Band-Pass Response Properties of Rat SI Neurons

Catherine E. Garabedian,1 Stephanie R. Jones,2 Michael M. Merzenich,1 Anders Dale,2 and Christopher I. Moore3

1University of California, Keck Center for Integrative Neuroscience, San Francisco, California 94143; 2Massachusetts General Hospital Nuclear Magnetic Resonance Imaging Center, Charlestown, Massachusetts 02141; and 3Massachusetts Institute of Technology, McGovern Institute for Brain and Cognitive Sciences, Cambridge, Massachusetts 02139

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Garabedian, Catherine E., Stephanie R. Jones, Michael M. Merzenich, Anders Dale, and Christopher I. Moore. Band-pass response properties of rat SI neurons. J Neurophysiol 90: 1379–1391, 2003. First published May 15, 2003; 10.1152/jn.01158.2002. Rats typically employ 4–12 Hz “whisking” movements of their vibrissae during tactile exploration. The intentional sampling of signals in this frequency range suggests that neural processing of tactile information may be differentially engaged in this bandwidth. We examined action potential responses in rat primary somatosensory cortex (SI) to a range of frequencies of vibrissa motion. Single vibrissae were mechanically deflected with 5-s pulse trains at rates =40 Hz. As previously reported, vibrissa deflection evoked robust neural responses that were adapted to stimulus rates =3 Hz. In contrast with this low-pass feature of the response, several other characteristics of the response revealed band-pass response properties. While average evoked response amplitudes measured 0–35 ms after stimulus onset typically decreased with increasing frequency, the later components of the response (>15 ms post stimulus) were augmented at frequencies between 3 and 10 Hz. Further, during the steady state, both rate and temporal measures of neural activity, measured as total spike rate or vector strength (a measure of temporal fidelity of spike timing across cycles), showed peak signal values at 5–10 Hz. A minimal biophysical network model of SI layer IV, consisting of an excitatory and inhibitory neuron and thalamocortical input, captured the spike rate and vector strength band-pass characteristics. Further analyses in which specific elements were selectively removed from the model suggest that slow inhibitory influences give rise to the band-pass peak in temporal precision, while thalamocortical adaptation can account for the band-pass peak in spike rate. The presence of these band-pass characteristics may be a general property of thalamocortical circuits that lead rodents to target this frequency range with their whisking behavior.

INTRODUCTION

The rat primary somatosensory cortex (SI) is a popular model for studies of spatial cortical representation because of the discrete one-to-one topographic correspondence of vibrissae to cortical layer IV “barrels” (Woolsey and Van der Loos 1970). The rat vibrissa system also engages a range of temporally specific information-sampling behaviors. During rest or inactivity, the facial vibrissae are stationary. After an alerting stimulus, general alertness to incoming stimuli is crucial, whereas during whisking, the ability to make fine and rapid discriminations between stimuli is potentially more important. Consistent with this hypothesis, the cortical representation of a single vibrissa is more spatially focused during high-frequency (5–10 Hz) vibrissa stimulation than low-frequency (1 Hz) stimulation (Sheth et al. 1998). Further, inter-vibrissa lateral inhibition is robust within rat SI, suggesting that multi-vibrissa contact enhances the functional isolation power spectrum with a peak between 4 and 12 Hz and a relatively narrow band-width (typically <3 Hz) (Carvell and Simons 1990, 1995; Fanselow and Nicolelis 1999; Gao et al. 2001; Harvey et al. 2001; Nicolelis and Fanselow 2002; Welker 1964). Whisking frequency can vary during sampling epochs and can be modified as the result of learning (Harvey et al. 2001). In addition to the predominant whisking behavior, two other frequency-specific vibrissa motion patterns have been observed: vibrissa twitching, a brief period of low-amplitude vibrissa motion between 7 and 12 Hz (Berg and Kleinfeld 2003; Nicolelis et al. 1995; Nicolelis and Fanselow 2002), and a second, higher frequency motion of protracted vibrissae, peaking in a range from 15 to 25 Hz (Berg and Kleinfeld 2003; see also Carvell and Simons 1990; Harvey et al. 2001).

Electrophysiological studies of temporal processing in rat SI have reported robust adaptation of layer IV responses to repetitive stimulation of vibrissae >3 Hz (Ahissar 2000, 2001; Castro-Alamancos and Oldford 2002b; Chung et al. 2002; Simons 1978). In layer IV, differential adaptation patterns have been observed in distinct neuron populations. Regular spiking units, which are putative excitatory neurons, show action potential and excitatory postsynaptic potential (EPSP) adaptation at frequencies as low as 4 Hz (Chung et al. 2002; Simons 1978). In contrast, fast spiking units, which are putative inhibitory neurons, emulate ventral posterior thalamic neurons by responding robustly to stimulus rates as high as 40 Hz (Simons 1978). Robust adaptation is observed in the barrels and septa of layer IV, although the mechanistic underpinning of adaptation in these regions may be different (Ahissar et al. 2000, 2001).

The frequencies of vibrissa motion displayed during rest (<1 Hz) and whisking (4–12 Hz) may optimize the vibrissa processing system for the detection or discrimination of stimuli features, respectively (Moore et al. 1999; Nicolelis and Fanselow 2002). During rest, general alertness to incoming stimuli is crucial, whereas during whisking, the ability to make fine and rapid discriminations between stimuli is potentially more important. Consistent with this hypothesis, the cortical representation of a single vibrissa is more spatially focused during high-frequency (5–10 Hz) vibrissa stimulation than low-frequency (1 Hz) stimulation (Sheth et al. 1998). Further, inter-vibrissa lateral inhibition is robust within rat SI, suggesting that multi-vibrissa contact enhances the functional isolation...
of each vibrissa (Brumberg et al. 1996). These findings suggest that in the context of low frequencies of vibrissa motion (e.g., during rest), contact on any vibrissa may be more easily detected by the broader recruitment of cortical neurons, whereas during whisking, the somatotopic identity of a specific vibrissa may be better discriminated (Moore et al. 1999). Behavioral studies further support this framework. When rats were trained to whisk an object to obtain a reward, whisking frequency peaked from 2 to 5 Hz. However, when the same animals learned to discriminate between these objects for reward, a second peak emerged at 7–10 Hz. The power of this peak correlated with task performance level, demonstrating that higher frequency whisking may be used as a strategy to increase perceptual selectivity (Harvey et al. 2001).

