TRANSLATIONAL PHYSIOLOGY

Very Fast Oscillations Evoked by Median Nerve Stimulation in the Human Thalamus and Subthalamic Nucleus

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1Toronto Western Research Institute, University Health Network, 2Division of Neurology, Department of Medicine, 3Department of Physiology, and 4Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, Ontario M5T 2S8, Canada

Submitted 8 April 2004; accepted in final form 27 July 2004

Hanajima, Ritsuko, Robert Chen, Peter Ashby, Andres M. Lozano, William D. Hutchison, Karen D. Davis, and Jonathan O. Dostrovsky. Very fast oscillations evoked by median nerve stimulation in the human thalamus and subthalamic nucleus. J Neurophysiol 92: 3171–3182, 2004. First published May 19, 2004; doi:10.1152/jn.00363.2004. Very fast oscillations (VFOs; 500–1,500 Hz) are often observed with sensory-evoked potentials (SEPs), but their origin is unknown. To characterize the origins of VFOs, we studied 35 patients with deep brain stimulation (DBS) electrodes [15 with thalamic and 20 with the subthalamic nucleus (STN) electrodes]. We recorded median nerve stimulation–evoked SEPs from the thalamus and STN with microelectrodes during stereotactic surgery and from the contacts of the DBS electrodes postoperatively. We also examined the firing of individual neurons in the thalamus in relation to the VFOs. In the thalamus, VFOs with frequencies around 1,000 Hz were superimposed on slow potentials. Both slow and fast SEP components showed phase reversals in the somatosensory thalamus (ventralis caudalis Vc). Median nerve poststimulus time histograms showed that single thalamic neurons fired at preferred times at intervals between 0.8 to 1.2 ms that were synchronous with the VFOs, although the neurons fired once or a few times per trial. In the STN, low-amplitude SEPs with VFOs were observed at a latency similar to the thalamic SEPs. The STN was identified as the source of the VFOs from the volume conduction, possibly from the medial lemniscus. We conclude that the thalamic VFOs are generated within Vc and that they induce time-locked firing in a network of neurons.

INTRODUCTION

Very-high-frequency oscillatory activity (>500 Hz) associated with sensory evoked potentials [very fast oscillations (VFOs)] can be recorded in many levels of the somatosensory system (Calvin and Loeser 1975; Curio et al. 1994; Hashimoto et al. 1996; Ikeda et al. 2002; Kato et al. 2003). Components with frequencies of 500–700 Hz can be recorded from the human sensory cortex (S1) superimposed on the N20 wave (cortical potentials recorded from the scalp) (Curio 2000; Curio et al. 1994; Hashimoto 2000; Hashimoto et al. 1996). These VFOs are thought to be generated in the S1 by signals from thalamocortical terminals (Ikeda et al. 2002) and cortical inhibitory interneurons (Hashimoto et al. 1996; Jones et al. 2000; Kandel and Buzsáki 1997), although the mechanisms underlying the synchronization are not known. VFOs have also been observed in thalamus as small notches superimposed on positive sensory-evoked potentials (SEPs) recorded with microelectrodes or the contacts of deep brain stimulation (DBS) electrodes in the human thalamus (Katayama and Tsubokawa 1987; Klostermann et al. 1999; Morio et al. 1989). The thalamic VFOs have a higher frequency and shorter onset latency from median nerve stimulation than those from the cortex. Although it has been hypothesized that thalamic VFOs originate within or near the sensory thalamus and involve different generators from the VFOs of the S1 (Klostermann et al. 2000, 2002), this remains to be confirmed. Furthermore, the possible relationship between median nerve stimulation evoked neuronal responses and the VFOs has not been examined.

The aim of this study was to characterize the origin of the thalamic VFOs and their relationship, if any, with neuronal firing. Median nerve-evoked SEPs have also been reported in the subthalamic nucleus (STN), probably generated by activity in the medial lemniscus or thalamus, and so it is also of interest to determine whether VFOs can be observed in the STN. In this study we report the analysis of median nerve evoked SEPs and single unit responses recorded in the thalamus and STN with microelectrodes and from contacts of DBS electrodes (for SEPs) postoperatively.

