SECOND ANTONIO BORSELLINO COLLEGE ON NEUROPHYSICS: INCLUDING 25-26 MAY SYMPOSIUM ON "Plasticity of Sensory-Motor Systems"

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Miramare - Trieste, Italy

Computing the meaning of neural activity

Mikhail Lebedev
National Institute of Health Animal Center
Poolesville- MD - USA
Window discriminator is the most commonly used technique for single-unit recordings.

Disadvantage: only the best isolated units can be discriminated (i.e., sampling bias).

More sophisticated techniques:

1. Raw Record
2. Template Definition
3. Cluster Cutting
4. Sorted Waveforms
Peristimulus Time Histogram (PSTH)
Averaging spike counts across a number of trials (PSTH analysis) is used to determine task engagement of a unit. Units that exhibit average firing rate modulation in relationship to task events are classified as task related.

What about the fine temporal structure of neuronal spike trains? Does it represent a code? How can this code be investigated?
Rhythmic

Bursty

Tonic nonrhythmic

(The illustrated spike trains have equal mean firing rates)

trigger = 1, 2, 3, ...

Autocorrelation histogram describes spike occurrence probability at a certain time following a given spike

Autocorrelation histogram can identify the temporal firing pattern
Figure 3.2. Types of primary somatosensory cortical neurons.

A: Examples of expectation density histograms for rhythmically firing, nonrhythmically firing and bursty neurons. B: Circular diagram showing proportions of high-frequency vibratory sensitive (HFVS) and vibration-entrained (non-HFVS) neurons for the group of rhythmically firing neurons. C&D: Circular diagram showing proportions of rhythmically firing, nonrhythmically firing, bursty neurons and neurons with firing rate less than 10 spike/s for groups of vibration-entrained neurons and HFVS neurons, respectively.
Crosscorrelation histogram

spike train 2

spike train 1

n-1 n n+1

Next n

Common Input

Neuron 1

Neuron 2

Stimulus

Effective Connectivity

Spike train 1

Stimulus A

A ≠ B

Spike train 2

Stimulus B

CCH - Predictor, normalization

Correlated and normalized CCH

Correlation Coefficient
Joint ISI Plot

Positive Serial Correlation During Smooth ISI Modulations

Joint ISI Plot

Diagonal Band In Case of Rhythmic Firing with Interrupting Spikes

ISI Shuffling

(Autocorrelation Histogram --> Renewal Density)
Figure 6.1. Records for a rhythmically firing neuron entrained to a 27 Hz vibration

This neuron was located in a cortical area different from SI (possibly in SII; histological reconstructions have not been done yet). No clear receptive field was found. No-move trials are illustrated. Vibration was turned on for 1000 ms. A: Scattergram of interspike intervals. B: Histogram of activity. C: Raster of discharges. D: Phase scattergram. E-F: joint interval scattergrams for the consequent epochs of activity.
A. ISIs by Trial
B. Ranked by Trial Mean
C. Joint ISI Plot
D. Normalized ISI Plot
FIG. 3. Experimental EMG fragments (bottom) and corresponding estimates of EMG power and rectified EMG spectra (top, right); voluntary contraction of the soleus muscle was maintained on the back.}

In the rectified EMG spectrum, the peak is present in the frequency (100 Hz), while the peak is revealed by spectrum peaks at vibration frequencies. For a higher vibration (40 Hz), the influence due to vibration (a) and 40 Hz (b), the influence due to vibration of 100 Hz ground of vibration with a frequency of 100 Hz in the rectified EMG power spectrum (top, right).
Response variations of total power did not exceed ±15%. The EOG spectrum preceded the diminishment of the T reflex. The deterioration of the peak in the rectified EMG spectra (note the absence of spectral peaks in the compression) was conducted each 5 min after the onset of the vibrotactile stimulation (65 Hz) and the registration of the T reflex. The recordings of EMG during the course of ischemic block. The recordings of EMG during

Figure 2.1. Schematics of the manipulandum, the feedback display, and the task.

Figure 4.1. Cortical location of vibration-entrained neurons.

A: A digitized view of the dorsolateral surface of the brain (monkey H). The brain has been tilted 30° in the coronal and sagittal planes. Central sulcus (CS) and intraparietal sulcus (IP) are marked. B: A composite showing the relative location of recording sites. The locations of penetrations for monkeys C, F, and G were transposed into the surface map of the most extensively studied monkey (H). C: Representative parasagittal sections, indicating the location of neurons at three levels (lateral [L], intermediate [I], and medial [M]) are shown in C.
Figure 4.3. Epochs of neuronal activity.

A: Different epochs of neuronal activity in this reaction time paradigm. Background firing preceded vibratory stimulus onset. After a transitory response to the stimulus, a stabilized response was observed. Premovement activity then occurred (one or two events of mean firing rate change). The onsets of second events, if present, usually were close to electromyographic activity onset. B: Different types of premovement activity and the number of cases for which they were observed.
Table 4.1. Characteristics of Background Activity and Vibratory Responses

<table>
<thead>
<tr>
<th>Group of Neurons</th>
<th>Cutaneous RFs</th>
<th>Deep RFs</th>
<th>Not Tested for RF</th>
<th>All</th>
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<tr>
<td>Background Firing Rate (spikes/s)</td>
<td></td>
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<tr>
<td>Background Firing Rate (spikes/s)</td>
<td>21.5 ± 11.0*1</td>
<td>30.2 ± 13.5*1</td>
<td>37.5 ± 12.6</td>
<td>28.2 ± 13.6</td>
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<td>N = 20</td>
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<td>N = 9</td>
<td>N = 55</td>
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Latency of Vibratory Response (ms)

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<th></th>
<th>27 Hz</th>
<th>57 Hz</th>
<th>127 Hz</th>
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<tr>
<td>27 Hz</td>
<td>26.1 ± 7.3</td>
<td>23.5 ± 7.5</td>
<td>24.6 ± 10.0</td>
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<tr>
<td>N = 16</td>
<td>N = 17</td>
<td>N = 20</td>
<td>N = 14</td>
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<tr>
<td>27 Hz</td>
<td>27.0 ± 9.2</td>
<td>21.8 ± 8.6</td>
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<tr>
<td>N = 17</td>
<td>N = 26</td>
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<tr>
<td>27 Hz</td>
<td>28.8 ± 14.9</td>
<td>24.0 ± 6.3</td>
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<tr>
<td>27 Hz</td>
<td>28.8 ± 8.9*</td>
<td>22.8 ± 7.8</td>
<td>22.3 ± 8.8</td>
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<tr>
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Stabilized MFR (spikes/s)

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<tr>
<td>27 Hz</td>
<td>51.8 ± 18.3</td>
<td>45.7 ± 26.1</td>
<td>19.4 ± 11.4**3</td>
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<tr>
<td>N = 16</td>
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<tr>
<td>27 Hz</td>
<td>44.3 ± 13.9</td>
<td>48.6 ± 22.3</td>
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<tr>
<td>27 Hz</td>
<td>46.3 ± 20.0</td>
<td>54.3 ± 25.9</td>
<td>30.0 ± 31.6</td>
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<td>27 Hz</td>
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<td>N = 37</td>
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Stabilized Synch

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<tr>
<td>27 Hz</td>
<td>0.39 ± 0.18</td>
<td>0.39 ± 0.18</td>
<td>0.22 ± 0.17**2</td>
</tr>
<tr>
<td>N = 12</td>
<td>N = 17</td>
<td>N = 10</td>
<td>N = 14</td>
</tr>
<tr>
<td>27 Hz</td>
<td>0.39 ± 0.16</td>
<td>0.38 ± 0.15</td>
<td>0.26 ± 0.14**2</td>
</tr>
<tr>
<td>N = 16</td>
<td>N = 24</td>
<td>N = 14</td>
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<tr>
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<td>0.29 ± 0.11</td>
<td>0.32 ± 0.16</td>
<td>0.20 ± 0.10</td>
</tr>
<tr>
<td>N = 4</td>
<td>N = 9</td>
<td>N = 2</td>
<td>N = 2</td>
</tr>
<tr>
<td>27 Hz</td>
<td>0.38 ± 0.17</td>
<td>0.37 ± 0.16</td>
<td>0.24 ± 0.15*</td>
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<tr>
<td>N = 32</td>
<td>N = 50</td>
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Values represent mean ± standard deviation. N is the number of neurons. Significant level for both one-factor ANOVA with the Scheffé comparison test and Mann-Whitney U-test are shown: * p < 0.05; ** p < 0.01. 1 different from other RF type in the row; 2 different from other vibratory frequencies in the column; 3 different from all other combinations of RF type and vibratory frequency. The sample for calculating Synch is less than that for other parameters because cases with bimodal phase distribution were excluded.
Figure 4.9. Average traces for premovement activation.

Average traces of mean firing rate, mean phase, and synchronicity for premovement activation (A) and correlation analyses of activation onsets and onsets of mean phase (B) and synchronicity (C) changes. For averaging, the appropriate traces were centered on the onset of mean firing rate shift. Zero-phase in displays (B) was chosen arbitrary. In (C), data for F-statistics for linear regression and Spearman rank correlation analyses are shown.
Figure 4.10. Average traces for premovement suppression.

Conventions as in Figure 4.9.
Figure 5.1. Cortical locations of high-frequency vibratory sensitive neurons.

A: A drawing of the dorsolateral view of the brain. CS - central sulcus; IPS - intraparietal sulcus. B: A table showing the number of vibration-entrained and non-entrained neurons recorded in areas 3a, 3b, 1 and 2. C: Locations of recording sites for four monkeys (surface maps of electrode penetrations and sagittal sections through the cortex showing the neurons' locations).
Fig. 4A–E Spike train analyses of neuronal responses to 127-Hz vibration for three vibration-entrained neurons. A Histograms of activity aligned on vibration onset (bin width 5 ms; wrist flexion trials). Cortical locations of neurons, their types according to the degree of vibratory entrainment, movement directions, mean firing rates, and vibratory response latencies are indicated. B Raster displays of discharges. Trials are ordered by reaction time. C Histograms of interspike intervals (bin width 0.5 ms). D Joint interval scattergrams. E Cycle distribution histograms (bin width 10°). Vector representations of cycle distribution histograms are shown as insets. Mean vector lengths are indicated.
Fig. 5A–E  Spike train analyses of neuronal responses to 127-Hz vibration for three non-entrained neurons. Conventions as in Fig. 4.
Fig. 6A–F Analyses of the magnitudes and latencies of vibratory responses. A–C Plots depict mean firing rates during the hold period, 57-Hz and 127-Hz vibratory stimulation for E1 (A), E2 (B), and NE (C) neurons. D,E Scattergrams indicating latencies of the responses to 127-Hz (D) and 57-Hz (E) vibration for neurons of different types (E1, E2, NE), and cortical locations (areas 3a, 3b, 1, and 2). F Means and standard deviations of vibratory response latency by cortical location, neuronal type, and vibratory frequency.
Vibration-Entrained and Premovement Activity in Monkey Primary Somatosensory Cortex

MICHAEL A. LEBEDEV, JOHN M. DENTON, AND RANDALL J. NELSON
Department of Anatomy and Neurobiology, University of Tennessee, College of Medicine, Memphis, Tennessee 38163

SUMMARY AND CONCLUSIONS

1. Primary somatosensory cortical (SI) neurons exhibit characteristic activity before the initiation of movements. This premovement activity (PMA) may result from centrally generated as well as from peripheral inputs. We examined PMA for 55 SI neurons (10, 13, 28, and 4 in areas 3a, 3b, 1, and 2, respectively) with activity that was entrained to vibratotactile stimulation (i.e., was temporally correlated with the stimulus). We sought to determine whether the temporal characteristics of vibration-entrained discharges would change throughout the reaction time period, and, if they did, whether these changes might be accounted for by central inputs.

2. Monkeys made wrist flexions and extensions in response to sinusoidal vibration (27, 57, or 127 Hz) of their palms. Vibration remained on until the animal moved at least 5° from the initial hold position. Mean firing rate (MFR), a measure of the level of activity, was derived from the number of spikes per vibratory cycle. The correlation between the vibration and the neuronal firing was described by the mean phase (MP) of the vibratory cycle at which spikes occurred. The degree of entrainment was quantified as synchronicity (Synch), a statistical parameter that could change from 0 for no entrainment to 1 for responses at a constant phase.

3. Premovement MFR increases (activation) and decreases (suppression) were observed. Moreover, two changes in MFR were often observed for the same neuron (2-event PMA). Many MFR shifts, especially the first in the two-event PMA, preceded electromyographic (EMG) onset. The pre-EMG MFR shifts more often had the same sign both for flexion and extension movements rather than having opposite signs. However, with equal frequency, post-EMG PMA events had the same or opposite signs for different movement directions. We suggest that the pre-EMG PMA has an origin different from movement-related peripheral reafference.

4. Premovement activity was accompanied by shifts of MP corresponding to earlier responses to the ongoing vibratory stimulus and by decreases of response Synch. Premovement suppression was not associated with consistent shifts of MP and Synch. We suggest that during premovement activation, asynchronous (uncorrelated with vibration) signals are integrated with the vibratory input. These asynchronous signals may make neurons more likely to discharge and to do so earlier with respect to the vibratory stimulus. The asynchronous component may also disrupt the vibration-entrained activity pattern.

5. From these data we conclude that the activity of SI neurons that most faithfully represent the sensory periphery is modulated before voluntary movements. We suggest that inputs of central origin may contribute to this premovement modulation. Presumably, the role of the central inputs may be to prepare SI for changes in sensory activity that result from voluntary movement. Premovement asynchronous signals, both of central and peripheral origin, disrupt the fidelity of coding of the vibratory stimulus by SI neurons. This deterioration of the quality of representation of sensory inputs by SI neurons may be related to the phenomena of premovement elevation of the tactile threshold of perception and of premovement decrease of somatosensory-evoked potentials.

INTRODUCTION

Extracellular recordings from the primary somatosensory cortex (SI) of behaving monkeys have demonstrated that many neurons exhibit characteristic activity associated with voluntary movements of the forelimb made either in response to go-cues (Bioulac and Lamarre 1979; Evarts 1972; Fromm and Evarts 1982; Lamarre et al. 1983; Nelson 1984, 1987, 1988; Nelson and Douglas 1989; Nelson et al. 1991) or during self-paced tasks (Soso and Fetz 1980). Interestingly, the firing patterns of some SI neurons are modified before muscle activation (electromyographic (EMG)). It has been suggested (Jiang et al. 1991; Nelson 1987, 1988; Nelson and Douglas 1989; Nelson et al. 1991; Soso and Fetz 1980) that for these early firing SI neurons, premovement activity (PMA) may result from centrally generated preparatory signals. These central signals, presumably coming from motor centers, have been referred to as corollary discharge (Evarts 1971; von Holst 1954). Since the time of von Helmholz, it has been thought that sensation can be modulated by central influences (von Helmholz 1962; see Miles and Evarts 1979 for review). However, the functional significance and neuronal mechanisms of such modulatory influences are still not completely understood (Matthews 1988).

The presumed interaction between peripheral inputs to SI neurons and those of central origin can be studied with the use of an experimental paradigm in which monkeys make wrist movements in response to vibratotactile stimuli applied to the working hand (Nelson 1984, 1987, 1988). Several types of SI activity under these conditions have been found. It has been reported that some SI neurons exhibit quickly adapting phasic responses associated with vibratory stimulation (Nelson et al. 1991). Moreover, these same neurons resume firing before movement onset. In many cases, this reaction of neuronal firing occurs before EMG onset, suggesting the involvement of a centrally generated activity component. Analyzing the responsiveness of these neurons to the vibratotactile stimuli and the magnitude of their PMA showed that their PMA includes a stimulus-related component. The relative contribution of peripheral and central premovement inputs was also ana-
FIG. 1. A: digitized view of the dorsolateral surface of the brain (monkey H). The brain has been tilted 30° in the coronal and sagittal planes. Central sulcus (CS) and intraparietal sulcus (IP) are marked. B: composite showing the relative location of recording sites. Fifty-four surface locations are shown. The activity of 2 neurons, located in area 1, was recorded simultaneously. Locations of penetrations for monkeys C, F, and G were transposed into the surface map of the most extensively studied monkey (H). Representative parasagittal sections, indicating the location of neurons at 3 levels [lateral (L), intermediate (I), and medial (M)] are shown in C.

In the present study we examined the activity during initiation of vibratory-cued movements in a special class of SI neurons characterized by the faithful way in which they represented the sensory periphery. They responded to ongoing vibratory stimuli by sustained, entrained discharges. The entrainment of neuronal activity to periodic somatosensory stimuli (i.e., close temporal correlation between the stimuli and responses) is a well-known phenomenon. Entrainment has been demonstrated for cutaneous and deep afferents (Bianconi and van der Meulen 1963; Burke et al. 1976a,b; Johansson et al. 1982; Morley and Goodwin 1987; Ribot-Ciscar et al. 1989; Roll and Vedel 1982; Talbot et al. 1968; Wall and Cronly-Dillon 1960), motoneurons (Burke and Schiller 1976; Desmedt and Godaux 1980; Homma 1976; Lebedev and Poliakov 1991, 1992; Person and Kozhina 1992), spinal interneurons (Honda et al. 1986), as well as for neurons in somatosensory cortical areas (Burton and Sinclair 1991; Ferrington and Rowe 1980; Mountcastle et al. 1969, 1990; Nelson 1988). The entrainment of neuronal activity to the temporal characteristics of peripheral stimuli is believed to be an important coding mechanism (Morley and Goodwin 1987; Mountcastle et al. 1969, 1990; Nelson 1988; Talbot et al. 1968).