In this paper, we present physiological evidence that several temporal response properties are amplified by vibrissa stimulation in the whisking frequency range, supporting the idea that information processing at these sampling rates is differentially represented in SI. We characterized responses of 64 SI recording sites to stimulation of individual vibrissae at rates ≤40 Hz. In agreement with previous studies (Ahissar et al. 2001; Castro-Alamancos and Oldford 2002; Chung et al. 2002; Simons 1978), steady-state responses showed adaptation at high stimulation rates. Several other features of the evoked neural responses showed band-pass effects. Between 5 and 10 Hz, late components of the steady-state response were facilitated, total spike count over the steady-state period of the train increased and vector strength (VS), a measure of temporal fidelity, was maximal. Results from a model of the layer IV “barrel” cortical network with feedforward thalamic input replicated these band-pass effects, suggesting that input layer cortical circuitry can account for these phenomena. These results, taken with previous findings, suggest that cortical representations of sensory stimuli are selectively optimized for this behaviorally relevant range of processing frequencies.

METHODS

Preparation

Adult Sprague-Dawley rats (275–325 g) were anesthetized with pentobarbital sodium (50 mg/kg ip), and a craniotomy and durotomy were performed to expose the left SI. A tracheotomy and a cisternum magnum drain were performed. Animals were maintained at a constant level of anesthesia with supplemental doses of pentobarbital as needed (10% of the induction dose) so that they remained unresponsive to hindpaw pinch, with a stable breathing rate (30–60 breaths/min) and heart rate (4–7 beats/s). At the end of each experiment, animals were killed with an overdose of pentobarbital sodium (150 mg/kg), and a bilateral thoracotomy was performed.

Stimulation and electrophysiology

We recorded multiunit activity from 64 recording sites in the primary somatosensory cortex of 12 rats. Recordings were made with tungsten microelectrodes (FHC No. UEWMC1E2PG4, 2–4 MΩ) from the middle layers (500–750 μm), depths that typically correspond to layer IV in rat SI (Diamond et al. 1994). The time resolution for data collection was 25 kHz. Activity was band-pass filtered between 300 Hz and 10 kHz; spike times and shapes were recorded using a window discriminator, which was set well above noise level to isolate only action potential responses. Before each recording, the tip of the electrode was placed at the surface of the cortex and lowered down incrementally while monitoring the depth with microdrive readings. The primary vibrissa corresponding to each recording site was identified by hand mapping. Sites that responded robustly to a single vibrissa were identified as being putative barrel sites, while signals that showed weak responses to vibrissa stimulation or that responded equally well to more than one vibrissa were rejected as putative septal or non-layer IV sites and were not used in this study. Responses were collected from the vibrissae in columns 1–3, rows C–E, and from the gamma and delta vibrissae. A piezoelectric stimulator with a 3-cm extension attached to a wire loop was positioned so that the ventral surface of the vibrissa just contacted the loop one cm from the face. Mechanical dorsal deflections of the vibrissa were presented in trains of half-sinusoidal symmetric pulses (from trough to trough; 14-ms duration, ~100-μm maximal amplitude), for a vibrissa velocity of 20 mm/s at the point of simulator contact. Five-second-long pulse trains were presented at each frequency 10 times each in random order, with 3-s intervals between trains. At each recording site, we presented at least nine frequencies, including 1, 2, 3, 5, 8, 10, 12, 15, 20, 25, 30, 35, and 40 Hz (1, 3, 20, 30 and 40 Hz, n = 59; 5, 8, 10, 15 Hz, n = 64). Because significantly fewer responses were collected across recordings at 2, 12, 25, and 35 Hz, those frequencies were not included in the present analysis.

Analysis

We applied several different analyses to the cumulative data set. For each of the analyses described in the following text (repetition rate transfer function, vector strength, spike rate, and latency), the analysis of responses to frequency trains from 1 to 40 Hz were performed on the steady state response, defined as the period 1–5 s after the onset of the stimulus train. This time period was chosen for analysis to eliminate confounding effects of the dynamic changes in response latency or amplitude that characterized the first second (the dynamic period) of the response to each stimulus train. Unless otherwise stated, all analyses were performed with a resolution of 1-ms time bins.

REPETITION RATE TRANSFER FUNCTION (RRTF). The number of spikes evoked by each vibrissa deflection during the steady-state (1–5 s post-stimulus) period of the stimulus train was averaged for a given recording and normalized by the average number of spikes evoked by the first deflection of the stimulus train. The period over which individual response amplitudes were integrated for the RRTF calculation was defined in two ways. In the first analysis, spikes 0–35 ms post-pulse onset were included, which was sufficient time to include all evoked spikes. This analysis was performed separately for each individual recording site. An RRTF value of 1 indicates no adaptation; a value >1 indicates increased spike rate in the steady state, and a value <1 indicates a decrease in response rate. In the second analysis, 5-ms time windows (5–10, 10–15, 15–20, 20–25, 25–30, and 30–35 ms post stimulus) after each vibrissa deflection were analyzed. Because the number of evoked responses in these short time windows were small and variable, this analysis was conducted only on the averaged PSTH over all recording sites. Because each 5-ms time window included only a subset of the evoked spikes at each frequency, the resulting RRTF values quantifies the relative response amplitude during a particular time epoch and is meant to capture changes in the latency as well as the amplitude of responses at different frequencies. For both RRTF analyses, the same time window was used to quantify responses to the first deflection and deflections during the steady-state period.