METHODS

Subjects

We studied 35 patients undergoing surgery and programming for chronic DBS of the thalamus or the STN (Table 1). Ten patients had DBS macroelectrodes implanted in the nucleus ventrointermedialis of the thalamus (Vim; cerebellar thalamus) for the treatment of tremor, 5 patients who suffered chronic pain had DBS electrodes implanted in the nucleus ventrocaudalis of the thalamus (Vc; sensory thalamus), and 20 patients with Parkinson’s disease had contacts targeted to the STN bilaterally. The poststroke pain patients had lesions in sites that did not directly affect thalamus. In 17 patients, the effects of median nerve stimulation on neuronal firing were also examined. All patients gave free and informed consent to the procedures approved by the University Health Network Research Ethics Board.

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TABLE 1. Patients undergoing chronic DBS of the thalamus or STN

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<th>No.</th>
<th>Age</th>
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<th>DBS</th>
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<td></td>
<td></td>
<td></td>
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<tr>
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<td>70</td>
<td>M</td>
<td>ET</td>
<td>L</td>
<td>–</td>
<td>+</td>
</tr>
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<td>R</td>
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<tr>
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<td>+</td>
</tr>
<tr>
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<td>L</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
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</tr>
<tr>
<td>9</td>
<td>56</td>
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<tr>
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<td>46</td>
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<td>Pain (lumbar spinal cord infarction)</td>
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<tr>
<td>1</td>
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<td>PD</td>
<td>R/L</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>PD</td>
<td>R/L</td>
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</tr>
<tr>
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<td>M</td>
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<td>PD</td>
<td>R/L</td>
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</table>

DBS, deep brain stimulation; STN, subthalamic nucleus; L, left; R, right; M, male; F, female; +, data acquired; –, no data acquired; ET, essential tremor; PD, Parkinson’s disease.

Surgical procedures

The targets were identified by MRI and located stereotactically (Davis et al. 1998; Tasker 1998). The use of microelectrode recordings to assist DBS electrode placement in the thalamus has previously been described in detail (Davis et al. 1998; Lenz et al. 1988; Tasker and Kiss 1995). For thalamic DBS placements, a tentative initial target was selected in the ventrocaudal nucleus (Vc), equivalent to VPLc in the monkey, where the hand representation was expected at 4–5 mm above to about 15 mm lateral to the midline. Neuronal recordings were obtained from 10 mm above to the tip of the electrode. The tip of the DBS electrodes targeted to Vim was often located in Vc. For 3–7 days after electrode implantation, the wires from each of the four contacts were led out through the scalp and could be connected to an amplifier for recording local field potentials and SEPs. At the second surgery, the leads were connected to an implanted programmable stimulator.
**Median nerve SEPs**

RECORDING POTENTIALS FROM DBS MACROELECTRODES, NECK, AND SCALP. These recordings were made in the few days between the two surgical procedures in 33 patients (Table 1). The subjects lay relaxed on a comfortable bed in an air-conditioned room. Stimuli (a square-wave pulse with duration of 0.2 ms and intensity 1.1–1.2 times the motor thresholds) were given to the median nerve at the wrist at 2 Hz. Ag-AgCl surface cup electrodes were placed on several points including NC (nonpeptidergic reference on the contralateral shoulder), CS2 (second cervical spine), Fz (midline frontal), and Cpc (centroparietal electrodes contralateral to the median nerve stimulation; International 10–20 system). Bipolar derivation of CS2–Fz was used to record N13 (potential generated in the cuneate nucleus) (Allison and Hume 1981; Araki et al. 1997; Desmedt and Cheron 1981; Kaji et al. 1986; Morioka et al. 1991; Sonoo et al. 1999). The derivation CPC–NC was used to evaluate P13/14 (potential generated in the medial lemniscus). These derivations are based on studies of patients with focal lesions. Cortical potentials (N20) were evaluated using CPC–Fz. Recordings from the four contacts (0, 1, 2, 3) of the DBS electrode were made with monopolar nonpeptidergic configurations (0-NC, 1-NC, 2-NC, 3-NC) and bipolar recordings (0–1, 1–2, 2–3). Responses were amplified and filtered between 2 and 2,500 Hz and sampled at 20 kHz. Two contiguous trials of 2,000 stimuli were averaged (Signal, Cambridge Electronic Design, Cambridge, UK), and the two averages were superimposed to confirm the reproducibility of the potentials. Latencies were measured to the peak and are expressed as the mean ± SD of all subjects. For analysis of the high-frequency components (VFOs) of SEPs from DBS contacts (see RESULTS), the band-pass filter was changed to 500–2,500 Hz using Scan software (Neuросcan Labs). The largest VFO was defined as the largest negative wave detected. The frequency of the VFOs was calculated from the mean interval between reproducible peaks. The amplitude of the VFOs was defined as the difference between the most negative and most positive peak.