We hypothesized that, for SI neurons that faithfully fol-
FIG. 2. Example of analyses of vibration-entrained firing for an area 1 neuron (monkey H). This neuron was activated by passive wrist extension. Activity pattern exhibited during active extensions in response to 57-Hz vibration is illustrated. A and B: histograms (binwidth = 2 ms) of activity and raster displays aligned on vibration onset (A) and on movement onset (B). Mean firing rate traces are superimposed on the histograms. In rasters, movement onset (A) and vibration onset (B), respectively, are shown by darker marks. Distribution histograms for these onsets are displayed in the top of the panels. The periodic pattern of the vibration-entrained activity is visible in A. However, this pattern is not evident in the movement-aligned display (B). Mean firing rate increased 80 ms before movement onset (B). C: representations of the phase of the vibration-entrained responses. D: vector representation of the phase. Expression of mean phase and of standard deviation of phase using this representation. E and F: raster displays of phase and traces of mean phase and synchronicity aligned on vibration onset (E) and movement onset (F). In E, for better visibility, individual dots were rearranged into minihistograms over the vibratory cycle. Onsets of mean phase shift and of synchronicity decreases were 75 and 100 ms before movement onset, respectively (F).
low vibratory stimuli, activity patterns associated with vibratocative stimulation can be distinguished from the activity induced by other inputs. We assumed that peripheral vibration would induce responses that were temporally correlated with the stimuli, whereas inputs from other sources would introduce an activity component in these neurons that was temporally uncorrelated with the stimuli (asynchronous component). Thus the degree of correlation of neuronal activity with vibratory stimuli can indicate the relative influence of peripheral vibratory inputs versus asynchronous signals. Asynchronous inputs that affect SI activity during movement initiation may be associated with peripheral reafference, or they may have a central origin. If PMA of SI neurons occurs early with respect to EMG onset, it is probably centrally generated. On the basis of these assumptions, we analyzed entrained neuronal activity in terms of parameters characterizing the temporal relationships between the vibratory stimuli and the neuronal discharges (phase) and the degree of entrainment (synchronicity). Firing rates were analyzed as well. Some of the data have been presented previously in preliminary form (Lebedev and Nelson 1992).

**Methods**

**Experimental set-up and behavioral paradigm**

Four adult male rhesus monkeys (Macaca mulatta; C, F, G, and H) were taught to make wrist flexion and extension movements after a vibratory stimulus to the palm (Nelson et al. 1991). The monkeys were cared for in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals, revised 1985. Each monkey sat in an acrylic monkey chair with his right forearm on an armrest and his right palm on a plate attached, at the end nearest to the wrist, to the axle of a brushless DC torque motor (Colburn and Evarts 1978). A load of 0.07 Nm was applied to the plate, which assisted extension and opposed flexion movements. The monkeys exerted a flexion force to maintain a centered wrist position. Animals viewed a visual display, located 35 cm in front of them at eye level. The display, consisting of 31 light-emitting diodes (LEDs), provided visual feedback of the current wrist position. A central, red LED indicated a centered wrist position. Each smaller, yellow LED above or below the central LED indicated a deviation of wrist position of 1°.

Each monkey made self-paced wrist flexions or extensions in response to vibratory go-cues (Nelson et al. 1991). Trials began when the monkey centered the plate. A movement direction instruction was given by the presence or lack of illumination of a red LED located in the upper left corner of the visual display. If this LED was illuminated, extension was the appropriate movement. Otherwise, the monkey was to flex. The monkey was required to maintain the centered (hold) position for 0.5, 1.0, or 1.5 s (pseudorandomized). Movements of >0.5° from center during the hold period cancelled the trial. If the animal held the center position, a 27-, 57-, or 127-Hz low-amplitude stimulus (sine wave <0.06° angular deflection) vibrated the plate. Vibratory stimuli, which served as the go-cues, remained on until the monkey moved at least 5° from the held position. If the monkey moved, the monkey received a fruit juice reward. A new trial began when the monkey once again held a steady position.

**Electrophysiological recordings and histology**

Once animals reached a steady daily performance level, stainless steel recording chambers were surgically implanted, and extracellular recordings were made of SI neurons by using platinum-iridium microelectrodes. Transdural penetrations were made daily into the somatosensory cortex, and the activity of single units was amplified, discriminated, and stored in a computer by conventional means (Evarts 1966; Lemon 1984; Nelson 1988; Nelson et al. 1991). At regular intervals, EMG recordings of the forearm muscles acting across the wrist were made. With the use of sterile 25-gauge needle electrodes as guides, intramuscular EMG wires (stranded stainless steel, Teflon insulated; Bergen Wire Rope) were temporarily implanted in muscles. The recorded EMG activity was converted into pulse data with a window discriminator (Vaidya et al. 1988) and stored in a computer in the same form as the neuronal data.

On the last recording day, electrolytic lesions were made in cortical locations of interest by passing 10 µA of current for 10–20 s. The animals were then deeply anesthetized with pentobarbital sodium and transcardially perfused with 10% buffered formalin. Histological sections of the cortex were prepared, and electrode tracks were reconstructed based on the depth of each recording site from the point where the cortical activity was first encountered and the location of the marking lesions (Nelson 1988; Nelson et al. 1991). Only those neurons from recording sites that could be clearly identified as to their cortical location were included in this analysis. The location of each recording site was subsequently transferred to schematic reconstructions of the
TABLE 1. Characteristics of background activity and vibratory responses

<table>
<thead>
<tr>
<th>Group of Neurons</th>
<th>Cutaneous RFs</th>
<th>Deep RFs</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Background firing rate, spikes/s</td>
<td>21.5 ± 11.0 (20)*&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30.2 ± 13.5 (26)*&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37.5 ± 12.6 (9)</td>
<td>28.2 ± 13.6 (55)</td>
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<td>Latency of vibratory response, ms.</td>
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<td>26.1 ± 7.3 (16)</td>
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<td>23.5 ± 7.3 (20)</td>
<td>21.8 ± 8.6 (26)</td>
<td>24.0 ± 6.3 (9)</td>
<td>22.8 ± 7.8 (55)</td>
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<td>21.3 ± 7.6 (16)</td>
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<td>Stabilized MFR, spikes/s</td>
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<td>44.3 ± 13.9 (17)</td>
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<td>57 Hz</td>
<td>45.7 ± 26.1 (20)</td>
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<td>57 Hz</td>
<td>0.39 ± 0.18 (17)</td>
<td>0.38 ± 0.15 (24)</td>
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<td>0.22 ± 0.17 (10)*&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.26 ± 0.14 (14)*&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.20 ± 0.10 (2)</td>
<td>0.24 ± 0.15 (26)*&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

Values represent means ± SD; number of neurons is in parentheses. Significance level for both 1-factor analysis of variance with the Scheffé comparison test and Mann-Whitney U test are shown. The sample for calculating Synch is less than that for other parameters because cases with binomial phase distribution were excluded. RF, receptive field; MFR, mean firing rate; Synch, synchronicity. * P < 0.05, *<sup>a</sup> P < 0.01. *<sup>b</sup> Different from other RF type in the row; *<sup>a</sup> Different from all other combinations of RF type and vibratory frequency.

recordings were performed after appropriate scaling and alignment of sections from individual animals based on the location of the central and intraparietal sulci (Fig. 1).

Analyses of entrained responses

SI neurons with activity entrained to vibratory stimuli were selected for analysis by visual inspection of raster displays and histograms. Entrained vibratory responses were characterized by a periodic pattern in the rasters and histograms when these were centered on vibration onset (Fig. 2A). In displays aligned on movement onset, the periodic pattern usually was obscured (Fig. 2B). The analyses of response phase were conducted to describe the dynamic changes in the pattern of entrainment quantitatively. The time of occurrence of each spike was related to the instantaneous phase of the vibratory stimulus (Fig. 2C). The phase of the vibratory stimulus at which spikes occur is a correlate of response latency. We defined the latency as the time from the beginning of a given vibratory cycle to the resultant spike. Variations of the phase, Δϕ, and of the latency, ΔL, are linearly related

$$Δϕ = 2π L \Delta L$$

where $\Delta ϕ$ is the frequency of vibration.

The phase at which spikes occur in response to external stimuli was defined as a statistical value depending on time. Floating mean phase (MP; Fig. 2, E and F) and the standard deviation of phase were calculated. From the standard deviation, a synchronicity (Synch) parameter was determined that characterized the degree of vibratory entrainment on a 0 to 1 scale (Fig. 2, E and F). To calculate the floating mean phases, circular statistics were used (Batschelet 1981; Zar 1974). The phase of the stimulus was represented as the angle of a unit vector in a circular diagram (Fig. 2D). Because a vibratory stimulus is a harmonic function of time, the unit vector can be thought of as rotating at a constant angular velocity corresponding to the frequency of vibration. With the use of complex values, this rotating unit vector, $e(t)$, can be expressed as

$$e(t) = \exp(i2π t)$$(2)

where $t$ is the time from vibration onset and $i$ is an imaginary unit [$i = (-1)^{1/2}$].

Floating mean parameters were calculated as average values in a time window having a width equal to one vibratory period at 27 Hz (37.0 ms), two periods at 57 Hz (35.1 ms), and four periods at 127 Hz (31.5 ms). The width of the time window was chosen to be equal to multiples of the vibratory period to provide average values over at least one vibratory cycle, and to smooth the "bursty" pattern of vibration-entrained activity. The number of spikes, $N(t)$, in the time window was used to calculate the mean firing rate (MFR), $F(t)$

$$F(t) = N(t)/(nT)$$

where $T$ is the time window width and $n$ is the number of trials averaged.

Mean vector, $m(t)$, was calculated as an average of unit vectors corresponding to individual response phases

$$m(t) = \frac{1}{N(t)} \sum_{i=1}^{N(t)} e(t_i) \quad T/2 < t_i < T/2$$

where $t_i$ is the time of the $i$th spike's occurrence. MP, represented as $\theta(t)$, was calculated as the angle of the mean vector

$$\theta(t) = \angle m(t)$$

The floating standard deviation of the response phase, $σ(t)$, was calculated by averaging the squared angular deviations of individual unit vectors with respect to the mean vector

$$σ(t) = \{1/N(t) \sum_{i=1}^{N(t)} \text{angle}(m(t), e(t_i))\}^{1/2}$$

In Eq. 6 the angle is defined as ranging between $−\pi$ and $\pi$ radians ($−180$ and $180°$).

Standard deviations calculated for small samples tend to be underestimated (Gurland and Tripathi 1971). To correct for this tendency, resulting from Eqs. 4–6, we used a numerical model. On the basis of this model, a correction factor was calculated in the form of a second-order polynomial of the number of samples. Standard deviation, $σ(t)$, was multiplied by this correction factor. For most cases, the number of samples was sufficiently large, so that the correction was small (<5% for $N_{\text{sample}} > 10$).

The Synch parameter was derived from the standard deviation. Synch served to compare the experimentally derived distribution...
with a uniform (completely random) distribution over the vibratory cycle. The standard deviation of a uniform distribution, \( \sigma_{\text{unif}} \), is equal to \( 3^{-1/2} \pi \text{ radians} \) (103.923°). Synch, \( e(t) \), was calculated as

\[
s(t) - [e_{\text{unif}} - e(t)]/\sigma_{\text{unif}}
\]

Synch could vary from 0 to 1, where 0 corresponds to the absence of entrainment (uniform distribution), and 1 corresponds to a neuron responding at a constant phase.

The analyses of response phase routinely revealed additional information. Figure 2, E and F, illustrates the results of applying these analyses to the same data more conventionally presented in Fig. 2, A and B. Raster displays also show the phase for the time preceding the vibratory stimulation onset. For this period, individual phases (automatically calculated by the computer) were scattered randomly within the graph limits. After stimulation onset, individual phases clustered around a particular phase value (i.e., MP). MP shifted at approximately the same time that the unit was activated before movement onset (~80 ms). This change of MP corresponded to an earlier response to the ongoing vibratory stimulus (see Eq. 1). In addition, Synch decreased with respect to the early poststimulus onset level.

**Onset of EMG and PMA**

EMG onsets were determined with the use of the cumulative sum methods (CUSUM) (Ellaway 1977; Jiang et al. 1991). A linear least-square interpolation curve was calculated for the CUSUM method.
SUM trace of EMG pulses recorded during the epoch of steady holding against the load. Then the computer program searched forward in time to find the first deviation from the interpolated curve of more than three standard deviations for at least 40 ms. This time was designated as the EMG onset. The latency of the initial vibratory response of SI neurons was determined in a similar way. Because of the bursty character of vibration-entrained firing, an estimate of PMA onset could not be made accurately with the use of the CUSUM methods. Average parameters were analyzed instead. A stable piece of the respective trace was labeled by visual inspection. Means and standard deviations of MFR, MP, and Synch were calculated for this epoch. Then the computer program searched forward in time to find the first change of more than three standard deviations for at least 40 ms. It should be stressed that the precision of estimation of this time was principally limited. The procedure for calculating floating mean parameters was analogous to low-pass filtering. It tended to broaden sharp edges (compare in Fig. 2.4 the 2-ms binned histogram with mean firing rate trace). The maximum error in determining the occurrence of change resulting from this broadening is equal to $T/2$ (~18 ms).

Statistical analyses

To analyze factors determining the characteristics of activity patterns in different neurons, factorial analysis of variance (ANOVA; including Scheffe's post hoc test) was used. Multifactorial ANOVA served to detect with which independent factors (i.e., cortical area, receptive field type, frequency of vibration, direction of movement, etc.) MFR, MP, and Synch covaried. If some factors were not statistically significant in their covariance, averaging was performed on the set of these factors. The data were grouped to isolate combinations of significant factors. The parametric $t$ test and the more robust nonparametric Mann-Whitney $U$ test were used to test the significance of differences between groups. In cases when correlations between certain parameters were suspected, parametric F-statistics for the linear regression and the nonparametric Spearman rank correlation analyses were conducted.

RESULTS

Database

From the recordings for 410 vibratory responsive SI neurons, 55 units (13%) were selected as entrained to the frequency of the vibratory stimulus. These vibration-entrained units represented a subpopulation of the group of neurons activated by the vibratory stimulus (60% of the vibratory responsive cells) (Nelson 1988). Monkeys C, F, G, and H contributed 10, 6, 12, and 27 units, respectively. The best entrainment for the selected units was observed at stimulus frequencies of 27 and 57 Hz, whereas the entrainment was less at the higher frequency (127 Hz). We did not include Pacinian-like neurons (Mountcastle et al. 1969) because of their qualitatively different activity patterns. Their best responsiveness was at the higher vibratory frequency of 127 Hz. (Pacinian-like neurons will be considered separately in following studies). Determination of cortical location was based on previously published criteria (Nelson et al. 1991). Figure 1 presents the distribution of surface locations of the recordings ($B$), their location in representative sagittal sections ($C$), and the respective number of neurons ($D$). No clear distribution patterns were evident, either within or across cortical areas. However, there was a tendency for the studied neurons to be located in the granular or infragranular cortical layers.

General activity patterns

We use the term "case" to indicate a set of activity recordings for a particular neuron at a single vibratory frequency for one direction of movement (Nelson et al. 1991). A total of 248 cases were analyzed. For 30 cases (from 10 neurons), response phases formed 2 bands rather than being grouped around a particular phase value. Probably this activity profile represented responses to both the application and withdrawal of the mechanical stimuli from the neuron's receptive field (RF). These cases were excluded from the analyses of MP and Synch. Figure 3A shows the typical epochs of neuronal activity that were observed: 1) background firing preceding the stimulus onset; 2) initial transient response to stimulus onset; 3) stabilized response to vibration; and 4) one of several types of PMA. We observed premovement increases of firing rate (activation) as well as firing rate decreases (suppression). Moreover, in some cases, two consecutive changes of firing rate occurred (2-event PMA). The different types of PMA are schematically illustrated in Fig. 3B.

Background activity and vibratory response

The results of statistical analyses of the MFR during background activity, of the vibratory response latency, and of MFR and Synch for the period of stabilized response are presented in Table 1. No significant differences dependent on the cortical area were found. The background MFR was, on average, higher for neurons with deep RFs than for neurons with cutaneous RFs. The latency of the vibratory response averaged ~23 ms. The latency was significantly longer at 27 Hz than at 57 and 127 Hz. The stabilized MFR was not significantly different for neurons with deep RFs at any of the studied frequencies nor for neurons with cutaneous RFs at 27 and 57 Hz. However, for neurons with cutaneous RFs, MFR was significantly less at the higher frequency (127 Hz). Stabilized MFR was, on average, higher than background MFR, except for neurons with cutaneous RFs at 127 Hz. An example of the activity of a neuron with a MFR increase during the stabilized response is presented in Fig. 8, A and B. In some instances, however, stabilized MFR remained virtually unchanged (e.g., Fig. 7, A and B) or even decreased (often for neurons with cutaneous RFs at 127 Hz). In these latter cases the sustained response to vi-

**FIG. 5.** Patterns of EMG activity of forearm muscles illustrated for 2 monkeys (Cand F). EMG was converted into pulse data with the use of a window discriminator. Histograms of these pulse data, centered on movement onset, are shown (gray, flexion; white, extension). EMG onsets estimated with the use of the cumulative sum (CUSUM) method are shown (4, suppression; 4, activation; negative value, before movement onset; positive value, after movement onset; Flex, flexor; Ext, extensor). The earliest EMG onset was 90 ms before movement onset (monkey F).
vation was characterized by groupings of spikes around a particular phase of the vibratory cycle, rather than by a firing rate increase. There were no significant differences in Synch during the stabilized response period that were dependent on the RF type. Synch was not significantly different at the vibratory frequencies of 27 and 57 Hz, but it was significantly lower at 127 Hz.

Onset of PMA and EMG

The onsets of PMA and EMG were determined relative to movement onset. PMA onset differed between individual monkeys with different reaction times (RTs). For two monkeys with longer RTs (monkeys C and G with mean RTs of 330 and 360 ms, respectively), PMA onset (but not EMG onset), on average, was earlier than for two monkeys with shorter RTs (monkeys F and H; mean RTs 200 and 220 ms). Therefore, we combined the data obtained from two monkeys with fast RTs into one group and the data from two monkeys with slow RTs into another. The differences in PMA onset related to RF type, cortical area, vibratory stimulus frequency, and sign of MFR shift (activation or suppression) were not significant. The onsets were analyzed separately for three groups of PMA: 1) first events for the two-event PMA (Fig. 4A); 2) second events for the two-event PMA (Fig. 4B); and 3) single-event PMA (Fig. 4C). The difference in PMA onsets between slow and fast monkeys was greater for first events than for second and single PMA events.