TOTAL SPIKE RATE (SR). In this analysis, the average spike rate during the entire steady state period of each stimulus train was calculated. All spikes, regardless of their post-stimulus latency, were included in this analysis.

VECTOR STRENGTH (VS). The temporal consistency of spike timing across stimulus cycles during the steady-state period was quantified using vector strength (VS). The VS was calculated as per Goldberg and Brown (1969)

$$VS = \sqrt{\sum (\cos \theta)^2 + \sum (\sin \theta)^2}/n$$

$$\theta = 2\pi f(t/T)$$
Where \( n \) is the total number of spikes evoked during the stimulus train, \( t \) is the time between the most recent previous vibrissa deflection and the evoked spike, and \( T \) is the period of the stimulus frequency. For each recording site and stimulus frequency, an average cycle histogram with 1-ms bins was constructed for the steady-state response to all repetitions of a stimulus train, and the VS was calculated from this histogram. The VS quantifies the precision with which spikes are locked to the same phase of a stimulus period during each repetitive cycle of stimulation. The VS measure is proportional to the amplitude of the Fourier component of the driving frequency of the period histogram normalized by the total number of spikes during this period. A value of 1 signifies perfect phase locking; a value of 0 signifies random spike timing. Latency shifts presumably did not affect this statistic because only steady state responses were analyzed.

**Latency.** The response latency for each frequency at each recording site was evaluated from the average cycle histogram at steady state. For the first deflection, the 10 repetitions of the first response to all stimulus trains were used to calculate latency. The latency was defined as the post-stimulus time at which the response amplitude reached 50% of its peak value. In separate analyses, histograms were convolved with a right triangle as in Ahissar et al. (2001), yielding similar results. Similarly, the latency to the declining slope of the PSTH was defined as the post-stimulus time after the peak response at which the response amplitude fell <50% of its peak value. We chose to use averaged steady-state histograms to calculate latency rather than averaging latencies for individual deflections because there were often insufficient spike responses to single deflections to make reliable latency estimations, particularly at high frequencies. To make statistical comparisons of onset and decay latencies at different frequencies, we chose 55 recording sites at which the VS was \( \geq 0.3 \) for frequencies between 3 and 15 Hz to eliminate recordings in which there were no significant periodic responses (see Fig. 3C). For these sites, the response width was defined as the difference in time between the latency onset and decline at each frequency.

In analyses of latency, a sign test was applied to assess whether a significant subset of recordings demonstrated a given trend (\( P < 0.05 \)), for example, a higher probability of longer-latencies to response onset with increasing frequency.

**Depth comparisons.** Recording sites were divided into five groups based upon recording depth as measured on a microdrive (500–550, 551–600, 601–650, 651–700, and 701–750 \( \mu \)m). The mean RRTF, SR, and VS, as well as onset and decay latencies, were calculated for each group independently. For each analysis, a one-way ANOVA was performed to test for any significant differences between the five groups. For RRTF, SR, and VS analyses, \( n = 20 \) for 500–550 \( \mu \)m, \( n = 18 \) for 551–600 \( \mu \)m, \( n = 9 \) for 601–650 and 651–700 \( \mu \)m, and \( n = 8 \) for 701–750 \( \mu \)m. For latency analyses, \( n = 12 \) for 500–550 and 551–600 \( \mu \)m and \( n = 5 \) for 601–650, 651–700, and 701–750 \( \mu \)m. Only sites at which VS \( \geq 0.3 \) for 3–15 Hz were included in the latency analyses.

**Minimal cortical model.**

The numerical simulations were performed on a model representing a layer IV vibrissa barrel circuit. The circuit consisted of two cells—an excitatory cell (E cell) and an inhibitory cell (I cell). Both cells were modeled with Hodgkin-Huxley-based current-balance equations as follows

\[
C \frac{dV_e}{dt} = I_e + I_{\text{NA}} + I_k + I_{\text{app}} + I_{\text{GABA}_A} + I_{\text{GABA}_B} + I_{\text{thd}} + \text{noise}
\]

\[
C \frac{dV_i}{dt} = I_i + I_{\text{NA}} + I_k + I_{\text{app}} + I_{\text{GABA}_A} + I_{\text{GABA}_B} + I_{\text{thd}} + \text{noise}
\]

\[
I_{\text{ion}} = g_{\text{ion}}m^n h(V_{\text{ion}} - V)
\]

Here, \( C \) is the membrane capacitance, \( V_e \) is the membrane potential of cell \( j \), \( I_{\text{ion}} \) is an ionic current, \( g_{\text{ion}} \) and \( m \) and \( h \) are, respectively, the maximal conductance, and the dynamic activation and inactivation variables for that current, \( V_{\text{ion}} \) is the associated reversal potential, and \( p \) and \( q \) are integers.