RECORDING POTENTIALS FROM MICROELECTRODES. We recorded field potentials and responses of single units elicited by median nerve stimulation from microelectrodes during the operation. The parylene-C–coated tungsten microelectrodes had an exposed tip size of 15–25 μm, and the tips were plated with gold and platinum to reduce the impedance to about 0.1–0.5 MΩ at 1 kHz. We used two microelectrodes separated horizontally by 600 μm. The stimulating and recording techniques for evoked potentials were similar to those used for the DBS electrode recordings except that band-pass filters were 10 Hz to 5 kHz for the field potentials and 500 Hz to 5 kHz for single unit responses (GS3000 system, Axon Instruments, Foster City, CA). Slow wave averages and poststimulus histograms were calculated for 140–200 repetitions of the stimulus (at 2 Hz), using Spike2 software.

To compare field potentials recorded with microelectrodes to the results of VFOs from macroelectrodes, we digitally changed the band-pass to 500 Hz to 2.5 kHz (Spike 2, Cambridge, UK) and obtained the averaged field responses. The sampling rate was 12–15 kHz. In two patients, the averaged potentials were recorded at several successive depths 1 mm apart.

We also recorded responses of cells to median nerve stimulation. In Vc, we studied tactile cells, which responded to tactile stimuli to the contralateral hand. In the STN, we studied cells that reacted to passive joint movements in the hand. The same stimulation was used as for the macroelectrodes recording. Data were stored and analyzed off-line (Spike 2). Poststimulus time histograms (PSTHs) triggered by the median nerve stimulation were made from the single-unit data. We also analyzed the interspike intervals.

**MRI**

Every patient had postoperative three-dimensional MRI of the brain to identify the location of each DBS contact using a high-resolution T2-weighted fast spin echo sequence developed to reduce magnetic susceptibility artifacts and minimize noise (Saint-Cyr et al. 2002). The position of the contacts in relation to the anterior commissure (AC) and posterior commissure (PC) and the height from the AC–PC line were determined. We then compared the amplitudes, polarities, and latencies of the SEPs recorded bipolarly from adjacent contacts of the DBS electrode with the locations of the center of contact artifacts determined from MRI scans.

**RESULTS**

**SEPs from thalamus**

POETENTIALS FROM DBS CONTACTS RECORDED POSTOPERATIVELY. Recordings of median nerve stimulation–evoked SEPs from DBS electrodes were made from 15 sites in 14 patients. Figure 1A shows examples of SEPs recorded from the scalp and from the contacts of a DBS electrode in one patient (case 1). Between CS2 and Fz, we recorded a N13 potential with a latency of 15.9 ms. A N20 potential was evoked at a latency of 24.8 ms in CPC–Fz channels. From the contacts of the DBS electrode in the thalamus (Thal 0–1, 1–2, 2–3), large potentials were recorded. The latency of the peak of the positive potential was 19.6 ms, which was between the latencies of N13 and N20 in this patient.

The small high-frequency oscillations superimposed on the slow thalamic potentials in Fig. 1A are shown in Fig. 1B with higher gain (top 3 traces). When the signal is band-pass filtered between 500 and 2,500 Hz, the VFOs become more obvious (Fig. 1B, bottom 4 traces). The VFOs occurred throughout the duration of the large negative potentials with peak latency of 19.6 ms starting at about 15 ms and extending to 25 ms, and their amplitude corresponded approximately to the amplitude of the SEP at each point on the potential. The frequency of the VFOs in this subject varied from 1 to 1.4 kHz.

