modafinil is a vigilance-promoting agent and rivastigmine is an inhibitor of central acetylcholinesterase. Although their administration did not affect the latency and the amplitude of N20, both enhanced the HFO activities[20,21]. These findings suggest that the scalp HFOs in part reflect the somatosensory arousal activities and are subcortically generated at the thalamic level[11,30].

Although we did not have enough sample number to analyze the aging effect, our case observation tended to prove that the HFO amplitudes were higher in the aged subject[28] (Fig. 4). The effects of aging on SEPs have been extensively studied[31-33]. The short latencies of cortical response tend to be larger in the aged and present with a pattern of a U-shaped curve. The amplitudes are higher in the adolescent group, lower in the middle-age

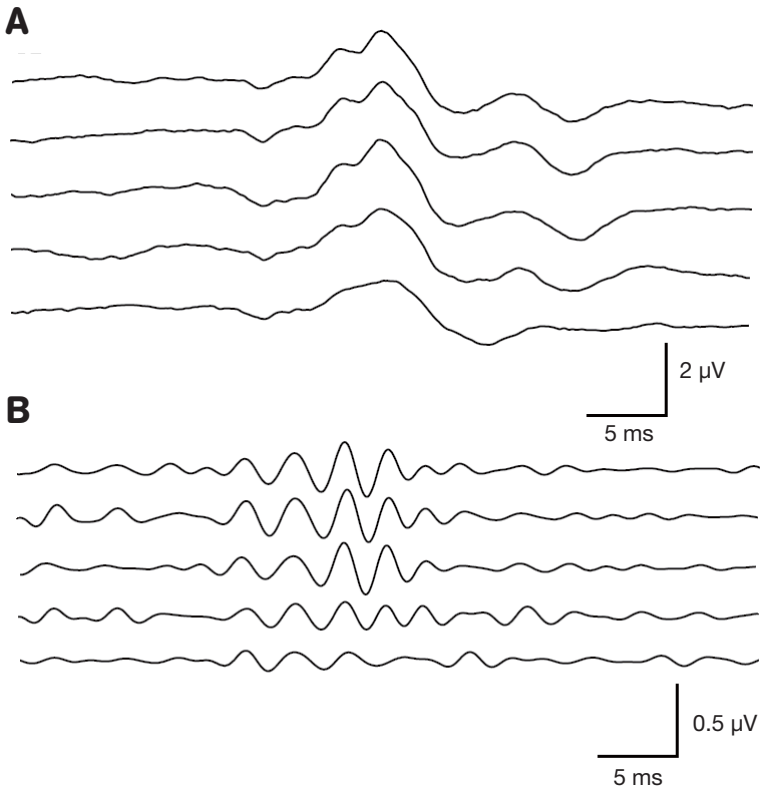

Figure 3. Effects of the vigilance on low- and high-frequency somatosensory evoked potentials.

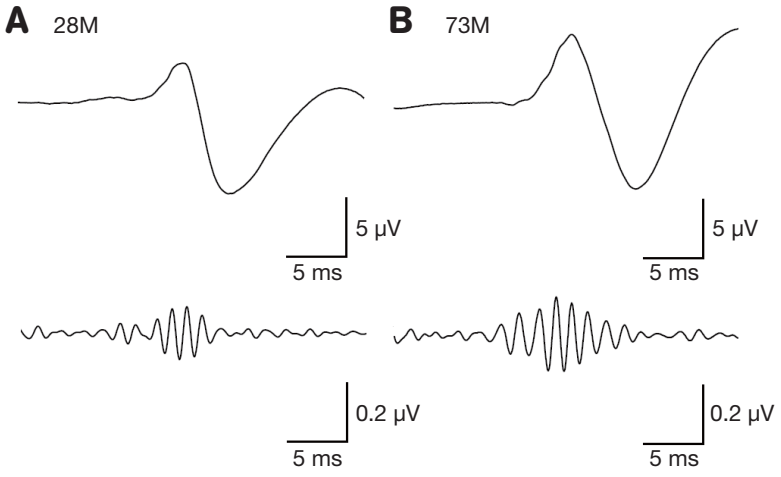

Figure 4. A comparison of low- and high-frequency somatosensory evoked potentials between a 28 year-old young man and a 73 year-old aged man.

group, and became higher again in the old-age group. The aging effect on somatosensory evoked HFOs was also studied by Nakano et al.[28]. In their study, the late HFOs had higher amplitude, longer duration and larger area and more number of negative peaks in the aged subjects. However, there is no difference in the early HFO between the young and the aged groups. The longer duration and larger number of negative peaks in HFOs in

the aged subject are probably due in part to the longer duration of the primary response as a result of increased variability in the conduction velocity of the sensory pathways with a temporal dispersion, degradation of inhibiting mechanism, and a relative insensitivity of the pyramidal neurons to the feed-back inhibitory input[28].

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