The sodium (\( I_{\text{NA}} \)), potassium (\( I_k \)), and leak (\( I_l \)) currents represent voltage-dependent currents of regular spiking cells (Simons 1978) and cause each cell to display a typical spike pattern of a suprathreshold spike followed by a brief refractory period. The applied currents (\( I_{\text{app}} \) and \( I_{\text{thd}} \)) represent constant tonic drive to each cell. Thalamic input was also captured by an applied current (\( I_{\text{thd}} \)) and was modeled as a 30-ms square-wave pulse delivered to each cell at various frequencies (1–20 and 30 Hz). The thalamic input was stronger for inhibitory than excitatory cells (Simons 1995). The intrinsic currents were modeled as follows

\[
I_c = g_c(E_c - V)
\]

\[
I_{\text{NA}} = g_{\text{NA}}m^n h(E_{\text{NA}} - V)
\]

\[
\alpha_c(v) = 0.32^*(54 + v)/(1 - \exp(-(v + 54)/4))
\]

\[
\beta_c(v) = 0.28^*(v + 27)/(\exp((v + 27)/5) - 1)
\]

\[
\alpha_k(v) = 0.128^*\exp(-(50 + v)/18)
\]

\[
\beta_k(v) = 4/(1 + \exp(-(v + 27)/5))
\]

\[
I_k = g_{\text{NA}}^m h(E_k - V)
\]

\[
\alpha_k(v) = 0.032^*(v + 52)/(1 - \exp(-(v + 52)/5))
\]

\[
\beta_k(v) = 0.5^*\exp(-(57 + v)/40)
\]

The functions \( \alpha_c \) and \( \beta_c \) capture the forward and backward rates of the activation and inactivation variables \( y \) of each of the currents, as in standard Hodgkin-Huxley notation, where \( dy/dt = \alpha_y(1 - y) - \beta_y y \). Time is in milliseconds. The local two-cell circuit was established by synaptically coupling the cells using a model fast excitatory synapse (AMPA) and model fast and slow inhibitory synapses (GABA_A and GABA_B, respectively).

The synapses are given by the following equations (Koch and Segev 1998)

\[
I_{\text{AMPA}} = g_{\text{AMPA}}\text{AMPA}(E_{\text{AMPA}} - V)
\]

\[
I_{\text{GABA}} = g_{\text{GABA}}\text{GABA}(E_{\text{GABA}} - V)
\]

\[
I_{\text{GABA}} = g_{\text{GABA}}(GABA_A^d/(GABA_A^d + 5))(E_{\text{GABA}} - V)
\]

\[
\frac{d\text{AMPA}}{dt} = k_e(V_e)(1 - \text{AMPA}) - \text{AMPA}/\tau_d
\]

\[
\frac{d\text{GABA}}{dt} = k_i(V_i)(1 - \text{GABA}_A) - \text{GABA}_A/\tau_i
\]

\[
\text{ke}(V) = 5*(1 + \tanh(V/4))
\]

\[
\text{ki}(V) = 2*(1 + \tanh(V/4))
\]

\[
\text{dGABA}_A = 1.8(\text{r}_d) - 0.34\text{GABA}_A
\]

\[
\frac{d\text{r}_d}{dt} = 0.9\exp(1 - \text{r}_d) - 0.012\text{r}_d
\]

where \( \text{trans} \) is set to one for 1 ms when \( V_i \) crosses zero.

To capture thalamocortical input on each cycle of the square-wave thalamic input (\( I_{\text{thd}} \)) the height, \( h \), of the square-wave pulse changed according to \( h \rightarrow d \ast f \), where \( d \) is a depression term that resets to \( d \ast C_d \) during each cycle of the thalamic input. Between cycles of the thalamic input \( d \) changes according to \( d' = (1 - d')/\tau_d \). Similarly, \( f \) is a facilitation term that resets to \( f \ast C_f \) during each cycle of the thalamic input and between cycles changes according to \( f' = (f' - f)/\tau_f \).
The time constants $d$ and $f$ were chosen so that the RRTF curve resulting from data generated by the model matched the RRTF curve generated experimentally. The input activity is shown in Fig. 7B to demonstrate the interaction between depression and facilitation at each frequency. The additional noise current (noise) in each cell was modeled as a noisy excitatory (AMPA) synapse that comes from a presynaptic cell outside of the two-cell circuit. The presynaptic cell fires randomly with a uniform distribution in time.

The values of the parameters employed were derived from the experimental data and from other models of the rat somatosensory system (Jones et al. 2000; Kyriazi and Simons 1993; Pinto et al. 1996) and are as follows: $I_{gpe} = 0.5$, $I_{qpe} = 0.5$, $E_{c} = 100$, $E_{s} = 50$, $E_{l} = -67$, $E_{GABA_{c}} = -80$, $E_{GABA_{s}} = -80$, $E_{AMPA} = 0$, $g_{s} = 0.1$, $g_{c} = 80$, $g_{NA} = 100$, $g_{AMPA} = 0.1$, $g_{GABA_{c}} = 0.2$, $g_{GABA_{s}} = 0.2$, $\tau_{c} = 2$, $\tau_{s} = 10$, $\tau_{d} = 80$, $C_{d} = 1.000$, $C_{s} = 0.5$, $C_{j} = 0.6$, $f_{sat} = 0.2$. All simulations were performed using G. B. Ermentrout’s package for solving ordinary differential equations, XPPAUT. This package is available from ftp://ftp.math.pitt.edu/-pub/bardware. The usual method of integration was a fourth-order Runge-Kutta method with a time step of $dt = 0.02$.

Results

Adaptation to repetitive stimuli

The average poststimulus time histogram (PSTH) for all 64 recordings is shown in Fig. 1A. At 1 Hz, each repetition of the stimulus elicited a robust response. At higher frequencies, responses changed dynamically over the first ~1,000 ms of stimulation, typically decreasing in amplitude, and then stabilized to a steady state, defined as the last 4 s of the 5-s stimulus period. After each initial excitatory response, activity was suppressed below spontaneous rates for ~130 ms after stimulus onset (Fig. 1B). At high stimulus rates, deflections during this time resulted in few, if any, evoked spikes. At lower frequencies with periods >130 ms (1–5 Hz), a “rebounce” back to or above spontaneous activity levels was observed after this suppression (Fig. 1B). At most recording sites, a frequency was reached above which no systematic or periodic spiking was evoked after the first ~1 s of stimulation. At this frequency, sites often responded to every other repetition of a stimulus, firing at half the stimulus frequency presented to the vibrissa.