PMA onset was compared with the EMG onset. Figure 5 illustrates the EMG patterns of different forearm muscles for two animals, one slow (monkey C) and one fast (monkey F). The earliest EMG onset was 90 ms before movement onset (monkey F). The minimum conduction time necessary for peripheral signals to arrive at SI has been estimated to be 11 ms (Wiesendanger and Miles 1982). We suggest, therefore, that the peripheral reafference associated with EMG onset does not reach SI earlier than 79 ms before movement onset. In the present analyses a time-averaging procedure was used to calculate MFR, MP, and Synch. Because this procedure depends on time-window measurements, a maximal error of one-half the time window width (18 ms) was possible in estimating PMA onset. Therefore, we suggest that the earliest peripherally induced changes in SI activity occur no earlier than 97 ms before movement onset. The majority of the first events occurred earlier than 97 ms before movement onset. The PMA onsets for the slow group were especially early. Most of the second events, however, began <97 ms before movement onset. Approximately an equal number of the single events occurred before and after the 97-ms boundary.

PMA patterns

Premovement changes in MFR were accompanied by changes in MP and Synch. For a given neuron and a given movement direction, the general pattern of changes in MFR, MP, and Synch usually was consistent at different vibratory frequencies (e.g., Fig. 6). The magnitude of these changes differed depending on the vibratory frequency. During premovement activation an increase of MFR was typically accompanied by a shift of the MP toward earlier responses to vibratory stimuli and a decrease in Synch (e.g., Fig. 2). Usually, the decrease of Synch was greatest at lower vibratory frequencies (e.g., 27 Hz in Fig. 6, A and B) than at higher frequencies (e.g., 127 Hz in Fig. 6, C and D). However, greater phase shifts were characteristic at the higher frequencies of vibration (Fig. 6, C and D). The magnitude of the change in MFR was not necessarily correlated with the magnitude of accompanying changes in MP and Synch. For example, MFR of the unit presented in Fig. 7, A and B, only slightly increased 150 ms before movement onset, whereas the MP and the Synch substantially changed before movement. Another unit (Fig. 7, C and D) exhibited a small increase in MFR occurring at 120 ms before movement. In this instance, although the shift of MP was quite pronounced, no substantial changes in Synch took place.

In general, no consistent shifts in MP and Synch were temporally correlated with premovement suppression. An example of a single-event premovement suppression (S pattern; Fig. 3B) is presented in Fig. 8, A and B. In this case the MFR decreased ~150 ms before movement onset. No substantial phase shift was observed in this instance, whereas a desynchronization occurred ~30 ms before movement onset. An example of a neuron with a two-event pattern with consecutive activation and suppression (AS pattern; Fig. 3B) is presented in Fig. 8, C and D. In this case MFR increased ~200 ms before movement onset. A reduction in MP and a slight decrease in Synch also took place. These events, characteristic for the premovement activation, were followed by MFR decrease, which occurred ~80 ms after movement. Although the increase in MFR subsequently reversed, the MP continued to shift toward earlier responses, and the Synch decreased.

To estimate the mean time course of changes in the characteristics of vibration-entrained firing during PMA, we averaged across cases by aligning MFR, MP, and Synch traces on the onset of the MFR shift. The average traces for the patterns of the one-event cases were similar to those.

FIG. 6. Changes in mean phase and synchronicity during premovement activation at low (27 Hz; A and B) and high (127 Hz; C and D) vibratory stimulus frequencies. Activity patterns of an area 1 neuron (monkey H) during wrist extensions made in response to vibration. This neuron had a cutaneous receptive field located on the radial base of the 1st digit. Conventions as in Fig. 1. At 27 Hz, the neuron fired approximately twice per the vibratory cycle (A; see the traces of firing rate). Premovement activation occurred at 80 ms before movement onset at 27 Hz. During this activation the vibration-entrained firing was desynchronized. At 127 Hz, during the stabilized response, this neuron discharged once every 3 cycles. However, during premovement activation (at 110 ms before movement onset), a 1-to-1 following of the vibratory stimulus frequency was observed (D). Premovement activation was accompanied by changes of mean phase and synchronicity. The shift of mean phase was greater at 127 Hz (D) than at 27 Hz (B). The synchronicity decrease was greater at 27 Hz (B) than at 127 Hz (D).
calculated for the shift of MFR of the same sign in the
two-event cases. In Fig. 9A, averaged traces for premove-
ment activation are shown (1-event and 2-event cases were
not segregated). Average traces of MP and Synch revealed a
phase shift toward earlier responses and a desynchroniza-
tion that were correlated with the increase of MFR. The
changes in MP and Synch were similar for neurons with
cutaneous and deep RFs. The average MP shift was approxi-
mately the same at the two higher vibratory frequencies, 57
and 127 Hz. The phase shift was less at the lower frequency
(27 Hz). However, desynchronization was greater at 27 Hz
than at the higher frequencies. The onsets of both MP (Fig.
9B) and Synch (Fig. 9C) shifts were correlated with the
beginning of MFR increase.

The average traces of MFR for premovement suppress-
on (Fig 10A) indicated that an activation often preceded
suppression. An average shift of MP toward earlier re-
sponses and a desynchronization was also evident. How-
ever, these changes of MP and Synch did not begin at the
onset of MFR decrease. Rather, they occurred before sup-
pression in many instances. Therefore changes of MP and
Synch may be related to the activation that often preceded
the suppression. No significant correlation was evident be-
tween the onset of MFR decrease and the shifts of MP and
Synch (Fig. 10, B and C).

**PMA for different directions of movement**

The PMA pattern depended on the subsequent direction
of movement. Figure 11 presents the records from a neuron
that increased activity at 50 ms before the onset of wrist
flexions (A and B) and decreased activity at the same time
before the onset of wrist extensions (C and D). This unit
also showed slight increases in MFR at 120 ms before
movement onset during both extension and flexion trials
(superimposed traces in Fig. 11F). An MP shift toward
earlier responses beginning 120 ms before movement onset
was also present for both directions of movement (Fig.
11G). During the suppression of the firing for extension
trials, the MP continued to shift. In addition, a desynchroni-
zation was observed for both types of movement.

In analyzing the dependence of PMA upon movement
direction, only those PMA events were selected that had
onsets in extension and flexion trials separated by <30 ms.
The onset of these selected PMA events was estimated as an
average for different movement directions (and vibratory
frequencies, if PMA satisfied the 30-ms criterion at several
frequencies). PMA events were split into two groups ac-
cording to the position of their onset with respect to EMG
onset: those that occurred earlier than 97 ms before move-
ment onset and those that occurred after this boundary.
Most pre-EMG MFR shifts had the same sign for both flex-
ion and extension movements (22/29). However, with
equal frequency, post-EMG PMA events had the same or
opposite sign for different movement directions (the same
sign: 19/41; opposite signs: 22/41).

**DISCUSSION**

**Centrally generated PMA and SI**

PMA of SI neurons, often preceding the EMG onset, has
been reported in a number of studies (Bioulac and Lamarre
1979; Evarts 1972; Fromm and Evarts 1982; Lamarre et al.
Nelson et al. 1991; Soso and Fetz 1980). Each study indi-
cates that post-EMG PMA contains a substantial compo-
est associated with peripheral reafference. However, sug-
gestion involvement of centrally generated signals in pre-
EMG PMA is controversial. One argument against
centrally generated PMA in SI is based on the fact that
PMA occurs in SI later than in the motor cortex (Evarts
1972). However, if PMA in the SI is a corollary motor
cortical discharge (Matthews 1988), then this difference in
PMA onsets should be a prerequisite. Another argument is
that most movement-related discharges in SI disappear
after extensive deafferentation of the arm (Bioulac and La-
marre 1979). However, this result does not rule out the
possibility of centrally generated PMA in SI under normal
conditions. After deafferentation, the functioning of SI as a
unit for somatosensory information processing may be dra-
matically altered. SI may no longer be capable of participat-
ing in movement control. Thus it may be excluded from
the motor control loop, and therefore there might no longer be
a reason to adjust SI neuronal responsiveness.

We examined PMA for a group of SI neurons that faith-
fully represented the somatosensory periphery. The firing
of these neurons was entrained to vibratormctile stimuli. We
hypothesized that, for the selected neurons, the activity pat-
terns related to peripheral vibration can be distinguished
from inputs coming from other sources. It was expected
that signals that are temporally uncorrelated with vibration
(asynchronous signals) would disrupt the vibration-en-
trained neuronal firing patterns. Asynchronous inputs may
be associated with peripheral reafference, or they may have
central origins. To reveal the changes in vibration-en-
trained neuronal activity that may be produced by
asynchronous signals, we analyzed the temporal relation-
ship between the vibratory stimuli and the neuronal re-
sponses to them in terms of the phase of the vibratory cycle.
at which individual spikes occurred. The phase was considered as a statistical value varying in time. This value was described with the use of floating mean parameters, MP and Synch, which characterized, respectively, the preferred phase of responses and the degree of vibratory entrainment. For the majority of the selected neurons, the pattern of responses to ongoing vibration changed before movement onset. Changes in firing rate were accompanied by changes in MP and in Synch. Typically, the vibration-entrained pattern was disrupted before movement onset. In many cases, premovement changes in activity began before EMG changes. We suggest that inputs of central origin may contribute to premovement changes in the activity of the studied SI neurons.

Background activity and responses to vibration

During the hold phase of the paradigm, most neurons typically were active with a firing rate of ~30 spikes/s. On average, neurons with deep RFs had higher background firing rates than those with cutaneous RFs. It is possible that the higher background firing of neurons with deep RFs was related to tonic muscle activity that occurred during holding of the handle against a load. Muscle spindle activity is activated during maintained voluntary contractions due to γ-motoneuron discharges (Hagbarth and Vallbo 1968; Vallbo 1970). The latency of vibratory responses was significantly longer for the lowest tested vibratory frequency (27 Hz) than for 57 and 127 Hz. Probably, this longer latency was related to a less steep onset of the vibratory stimulus at 27 Hz than at the higher frequencies. During the stabilized response to vibration, MFR did not vary significantly with different vibratory frequencies, with the exception of the responsiveness of neurons with cutaneous RFs at 127 Hz. Relatively constant MFRs of somatosensory cortical neurons despite changes in peripheral stimulus frequency have been reported (Burton and Sinclair 1991; Gardner et al. 1992; Mountcastle et al. 1969, 1990). It has been suggested that the characteristics of vibrotactile input are encoded by the temporal pattern of neuronal responses rather than by MFR. The decreased activity that was observed for the neurons with cutaneous RFs at 127 Hz may be due partially to reduced responsiveness of cutaneous receptors at higher stimulus frequencies (Talbot et al. 1968). However, this is probably not the only reason, because in a number of cases, pronounces entrained responses were observed before movement onset in 127-Hz trials (Fig. 6, C and D). Thus the decrease in MFR of neurons with cutaneous RFs at 127 Hz may be due to inhibitory mechanisms dependent on the stimulus frequency. The SI activity pattern characterized by rapid adaptation of neuronal responses to the vibratory stimuli, and then a reactivation of sensory responsiveness before movement onset, has been analyzed previously (Nelson et al. 1991).

PMA patterns

Several types of PMA were observed and classified according to models of MFR changes (Fig. 3B). For the cases in which two consecutive changes in MFR occurred (2-event PMA), most of the first MFR changes occurred before EMG onset, whereas most of the second MFR changes occurred after EMG onset. Approximately an equal number of the single events began before and after EMG onset. EMG onset reflects the time when the muscle force and, consequently, the force on the receptive field may begin to change. Therefore we suggest that pre-EMG PMA is not caused by peripheral reactivation, whereas post-EMG PMA probably is. It would be reasonable to expect that peripherally induced MFR shifts have opposite signs for flexion and extension movements, at least in some cases. Indeed, a considerable number of the post-EMG MFR shifts of this type were observed. However, pre-EMG MFR shifts more often had the same sign both for flexions and extensions rather than having opposite signs. This fact provides indirect evidence that these PMA events were not peripherally induced. PMA onset was earlier with respect to movement onset for monkeys with slower RTs. Probably the difference in PMA onsets between monkeys reflects the difference in sensorimotor strategies used by the animals during movement preparation. We presume that this difference would not occur if the PMA was induced exclusively by peripheral movement-related reafference, because there was no evidence of faster peripheral conduction for slow monkeys. Also, no similar differences were observed for EMG onsets. Moreover, the difference between slow and fast monkeys was greater for pre-EMG PMA events that presumably were not associated with peripheral reafference, because of their early occurrence.

Premovement activation was typically accompanied by shifts in MP toward earlier responses to stimuli and by decreases in Synch. We suggest that the decrease in Synch signifies that the activation is produced by inputs uncorrelated with the vibratory stimulus (asynchronous inputs). Adding an asynchronous component to a neuron’s entrained response would induce a shift in the response phase. When two excitatory signals are superimposed, the membrane potential may be brought to threshold earlier compared with when it is activated by only one input. Desynchronization was most pronounced at the lowest vibratory frequency (27 Hz). The changes in MP, on the other hand, were greater at the higher vibratory frequencies (57

![Image](https://example.com/image.png)
and 127 Hz). We suggest that the above differences, dependent on the vibratory stimulus frequency, reflect an interaction between the frequency components of the vibration-entrained input and those of asynchronous signals. It is possible that, when two excitatory components are added, the membrane potential will more often cross the threshold on the rising edge of the higher frequency signal.

Premovement suppression of MFR was sometimes accompanied by MP shifts and desynchronization. However, the decrease of MFR and the changes of MP and Synch were not related. For some two-event cases, premovement suppression may have been superimposed on an activation pattern. The first premovement event in these cases was an activation associated with changes of MP and Synch. The second event was a suppression. However, MP and Synch continued to shift in the same direction (Fig. 8, C and D). The neuronal mechanism for the interaction between premovement facilitatory and inhibitory signals cannot be resolved from the present data. It is unclear whether this mechanism is based on the convergence of different inputs onto a single neuron or on network interactions.

Possible roles of centrally generated PMA

Several sources are possible for centrally generated PMA (Nelson et al. 1991). First, PMA may result from inputs coming from motor centers (Evarts 1971; Miles and Evarts 1979; Soso and Fetz 1980; von Holst 1954). Second, PMA may originate in SI itself and provide an output signal driving or subserving the drive of movements. Third, PMA may reflect some intrinsic regulation of SI activity. It has been suggested that PMA in SI pyramidal tract neurons contributes to the motor drive (Fromm and Evarts 1982). We do not have direct evidence of what class of SI neurons, having vibration-entrained responses, were studied. However, we assume that, because these are neurons that faithfully respond to peripheral inputs, they are likely to be close to the input site for somatosensory afference. Therefore it is un-
likely that the studied neurons generate a direct motor control signal. Rather, their activity provides an input for other regions involved in sensorimotor integration. We assume that centrally generated PMA in these neurons may be induced either by inputs from motor centers or by intrinsic signals.

Signals originating in the motor cortex can influence SI activity. This was demonstrated with the use of microstimulation of area 4 during monitoring of somatosensory-evoked potentials in monkey areas 1 and 3b (Jiang et al. 1990a). However, motor cortical discharges may reach SI via indirect pathways. Besides providing direct input to SI (Jones and Porter 1980; Vogt and Pandya 1978), these discharges may interact with ascending somatosensory transmission at the level of the dorsal column nuclei and the thalamus (see Mountcastle 1984 for review). Changes of afferent transmission have been observed in the medial lemniscus and ventroposterolateral nucleus of the thalamus during arm movements in monkeys (Chapman et al. 1988) and during locomotion in rats (Shin and Chapin 1990). However, these changes were always less than those observed in the SI itself. Thus it is reasonable to assume that the strongest influence of motor cortex over SI responsiveness is at the cortical level.

Several functional roles can be suggested for centrally generated PMA. The first possibility is that centrally generated PMA is a component of the corollary discharge, or a sensory signal originating in the brain itself rather than coming from periphery (Miles and Evarts 1979; Soso and Fetz 1980). This corollary discharge may subserve kinesthetic sensation during self-initiated as opposed to passive movements (Matthews 1988). Premovement modulation of sensory activity may make the system work as a system with anticipation, which could be more effective for motor control (Prochaska 1989). Evidence supporting the theory of corollary discharge has been provided by experiments in which a sense of movement was elicited by magnetic stimulation of human motor cortex when the forearm was ischemically paralyzed (Amassian et al. 1989).

Another possibility is that PMA may reflect gating of so-
FIG. 11. Variability of premovement activity patterns with respect to movement direction (flexion or extension). The activity of an area 1 neuron (monkey F) during flexions (A and B) and extensions (C and D) made in response to 57-Hz vibration is illustrated. This neuron was activated during palpation of flexor carpi ulnaris and during passive flexions of the 3rd metacarpophalangeal joint. An activation-activation (AA) pattern was observed during flexions, and an activation and suppression pattern was observed during extensions (see Fig. 3B). Thus the activity change associated with the 1st event that occurred 120 ms before movement onset had the same sign for different movement directions. That occurring for the 2nd event (60 ms before movement onset) had the opposite signs for flexions and extensions (E and F). F: superimposed traces of mean firing rate. G: superimposed traces of mean phase. H: superimposed traces of synchronicity.
mato sensory responsiveness that depends on the phase of a behavior. Initially, the vibrotactile stimulus in our paradigm serves as the go-cue, and its detection is particularly important. However, during movement execution, this stimulus may interfere with afferent signals providing feedback about movements (Nelson 1988; Nelson et al. 1991; Wiesendanger and Miles 1982). It has been shown that vibratory stimulation of muscle receptors during voluntary movements leads to errors in planned movement trajectories (Capaday and Cooke 1981; Cody et al. 1990; Inglis and Frank 1990). Thus it may be important to suppress the sensory responsiveness to vibration before movement onset. We indeed observed premovement suppression for a number of neurons. These observations are consistent with the results of other studies (Jiang et al. 1991; Nelson 1987, 1988).