Combining the results from all the patients, the mean latency of the first clear VFO was 14.8 ± 1.5 (SD) ms. The difference between the latencies of the first VFO and the N13 was 0.2 ± 0.3 ms. The oscillation with the largest peak tended to be located in the middle of the VFOs. The latency of the largest oscillation was 17.3 ± 1.9 ms (2.9 ± 1.1 ms later than N13), which was similar to the peak latency of the slow component of the thalamic potentials (17.7 ± 1.9 ms; 2.9 ± 0.6 ms later than N13). The duration of the VFOs was 9.2 ± 2.7 ms. The frequency of the VFOs was 1.408 ± 170 Hz (at a band-pass of 500–2,500 Hz). When we changed the band-pass filtering to 500–1,500 Hz as in previous studies (Klostermann et al. 1999, 2000, 2002), some of the smaller waves of the VFOs disappeared, and the frequency was about 1,000 Hz. In 3 of 15 recordings, both the slow components of thalamic potentials and the VFOs showed phase reversal at the same contact (Fig. 2A, *). In the other 12 recordings, there was no phase reversal of the slow component; however, in 9 of these cases, the VFOs showed phase reversal (Fig. 2B, *).

Figure 3 plots the absolute values of the amplitude of SEPs recorded from each of the three pairs of DBS contacts as a function of their vertical distance from the AC–PC line and their distance anterior or posterior to PC for all elec-
trodes. The mean values of all points are shown as filled circles. Both the slow component of the SEPs and the SEP VFOs recorded from the thalamus showed maximum amplitude around the AC-PC line in the vertical axis (Fig. 3, A and C) and just anterior to the PC in the anterior-posterior axis (Fig. 3, B and D).

**Intraoperative recordings**

**FIELD POTENTIALS.** Twenty-four monopolar microelectrode recordings referenced to the ground were obtained in seven thalamic patients. Figure 4 shows an example of the averaged field potentials recorded from a microelectrode at successive depths 1 mm apart in response to median nerve stimulation in one patient (case 11; 0 mm is the level of the AC-PC line calculated with preoperative MRI). Single-unit recordings in this patient revealed responses to tactile stimuli to the contralateral hand from 0 to 3 mm above the AC-PC line. At 0 mm, the cells responded to brushing of the second digit, suggesting that the electrode was in the Vc. At 2 mm below the AC-PC line, electrical stimulation at 300 Hz through the microelectrode evoked parasthesia in the entire contralateral half of the body. This site was considered to be in the medial lemniscus (ML). VFOs can be seen superimposed on the slow waves and become more obvious when the band-pass filter is changed to 500–5,000 Hz. The VFOs of the evoked field potentials recorded from the microelectrode had the largest amplitude between 1 and 2 mm (Fig. 4A). When the differences between SEPs recorded at successive sites were computed (Fig. 4B), phase reversal of VFOs occurred at the same position as the phase reversal of the slow components of SEPs (0 mm). The amplitudes of these potentials were largest from the sites close to the AC-PC line. We obtained similar positive waves for the slow component of the SEP with VFOs around the AC-PC line from the other 23 recordings.

**UNIT RECORDINGS.** We recorded the activity of seven single Vc neurons responding to the median nerve stimulation in six patients. Figure 5 shows the PSTH of the firing of a single unit (Fig. 5A) and the averaged field potentials (Fig. 5B) recorded by the microelectrode. Four peaks were detected in the PSTH (Fig. 5A), and they tended to occur 1.0–1.6 ms apart. The peaks of the VFOs shown in Fig. 5B appear to be closely related to the firing of the single unit as
can be seen in the raster plot (Fig. 5C) and PSTH (Fig. 5A). These PSTH peaks were not caused by repetitive firings of the single cell as can be seen in the raster plot (Fig. 5C), which shows that the cell usually only fired once per stimulus. Additionally the interspike interval histogram (Fig. 5D) shows that there were only a small number of short intervals and none <2 ms. The occurrence of spikes in response to median nerve stimulation usually corresponded with one of the peaks of the VFOs. The VFOs recorded with the microelectrodes, although not identical to the VFOs recorded subsequently with DBS contacts in the same patient, showed similar features (Fig. 5E, see also Fig. 7).

Figure 6 shows an example of a neuron responding to median nerve stimulation with a brief burst of spikes (Fig. 6A). A PSTH of the unit’s discharges using all spikes aligned to median nerve stimulation indicates multiple peaks with shorter intervals (0.4–1.2 ms) than the intervals within the bursts (Fig. 6B), similar to those of the peaks in the averaged field potential waveform. Furthermore, a PSTH aligned to median nerve stimulation constructed using only the first spike in the burst response showed multiple peaks with short intervals, between 0.6 and 1.2 ms (Fig. 6C). This indicates that firing within the burst and its onset are related to VFOs recorded in the field potential. In contrast, in time histograms triggered by the first spike of each burst, the interval between the first and the second spikes was around 2.6 ms and that between the second and the third spikes was around 2.8 ms (Fig. 6D). These intervals were longer than those of the VFOs or PSTH peaks, indicating that VFOs cannot be accounted for by the timing of spikes within the bursts.