This type of response is reflected in the average PSTH at 15 Hz (Fig. 1, A and B), where responses to every other stimulus during the first second of the train are enhanced. To quantify a commonly measured feature of adaptation, we calculated a RRTF for the responses in our sample. For each site, the average amplitude of the response to vibrissa deflections (0–35 ms post-stimulus) at steady state was normalized to the amplitude of the first response to the train. At low frequencies, a high-amplitude response was maintained during the course of the train that is reflected in high RRTF values (Fig. 2, A and B). Although facilitation was not uncommon at low frequencies (42/64 sites showed facilitation at some frequency, 20 of these at 1 Hz), an inspection of the individual RRTF curves shows that all responses had predominantly low-pass RRTF characteristics that saturated by 20 Hz (Fig. 2B). The slope of the mean RRTF curve was steepest between 5 and 10 Hz. These results confirm previous reports of low-pass response adaptation of cortical neurons to repetitive vibrissa stimulation (Ahissar et al. 2001; Castro-Alamancos and Oldford 2002; Chung et al. 2002; Simons 1978).

Band-pass properties of adaptation

Although the net evoked response to a given stimulus within a train decreased with frequency, this adaptation was dependent on the time window in which responses were calculated. The steady-state responses at different frequencies of stimulation exhibited a small but consistent (0–5 ms) latency shift compared to the average first deflection in a train (Fig. 3). This effect was found to be significant for all frequencies evaluated ($P < 0.01$ for rates from 3 to 15 Hz, $P = 0.073$ for 1 Hz, sign test for incidence of longer latencies at each recording site for each frequency vs. first pulse latency). Increased latency was paralleled by a latency shift that is demonstrated by the normalized and averaged cycle histograms at each frequency (Fig. 3B, $P < 0.01$ for rates ≤ 15 Hz, sign test). Even at rates as low as 1 Hz, the average steady-state response began later than the response to the first deflection, and there was a systematic increase in both onset and decline time with increasing frequency and a trend toward longer lasting responses at higher frequencies ($P < 0.05$ for 8, 10, and 15 Hz, sign test). This latency shift suggests that although average response amplitudes decreased with increasing repetition rates, within specific longer-latency time windows, responses were facilitated relative to onset amplitude. To characterize this phenomenon, we calculated an RRTF of the averaged PSTH in 5-ms post-stimulation time windows (Fig. 3D). During the 5- to 10- and 10- to 15-ms post-stimulus time windows, steady-state responses were smaller than responses to the first deflection, as suggested by the overall RRTF value from 0 to 35 ms. However, for time windows beginning ≥ 15 ms after vibrissa deflection, responses showed band-pass facilitation at intermediate frequencies due to fast decline of first pulse responses and increased latency of steady-state responses. At 15–35 ms post-stimulus, facilitation of later time window responses peaked at rates between 3 and 10 Hz, with a systematic increase in facilitation in later time windows.

Band-pass temporal and SR responses

Additional analyses assessed overall SR and spike timing (VS) as a function of the frequency of vibrissa movement. The SR at each recording site was plotted as a function of stimulus frequency. In the majority of individual examples (70%, $n = 45/64$) and in the grand average, neurons displayed a peak in mean SR between 5 and 10 Hz (Fig. 4, A and B). Above 15 Hz, firing rate at individual recording sites and in the average response were consistently lower.

The temporal fidelity of each response to the stimulus rate was quantified by calculating the VS for each frequency. The VS reflects the precision with which a response locks its firing to the same phase of the stimulus period across deflections, with higher values signifying more consistent spike timing between cycles. Figure 5 shows the average VS (A) and the VS for each recording (B). Like the overall SR measure, VS peaked at 5–10 Hz in the grand average, and in almost all individual cases (89%, $n = 57/64$).

Comparison of responses by recording depth

We divided recording sites into five groups based on electrode depth to determine whether any of the observed temporal responses might vary with recording position. The RRTF, VS,
and SR measures, as well as onset and decay latency, were independently quantified for sites between 500 and 550, 551 and 600, 601 and 650, 651 and 700, and 701 and 750 μm depths (Fig. 6). For each group, RRTF values decreased with increasing frequency, while VS and SR responses showed band pass peaks between 5 and 10 Hz, as in the cumulative data set.
For each characteristic, a one-way ANOVA at each frequency showed no statistical difference between responses at each recording depth (P > 0.1 for RRTF, VS, SR, and onset latency at all frequencies, P > 0.08 for decay latency at all frequencies).

**Modeling of cortical transformations**

We employed a minimal cortical model including basic features of layer IV circuitry to provide insight into the mechanistic bases of the observed temporal phenomena. The model consisted of a spiking inhibitory and excitatory cell that were synaptically coupled via fast excitation (AMPA) and fast and slow inhibition (GABA_A and GABA_B) (Fig. 7A). Each cell also received adapting depolarizing thalamic input and additional noisy excitatory drive. Calculations of RRTF, VS, and SR from simulations of the model produced results similar to our physiological data (Fig. 7).

The experimentally observed facilitation at the lowest sampled frequencies, and low-pass adaptation at higher frequencies were built into the model via thalamocortical input (Fig. 7B).

Adaptation and facilitation parameters where chosen while holding all other variables constant so that the RRTF curve generated from numerical simulations (Fig. 7D, black curve) matched those generated from the physiological data (compare to Fig. 2A). Thus the origin of the adaptation in the model is non-explicit and may capture either the adaptation at the thalamocortical synapse or a reduction in thalamic or prethalamic firing. The relative amplitude of the input activity during the stimulus train is shown for each frequency in Fig. 7B. At 1 Hz, facilitation dominates over depression during the steady state, while at frequencies >3 Hz, the input activity shows varying degrees of depression. When the adaptation is removed from the model, the height of the square-wave impulse train remains 1 (data not shown).