PMA and the quality of peripheral stimulus representation

PMA often was associated with a disruption of the pattern of vibrotactile stimulus representation in SI neuronal activity. First, the quality of peripheral stimulus representation deteriorated because the firing of some neurons was suppressed. Second, during premovement activation, neuronal sensory responsiveness was also effectively suppressed because of desynchronization. We suggest that these mechanisms of masking peripheral stimuli are related to the previously demonstrated elevation of the threshold for tactile perception before and during voluntary movements (Coquerey 1978; Dyhre-Poulsen 1978; Schmidt et al. 1990a,b). PMA may result in premovement decreases of somatosensory-evoked potentials (Cohen and Starr 1987; Coquerey et al. 1972; Jiang et al. 1990b; Rushton et al. 1981). From our data showing premovement changes in the phase of responses to ongoing vibration, it may be predicted that similar premovement changes may occur in the latency of responses evoked by other stimuli (evoked potentials, air puff, etc.).

Conclusions

When monkeys make wrist movements in response to vibrotactile stimulation of their hands, some SI neurons exhibit sustained sensory responses that faithfully follow the vibratory stimulus frequency. However, the vibration-entrained firing pattern of these neurons changes before movement onset. Some neurons exhibit additional activation, whereas the firing of others is suppressed. Premovement changes in the phase of responses to vibration and in the fidelity of entrainment, both of which are correlated with the changes of firing rate, also occur. We suggest that the patterns of premovement activity result from the interaction between periodic vibration-related inputs and signals uncorrelated with vibration. In many cases, premovement changes precede EMG onset, indicating that they probably do not originate from movement-associated peripheral reafference. We suggest that inputs of central origin contribute to premovement activity. Presumably, the role of the central inputs is to prepare sensory cortical neurons for reafference resulting from voluntary movement, even if these neurons previously responded to peripheral stimuli with entrained activity.

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High-frequency vibratory sensitive neurons in monkey primary somatosensory cortex: entrained and nonentrained responses to vibration during the performance of vibratory-cued hand movements

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Abstract The activity of high-frequency vibratory sensitive (HFVS) neurons was recorded in monkey primary somatosensory cortex (SI) while animals performed wrist flexions and extensions in response to 57-Hz or 127-Hz palmar vibration. HFVS neurons were distinguished by their exquisite responsiveness to the higher frequency vibration (127 Hz). These neurons probably received input from Pacinian afferents. Systematic selection of HFVS neurons was made using K-means cluster analysis of neuronal firing rates during stimulating at 127 Hz and 57 Hz. HFVS neurons constituted ~4% of all recorded cells and more frequently were found in areas 3b, 1, and 2 (~5% of total in each area) than in area 3a (~1%). Using circular-statistics analyses for nonuniformity of discharges over the vibratory cycle, HFVS neurons were split into two groups of vibration-entrained neurons (E1 and E2 neurons) and one group of nonentrained neurons (NE neurons). E1 neurons were entrained to vibration at both 127 Hz and 57 Hz, whereas E2 neurons were entrained only at one of these vibratory frequencies. Vibration-entrained neurons often exhibited multimodal distributions of interspike intervals (ISIs), with the modes at multiples of the period of vibration. In addition, for these neurons, ISI clusters in joint interval plots commonly had diagonal orientations that were indicative of negative serial correlations of the ISIs, a feature of extrinsically driven rhythmic activity. HFVS neurons located in areas 3a, 3b, and 1 responded to vibration onset at shorter latencies (16.5±1.6, 19.8±5.9, and 21.4±6.4 ms, respectively, during 127-Hz stimulation) than those located in area 2 (35.6±13.8 ms). These observations are consistent with a scheme in which HFVS area 2 neurons receive their inputs from more anterior areas of SI. Moreover, entrained neurons exhibited shorter response latencies than nonentrained neurons. During 127-Hz stimulation, response latencies were 17.3±3.0, 17.5±2.6, and 25.7±6.4 ms for E1, E2, and NE neurons, respectively, located in areas 3a, 3b, and 1. Thus, entrained and nonentrained HFVS neurons may belong to different hierarchical stages of information processing.

Key words Somatosensory cortex · High-frequency vibrotactile stimulation · Stimulus-entrained activity · Pacinian afferent · Monkey

Introduction

Somatosensory afferent fibers of different submodalities (slowly adapting, rapidly adapting and Pacinian afferents) are preferentially sensitive to vibratory stimulation at characteristic frequency ranges (Talbot et al. 1968). Pacinian afferents are preferentially activated by high-frequency (80–400 Hz) vibration (Sato 1961; Talbot et al. 1968). During high-frequency vibratory stimulation, the discharges of Pacinian afferents commonly are entrained to the stimulus frequency (i.e., they are temporally correlated with the stimulus pattern). However, the precision of entrainment of neuronal activity with vibration declines as the signals from Pacinian afferents ascend to cortical levels (Burton and Sinclair 1991; Ferrington and Rowe 1980; Mountcastle et al. 1969). In primary somatosensory cortex (SI), not all high-frequency vibratory sensitive (HFVS) neurons are vibration-entrained (Ferrington and Rowe 1980; Mountcastle et al. 1969). Mountcastle and coworkers (1969) suggested that the predominant inputs to vibration-entrained SI neurons are from direct thalamocortical projections, whereas nonentrained (NE) SI neurons may receive higher-order intracortical projections.

Little is known about the role that different types of cortical HFVS neurons play during attentive behavior. In this study, we examined the activity of SI HFVS neurons recorded while monkeys performed vibratory-cued wrist movements. Temporal characteristics of the neuronal responses to vibration were analyzed using circular statistics (Batschelet 1981; Zar 1974) and spike train analysis methods (Mountcastle et al. 1969, 1990; Perkel et al.
1967; Poggio and Viernstein 1964; Rodieck et al. 1962; Surmeier and Towe 1987a,b). Based on the results of these analyses, the activity patterns of groups of vibration-entrained and NE HFVS neurons were compared. Our results suggest that entrained and NE neurons may belong to different hierarchical stages of information processing (Ferrington and Rowe 1980; Mountcastle et al. 1969). Some of these data have been presented previously in preliminary form (Lebedev and Nelson 1994).

Materials and methods

Experimental apparatus and behavioral paradigm

Four adult male rhesus monkeys (Macaca mulatta; monkeys F, G, H, and N) were trained to make wrist flexions and extensions in response to vibrotactile go-cues. The monkeys were cared for in accordance with the NIH Guide for Care and Use of Laboratory Animals (revised 1985). Experimental protocols were approved by the Animal Care and Use Committee of the University of Tennessee, Memphis. The experimental apparatus and behavioral paradigm have been described in detail elsewhere (Nelson 1988; Nelson et al. 1991). Briefly, each animal sat in an acrylic monkey chair with its right forearm on an armrest and its right palm on a moveable plate. One end of the plate was attached to the axle of a brushless d.c. torque motor (Colburn and Evarts 1978). A load of 0.07 Nm was applied to the plate, which assisted wrist extensions and opposed flexions. Feedback of current wrist position was provided by a visual display located 35 cm in front of the animal. This visual display consisted of 31 light-emitting diodes (LEDs). The middle, red LED corresponded to a centered wrist position. Yellow LEDs above and below the middle LED indicated successive angular deviations of 1°. An instructional, red LED was located in the upper left corner of the visual display.

A trial began when the monkey centered the plate. At this time, a movement direction request was given by the instructional LED. If this LED was illuminated, the appropriate movement was extension. Otherwise, flexion was requested. The monkey was required to hold the plate in the centered position until a go-cue was presented. Movements of more than 0.5° from the center position during this hold period canceled a trial. After the center position was held for the required time (e.g., 1.0, 1.5, or 2.0 s; pseudorandomized), the plate was vibrated by driving the torque motor with a sine wave (27, 57, or 127 Hz presented in different blocks of trials). The onset of vibratory stimulation signaled to the monkey that it could make a movement. The amplitudes of angular deflection of the torque motor axle were 0.04°, 0.02°, or 0.005° during 27-, 57-, or 127-Hz vibration, respectively. The resulting plate movements were 69.8, 34.9, or 8.7 μm peak-to-peak, respectively, measured 10 cm distal to the coupling of the handle to the motor. These values of the stimulus frequency and amplitude parallel the frequency-threshold curve for vibrotactile sensitivity in monkey (Mountcastle et al. 1972). Thus, we presumed that the 27-Hz stimulus was detected by adapting cutaneous afferents, whereas the 127-Hz stimulus was better for activating Pacinian afferents, and the 57-Hz stimulus might activate both of these types of cutaneous afferents (Talbot et al. 1968).

Electrophysiological recordings and histology

A stainless steel recording chamber was surgically implanted in order to make extracellular recordings of the activity of SI neurons (see Nelson et al. 1991 for details). The recordings were performed using platinum-iridium microelectrodes (1–2 MΩ). Transdermal penetrations were made daily into the hand representation in SI. The activity of single neurons was amplified and converted into an oscilloscope with a time-amplitude window discriminator (Evarts 1966; Lemon 1984; Nelson 1988; Nelson et al. 1991). Neuronal receptive fields (RFs) were examined by lightly touching punctate skin surfaces, manipulating joints, and palpating muscles. In a series of experiments, the electromyographic (EMG) activity patterns of forearm muscles acting across the wrist were recorded using intramuscular EMG wires (Nelson 1987). EMG activity was converted into pulse data (Nelson 1987; Vlaadia et al. 1988).

At the end of the experiments, electrolytic lesions were made in the cortex by passing a current of 10 μA through a recording electrode for 10–20 s. These lesions provided references for histological reconstruction of the recording sites. The animals were then deeply anesthetized with pentobarbital sodium and transcardially perfused with 10% buffered formol-saline. Histological sections (50 μm) of the cortex were prepared, and recording sites were reconstructed based upon the location of electrode penetrations in sagittal Nissl-stained sections relative to the marking lesions and the recording depth from the cortical surface (see, e.g., Figs. 11, 21). Detailed histological data for these animals have been published elsewhere (Lebedev and Nelson 1995).

Selection of HFVS neurons

We selected neurons that were exclusively sensitive to high-frequency (127 Hz) vibratory stimulation. Neuronal responsiveness to vibratory stimulation at different frequencies was estimated during experimental sessions by running short groups of trials (approx. five trials) at each vibratory frequency and visually inspecting retentive records of neuronal discharges. Next, recording sessions were conducted consisting of ~40 trials for each direction of movement for a given type of go-cue. Recordings using a 57-Hz vibratory go-cue were made first. If a neuron was previously classified as exhibiting greater responsiveness to vibration at either 27 or 127 Hz, the direction of movement was chosen for the next recording session. Recordings at the frequency of least responsiveness were conducted last. Because isolation of action potentials deteriorated during some experimental sessions, recordings at each vibratory frequency were not conducted for every neuron. However, recordings at 57 Hz and at the frequency of maximum responsiveness (if different from 57 Hz) usually were conducted.

Systematic selection of HFVS neurons for this study was done by comparing the neuronal activity during 57-Hz and 127-Hz vibratory stimulation for each neuron that satisfied the following criteria: (1) the neuron's firing rate increased after vibratory stimulus onset at least at one vibratory frequency; (2) this firing rate increase was sustained for at least 75 ms. The onset of vibratory response was calculated using cumulative sum methods (for details, see Lebedev and Nelson 1995; Lebedev et al. 1994; also see Ellaway 1977; Jiang et al. 1991). The magnitude of neuronal activity during vibratory stimulation was quantified as the mean firing rate for the epoch from the vibratory response onset until 125 ms after Fig. 1A–J Records for a vibration-entrained area I neuron. A–H Vibrat...
Fig. 3A,B Classification of neurons. A Scattergram showing the magnitude of vibratory response at 127 Hz and the difference between the responses at 127 Hz and 57 Hz (normalized to the 57-Hz response) for the sample of neurons whose firing rates increased during vibratory stimulation. The group of high-frequency vibratory sensitive (HFVS) neurons was selected using K-means cluster analysis. This method selected four clusters having values that varied across the two data dimensions. The bar graphs to the left side and bottom illustrate the distributions of values across a single dimension and the best-fit Gaussian of that distribution. Hatched bars in these plots and filled circles in the scattergram indicate data from three clusters (not shown) that constituted the HFVS neurons based on the classification scheme described in the text and illustrated in B. B Scattergram showing mean vector lengths (r) during stimulating at 127 Hz and 57 Hz. Entrained type 1 (E1), entrained type 2 (E2), and nentrained (NE) types of neurons were selected initially using the Rayleigh and Rao tests. To the initial group of eight NE neurons, four entries were added (see text). The circled cross-hairs indicates the mean r values (\( \mu \)) in both dimensions for the eight initial NE neurons; dashed lines indicate \( \pm 2 \) SD from these values. The double cross indicates a case for which the r in one dimension was greater than the cutoff value but that had cycle distributions for both stimulation frequencies that were not statistically different from random.

Fig. 2A–J Records for a nonentrained area 1 neuron. Conventions as in Fig. 1. A–H Vibrotactile stimulation at 127 Hz; A′–H′ vibrotactile stimulation at 57 Hz. This neuron had a cutaneous RF located on the fourth digit (I) vibration onset. This endpoint preceded the earliest onset of movement-associated activity. If no vibratory response was detected, the initial point of this analysis epoch was set at 30 ms (i.e., mean onset of vibratory responses). Groups of HFVS and non-HFVS neurons were determined by analyzing two parameters (Fig. 3A). The first parameter, mean firing rate during 127-Hz vibratory stimulation, characterizes the responsiveness to high-frequency vi-
bration. The second, the difference between the firing rate during stimulation at 127 Hz and at 57 Hz, divided by the firing rate during 57-Hz stimulation, describes the relative difference between the responsiveness to the higher and lower frequency vibration. K-means cluster analysis of these parameters separated groups of HFVS and non-HFVS neurons (Everitt 1980; Hartigan 1975).

Analyses of neuronal activity

Neuronal activity exhibited during the performance of the task can be illustrated using multipanel displays (Figs. 1, 2). These displays include conventional discharge histograms (Figs. 1B, B', 2B, B') and raster plots (Figs. 1C, C', 2C, C'). In addition, rasters of inter-spike intervals (ISIs) display the time of occurrence of each spike on the y-axis and that of the succeeding ISI on the x-axis (Figs. 1A, A', Figs. 2A, A'; Wall and Cronly-Dillon 1960). ISI rasters provide additional information about the temporal patterns of neuronal activity and the changes in these patterns during the performance of the task.

Spikes train analyses demonstrated the temporal correlation between the activity of HFVS neurons and the vibratory stimuli. A measure of this correlation is provided by the histograms of spike occurrences with respect to the vibratory cycle (e.g., Figs. 1G, G', 2G, G'). Neurons that preferentially discharge at a particular phase of the vibratory cycle were termed vibration-entrained by convention (Mountcastle et al. 1969). We quantified the degree of entrainment using a circular-statistics parameter, the mean vector length (Batschelet 1981; Zar 1974):

\[ r = \frac{1}{\sqrt{n}} \sqrt{ \left( \frac{1}{n} \sum_{i=1}^{n} \sin(2\pi f_i t) \right)^2 + \left( \frac{1}{n} \sum_{i=1}^{n} \cos(2\pi f_i t) \right)^2 } \]  

(1)

where \( r \) is the mean vector length, \( f_0 \) is the frequency of vibration, \( t \) represents the time of spike occurrence, and \( n \) is the number of spikes. The value of \( r \) can change in the range of 0.0–1.0, where 0.0 corresponds to the uniform cycle distribution and 1.0 corresponds to discharges at a constant phase relative to the stimulus cycle. For cases of bimodal cycle distributions (see, e.g., Fig. 4E, right-hand column) doubling of the angles (i.e., using \( 4\pi f_i t \) instead of \( 2\pi f_i t \) in Eq. 1) was performed during the calculation of \( r \) (Batschelet 1981). To test whether the distributions of neuronal discharges over the stimulus cycle were significantly different from a uniform distribution, we employed the Rayleigh test and Rao’s spacing test (Batschelet 1981; Zar 1974). The Rayleigh test evaluates statistics for \( r \). It is powerful in detecting unimodal angular distributions, whereas Rao’s spacing test is more powerful for detecting multimodal angular distributions.

Additional information about the characteristics of neuronal responses to vibration was provided by examining ISI histograms. During vibratory entrainment, ISIs preferentially occurred near multiples of the vibratory period (e.g., Fig. 1E; Mountcastle et al. 1969; Talbot et al. 1968). In addition to analyzing ISI distributions, we evaluated any serial dependencies of the ISIs that were related to entrainment of neuronal activity to the vibratory stimulus. Serial dependencies were analyzed using joint interval scattergrams, which plot the relationship between immediately adjacent ISIs (e.g., Fig. 1F; Rodieck et al. 1962; Sieber et al. 1991; Surmeier and Towe 1987a,b).

Quantitative characteristics of neuronal activity were compared statistically across groups of neurons (e.g., neurons from different cortical areas, entrained and nonentrained neurons, etc.) using a multifactorial ANOVA (with the Scheffé post hoc test).

**Results**

**Database**

Of a total 808 task-related SI neurons, recorded from the four monkeys, whose firing rates changed in association with go-cue or movement onset, 156 neurons were selected. These were recorded during stimulation at both 57 Hz and 127 Hz and responded to vibration with sustained increases in activity at least at one stimulus frequency (Table 1). Most of these neurons did not exhibit any enhanced responsiveness during 127-Hz vibratory stimulation. The points in Fig. 3A, corresponding to these neurons, formed a compact cluster in the scattergram. However, a small number of neurons had either (1) high firing rates during 127-Hz vibratory stimulation or (2) significant differences between the responsiveness at 127 Hz and 57 Hz when normalized to the latter. Because the separation of these neurons from the rest was not absolutely clear, we used an objective statistical algorithm, a K-means cluster analysis (Everitt 1980; Hartigan 1975), to classify HFVS neurons. This was done to facilitate a binary separation across each of the two data dimensions enumerated above. Thus, for the initial separation, four clusters were used. The cluster with the most members (n=123) corresponded to non-HFVS neurons. The other three clusters were defined as representing HFVS neurons (n=33). Because there was no clear relationship of these clusters to either the cortical location of the neurons or to the temporal characteristics of their activity, all three clusters were grouped together (n=33).