Similar VFOs were obtained from the five other single units. PSTHs to median nerve stimulation also revealed multiple peaks with intervals between 0.4 and 1.6 ms (0.9 ± 0.25 ms). The mean onset latency of the first PSTH peak was 16.1 ± 2.7 ms (2.6 ± 2.2 ms later than N13). In the seven patients who had both intraoperative and DBS recordings, the latency of the largest peak in the PSTH was 17.7 ± 2.4 ms, which was 4.2 ± 1.8 ms later than the N13 peak and 1.1 ± 0.3 ms later than the peak of the slow component of the thalamic potentials from DBS electrodes.

We compared the latency of the peaks of the PSTH for different neurons in different locations within a patient. For this purpose, we used both single and multiple unit activity (n = 16 sites). Figure 7 shows multiple unit PSTHs from three different sites in a single patient (+4 mm, +4 mm
from another microelectrode separated by 600 μm, +4.5 mm). All three PSTHs showed multiple peaks. The top two PSTHs show peaks at a similar latency. The lowest PSTH was derived from a single unit that had slightly different latencies. In each case, the negative peaks for the lower contact on the traces representing the averaged analogue waveform corresponded to the latencies of the PSTH peaks. Although the peak latencies were slightly different in the three traces, the frequency of the peaks was similar and the peaks of VFOs from the DBS electrode were related to the peaks recorded with microelectrodes.

**SEPs from the STN**

Recordings in STN were made from 17 patients (32 sides). An example of the SEPs recorded from scalp and STN electrodes is shown in Fig. 8A. Small potentials with the lower contact being more negative were recorded from the contacts of the DBS electrode (STN 0–1, 1–2, 2–3). The latency (20.1 ms) was between the latency of the N13 (16.5 ms) and N20 (22.0 ms). Very small VFOs were superimposed on the small potentials and could be seen more clearly with a band-pass of 500–2,500 Hz (Fig. 8B). The amplitude of the VFOs was highest at STN 0–1, while the small slow component had the highest amplitude at STN 2–3. There was no phase reversal of the slow waves or VFOs. The latency of the largest VFO (16.6 ms) was earlier than the peak of the slow component (20.1 ms) and was similar to the latency of N13 (16.5 ms).

Similar results were obtained from all patients. The phase and the latency of the VFOs recorded from each pair of contacts in the DBS electrode were similar. The largest amplitude of the VFOs and the slow components of SEP were recorded at different contacts.

The mean latency of the first peak of the VFOs from contact 0–1 was 15.2 ± 1.5 ms. This was 0.4 ± 0.3 ms later than the N13 latency. The largest VFO was usually the first
The latency of the largest VFO from STN 0–1 was 16.1 ± 1.7 ms, which was 1.3 ± 0.7 ms later than N13. These latencies were significantly shorter than those of the peak of the slow component from STN 2–3 (17.9 ± 1.4 ms; Student’s paired t-test, P < 0.001). The difference in latencies between the largest VFO and N13 was significantly shorter for STN 0–1 than for the thalamus (Student’s t-test, P < 0.01).

The interval between the peaks of the VFOs from the STN 0–1 was 0.74 ± 0.14 ms. Therefore the mean frequency of the STN VFOs was about 1,400 Hz. This frequency was similar to the frequency of the VFOs from the thalamus described above (Student’s t-test, P > 0.05). The latencies of the peaks of the VFOs recorded in the STN were the same from each of the contacts in a given patient.

The potentials from STN were much smaller than those from the thalamus. MRI confirmed that the DBS electrodes in STN were more anterior and deeper than those in the thalamus. The slow components of the SEPs from the STN tended to be recorded from higher contacts than those showing VFOs. We detected larger slow components from STN2-3 than from STN 0–1 (paired Student’s t-test, P < 0.05), and larger VFOs were obtained from STN0-1 than from STN 2–3 (paired Student’s t-test, P < 0.01). These findings suggest that these two potentials originated from different structures. PSTHs of single units in the STN did not show preferred timing of unit firing.