When thalamocortical adaptation alone was removed from the model, the low-pass phenomenon disappears (Fig. 7D, mid-gray curve). Slow suppressive intra-cortical mechanisms also influence the shape of the RRTF curve in the model. When the GABA_B synapse alone was removed from the model (Fig. 7D, light gray curve), less intra-cortical inhibition is evoked overall on subsequent cycles of stimulation, leading to an increase in the normalized RRTF value. Interestingly, the contribution of modeled GABA_A was not observed in the absence of thalamocortical adaptation (Fig. 7D, light gray curve), suggesting a non-linear addition of these suppressive influences. The requirement that other concomitant inhibitory factors are present for the expression of GABA_A affects has recently been observed in other sensory cortices (Wang et al. 2002).

Although no further manipulations were made in the model to capture the band-pass temporal features observed experimentally, SR and VS curves qualitatively similar to those generated from the physiological data emerged (compare black curves in Fig. 7, E and F to Figs. 4A and 5A). Removal of thalamocortical adaptation evoked a linear rise in SR with stimulus frequency (Fig. 7E, mid-gray curve). Slow intra-cortical inhibitory mechanisms also affected SR values. When the GABA_A synapse alone was removed from the model (Fig. 7E, light gray curve), SR values were higher and the band-pass character of this feature was diminished (compare black and light gray curves in Fig. 7E). Unlike the SR response, the band-pass character of the VS was not influenced by thalamocortical adaptation (Fig. 7F, mid-gray curve). However, slow intra-cortical inhibition played a dominant role in defining this band-pass peak as verified by the lower degree of band-pass VS modulation in the light gray curve in Fig. 7F, generated with GABA_B removed from the model. The inhibitory influence of GABA_B on the observed band-pass phenomena was specific to the dynamics of this current, and not a general effect of inhibition. When GABA_A was removed from the model, higher spike rates were observed but there was little influence on the shape of the VS and RRTF curves (data not shown).

**Discussion**

In this study, we replicated previous reports that described low-pass adaptation of the evoked responses of layer IV cortical neurons to vibrissa deflection. In agreement with earlier studies (Ahissar et al. 2001; Castro-Alamancos and Oldford 2002; Chung et al. 2002; Simons 1978), almost all individual recording sites and the grand average of responses adapted to repetitive stimulation, and this adaptation was more robust.
with increasing frequency. Further analyses revealed several band-pass characteristics of the evoked responses. The relative response amplitude in late periods of the evoked response and the average SR and VS during the steady state peaked with repetitive stimulation between 5 and 10 Hz. These band-pass characteristics of SI neurons overlap closely with the reported range of whisking sampling frequencies of the vibrissae, suggesting that whisking frequencies reflect the optimal range for sensory information processing in the vibrissa to cortex pathway. The replication of the key features of these findings by a reduced computational model of layer IV circuitry suggests that, while many levels of information processing may contribute to the existence of these band-pass phenomena, basic features of layer IV cortical circuitry can account for their generation.

Implications for whisking behavior and sensory coding

We have previously proposed that cortical dynamics transform sensory representations to optimize perceptual performance in the whisking frequency range. Specifically, low-frequency input facilitates detection of tactile stimuli through spatially extensive recruitment of a greater number of cortical neurons by a given vibrissa, whereas stimulation at higher rates, initiated by whisking, facilitates spatial discrimination of distinct vibrissae through the restriction of activation extent (Moore et al. 1999). The current findings are consistent with the proposal that rat SI processing is differentially transformed in the whisking frequency range and appear to extend the applicability of this framework to the temporal processing domain.

Each of the observed band-pass properties, the precise timing of spiking activity, the mean spike rate over an extended period, and response latency, have been central features of proposed somatosensory neural codes for frequency discrimination and spatial localization (Hernandez et al. 2000; Mountcastle et al. 1967, 1969, 1990; Recanzone et al. 1992; Salinas et al. 2000). Analyses of neural responses in monkeys discriminating the frequency of tactile stimuli on their fingers suggest that either the mean spike rate and/or temporal pattern of responses optimally predict perceptual performance (Hernandez et al. 2000; Mountcastle et al. 1967, 1969, 1990; Recanzone et al. 1992; Salinas et al. 2000). While parallel electrophysiological studies have not, to our knowledge, been conducted in the vibrissa to barrel system, the observed increase in spike count at 5–10 Hz may optimize the confidence of spike-rate based discriminations made in this frequency range. Similarly, the peak in the fidelity of spike timing (VS) at the whisking sampling rate, particularly in the context of a robust number of total spikes, might reflect enhanced ability of rats to discriminate frequencies in this range. Recently, Kleinfeld et al. (2002) found that spiking activity of awake rat primary motor cortex neurons selectively extracted the fundamental
frequency of repetitive vibrissae stimulation at rates from 5 to 15 Hz. This band-pass phenomenon parallels and may be related to those reported here and underscores the importance of processing in this frequency range in the awake behaving animal.

We also observed band-pass enhancement of responses that resulted from small, frequency-specific latency shifts with increasing frequency. Previous studies have reported latency shifts in the septa and in layers Va and II/III (Ahissar et al. 1997, 2000, 2001). In these layers, onset latency shifts could be as great as 45 ms and increased with higher stimulus rates, while decline latencies remained constant. This combination of phenomena resulted in a rate code for stimulus frequency that is hypothesized to be important for coding object localization. In contrast, layer IV responses were hypothesized to be important for coding temporal information because latencies were stable (Ahissar and Arieli 2001; Ahissar et al. 2000). Our data showed small onset latency shifts that were significantly shorter than latency shifts reported in other cortical layers but were not inconsistent with previously reported data showing slight latency shifts on the scale of a few milliseconds in layer IV (e.g., Fig. 2B in Ahissar 2001). We also observed small decline-latency shifts and a trend toward longer response widths, which differ from the non-granular pattern of responses. Although the latency shifts we observed are small in comparison with shifts in other layers, temporal processing on the millisecond time scale may be important for a variety of tasks, including texture discrimination (Carvell and Simons 1995).