HFVS neurons were observed in all regions of SI. However, they were found more frequently in areas 3b, 1, and 2 than in area 3a (Table 1). Thirty HFVS neurons were tested for RFs. Of these, 22 of 30 neurons were activated by touching the surfaces of the hand. These neurons probably received inputs from dermal or subcutaneous Pacinian corpuscles (Cauna and Mannan 1958; Kumamoto et al. 1993; Sato 1957). Two neurons were activated by passively manipulating single joints. One of these neurons was located in area 3b and one in area 1. These neurons may have received inputs from the Pacinian afferents located in the connective tissue of joints or muscles (Quilliam 1966). Alternatively, these two neurons may have received muscle spindle input. The latter possibility, however, seems less likely because, under these experimental conditions, neurons having clear muscle RFs exhibited neither greater re-
sponsiveness at 127 than 57 Hz stimulation nor exquisitely high firing rates during stimulating at 127 Hz (Lebedev et al. 1994). For each of six neurons, no clear RF was found.

Classification of entrained and nonentrained neurons

Consistent with the results of previous studies (Ferrington and Rowe 1980; Mountcastle et al. 1969), we observed both entrained and NE vibratory responses for HFVS neurons. Figure 1 shows records of an area 1 HFVS neuron whose activity was entrained to the vibratory stimulation at both 127 Hz and 57 Hz. This neuron was more responsive to vibratory stimulation at 127 Hz (Fig. 1A–C) than at 57 Hz (Fig. 1A’–C’). The entrainment to vibration at both frequencies was evident because, in the ISI scattergram, bands were present that corresponded to multiples of the vibratory period (Fig. 1A,A’). Also, peaks at multiples of the vibratory period occurred in the ISI histogram (Fig. 1E,E’). Clusters of ISIs around multiples of the vibratory period also were evident in the joint interval scattergram (Fig. 1F,F’). Cycle distributions and vector plots for both 127 Hz and 57 Hz stimulation showed that neuronal discharges occurred most frequently at preferred phases of the stimulus cycle (Fig. 1G,F,G’,F’). Mean vector lengths (r) were 0.60 and 0.66 at 127 Hz and 57 Hz, respectively. These values were statistically different from those for a uniform cycle distribution (P<0.001, Rayleigh test). Thus, this neuron was vibration-entrained.

In Fig. 2, records are presented for another area 1 HFVS neuron. This neuron responded to 127-Hz vibration with a sustained increase in firing rate (Fig. 2A–C), whereas only a slight transient response occurred during 57-Hz stimulation (Fig. 2A’–C’). This neuron was not vibration-entrained. There was no clustering of ISIs at multiples of the vibratory period (Fig. 2A,E,F,A’,E’,F’), and the cycle distributions were not statistically different from a uniform distribution (r=0.05 at 127 Hz and 57 Hz; P>0.1 for both Rayleigh and Rao’s tests; Fig. 4G,H,G’,H’).

HFVS neurons were separated into groups according to their degree of vibratory entrainment (Fig. 3B). The characteristic mean vector lengths used to classify neurons as entrained or NE were calculated in the following manner. First, the neurons were classified as NE if they had cycle distributions for both vibratory frequencies that were not statistically different from a uniform distribution (n=8; P>0.05 for both the Rayleigh and Rao’s test). The mean and standard deviation of r for this group were calculated for each vibratory frequency. Cutoff values were then set to the NE mean values of r plus 2 SDs for 57 Hz and 127 Hz, respectively (Fig. 3B). This procedure resulted in the addition of four neurons having low r values to the NE group (n=12). The remaining HFVS neurons were separated into two additional groups. The entrained type 1 (E1) group included 16 neurons having r values that were greater than the cutoff values for both 57 Hz and 127 Hz. The entrained type 2 (E2) neurons consisted of 5 neurons with r values greater than the cutoff for only one vibratory frequency.

Spike train analyses

The temporal characteristics of entrained responses to vibration differed depending on the magnitude of the vibratory response. In Fig. 4, the results of spike train analyses are presented for three entrained neurons that had different firing rates during 127-Hz vibratory stimulation. One neuron had a firing rate of 111 spikes/s (Fig. 4A–E, left-hand column). This neuron was classified as an E1 neuron. Its cycle distribution was unimodal (Fig. 4E, left). The ISI histogram (Fig. 4C, left) and joint interval scattergram (Fig. 4D, left) showed the presence of ISIs at multiples of the vibratory period, as well as the presence of short ISIs (less than 5 ms). The ISI clusters in the joint interval scattergram corresponding to multiples of the vibratory period had visible diagonal orientations. Diagonal orientations of ISI clusters indicate that ISIs which are shorter than the average are likely to be followed by ISIs longer than the average. This type of serial dependency commonly occurs when neuronal responses to rhythmic driving fluctuate in time because of synaptic noise (Surmeier and Towe 1987b). Similar serial dependencies have been described as negative serial correlations, because they typically have negative serial correlation coefficients (Perkel et al. 1967). In this study, the analyses of serial correlations were restricted to qualitative observations. We did not calculate serial correlation coefficients by the conventional algorithm (i.e., by calculating mean ISI and considering differences between each ISI and the mean) because, in our case, ISIs were distributed in clusters rather than unimodally.

The other two neurons whose records are shown in Fig. 4A–E, middle column and right-hand column, discharged, on average, more often than once per stimulus cycle in response to 127-Hz vibratory stimulation. These neurons were from groups E2 and E1, and their firing rates were 154 spikes/s and 178 spikes/s, respectively. For these neurons, the proportions of ISIs at multiples of the vibratory period were less and the proportions of short intervals were more than for the neuron illustrated in Fig. 4A–E, left-hand column. In addition, the joint interval histograms for these neurons contained diagonal bands spanning the points corresponding to the vibratory period on both axes (7.87 ms). These bands, signifying another form of negative serial correlation, are indicative of “interrupting” spikes that occurred between responses to rhythmic driving inputs (Surmeier and Towe 1987a,b). For the neuron with the highest firing rate, the cycle distribution was bimodal (Fig. 4E, right-hand column). It contained two peaks separated by approximately 120° of phase. Probably, these peaks occurred because of responses to both the application and
Fig. 4A–E  Spike train analyses of neuronal responses to 127-Hz vibration for three vibration-entrained neurons. A Histograms of activity aligned on vibration onset (bin width 5 ms, wrist flexion trials). Cortical locations of neurons, their types according to the degree of vibratory entrainment, movement directions, mean firing rates, and vibratory response latencies are indicated. B Raster displays of discharges. Trials are ordered by reaction time. C Histograms of interspike intervals (bin width 0.5 ms). D Joint interval scattergrams. E Cycle distribution histograms (bin width 10°). Vector representations of cycle distribution histograms are shown as insets. Mean vector lengths are indicated withdrawal of the stimulus (Alloway et al. 1988; Talbot et al. 1968).

The spike trains of NE neurons recorded during vibratory stimulation had unique temporal properties. Most notable were the shapes of ISI distributions and the patterns within the joint interval scattergrams. However, these properties did not reflect any temporal "signature" of the vibratory stimulus. In Fig. 5, the results of spike train analyses are presented for three NE neurons. The shapes of
the ISI distributions and of the joint interval histograms varied with the firing rates of the neurons. No signs of correlations of neuronal discharges with the vibratory stimuli were present in the ISI distributions (Fig. 5C), joint interval scattergrams (Fig. 5D), or cycle distributions (Fig. 5E).

Vibratory response magnitude and latency

The firing rates exhibited during different epochs of the paradigm and the latencies of neuronal responses to vibration were compared for E1 and E2 and the NE neurons. In Fig. 6A–C, mean firing rates exhibited during the hold period and during stimulating at 57 Hz and 127 Hz are presented for each type of HFVS neurons. For E1 neurons, the values for each measure were less
Fig. 6A–F Analyzes of the magnitudes and latencies of vibratory responses. A–C Plots depict mean firing rates during the hold period, 57-Hz and 127-Hz vibratory stimulation for E1 (A), E2 (B), and NE (C) neurons. D,E Scattergrams indicating latencies of the responses to 127-Hz (D) and 57-Hz (E) vibration for neurons of different types (E1, E2, NE), and cortical locations (areas 3a, 3b, 1, and 2). F Means and standard deviations of vibratory response latency by cortical location, neuronal type, and vibratory frequency.

variable (Fig. 6A) than for E2 (Fig. 6B) and NE neurons (Fig. 6C). In general, NE neurons had lower firing rates. The difference between the firing rates of E1 and NE neurons was statistically significant only for 57-Hz stimulation ($P=0.005$, ANOVA). Given the large variability in firing rates, this mean difference could result from a greater number of neurons with low firing rates (less than 50 spikes/s) in the NE group, as compared to the E1 group. Firing rates were not different statistically as a function of cortical location within SI.

Vibratory response latencies may provide information about whether or not there is a hierarchical relationship between the neurons of different types. In Fig. 6D,E, vibratory response latencies for different types of neurons are presented in scatterplots. Statistical analyses (ANOVA) showed significant differences in response latencies that were related to cortical location of the neurons and the degree of entrainment. Area 2 neurons responded to 127-Hz vibration onset, on average, later than the neurons located in areas 3a, 3b, and 1 ($P<0.005$; see an example in Fig. 5A,B, left-hand column). However, re-
spontaneous latencies were not significantly different for neurons located in areas 3a, 3b, and 1. Means and standard deviations of these latencies by area were 16.5±1.6, 19.8±5.9, 21.4±6.4, and 35.6±13.8 ms, for areas 3a, 3b, 1, and 2, respectively. Thus, when comparing response latencies of entrained and NE neurons, we considered area 2 neurons separately, and area 3a, 3b, and 1 neurons as one group (Fig. 6F). For the latter group, vibratory response latencies for E1 neurons were significantly less than those for NE neurons during both 57-Hz and 127-Hz stimulation. Latencies for E2 neurons were intermediate between latencies for E1 and NE neurons, but statistically different only from NE neurons during 127-Hz stimulation. For area 2 neurons, there was a trend for type E1 neurons to have short response latencies than type E2 and NE neurons. The sample of area 2 neurons was too small to determine statistically significant differences.

Premovement changes in activity

Like the activity patterns of other SI neurons (Cohen et al. 1994; Evarts 1972; Fromm and Evarts 1982; Lebedev and Nelson 1995; Lebedev et al. 1994; Nelson 1987, 1988; Nelson and Douglas 1989; Nelson et al. 1991; Shin and Chapin 1990; Soso and Fetz 1980), firing rates of HFVS neurons changed prior to movement onset. However, these changes often were small and/or inconsistent from trial to trial (see Figs. 1, 2, 4, 5). When activity changes occurred, these more often were decreases in firing rate that began before movement onset. During 127-Hz vibratory-cued trials, decreases, increases, or no change in firing rate were observed in 14, 7, and 12 instances, respectively, for flexion movements, and in 15, 7, and 11 instances for extension movements. For 17 neurons, in addition to vibratory-cued trials, records also were obtained during visually cued trials (for details, see Nelson and Douglas 1989; Nelson et al. 1991). Unlike premovement changes in activity during vibratory cued trials, firing rate increases more often were observed during visually cued trials (3, 13, and 1 instances of decreases, increases, and no change, respectively, during flexion movements; and 1, 14, and 2 instances during extension movements). It should be noted, however, that, although firing rates decreased during vibratory-cued trials, these firing rates typically were higher than those during corresponding epochs of the visually cued trials. Similar differences in premovement activity patterns during vibratory and visually cued trials have been described and discussed elsewhere (Nelson and Douglas 1989). The onsets of premovement activity for HFVS neurons were compared with the EMG onsets for different forearm muscles for two of the monkeys (Nelson 1987; Lebedev et al. 1994). EMG onsets provided estimates of the probable time of arrival of movement-related peripheral activity in SI. A minimal conduction time of 11 ms from periphery to cortex was subtracted from the EMG onsets (Wiesendanger and Miles 1982). The earliest time at which muscle activity preceding movement might arrive in SI was thus ~100 ms prior to movement onset. Most (~80%) of the premovement activity changes of HFVS neurons occurred closer to movement onset. Thus, these changes certainly could be related to those in the periphery that resulted from impending movements.

Discussion

We examined the activity of HFVS neurons located in monkey SI during the performance of vibratory-cued hand movements. The small proportion of HFVS neurons constituting ~4% of the total sample of recorded task-related neurons is consistent with those reported in previous studies. Mountcastle et al. (1969) reported that only about 6% of SI neurons belonged to the Pacinian class. The relative number of HFVS neurons in SI is comparable with the proportion of Pacinian fibers in peripheral nerves (~9%; Talbot et al. 1968). HFVS neurons more frequently were observed in areas 3b, 1, and 2 than in area 3a, perhaps because area 3a neurons receive inputs mostly from muscle afferents (see Jones 1986; Kaas 1993 for review). Several previous studies demonstrated concentrations of Pacinian-like neurons in area 1, but not in area 3b (Hyvärinen and Poranen 1978; Iwamura et al. 1983a, 1993; Paul et al. 1972). However, Mountcastle et al. (1969, 1990) observed Pacinian-like neurons in both areas 1 and 3b, although reporting them to be somewhat more numerous in area 1. We observed HFVS neurons in approximately equal proportions in areas 1 and 3b. Our selection of HFVS neurons was based on the comparison of neuronal responses to a lower (57 Hz) and a higher (127 Hz) frequency vibration which served as go-cues in our behavioral task. The necessity of detecting vibratory stimuli in an active movement task may influence sensory responsiveness. Some HFVS neurons that we recorded were vibratory-responsive during the task, yet did not exhibit clear responses during passive RF tests. In the studies of Hyvärinen and Poranen (1978), Iwamura et al. (1983a, 1993), and Paul et al. (1972), animals were not engaged in task performance. Thus, the manner in which neuronal responsiveness was tested in these studies was different from ours. In addition, in these studies, large RF size was regarded as one of the essential criteria for selecting Pacinian-like neurons. Since neurons in area 1 generally have larger RFs than those in area 3b (Hyvärinen and Poranen 1978; Iwamura et al. 1983b, 1993), this selection criterion may have favored the selection of area 1 cells.

Area 2 HFVS neurons responded to vibration onset with longer latencies than the neurons located in areas 3a, 3b, and 1. This observation is consistent with the known pattern of corticocortical connectivity of SI, in which area 2 receives substantial input from the more anterior SI areas (Jones 1975, 1986; Jones and Powell 1970; Kaas 1993; Vogt and Pandya 1978). In addition, longer vibratory response latencies of area 2 neurons are...
consistent with the progressive spatial convergence of connections of SI neurons along the rostrocaudal axis (Hyyräinen and Poranen 1978; Iwamura et al. 1983b, 1993).

HFVS neurons were split into three groups based on the degree of correlation between the neuronal activity and the temporal characteristics of the vibratory stimulus. We proposed two groups of vibration-entrained neurons, groups E1 and E2, and one group of NE neurons. For both types of vibration-entrained neurons, clustering of ISIs at multiples of the vibratory period was observed. In some instances, ISI clusters in joint interval scattergrams had diagonal orientations that can be described as negative serial correlations of the ISIs (Perkel et al. 1967; Surmeier and Towe 1987a, 1987b). Diagonally oriented ISI clusters occur, in some cases, because of nonprecise time-locking of neuronal discharges to the stimulus and, in other cases, because of the presence of “interrupting” spikes at less than the modal interval (Surmeier and Towe 1987a, 1987b). In our case, these spike train features were related to the extrinsic origin of rhythmic activity (i.e., rhythmic peripheral stimulus). We suggest that similar spike trains may occur in cases when rhythmic driving originates in the cortex itself rather than coming from the periphery, for example during 40-Hz cortical oscillations (for review, see Gray 1994).

NE neurons had low indices of entrainment, which corresponded to little or no correlation of their activity to vibration. Spike trains had unique features (i.e., the shape of ISI distribution) which probably reflected intrinsic discharge properties of these neurons, as well as the temporal properties of their inputs. However, no indications of temporal correlation of discharges with the stimulus were evident in ISI histograms and joint interval plots.

The activity of vibration-entrained and NE HFVS neurons previously has been described (Ferrington and Rowe 1980; Mountcastle et al. 1969). In these studies, it was suggested that entrained neurons are the major targets of thalamocortical projections, and may actually be stellate neurons of cortical layers 3 and 4. Furthermore, it was suggested that NE neurons probably are pyramidal cells that receive inputs from the entrained neurons. During transmission of vibration-related activity and its integration with other inputs, the fine temporal characteristics of vibratory signals may become obscured. Our data may be interpreted to suggest that information flows from entrained to NE neurons. Indeed, the latency of the vibratory response was shorter for entrained neurons (e.g., E1 neurons) in comparison with NE neurons. Therefore, entrained neurons may receive thalamocortical signals first and then transmit them to NE neurons.

Mountcastle et al. (1969) suggested that Pacinian information may be encoded differently by entrained and NE neurons. For entrained neurons, the fine temporal structure of spike trains appears to encode the frequency and amplitude characteristics of the vibratory stimulus. From our observations, several encoding principles may be suggested for entrained neurons. Spike periodicity may encode the stimulus frequency (Mountcastle et al. 1969). The stimulus amplitude may be indicated by the relative number of ISIs around the vibratory period. Thus, with decreases of stimulus amplitude, more ISIs may occur around multiples of the vibratory period than around the vibratory period itself. In addition, short ISIs (less than 5 ms) may contribute to the encoding of stimulus amplitude. Spikes that are separated by short ISIs may produce stronger effects at postsynaptic sites than those separated by long ISIs because of temporal summation of PSPs (Eccles 1964). The encoding principles for NE neurons remain unclear. A rate code, and/or a population code are the probable coding principles for these neurons (Mountcastle 1969; Nicolelis et al. 1995; Perkel 1970; Stein 1967).