**DISCUSSION**

**SEPs recorded with electrodes in the human thalamus have VFOs**

The SEPs recorded from DBS contacts in the thalamus in response to median nerve stimulation have both slow and fast components. The slow components likely arise from excitatory postsynaptic potentials (EPSPs) in thalamic neurons (Hanajima et al. 2004; Katayama and Tsubokawa 1987; Morioka et al. 1989). The fast components (1,000–1,400 Hz) are best seen with a band-pass filter of 500–2,500 Hz. The VFOs recorded from the thalamus are not artifacts due to bipolar recordings, because similar VFOs were detected with noncephalic NC recordings.

There have been several reports of VFOs associated with the SEP in the thalamus (Katayama and Tsubokawa 1987; Klostermann et al. 1999; Morioka et al. 1989). The frequency of the VFOs we recorded (1,408 ± 170 Hz) was slightly faster than
those previously reported (about 1,000 Hz) (Klostermann et al. 1999, 2000, 2002). This was probably because we used a high-frequency cut-off of 2,500 or 5,000 Hz. When the high-frequency cut-off was changed to 1,500 Hz as used by Klostermann et al. (1999, 2000, 2002), some of the smaller and narrower peaks were filtered out, and the frequency of the VFOs was reduced to about 1,000 Hz. It is noteworthy that the period between oscillations varies somewhat during the oscillatory event.

VFOs are generated in the sensory thalamus (Vc)

The VFOs we recorded showed phase reversal between DBS contacts straddling the thalamus (Fig. 1); their amplitudes were largest near to the AC-PC line (Fig. 3), i.e., at the level of the sensory thalamus. We recorded similar VFOs with microelectrodes, and these also had phase reversals in the Vc (Fig. 4). Klostermann et al. (2002) observed that the amplitude of the VFOs with monopolar recordings decreased with distance from the thalamus, and there was no phase reversal 10–20 mm above the target position. They suggested that VFOs were generated in the thalamus probably by the thalamocortical projection neurons (Klostermann et al. 2002). Our data provide direct support for this hypothesis. In addition, the microelectrode recordings (e.g., Fig. 4) showed that the VFOs were fairly constant in amplitude over a distance of about 4 mm, which corresponded to Vc, but their amplitude dropped off rapidly above and below this region. Interestingly, in some patients, part of the VFOs reversed their phases, but the slow components did not show phase reversal at the same contact, thus suggesting that the generators of the slow and the fast components of SEPs are not identical.

VFOs from DBS electrodes

Even though the contacts of the DBS electrode were much larger than the microelectrodes, the shape and timing of the VFOs recorded with DBS contacts correspond to those recorded with microelectrodes. Although there were differences in the detailed structure of the VFOs at different sites within Vc...
(e.g., Figs. 5E and 7), the major components were very similar, suggesting a large degree of synchrony between the generators. This is consistent and necessary to be able to record these VFOs from the large contacts of the DBS electrode, which essentially provide an average of the local field potentials generated in the region of the electrode. However, the fact that there are subtle differences when examining the recordings from the microelectrode indicates that there are probably local zones within which the neurons are more tightly synchronized.

**Preferred firing times of neurons in the Vc thalamus are related to the VFOs**

The most novel and instructive part of this study was the observation that neuronal firing was highly correlated with the VFOs (Figs. 5–7). Although the neurons do not fire to each successive oscillation, when they do fire, their action potentials are highly correlated with the oscillation, even though they may only fire once or twice to each stimulus as shown in Fig. 5. This observation suggests that the VFOs may either determine the exact time of firing of neurons in Vc or that the firing of Vc neurons is somehow timelocked in a repetitive pattern and gives rise to the oscillatory VFO.

One possible explanation is that the VFOs are generated by the action potentials comprising the response to stimulation. However, this would require that the neurons fire in a high-frequency burst following each stimulus and that these bursts would be very similar in timing among different neurons so that summation would occur to give rise to the widespread oscillatory LFPs. This mechanism is unlikely to be the case since, except for neurons in CL, thalamic neurons (Steriade and
Glenn 1982; Steriade et al. 1993) do not display such high-frequency bursts. CL is very unlikely to be source of these potentials since it does not receive a projection from the medial lemniscus and also our data point to Vc as the source. In our recordings, the frequency of the burst discharge for those neurons in Vc that responded in a burst was much lower (e.g., Fig. 6).