In addition to the possible utility of band-pass responses at whisking frequencies, several characteristics of low-pass adaptation could improve information coding over these frequencies. The slope of the RRTF adaptation function was greatest from 5 to 10 Hz, and the highest frequency at which cortical responses had not completely adapted occurred at ~8 Hz, where the RRTF slope is greatest. Sampling tactile information at this frequency could mediate a compromise between having an ample number of spikes per stimulus (highest statistical power observation) and collecting information at an optimal rate. A further possible advantage of the rapid change in response amplitude in the whisking frequency range is that rapid or long-term plasticity of responses would be expected to optimally effect sensory processing in this frequency range. Auditory plasticity studies in rodents have shown experience-dependent changes in temporal properties of cortical neurons.
around the frequency range where RRTF curves were steepest (Kilgard and Merzenich 1998).

Possible mechanisms for the observed phenomena

Previous biological studies as well as findings from our minimal cortical model suggest the following mechanisms for our results. With regard to the RRTF adaptation phenomenon observed in layer IV, several studies have demonstrated that the magnitude of adaptation within the VPm is significantly smaller than that observed in the cortex (Chung et al. 2002; Diamond et al. 1992; Hartings and Simons 1998; Sosnik et al. 2001; J. A. Hartings and D. J. Simons, personal communication). Data from whole cell recordings in barrel cortex have demonstrated that repetitive vibrissa stimulation depressed EPSPs evoked at the thalamocortical synapse and that depression at this synapse can account for the consistently observed cortical adaptation in spiking activity (Chung et al. 2002). Thalamocortical adaptation was also crucial, in our model, to the emergence of the other spike count phenomenon observed, the band-pass characteristic of the SR. Because the SR was calculated from the entire steady-state period, the initial increase in SR at low frequencies reflects the increased number of vibrissa stimuli per second at increasing stimulus rates. At higher frequencies (>5–10 Hz), adaptation overcame this increase in SR even though the number of stimuli continued to increase. Thus the band-pass peak in SR reflects a trade off between an increase in the number of stimuli per second at higher rates and the adaptation resulting from high-frequency vibrissa stimulation.
In contrast to these spike count measures, VS appears to depend largely on long-lasting inhibitory influences. Post-stimulus suppression commonly has been observed in intracellular and extracellular studies of somatosensory cortex (Carvell and Simons 1988; Hellweg et al. 1977; Kyriazi et al. 1996; Moore and Nelson 1998; Simons 1985; Zhu and Connors 1999). Application of GABA_B antagonists to the cortex eliminates the slow component of this suppression that lasts for hundreds of milliseconds (Kyriazi et al. 1996). We observed suppression of spontaneous activity after initial vibrissa deflections that lasted \( \sim 130 \) ms (Fig. 1B). Recovery from this suppression coincided exactly with subsequent excitation by a second deflection at 8 Hz. A parsimonious explanation for the observed band-pass characteristic in VS is that at low frequencies, inhibition does not suppress the “noisy” spikes that occur between longer inter-stimulus intervals (i.e., \( >130 \) ms). These spikes degrade the measured phase locking of the response to subsequent deflections. At higher frequencies (e.g., \( >10 \) Hz), interactions between the slow inhibition and thalamocortical depression effectively diminish the response and undermine the consistency of a greater number of spikes from cycle to cycle (e.g., see the response to the second pulse of stimulation at 15 Hz, Fig. 1B). These suppressive interactions effectively impose an inherent periodicity on processing in this system. In agreement with this prediction, removal of slow suppression from the model by removal of GABA_B largely eliminated the band-pass VS characteristics.

Although we have shown that a cortical circuit model can account for the temporal response properties observed, other cellular or network mechanisms likely also contribute to these phenomena. The sustained inhibition in our model was constructed to represent GABA_B synaptic currents derived from in vitro studies (Connors et al. 1988) and implicitly demonstrated by pharmacological blockade in the cortex in vivo (Kyriazi et al. 1996). However, these currents have been found to be less prominent in vivo than in vitro (Steriade 2001). A variety of other mechanisms may contribute to the increased band-pass temporal fidelity observed. Studies of cellular subthreshold oscillations have shown that the temporal reliability of cortical pyramidal neurons peaks at rates between 5 and 20 Hz when these cells are injected with sinusoidal current (Fellous et al. 2001). Further, the time course of the sustained slow inhibitory period and rebound burst observed here follows the activation kinetics of intrinsic low-threshold calcium currents \( (I_h) \) and hyperpolarization activated currents \( (I_h) \) observed in thalamic and cortical neurons (Destexhe et al. 1993; Foehring and Waters 1991; Monteggia et al. 2000). Several intrinsic currents in cells within the cortex and thalamus also influence adaptation (i.e., \( Ca^{2+} \) - or Na\(^{+}\)-dependent K\(^+\) currents and persistent Na\(^{+}\) currents) and may hence contribute to the observed phenomena (Fleidervish and Gutnick 1996; Fuhrmann et al. 2002; Sanchez-Vives et al. 2000a,b). Corticothalamic loops have been hypothesized to help increase the sensitivity of thalamic and cortical responses during brief thalamic bursting modes that correspond to vibrissa twitching states but not to play this role during tonic thalamic firing (Nicolelis and Fanselow 2002). Periodicity imposed by the time constants of corticothalamic connectivity could also contribute to enhancing this band-pass fidelity of neuronal firing (Destexhe et al. 1998). While any of these response components may contribute to the observed phenomena, we have shown that a minimal spike generating cortical circuit with adaptation arising at the level of the thalamocortical synapse is sufficient to produce the observed results.