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Fig. 1. Long-range synchronization is influenced by stimulus coherence. Multunit activity was recorded from two sites in area 17 of cat visual cortex that were separated by 7 mm. The two cell groups preferred vertical orientations. (A), (B), (C) Plots of the receptive fields. The collinear arrangement of the fields allowed the comparison of three different stimulus paradigms: a long continuous light bar moving across both fields (A), two independent light bars moving in the same direction (B), and the same two bars moving in opposite directions (C). The circle represents the center of the visual field, and the thick line drawn across each receptive field indicates the preferred orientation. (D), (E), (F) The respective crosscorrelograms obtained with each stimulus paradigm. Using the long light bar, the two oscillatory responses were synchronized, as indicated by the strong modulation of the correlogram with alternating peaks and troughs (D). If the continuity of the stimulus was interrupted, the synchronization became weaker (E), and it totally disappeared if the motion of the stimuli was incoherent (F). This change of the stimulus configuration affected neither the strength nor the oscillatory nature of the two responses (not shown). The graph superimposed on each of the correlograms represents a Gabor function that was fitted to the data to assess the strength of the modulation. The number in the upper right corner indicates the 'relative modulation amplitude', a measure of correlation strength that was determined by computing the ratio of the amplitude of the Gabor function to its offset. Abbreviation: ns, not significant. Scale bars indicate the number of spikes.
Baker, Olivier, Lemon (1997)

Figure 1. Synchronous slow wave oscillations during precision grip task
Example of a section of recording showing slow waves from two cortical sites (SW1 and SW2), together with the position of finger and thumb levers. Oscillations appear during the hold period of the task, which appear synchronous between the two sites. Data in this and subsequent figures are from monkey 29, unless otherwise specified.
Cortical population oscillations

In visual cortex
Occur during visual stimulation
Occur in groups of neurons whose firing represents different features of the same visual object
May, therefore, have a role in perceptual binding

In sensorimotor cortex
- Occur during attentive behavior
- Precede movements
- The role is unclear

Single-unit records may provide a more detailed information about oscillations

Primary somatosensory cortical neurons entrained to vibrotactile stimulation: a model of single-unit oscillator

Rhythmically firing primary somatosensory cortical neurons: any specific activity modulation in a reaction-time task?

Dorsal premotor cortical neurons: these neurons are active during epochs preceding movements. Do they oscillate?
Figure 3.4. Analyses of rhythmic activity.

Spike trains for the hold period (500 ms epoch preceding vibration onset; same records as in Figure 3.5) were analyzed. A: Hold period interspike interval (ISI) scattergram for 40 consecutive trials. Each column represents a trial. B: Joint interval scattergram showing the relationship between immediately adjacent ISIs. C: Interspike interval distribution. D: Expectation density histogram. E: Renewal density histogram. In panels C - E, bin width is 1 ms.
A: An example of expectation density (ED) histogram. The spike train was computer-generated to have a normal distribution of the interspike intervals and a coefficient of variation of 0.15. \( R \) is the stabilized level of the histogram, \( E_1, E_2 \) are the heights, and \( t_1, t_2 \) are the times of the initial two peaks. B: Histograms of the distribution of the ratio of the first peak to stabilized ED level (\( E_1 / R \)) for rhythmically firing and nonrhythmically firing SI neurons. C-D: Scattergrams illustrating selection of rhythmically firing neurons based on the heights of ED peaks and the jitter of interpeak intervals.
Figure 3.6. Histogram of the distribution of the firing frequency for the total sample of rhythmically firing neurons
Figure 3.10. A typical example of premovement activity.

A: Records for a rhythmically firing (~44 Hz) area 2 neuron (conventions as in Figure 3.5). Vibratory frequency was 57 Hz. B: No clear receptive field was found for this neuron. C: The neuron’s cortical location. D: Analyses of rhythmic activity during the hold period (conventions as in Fig. 3.4). E: A schematic illustration of the typical premovement activity (PMA) pattern, i.e., an activity decrease. F: The frequency distribution histogram of PMA onsets with respect to movement onset.
Figure 3.11. Transition of neuronal activity from a rhythmic to a nonrhythmic pattern during activation.

A: Records for a rhythmically firing (~28 Hz) area 1 neuron (conventions as in Figure 3.5). B: Receptive field schematic. This neuron was activated by passive extension of the second digit at the metacarpophalangeal joint. C: The neuron’s cortical location. D: Analyses of rhythmic activity during the hold period (conventions as in Figure 3.4). E: Analyses of activity for the epoch of activation (50-150 ms with respect to movement onset; conventions as in Figure 3.4; expectation and renewal density histograms were not calculated).
Gray and McCormick (1996)
Fig. 2. Electrophysiology of sparsely spinous neurons of the cortex. (A) Subthreshold oscillation at approximately 42 Hz generated by a depolarizing current pulse. The autocorrelogram shows a 24-msec peak-to-peak interval. (B) Same recording as A but at a slower sweep speed demonstrates the all-or-none nature of oscillatory events. The first pulse generated an oscillatory response that outlasted the duration of the stimulus. The second pulse depolarized the cell slightly and produced two action potentials. Note that the subthreshold oscillatory frequency was not modified by the prolonged current pulse (A and B). The plateau potential that generated the oscillation disappeared abruptly in the middle of the second current pulse. (C) Subthreshold oscillation in another neuron having a frequency of the order of 38 Hz and generated by a DC current injection. Upon further depolarization (between arrows) spikes were generated at the peaks of subthreshold oscillatory events without modifying the oscillatory frequency. (D) Superposition of six action potentials from the cell in C demonstrates their time course and AHP waveform. (E) Characteristics of the action potentials are illustrated at a faster sweep speed. (F–H) Effect of TTX on a third cell. (F) Control. (G) TTX blocked the oscillatory potentials after 2 min. (H) TTX blocked all activity after 5 min. (Differences in the blocking time between these records and those in Fig. 3E reflect a difference in the depth of the recorded cells rather than a different sensitivity to TTX.) (I) Camera lucida drawing of narrow-frequency oscillatory neuron labeled intracellularly with horseradish peroxidase. (Inset) Location of neuron in cortical layer 4.
Fig. 12. A model of rhythmically active SI neurons as tonic inhibitory interneurons that gate the activity of cortical output neurons. Synapses marked black represent inhibitory interactions, while those marked white represent excitation. Line thickness corresponds to the strength of the connections.
A

All Spikes

Murthy and Fetz (1996)

B During Oscillations

C Outside Oscillations

-100 0 100

Delay (ms)

40 Hz

0
Unit 12-7; Rightward Movements

Unit 12-6; Leftward Movements

dol2-7/6-DIR-right/left
Rhythmically Firing (20–50 Hz) Neurons in Monkey Primary Somatosensory Cortex: Activity Patterns During Initiation of Vibratory-Cued Hand Movements

MICHAEL A. LEBEDEV AND RANDALL J. NELSON
Department of Anatomy and Neurobiology, University of Tennessee, Memphis, 875 Monroe Ave, Memphis, TN 38163, USA
nelson@utmem1.utmem.edu

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Rhythmically Firing (20–50 Hz) Neurons in Monkey Primary Somatosensory Cortex: Activity Patterns During Initiation of Vibratory-Cued Hand Movements

MICHAEL A. LEBEDEV AND RANDALL J. NELSON

Department of Anatomy and Neurobiology, University of Tennessee, Memphis, 875 Monroe Ave, Memphis, TN 38163, USA
mlenson@utmem1.utmem.edu

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Abstract. The activity patterns of rhythmically firing neurons in monkey primary somatosensory cortex (SI) were studied during trained wrist movements that were performed in response to palmar vibration. Of 1,222 neurons extracellularly recorded in SI, 129 cells (~11%) discharged rhythmically (at ~30 Hz) during maintained wrist position. During the initiation of vibratory-cued movements, neuronal activity usually decreased at ~25 ms after vibration onset followed by an additional decrease in activity at ~60 ms prior to movement onset. Rhythmically firing neurons are not likely to be integrate-and-fire neurons because, during activity changes, their rhythmic firing pattern was disrupted rather than modulated. The activity pattern of rhythmically firing neurons was complimentary to that of quickly adapting SI neurons recorded during the performance of this task (Nelson et al., 1991). Moreover, disruptions of rhythmic activity of individual SI neurons were similar to those reported previously for local field potential (LFP) oscillations in sensorimotor cortex during trained movements (Sanes and Donoghue, 1993). However, rhythmic activity of SI neurons did not wax and wane like LFP oscillations (Murthy and Fetz, 1992; Sanes and Donoghue, 1993). It has been suggested that fast (20–50 Hz) cortical oscillations may be initiated by inhibitory interneurons (Cowan and Wilson, 1994; Llinas et al., 1991; Stern and Wilson, 1994). We suggest that rhythmically firing neurons may tonically inhibit quickly adapting neurons and release them from the inhibition at go-cue onsets and prior to voluntary movements. It is possible that rhythmically active neurons may evoke intermittent oscillations in other cortical neurons and thus regulate cortical population oscillations.

Keywords: hand movement, monkey, neuronal activity, rhythmic firing, somatosensory cortex, vibration

Introduction

During the execution of motor tasks, large groups of sensorimotor cortical neurons intermittently become involved in coherent rhythmic activity (Murthy and Fetz, 1992; Sanes and Donoghue, 1993). Rhythmic activity has been suggested to be a functionally important type of neuronal firing that may serve to switch between behavioral modes and to establish dynamic coupling between cortical areas (for review, see Gray, 1994; Llinas, 1990; Lopes da Silva, 1991; Sheer, 1989; Singer, 1993; Steriade, 1993). Rhythmic activity in the form of local field potential (LFP) oscillations at ~40 Hz has been studied most extensively in cat visual cortex (Eckhorn et al., 1988; Gray and Singer, 1989; for review, see Engel et al., 1992; Gray et al., 1991; Gray, 1994; Singer, 1993). Similar LFP oscillations have been demonstrated in sensorimotor cortex in cat (Bouyer et al., 1981, 1987) and in monkey (Murthy and Fetz, 1992; Rougol et al., 1979; Sanes and Donoghue, 1993). In these studies, it was suggested that oscillations in motor and sensory cortical areas play a role during behavior in sensorimotor integration and focal attention.

Individual neurons having oscillatory properties may be important for the initiation of cortical oscillations (Llinas, 1990; Steriade, 1993). Single morphologically identified neurons with 40-Hz rhythmicity, probably inhibitory interneurons, have been recorded in cortical slice preparations (Llinas et al., 1991). The
presence of fast (~40 Hz) rhythmic IPSPs has been demonstrated while recording from pyramidal cortical neurons in vivo in urethane-anesthetized rats (Cowan and Wilson, 1994; Stern and Wilson, 1994). These rhythmic IPSPs may have resulted from cortical interneuronal inputs. In addition, depolarization-induced 20- to 40-Hz oscillations have been reported for a subset of cortical neurons with long axons recorded in vivo in urethane-anesthetized cats (Núñez et al., 1992). Therefore, both intrinsic properties and extrinsic circuitry may be involved in generating rhythmic activity.

While the majority of data demonstrating oscillations in sensorimotor cortical areas has been obtained while recording LFPs during behavior (Bouyer et al., 1981; 1987; Murthy and Fetz, 1992; Rougeul et al., 1979; Sanes and Donoghue, 1993), some studies have examined rhythmic activity of single neurons. Murthy and Fetz (1994) described monkey sensorimotor cortical neurons that intermittently generated rhythmic discharges during episodes of LFP oscillations. Ahissar and Vaadia (1990) reported that second somatosensory cortical (SII) neurons recorded in awake monkeys often exhibited rhythmic activity that was sustained during immobility. The pattern of rhythmic firing of these SII neurons was disrupted by tactile stimulation or during voluntary movements. Ahissar and Vaadia (1990) suggested that oscillatory activity of SII neurons may be important for texture analysis. The functional role of rhythmically active neurons in the primary somatosensory cortex (SI) of behaving animals is not completely understood.

To determine the changes in activity patterns of rhythmically firing SI neurons during the initiation of somatosensory-cued movements, we analyzed data from experiments in which monkeys performed voluntary wrist flexions and extensions in response to vibrotactile go-cues. We examined the characteristics of rhythmic spike trains during a period when vibration was not present as well as how these spike trains changed in association with the presentation of vibrotactile go-cues and movement initiation. Also, we sought to relate the activity of rhythmically firing neurons with that of other SI neurons recorded during the same experimental paradigm (Nelson, 1988; Nelson et al., 1991; Lebedev et al., 1994). Based on these observations, we constructed a model depicting how rhythmically firing neurons may influence the firing patterns of other cortical neurons. Some of the data have been presented previously in preliminary form (Lebedev and Nelson, 1993).

**Methods**

**Experimental Apparatus and Behavioral Paradigm**

Six adult male rhesus monkeys (Macaca mulatta; monkeys C, F, G, H, M, and N) were trained to perform sensory-triggered wrist movements. The monkeys were cared for in accordance with the NIH Guide for Care and Use of Laboratory Animals, revised 1985. Each animal sat in an acrylic monkey chair with its right forearm on an armrest and its right palm on a moveable aluminum plate (Fig. 1(A)). One end of the plate was attached to the axle of a brushless DC torque motor (Colburn and Evarts, 1978). A load of 0.07 Nm was applied to the plate, which assisted wrist extensions and opposed flexions. Thus, to maintain a centered wrist position, the monkeys had to maintain pressure upon the plate using the palmar surface of their hands. Feedback of wrist position was provided by a visual display located 35 cm in front of the animals. This display consisted of 31 light-emitting diodes (LEDs) (Fig. 1(B)). Current wrist position was indicated by illuminating one of the LEDs. The middle, red, LED corresponded to a centered wrist position. Yellow LEDs above and below the middle LED indicated successive angular deviations of 1°.

Each monkey was trained to make untargeted ballistic wrist flexions or extensions in response to vibrotactile stimulation of their palms through the plate (Nelson, 1988; Nelson et al., 1991). Movements were executed by the same hand that was stimulated. The experimental paradigm is illustrated in Fig. 1(C). To begin a trial, the monkey first centered the plate. At this time, a movement direction request was given by the presence or absence of illumination of an instructional red LED. This LED was located in the upper left corner of the visual display (Fig. 1(B)). Illumination of this LED signaled that extension was the appropriate movement. If this LED was not illuminated, the appropriate movement was flexion. The monkey was required to hold the plate in the centered position for 0.5, 1.0, 1.5, or 2.0 s (pseudorandomized). Movements of more than 0.5° from the center during this hold period canceled the trial. After the monkey successfully completed the hold period, the plate was vibrated by driving the torque motor with a sine wave at 27, 57 or 127 Hz. The angular deflection of the handle during the vibration was less than 0.06°. The onset of vibratory stimulation thus served as a cue for movement. When a movement of at least 5° in the required direction was
made, the vibration was turned off, and the animal received a fruit juice reward. A new trial began when the animal once again centered the plate.

**Electrophysiological Recordings and Histology**

Once an animal achieved stable performance in the task (~2,000 rewarded trials per experimental session), a stainless steel recording chamber was surgically implanted over the skull to allow for extracellular recordings of the activity of SI neurons (see Nelson et al., 1991, for details). Transdural penetrations were made daily into the region of SI that represented the contralateral hand. Platinum-iridium microelectrodes with impedances of 1–2 MOhms were used for recordings. The depth of the electrode was varied to achieve the best isolation between the neuronal waveform in question and other visible neuronal activity. The activity of single units was amplified and discriminated using a time window discriminator having two independently controllable window thresholds. Each channel (upper and lower window) of the discriminator was armed by a waveform's first crossing of that threshold. An acceptance pulse of 0.2 ms was issued when that threshold was recrossed. The time from initial threshold crossing to the end of the acceptance pulse was typically on the order of 0.5 ms. As well, the electronic refractory period of the entire data collection system while running the paradigm was confirmed to be on the order of 0.4 ms by analyzing recordings of white noise. Pulse data was stored in a computer by conventional means (Evarts, 1966; Lemon, 1984).

Neuronal receptive fields (RFs) were manually examined outside the task by lightly touching skin surfaces with hand-held probes, manipulating joints, and palpating muscles. An RF was classified as "cutaneous" if the neuron preferentially responded to light touch, and as "deep" if the neuron responded to bending a joint or to muscle palpation. To ensure that stimulation of overlying skin was not mistaken as a response from a muscle, the skin was displaced laterally and the muscle again palpated. For some neurons, no clear RF could be found.

At regular intervals, the EMG activity of forearm muscles acting across the wrist was recorded (Nelson, 1987). Intramuscular EMG wires (stranded stainless steel, TEFLO® insulated; Bergen Wire Rope Co.) were temporarily implanted in muscles by using sterile 25-gauge needles as guides. EMG activity was converted into pulse data with a window discriminator (Vaadia et al., 1988; Lebedev et al., 1994) and stored in the same form as the neuronal data.

On the last recording day, electrolytic lesions (10 μA of current for 10–20 s) were made in the cortex to mark locations of interest. The animals were then deeply anesthetized with sodium pentobarbital and
transcardially perfused with 10% buffered formol-saline. Histological sagittal sections of the cortex were prepared, and recording sites were reconstructed based upon the depth of each electrode penetration and its location with respect to the marking lesions (Fig. 2) (Nelson, 1988; Nelson et al., 1991).

Analyses of Rhythmic Spike Trains

Rhythmically firing SI neurons were selected by examining the 500-ms epoch of the spike trains that immediately preceded vibration onset. This corresponded to the shortest duration of the hold period during which an animal actively maintained a stable wrist position. Because of this time limit, slow rhythmic activity (<8 Hz) could not be detected. Conclusions on whether neurons fired rhythmically or nonrhythmically were made by examining the expectation density (ED) histograms (Mountcastle et al., 1969, 1990). ED, also termed the "autocorrelation function" (Zadeh, 1957), represents the probability of a neuronal discharge at a certain time after a given discharge. For rhythmic spike trains, ED histograms contain peaks at multiples of the rhythmic period (Fig. 3(A)) (Perkel et al., 1967; Poggio and Viernstein, 1964; Segundo et al., 1968). The average height of subsequent bins in the ED histogram gradually flattens to a stabilized level (Fig. 3(A)). We quantified the degree of rhythmicity as the ratio of the height of the first ED peak to the stabilized level of ED histogram:

\[
E_1' = \frac{E_1}{R},
\]

where \(E_1'\) is the normalized height of the first peak measured from zero level, \(E_1\) is the height of the first peak, and \(R\) is the stabilized level. The stabilized level was calculated by averaging ED bins in the range 0 to 200 ms.