A second possibility is that some other and unknown mechanism generates the VFO, and these LFP oscillations tend to synchronize the firing of the neurons, so that when they do discharge, the time of discharge is modulated by the phase of the oscillation and occurs near the peak of membrane depolarization. This hypothesis predicts that at least part of the oscillatory LFP results from membrane oscillations of the neurons in Vc. Perhaps the VFOs result from a high-frequency resonance phenomenon in the Vc region, but it remains a mystery how and why these would be generated and synchronized. It has been hypothesized that gap junctions may play a role in high-frequency synchronization between neurons in the cortex and in the dorsal lateral geniculate nucleus of the thalamus (Hughes et al. 2002). Hughes et al. (2002) reported that the thalamocortical neurons in the cat dorsal lateral geniculate nucleus were electrotonically coupled via gap junctions, with spikelets representing attenuated action potentials from adjoining cells. However, even electrotonic conduction via gap junctions involves some delay and may not be fast enough (e.g., Traub et al. 1999) to mediate the very high-frequency oscillatory activity observed in thalamus.

Our findings are similar to those recently observed in animal studies in the somatosensory cortex. For example, Barth (2003) reported that the neuronal responses to vibrissa stimulation are time-locked to the VFO field potentials elicited by the same stimuli. Blockade of cortical inhibitory circuits by application of the GABA antagonist bicuculline fails to block these cortical VFOs, indicating that inhibitory interneurons are not involved (Jones and Barth 2002). In the hippocampus, there are also VFOs termed ripples, although...
their frequency is much lower (200–400 Hz) than those observed in thalamus, and these may be generated by a similar mechanism to those generated in thalamus and cortex. It has been suggested that population ripples in hippocampus may be generated by a mechanism involving axonal gap junctions (Traub et al. 1999).

**VFOs from the STN**

We examined the STN because sensory input is known to modify the firing characteristics of some STN neurons as they respond to passive or active movements. VFOs from the STN have not been examined in detail in previous studies. Small slow waves and VFOs can be recorded with DBS contacts in the STN following median nerve stimulation. However, the largest VFOs were obtained at different positions compared with where the slow wave component of the SEPs was localized. Although it has been suggested that the N18 component of the SEP from median nerve stimulation originates from the STN (Pesenti et al. 2003), the slow components are likely to represent volume conduction from the thalamus (Dinner et al. 2002; Hanajima et al. 2004), because their amplitude is largest at the upper contacts (nearest to the thalamus), and they do not show phase reversal and have a latency similar to slow components recorded in the thalamus.

The VFOs, on the other hand, were largest at the lowest contacts and did not show phase reversal. The latencies of the largest VFOs in the lowest contacts in the STN were shorter than those of thalamic VFOs, and the position where the VFOs were largest was below Vc. Recording from single units in the STN did not show preferred firing timing in PSTHs following median nerve stimulation at short latency (0–30 ms). These findings suggest that the VFOs recorded in the STN represent volume conduction from another source, possibly the ML in the midbrain.

**Potential role of VFOs in sensory functions**

VFOs have been observed at several sites in the somatosensory system such as the cuneate nucleus (Canedo et al. 1998; Rasmussen and Northgrave 1997), the thalamus, and S1 (Curio 2000; Curio et al. 1994; Hashimoto 2000; Hashimoto et al. 1996), as well as in other systems. Although the frequency of oscillation differs by region, the underlying mechanisms and function may be similar. VFOs have also been observed in response to natural stimuli (Baker et al. 2003; Barth 2003) and thus appear to be a normal manifestation of brain function. The function and consequence of such VFOs is unknown but may be to synchronize and perhaps prolong important inputs, thus increasing the signal-to-noise ratio.

**ACKNOWLEDGMENTS**

We thank Dr. F. Skinner (Department of Medicine and Institute of Biomaterials and Biomedical Engineering, University of Toronto) for useful comments.
This work was supported by Canadian Institutes of Health Research Grants 85102 to P. Ashby, MOP15128 to R. Chen, MOP-42505 to J. O. Dostrovsky, National Institute of Neurological Disorders and Stroke Grant RO1 NS-40872 to J. O. Dostrovsky, and the Japan Society for the Promotion of Science to R. Hanajima.

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