The selection of rhythmically firing neurons was made using four criteria: (1) mean firing rate of the selected neurons during the hold phase of the paradigm exceeded 10 spikes/s; (2 and 3) the heights of the first and second ED peaks were greater than 1.5 \(R\) and 1.2 \(R\), respectively (Fig. 3(C), (D)); (4) time intervals from zero to the first peak \((t_1, \text{Fig. } 3(A))\) and from the first to the second peak \((t_2 - t_1)\) differed by less than 15% (percentage Jitter, Fig. 3(D)). Criterion 1 was used to initially select the population of tonically active neurons. Criterion 2 was chosen because the distribution of \(E_1'\) for tonically active neurons indicated a major subpopulation with \(E_1'\) in the range of nonrhythmically firing (1~1.5) and a smaller subpopulation of the neurons with \(E_1' > 1.5\) (Fig. 3(B)~(D)). Criteria 3 and 4 previously have been used by Ahissar and Vaadia (1990) and confirmed the presence of multiple peaks in ED histogram. The distributions of \(E_1'\) for the selected groups of rhythmically and nonrhythmically firing neurons were statistically different \((p < 0.0001\); unpaired \(t\)-test) and had a small overlap in the range of \(E_1'\) from 1.5 to ~2.0 (Fig. 3(B)). For rhythmically active neurons, their rhythmic frequency was calculated as

\[
f = \frac{2}{(t_1 + (t_2 - t_1))},
\]

where \(f\) is rhythm frequency and \(t_1, t_2\) are the intervals from zero to the first and second peaks, respectively. Some ED histograms showed qualitative features that were characteristic of bursty activity pattern (Wilson et al., 1977; Wilson and Groves, 1981). These ED histograms indicated high probability of firing at very short intervals after spike generation (<10 ms). Firing probability then decayed gradually to the stabilized level over a period of 20~50 ms. Bursty neurons were excluded from these analyses.

Renewal density (RD) histograms and joint interval plots were calculated to determine the degree of serial dependency in the spike trains. We sought to determine whether the rhythmic spike sequences of SI neurons were reset after the occurrence of each discharge (that is, could be described as a renewal process) (Perkel et al., 1967) or more complex serial dependencies of the ISIs were present. Nonrenewal spike trains often occur when a neuron is rhythmically driven by external inputs (Mountcastle et al., 1969, 1990; Surmeier and Towe, 1987a, 1987b). Joint interval scattergrams display each ISI as a function of its immediately preceding ISI (Fig. 4(B)). Joint interval methods have been used to analyze serial dependencies of the ISIs (Rodieck et al., 1962; Surmeier and Towe, 1987a, 1987b; Siebler et al., 1991). Another technique for detecting serial dependencies of the ISIs is the RD method (Mountcastle et al., 1969, 1990; Perkel et al., 1967; Poggio and Viernstein, 1964). RD is the ED calculated for randomly shuffled ISI sequences (Fig. 4(D), (E)). For a simple renewal process, ED and RD histograms are not different. However, if serial dependencies of the ISIs are present, these histograms may be different. Thus, in the case of externally driven activity, a peak in a RD histogram is smaller than the corresponding peak in the ED histogram (Mountcastle et al., 1969, 1990). To estimate the difference between ED and RD histograms, we compared the magnitudes of the first and second
Fig. 2. Cortical locations of rhythmically firing SI neurons. (A) A drawing of the dorsolateral view of the brain. Central sulcus (CS) and intraparietal sulcus (IPS) are indicated. (B) A table showing the number of rhythmically firing neurons by receptive field (RF) type recorded in each SI region (areas 3a, 3b, 1, and 2). (C) Locations of recording sites for six monkeys. The illustration for each monkey consists of four panels. The top panel presents a surface map of electrode penetrations with respect to CS and IPS. The penetrations where rhythmically firing neurons were recorded are indicated by larger marks. The lower panels illustrate three sagittal sections through the cortex (lateral, intermediate, and medial). Locations of the neurons are shown as projections to the nearest of the three sections. RF types are marked according to the convention of panel B.
Fig. 3. Selection of the group of rhythmically firing neurons. (A) A computer-generated example of an expectation density (ED) histogram. The spike train constructed to have a normal distribution of interspike intervals corresponding to 30 Hz and a coefficient of variation of 0.15. R is the stabilized level of the histogram, $E_1$, $E_2$ are the heights, and $t_1$, $t_2$ are the times of the initial two peaks. (B) Histograms of the distribution of the ratio of the first peak to stabilized ED level ($E_1/R$) for rhythmically firing and nonrhythmically firing neurons. (C)–(D) Scattergrams illustrating selection of rhythmically firing neurons based on the heights of ED peaks and the jitter of first interpeak interval. Jitter is the time of the first peak minus the time between the first and second peaks divided by the time of the first peak. (E) Histogram of the distribution of the firing frequency for the total sample of rhythmically firing SI neurons.

peaks in the ED histogram normalized by the stabilized level with those of corresponding peaks in the RD histogram.

Analyses of Changes in Neuronal Activity and EMG

Changes in neuronal activity associated with go-cues and movements were analyzed using conventional discharge histograms (Fig. 5B) and raster displays (Fig. 5C). In addition, ISI rasters were plotted that displayed the time of occurrence of each spike on the x-axis and the succeeding ISI on the y-axis (Fig. 5A). To analyze vibration-related changes in activity, the occurrences of individual discharges were expressed as times with respect to vibration onset (Fig. 5A–E, left panels). For the analysis of movement-related changes,
spike occurrences were expressed with respect to movement onset (Fig. 5(A)–(E), right panels).

The onsets of changes in neuronal firing rate and of changes in EMG were determined using the cumulative sum methods (CUSUM) (Ellaway, 1977; Jiang et al., 1991). The CUSUM at a given time is the total number of discharges accumulated for all trials from some starting time. The average CUSUM was calculated by rescaling this count by dividing it by the number of trials (Fig. 5(D)). The CUSUM for an impulse train for which the probability of discharge is constant over time is a linearly rising curve with a slope equal to the mean firing rate. To calculate the onset of deviations from the stationary level of activity, the largest epoch of linear rise in the average CUSUM prior to a behaviorally significant event was labeled by visual inspection. A linear least squares interpolation curve was calculated for this period. This curve was then extrapolated through the epoch containing the event. The standard deviation of the CUSUM from the fitted curve was calculated for the epoch that had a linear rise. The computer program searched forward in time to find the first change in the CUSUM from the curve of more than three standard deviations for at least 40 ms. This time was designated as the onset of a significant change in activity.

The correlation between the periodic vibratory stimulus and neuronal discharges was analyzed using a phase representation method (for details, see Lebedev et al., 1994). The phase of each spike with respect to the stimulus cycle was calculated and plotted in a scattergram as a function of time (see, e.g., Fig. 8(B)). In addition, the phase relative to the extrapolated stimulus sinusoid was automatically calculated by the computer for the epoch preceding vibration onset. For this epoch, phase was randomly scattered. Following vibration onset, if the activity was entrained to the stimulus, a band was present in the phase scattergram that corresponded
Fig. 5. Example of changes in neuronal activity associated with 57 Hz vibratory go-cue presentation and movement. Records in the left parts of panels A–B are centered on vibration onset, whereas those in the right parts are centered on movement onset. The activity pattern of a rhythmically firing (~39 Hz) area 1 neuron exhibited during flexion trials is illustrated. (A) Raster displays of interspike intervals (ISIs). For each spike, these displays show the time of its occurrence on the x-axis and plot the next ISI on the y-axis. (B) Histograms of discharge rate (bin width = 5 ms). Dotted lines represent average movement onset (left panel) and average vibration onset (right panel). (C) Raster displays of discharges. Each horizontal line corresponds to one trial, and each dot represents the time of a spike’s occurrence. Bold marks indicate movement onsets (on the left) and vibration onsets (on the right). The trials were rearranged in the order of increasing reaction time from top to bottom. (D) Plots of the average cumulative sum (CUSUM). The time of statistically significant deviations of the CUSUM trace are shown. (E) Average wrist position traces. (F) A schematic illustration of the neuron’s receptive field (RF). This neuron had a noncutaneous RF deeply located in the hand. (G) Cortical location of the neuron.
to the phase of preferential response. Cycle distribution histograms also were calculated that represented the probability of discharge occurrence in relationship to the phase of the stimulus cycle (see, e.g., Fig. 8(G)).

Statistical Analyses

The characteristics of neuronal activity for several groups of neurons (having specific RF types, located in given cortical areas, and so on) were statistically compared using a multifactorial ANOVA (with the Scheffé post hoc test). The parametric t-test and the more robust nonparametric Mann-Whitney U-test were used for two group comparisons.

Results

Cortical Locations and Receptive Fields

Of the total recorded 1,222 SI neurons, 706 (~58%) neurons had firing rates of more than 10 spikes/s during the hold period of the paradigm. Of this sample, 70/706 (~10%) neurons exhibited bursty firing patterns and were excluded. Eight of the remaining 636 neurons, were excluded from consideration because they had either a small number of ISIs shorter than 1 ms (approximately twice the spike duration) or inconsistent activity patterns during the experimental session. Either occurrence could indicate inclusion in the records of spikes from another nearby neuron. Thus, 129/1222 neurons (~11%) having rhythmic activity patterns were selected (Fig. 3(B)). The distribution of surface locations of the recording sites and their location in representative sagittal sections are shown in Fig. 2(C). No clear distribution patterns were evident, either within or across cortical areas (areas 3a, 3b, 1, and 2). Ninety-one neurons were tested for RFs. This sample contained more neurons with deep RFs than those with cutaneous RFs or no clear RF (Fig. 2(B)). Cutaneous RFs most frequently were associated with palmar surface of the hand. Deep RFs were associated with movements of fingers and the wrist or with deep hand tissues.

Characteristics of Rhythmic Activity

The activity of rhythmically firing neurons that occurred during the hold period was analyzed to determine its frequency characteristics as well as any serial dependencies of the ISIs. An example of spike train analyses for an area 1 neuron is presented in Fig. 4. The activity of the same neuron during task execution is illustrated in Fig. 5. In Fig. 4(A), a scattergram of ISIs during a 500-ms epoch preceding vibration onset is plotted for 40 consecutive trials. This scattergram shows that the ISI distribution remained virtually unchanged from trial to trial. In Fig. 4(B), a joint interval scattergram is presented. Fig. 4(C), (D), and (E) display ISI distribution, ED, and RD histograms, respectively. During the hold period, this neuron was rhythmically active at ~39 Hz. The majority of ISIs were distributed within the range of ±5 ms around the rhythmic period (~25.6 ms). Note, however, that a small number of outlying short and long ISIs occurred. ED and RD histograms were not substantially different.

Statistical analyses of the first normalized ED peaks ($E_1'$, Eq. 1) and the rhythmic frequencies ($f$; Eq. 2) for the sample of rhythmically active neurons did not show any significant differences depending on cortical location of the neurons nor on their RF type. The means and the standard deviations were, for $E_1'$, 2.62 ± 0.78 (Fig. 3(B)) and, for $f$, 32.1 ± 5.4 Hz (Fig. 3(E)).

We observed two features of spike trains that seem unlikely for a renewal model of rhythm generation (Perkel et al., 1967). These features were (1) multimodal ISI distributions and (2) the occurrence of a small but noticeable number of ISIs at less than the modal interval that formed diagonal bands in joint interval scattergrams. Multimodal ISI distributions were observed for 31/129 neurons (~24%). An example of an area 1 neuron with a multimodal ISI distribution is presented in Fig. 6(A)–(D) (also see Figs. 9 and 11). The ISI distribution of this neuron contained peaks at the modal interval ($T$) and at twice that interval (2$T$, Fig. 6(B)). The joint interval scattergram for this neuron had four clusters of ISIs pairs around points ($T$, $T$), ($T$, 2$T$), (2$T$, $T$), and (2$T$, 2$T$). ED and RD histograms were approximately the same for this neuron. For 32/129 neurons (~25%), we observed the occurrence of ISIs that were shorter than modal interval. Six neurons (~5%) exhibited both these short ISIs and multimodal ISIs. Short ISIs that form diagonal bands in joint interval plots have been attributed to "interrupting spikes" (Surmeier and Towe, 1987a, 1987b; Siebler et al., 1991). Joint interval scattergrams for such spike trains contain diagonal bands that connect points (0, $T$) and (T, 0). These bands occur when the sum of the ISIs that immediately precede and succeed the interrupting spikes is equal to the modal interval:

$$T_1 + T_2 = T,$$  (3)
Fig. 6. Examples of characteristics of rhythmic spike trains that seem unlikely for a renewal mechanism of rhythm generation. (A)–(D) Records for a rhythmically firing (~43 Hz) area 1 neuron with a multimodal ISI distribution. (A) Activity during task performance (conventions as in Fig. 5). (B) Analyses of rhythmic activity during the hold period (conventions as in Fig. 4). (C) Receptive field (RF) schematic. This neuron had a cutaneous RF located on the second digit. (D) Cortical location of the neuron. (E)–(H) Records for an area 3b neuron that had interrupting spikes. (E) Activity during task performance (conventions as in Fig. 5). (F) Analyses of rhythmic activity during the hold period (conventions as in Fig. 4). (G) No clear RF was found for this neuron. (H) Cortical location of the neuron.
where $T_1$ is the ISI preceding an interrupting spike and $T_2$ is the succeeding ISI. Records for an area 3b neuron that exhibited interrupting spikes are presented in Fig. 6(E)–(H). In addition to a cluster of ISIs around $T$, shorter ISIs were present (from 2 ms to $T$, Fig. 6(F)). In the joint interval scattergram, the presence of short intervals resulted in a diagonal band. Note that peaks in the RD histogram were less pronounced than those in the ED histogram.

The comparison of ED and RD histograms for the total sample of rhythmically firing cells showed a tendency for peaks in RD histograms to be smaller in amplitude than those in ED histograms. The results of a factorial ANOVA indicated that, for the neurons having interrupting spikes, the differences between ED and RD peaks were significantly greater compared with the rest of the total sample. For these neurons, the means and standard deviations of the differences between the first two ED and RD peaks were $13.4 \pm 9.7\%$ and $13.8 \pm 9.2\%$, respectively ($p < 0.0002$; paired t-test). When the neurons with interrupting spikes were excluded from the total sample, a small but statistically significant difference was found only for the first peaks ($1.8 \pm 5.0\%; p < 0.0002$).

**Vibration-Related Activity**

Changes in the activity of SI neurons in this experimental paradigm commonly occurred at vibratory go-cue onset and often preceded movement onset (Nelson, 1988). We analyzed the changes in activity of rhythmically firing neurons that occurred in association with these behaviorally significant events. For 67/129 rhythmically active neurons (~52%), the firing rate changed with vibration onset. Decreases in activity were the most common responses to vibration (60/67 cases, ~89%). An example of a typical response to vibration exhibited by an area 1 neuron is presented in Fig. 7(A). The neuron's firing rate decreased following palmar vibration with a latency of ~28 ms. The vibration-related activity decrease consisted of both transient and sustained changes in activity (schematic illustration, Fig. 7(E)). The analyses of the latency of vibratory responses are presented in Fig. 7(F). This latency (~26 ms at 57 Hz) was not significantly different as a function of cortical location or RF type.

In some cases, neuronal activity during ongoing vibration, although decreased, was stimulus-entrained. An example of an area 3a neuron with activity entrained to a 27 Hz vibratory stimulus is presented in Fig. 8. During the hold period, the neuron was rhythmically active at ~30 Hz. A transient decrease in activity occurred at ~27 ms after vibration onset and lasted for ~50 ms (Fig. 8(A)). Then, the activity recovered, although it was at a lower level than that during the hold period. Moreover, neuronal discharges were entrained to the ongoing 27 Hz vibration. The entrainment is clearly seen in phase raster (Fig. 8(B)) and in the cycle distribution histogram (Fig. 8(G)). The ISI distribution for the epoch of vibratory stimulation contained peaks at the vibratory period and at twice that period (Fig. 8(F)). Generally, entrainment was observed more often when stimulating at 27 Hz, which was close to the average rhythmic frequency of the studied neurons. Of 41 neurons recorded during stimulating at this frequency, 12 neurons (~29%) exhibited vibration-entrained activity. The majority of the data were collected while stimulating at 57 Hz. At this frequency, 12/129 neurons (~9%) exhibited vibratory entrainment. At the highest stimulus frequency (127 Hz), vibratory entrainment rarely was observed (1/38; ~3%).

**Premovement Activity**

The activity of each rhythmically firing neuron changed prior to movement onset for at least one movement direction. The earliest change of firing rate from the stabilized level of activity during vibratory stimulation was designated as the onset of premovement activity (PMA) (Nelson, 1988). PMA was detected in 124/129 instances for flexion movements and in 118/129 instances for extension movements. Decrease in firing rate was the most frequent type of PMA (~76% of PMA cases; Fig. 9(F)). Figure 9(A) illustrates this pattern. Records for an area 2 neuron are presented. The firing rate of this neuron did not change after vibration onset. However, its activity was dramatically decreased at ~40 ms prior to the onset of extension movements. The PMA onsets with respect to movement onset were not statistically different as a function of cortical location or RF type. These onsets also did not differ between instances of activity increases and decreases.

To estimate the temporal relationship between PMA and the earliest movement-related peripheral afferent signals, PMA onsets were compared with EMG onsets. The EMG onsets were analyzed for several forearm and arm muscles (Lebedev et al., 1994; Nelson, 1987; Nelson et al., 1991). A minimal afferent peripheral conduction time of 11 ms was subtracted from the actual EMG onsets (Wiesendanger and Miles, 1982).
to yield an estimate of the time at which afferent signals resulting from muscle activity might reach the cortex. The earliest time at which this might occur was thus 100 ms prior to movement onset, whereas given the average EMG onset, it was 60 ms prior to movement onset. A substantial number of PMA onsets for rhythmically firing neurons occurred after the earliest estimated time of afferent input arrival (194/242; ~80%) (Fig. 9(F)). Many PMA onsets occurred after the average estimated time of afferent input arrival (133/242; ~55%).

During activity decreases, rhythmic activity often was disrupted rather than modulated (e.g., Fig. 9(A)). In the cases when the rhythmic pattern of discharges was
preserved, the rhythmic frequency decreased slightly (by ~20%; e.g., sustained vibratory response in Fig. 5(A)). Activity increases usually occurred during movements and were characterized by transitions from rhythmic to nonrhythmic firing. In Fig. 10, records for an area I neuron are presented that show activation during voluntary extensions. This neuron also was activated by passive extension of the second digit at the metacarpophalangeal joint (Fig. 10(B)). Rhythmic firing decreased at ~27 ms following vibration...
onset and, additionally, at ~34 ms prior to extension movement onset. Then, a pronounced activation followed at ~45 ms after movement onset. This activation was characterized by a qualitative change in the ISI distribution (Fig. 10(D) and (E)). The ISI distribution shifted to the left, indicative of the faster firing rate. However, several ISIs occurred at the minimum value of 1.2 ms, possibly indicating the presence of small bursts of activity in this otherwise rhythmically spiking neuron. In some instances, transitions to irregular ISI patterns occurred without substantial changes in the mean firing rate (e.g., ~200 ms after movement onset in Figs. 6(E) and 11(A)).

Activity patterns were analyzed to determine if PMA types were dependent upon the direction of subsequent
movement. If the sign of the activity change was opposite for flexion and extension or if PMA occurred only for one movement direction, this instance of PMA was classified as directional. If the activity change was of the same sign for both movement directions, the PMA was classified as nondirectional. Nondirectional PMA occurred most frequently (84/129 neurons, ~65%); directional PMA was observed for 45/129 neurons (~35%). An example of an area 3a neuron with a nondirectional PMA pattern is presented in Fig. 11. For both flexions (Fig. 11(A)) and extensions (Fig. 11(D)), premovement decreases in activity of this neuron occurred at ~70 ms prior to movement onset.

**Comparison with Other SI Neurons**

We compared the activity pattern exhibited by rhythmically firing neurons with the types of activity of SI neurons that have been documented previously for this experimental paradigm (Nelson, 1988; Nelson et al., 1991). The typical activity pattern of rhythmically firing neurons resembled a mirror image of the activity of quickly adapting (QA) neurons recorded during similar behaviors (Nelson et al., 1991). QA neurons were activated at about the same time following vibratory cue onset (~30 ms) and prior to movement (~80 ms) as the firing rate of rhythmically firing SI neurons decreased.
Fig. 11. Comparison of the activity patterns seen during flexion and extension trials. Records for a rhythmically firing (~38 Hz) area 3a neuron are shown. Vibratory frequency was 57 Hz. (A) Records for flexion trials (conventions as in Fig. 5). (B) Analyses of rhythmic activity for the hold period during flexion trials (conventions as in Fig. 4). (C) Schematic illustration of the neuron's cortical location. (D) Records for extension trials. (E) Analyses of rhythmic activity for the hold period during extension trials.
Discussion

Activity of Rhythmically Firing Neurons During Trained Motor Tasks

We examined the activity of a population of rhythmically firing neurons in monkey SI while the animals performed trained motor tasks. The changes in activity of these neurons had common features during the initiation of vibratory-cued movements. Approximately one-half of rhythmically firing neurons responded to vibratory go-cues, typically with decreases in firing rates at $\sim$25 ms after vibration onset. In some cases, although the firing rate was decreased somewhat, the activity was entrained to the frequency of the ongoing vibration. It is possible that the entrainment observed was caused by IPSPs rather than by EPSPs (Cowan and Wilson, 1994; Lytton and Sejnowski, 1991; Stern and Wilson, 1994). The best vibratory frequency for this entrainment was close to the population's average frequency of rhythmic activity ($\sim$30 Hz). This observation is consistent with a model of texture perception proposed by Ahissar and Vaadia (1990). In this model, cortical oscillators are key elements in neuronal circuits that analyze the temporal properties of somatosensory discharges using a phase-locked loop algorithm (Horowitz and Hill, 1980). The model predicts that oscillatory neurons would follow somatosensory stimuli if the stimulus frequency is close to the frequency of spontaneous oscillations of these neurons. Although our experiments were not specifically designed to examine the role of rhythmically active neurons in somatosensory perception, our results generally support this prediction.

Decreases in the activity of rhythmically firing neurons often occurred at $\sim$57 ms prior to movement onset. Thus, a typical activity pattern consisted of a decrease in firing rate after vibration onset and an additional decrease in firing rate prior to movement onset. This activity pattern is complementary to the pattern previously reported for QA neurons that were recorded during the performance of this behavioral task (Nelson et al., 1991). QA neurons exhibit a short-duration burst of spikes after vibration onset. Then their activity decreases and is reactivated prior to movement onset. Nelson et al. (1991) suggested that QA activity patterns may occur because of gating of SI sensory responsiveness at behaviorally significant times. The function of gating may be to enhance sensory inputs that are important for the current behavioral task while suppressing others that are not (Chapin and Woodward, 1982; Chapman et al., 1988; Coquery, 1978; Dyhre-Poulsen, 1978; Nelson, 1988; Rushton et al., 1981). Because of the correspondence between the activity patterns of rhythmically firing and QA neurons, it seems reasonable to assume that rhythmically firing neurons may participate in gating SI activity.

Centrally generated as well as peripheral inputs to SI neurons may be involved in premovement gating of somatosensory activity (Chapin and Woodward, 1982; Chapman et al., 1988; Coquery, 1978; Dyhre-Poulsen, 1978; Lebedev et al., 1994; Nelson, 1987; Nelson et al., 1991; Soso and Fetz, 1980). Changes in the activity of rhythmically firing neurons that occurred before movement usually happened after the earliest EMG onset. Therefore, these changes certainly could be related to peripheral afferent signals associated with the onset of muscle activity that preceded movement onset as detected by the change in handle position. However, most premovement activity changes were of the same sign for both flexion and extension trials (that is, they were non directional). Peripheral reafferent signals commonly are directional, especially those of proprioceptive origin (Cohen et al., 1994; Soso and Fetz, 1980). Many of the rhythmically firing SI neurons in our sample had deep RFs. Nonetheless, they usually exhibited nondirectional premovement activity patterns. Therefore, the premovement changes in activity of rhythmically firing SI neurons probably are not simply replicas of peripheral reafferent signals but rather might reflect intracortical processing of peripheral information.

Rhythmically Active SI Neurons and LFP Oscillations

Our present observations suggest that there are similar features between the activity patterns of rhythmically firing SI neurons and the LFP oscillations in sensorimotor cortex reported by others. The mean firing frequency of the observed rhythmically firing SI neurons ($\sim$30 Hz) was close to the frequency often described for LFP oscillations (Bouyer et al., 1981, 1987; Murthy and Fetz, 1992; Rougeul et al., 1979; Sanes and Donoghue, 1993). In a manner similar to LFP oscillations, rhythmic activity of single SI neurons was disrupted with somatosensory stimulation and/or voluntary movements. LFP oscillations occur in sensorimotor cortex in the cat (Bouyer et al., 1981, 1987) and the monkey (Rougeul et al., 1979) during focused attention and immobility but usually disappear during movements. Disruptions of LFP oscillations in monkey motor cortex also occur prior
to movements performed during trained motor tasks (Sanes and Donoghue, 1993). In addition, Murthy and Fetz (1992) observed that LFP oscillations in monkey motor and somatosensory cortices occurred during exploratory movements requiring directed attention. Thus, LFP oscillations may vary as a function of attentive behavior and task requirements (for review, see Gray, 1994). Experimental conditions of Sanes and Donoghue (1993) are the most similar to ours. Disruptions of LFP oscillations in their experiments occurred around the same time as the disruptions of rhythmic firing of individual SI neurons in our experiments. We suggest, therefore, that LFP oscillations and rhythmic firing of SI neurons may be related.

Some characteristics of rhythmic activity of individual neurons, however, differ from those reported for LFP oscillations. LFP oscillations usually occur as occasional rhythmic bursts, 100–200 ms in duration and often with a variable frequency from one burst to another (Eckhorn et al., 1988; Gray and Singer, 1989; Murthy and Fetz, 1992; Sanes and Donoghue, 1993; Singer, 1993). The activity patterns of individual rhythmically firing SI neurons were consistent from trial to trial and were only briefly interrupted during vibratory stimulation and movements. We suggest that individual rhythmically firing SI neurons may maintain relatively independent activity. Further, it is possible that these neurons may intermittently evoke oscillations in other neurons. Murthy and Fetz (1994) observed sensorimotor cortical neurons that intermittently exhibited episodes of rhythmic activity during episodes of LFP oscillations. These neurons could be driven by neurons with sustained rhythmic activity. Driven oscillations of cortical neurons may become synchronized through cortico-cortical and thalamocortical interactions (Llinas, 1990; Llinas et al., 1991). Thus, rhythmically firing neurons may act to regulate cortical population oscillations.

Possible Models of Rhythmic Activity

Mechanisms causing rhythmic activity of SI neurons remain unclear. One possibility is that rhythmically active cells are integrate-and-fire neurons, and their regular firing occurs because of stable synaptic input (Segundo et al., 1968). Regular spiking cortical pyramidal neurons discharge very rhythmically in an integrate-and-fire mode, when they receive steady inputs (McCormick et al., 1985;Softky and Koch, 1993). Integrate-and-fire neurons respond to changes in the intensity of synaptic input by changing their firing frequency. If rhythmically firing SI neurons are integrate-and-fire neurons activated by stable peripheral inputs, then their firing frequency should follow changes in the intensity of peripheral inputs, for example, as might occur during movements. However, the rhythmic firing of SI neurons is disrupted rather than being modulated during movements. Thus, modeling rhythmically firing neurons as integrate-and-fire neurons does not describe all of our observations.

Alternatively, rhythm firing may result from extrinsic oscillatory drive. Rhythmic driving of cortical neurons produced by intracortical and/or subcortical inputs previously has been proposed. Ghose and Freeman (1992) suggested that visual cortical neurons may be driven by rhythmically active cells located in the lateral geniculate nucleus. Jagadeesh et al. (1992) demonstrated rhythm excitatory inputs to visual cortical neurons using in vivo patch clamp recording techniques. The source of rhythm drive may be from inhibitory, rather than excitatory, neurons (Cowan and Wilson, 1994; Llinas, 1990; Llinas et al., 1991). Some of our observations are consistent with an extrinsic drive model. We observed ISIs for some neurons that occurred at multiples of the modal interval. This may have occurred because of a neuron's occasional failures to respond to driving inputs as previously suggested (Ahissar and Vadia, 1990). In addition, we observed interrupting spikes that may reflect spikes that are uncorrelated with the rhythmic drive (Surmeier and Towe, 1987a, 1987b). However, from the manner in which these neurons were recorded, we cannot absolutely eliminate the possibility that interrupting spikes or ISIs at multiples of the modal interval could reflect occasional spurious inclusion spikes from adjacent neurons with similar waveforms or exclusion of spikes from the neuron in question. Further experiments are required to clarify this issue.

Rhythmic driving of SI neurons could arise from regular discharges of peripheral afferents. Single peripheral afferent fibers may have very regular firing patterns (e.g., Burke et al., 1987). However, the frequency of rhythmic discharge of peripheral afferents is modulated during movements (Burke et al., 1987; Prochazka, 1985). Since, typically rhythmic activity of SI neurons was disrupted periodically, these neurons were unlikely to be driven by peripheral afferent discharges throughout all phases of our behavioral task. Moreover, the SI neurons that seem to have been driven most securely by peripheral inputs did not exhibit rhythmic
activity. These neurons which had cutaneous or deep RFs faithfully responded to vibratory go-cues with entrained discharges (Lebedev et al., 1994). However, they did not fire rhythmically during the hold period of the paradigm (unpublished observations). Therefore, it seems unlikely that peripheral drive is the major source of rhythmic firing of SI neurons under these experimental conditions.

Rhythmic activity of some of the studied neurons could be the result of intrinsic oscillatory properties rather than extrinsic factors. For many rhythmically firing neurons (72/129; ~56%) we did not observe signs of extrinsic drive (that is, interrupting spikes and multimodal distributions of the ISIs). Moreover, ED and RD histograms for these neurons were virtually identical. Mountcastle et al. (1969, 1990) reported that ED and RD histograms were dramatically different when the firing of SI neurons was driven by peripheral vibration. Absence of such differences between ED and RD histograms for many rhythmically active SI neurons may indicate either that these neurons were not extrinsically driven or that they were driven by very secure oscillatory inputs.

Intrinsically oscillating cortical neurons have been reported. Two types of neurons recorded in vitro have been demonstrated to intrinsically oscillate at 10–50 Hz within layer 4 of guinea pig frontal cortex (Llinas et al., 1991). Neurons of the first type—that is, broadband oscillators—increased their firing frequency with membrane depolarization. Neurons of the second type, the narrow-frequency oscillators showed little change in firing frequency as a function of the level of depolarization. The narrow-frequency oscillatory neurons have been identified morphologically as sparsely spinous interneurons having axon collaterals in layers 3 and 4, and are probably inhibitory interneurons. Pyramidal cortical neurons typically do not generate fast (20–50 Hz) oscillations intrinsically (Silva et al., 1991). Rather, their activity is thought to be modulated by rhythmic IPSPs probably generated by cortical interneurons (Cowan and Wilson, 1994; Stern and Wilson, 1994; but see also Núñez et al., 1992). Thus observations tend to indicate that rhythmically firing neurons in the cortex may be inhibitory interneurons.

*Rhythmically Active Neurons and Tonic Inhibition of SI Activity*

Since cortical oscillatory neurons are likely to be inhibitory interneurons (Cowan and Wilson, 1994; Llinas et al., 1991; Stern and Wilson, 1994), there is the intriguing possibility that rhythmically active SI neurons may be involved in tonic inhibition of SI activity. The role of inhibitory interneurons as essential regulators of cortical activity is suggested by the observation that ~70% of intracortical connections are inhibitory (White, 1989). Tonic inhibition produced by local interneurons has been suggested to control RF size of cortical neurons and to increase spatial and temporal contrast (Brooks, 1959; Dykes et al., 1984). We further suggest that inhibitory interneurons may gate SI activity during behavior. The activity patterns of rhythmically firing neurons are complimentary to the activity patterns of quickly adapting (QA) neurons recorded during this behavior (Nelson et al., 1991). This observation is similar to that of Wilson et al. (1994), who observed that putative GABA-ergic interneurons and pyramidal neurons exhibited complementary patterns of activity while the monkeys performed visual and oculomotor tasks. These authors suggested that interneurons may hyperpolarize pyramidal neurons, whereas pyramidal neurons may depolarize interneurons. Similar reciprocal connections may be present between rhythmically firing and QA SI neurons.

Rhythmically firing neurons are candidates for one element of a model that was previously proposed to account for observed patterns of activity of QA SI neurons (Nelson et al., 1991). A task phase element was proposed that may suppress peripheral and motor inputs to QA neurons. In Fig. 12, a model is presented that is a modified form of the previous one. This model includes output neurons (such as corticocortical, corticothalamic or corticofugal), input neurons (presumably, layer IV spiny cells) (Jones, 1975) and two types of inhibitory interneurons, rhythmic and phasic interneurons. This model assumes the following functional relationships. Rhythmic interneurons exhibit sustained firing patterns, whereas phasic inhibitory interneurons respond to inputs with transient bursts of spikes. The model includes neurons that receive direct excitatory inputs from other regions. The model has been conceived such that rhythmically firing neurons tonically inhibit output neurons. Output neurons may be disinhibited because their inhibitors themselves receive inhibitory inputs from phasic interneurons. During increases in SI input, phasic inhibitory neurons would be transiently activated. Consequently, by this model, rhythmically firing neurons would be transiently inhibited. This scheme suggests that output neurons generate bursts of spikes when released from tonic inhibition and are excited by input signals. Quickly adapting activity patterns of output

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neurons may be important for signalling transient sensory events.

The model shown in Fig. 12 is consistent with the data on intracortical connectivity (Chagnac-Amitai and Connors, 1989; Istvan and Zarzecki, 1994; Jones, 1975). Nonpyramidal inhibitory neurons that may regulate activity of other cortical neurons previously have been studied (Kawaguchi, 1993; Kawaguchi and Kubota, 1993; Jones, 1975). One type of neuron, the double bouquet cell (Ramón y Cajal, 1911), has been shown to project to nonpyramidal cortical cells (Somogyi and Cowey, 1981). These cells are characterized by vertically oriented axonal arbor.

Recent findings suggest that GABA-ergic cortical neurons with this type of axonal arbor are immunoreactive for calbindin-28, whereas GABA-ergic neurons with horizontally oriented axonal arbor (for example, the basket cells) are immunoreactive for parvalbumin (Hendry et al., 1989; Kawaguchi and Kubota, 1993). Moreover, calbindin-28-immunoreactive neurons respond to current injections by firing phasically, whereas parvalbumin-immunoreactive neurons respond by firing repetitively with little or no spike frequency adaptation (Kawaguchi and Kubota, 1993). Therefore, calbindin-28 and parvalbumin-immunoreactive neurons are likely candidates for the phasic and rhythmic inhibitory elements of the model, respectively.

This model's circuitry may be capable of initiating network oscillations following the scheme proposed by Llinas et al. (1991). Rhythmically firing inhibitory neurons may induce rhythmic activity in output neurons. Output neurons, in turn, may induce rhythmic activity in their target regions, for example in the thalamus or in other cortical areas. Regions projecting back to the cortex would, thus, close the loop which would be necessary for the maintenance of network oscillations.

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