**Limitations of the experimental preparation**

We recorded responses from depths of 500–750 \( \mu \)m in rat SI, as determined from microdrive readings. A limitation of the present study is that we did not reconstruct the position of the electrode tip in each case, preventing the conclusive identification of the layer of recording. Several lines of evidence suggest that our recordings were located either within a barrel or within cell populations immediately superficial to the barrel that demonstrate overlapping response profiles. Physiologically, each site we recorded from showed strong single vibrissa responses that are typical of barrel responses (e.g., Armstrong-James et al. 1992; Simons and Carvell 1989). The location of these recordings was addressed in a separate experiment [5 sites in 3 rats (Garabedian and Moore, unpublished observations)] and in all cases, the position of the lesion overlapped both layer IV and layer III directly above a cytochrome oxidase-defined barrel. This lesion study also suggested that the more superficial depth recordings from our microdrive readings (500–550 \( \mu \)m) corresponded to layer III or IV of the barrel cortex and deeper recordings (700–750 \( \mu \)m) to layer IV. Comparison of the response measures at different depths showed that each trend (low-pass RRTF, consistent response onset shifting with increasing frequency and band-pass VS and SR curves) was replicated in a smaller range of recording depths. Further, no significant difference was observed in these properties as a function of depth nor were any trends in response profile observed to correlate with relative depth. Specifically, previous studies (Ahissar et al. 2001) suggest that were our more superficial recordings in layer III, a significantly greater onset latency shift should have been observed with increasing frequency at these depths.

In the present study, we recorded multi-unit responses: as such, these data contribute to the understanding of the net activity of the population of neurons sampled. Because our

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**FIG. 7.** A minimal network model replicates low-pass and band-pass responses. Black curves show data for control conditions, mid-gray curves show data when thalamocortical (TC) adaptation was removed from the model, and light gray curves show responses when slow inhibition was removed from the model. Temporal measures of RRTF, SR, and VS were calculated as described in the experimental procedures. Measures were generated from the spiking activity of the model excitatory cell and were averaged over 10 simulations for each frequency of stimulation. Error bars represent standard deviation. **A**: schematic diagram showing each element of the computational model consisting of thalamocortical input, 1 excitatory and 1 inhibitory unit, and AMPA, GABA_A, and GABA_B currents. **B**: normalized amplitude of the thalamocortical input function as a function of time for each frequency. The time at which the amplitude reached a steady state for each frequency was: 1 Hz: \( >5 \) s, 3 Hz: 3,030 ms, 5 Hz: 3,630 ms, 8 Hz: 2,530 ms, 10 Hz: 2,330 ms, 15 Hz: 1,630 ms, 20 Hz: 1,230 ms, 30 Hz: 930 ms. **C**: PSTHs for simulated data averaging 10 repetitions of stimuli from 1–20 Hz. **D**: RRTF as a function of stimulus rate. **E**: SR as a function of stimulus rate. **Inset**: SR as a function of stimulus rate, expanded scale. **F**: VS as a function of stimulus rate.
recordings focused on multi-unit responses, however, certain aspects of these findings have multiple possible interpretations. For example, intermediate levels of adaptation, where some but not all of the response was diminished with increasing frequency, can be interpreted either as the cumulative adaptation of single neurons at a given rate or as the complete adaptation of a subset of neurons that contributed incompletely to the response while other neurons maintained activity in an unadapted state. The latter scenario is unlikely based on previous reports showing that isolated single units and intracellular recordings also show temporal adaptation in the frequency ranges reported here (Chung et al. 2002; Simons 1978). In addition, although temporal properties of single units and clusters may vary, recent studies have emphasized the similarity in temporal features of both types of recordings, in somatosensory and auditory cortex (Ahissar et al. 2001; Eggermont and Smith 1995).

There are obvious concerns when extrapolating data from the anesthetized preparation, employed in the current study, to the awake animal. Although anesthesia allows greater control of stimulus presentation, a clear advantage when conducting precise temporal studies, it can modify barrel cortex response properties (Armstrong-James and George 1988; Friedberg et al. 1999; Simons et al. 1992). In anesthetized, sleeping, or unanesthetized animals, single-vibrissae deflections result in large cortical responses, whereas responses to repetitive stimuli show depression (Castro-Alamancos and Oldford 2002; Fanselow and Nicolelis 1999; Moore et al. 1999; Sheth et al. 1998). During arousal, thalamic firing rates are high, likely in part due to ongoing whisking (Fee et al. 1997) and in part due to depolarizing cholinergic input from the reticular formation: these high thalamic firing rates are hypothesized to maximize thalamocortical depression, resulting in smaller cortical responses (Castro-Alamancos 2002; Castro-Alamancos and Oldford 2002). Cortical responses to repetitive electrical stimulation of the fifth nerve have been characterized as showing little adaptation in awake, whisking animals (Fanselow and Nicolelis 1999), a response pattern that can be attributed to the already depressed/adapted state of the sensory pathway engaged by simultaneous whisking. As other authors have recently suggested, the steady state induced by repetitive stimuli in the anesthetized preparation is perhaps an appropriate model of the condition in the aroused animal during whisking (Castro-Alamancos and Oldford 2002). Whether the band-pass properties described here are also observed in the awake state and, more importantly, during repeated contact with an object during whisking, remains an open question.

Implications of band-pass phenomena for whisking behavior

The coincidence between the frequency range of whisking behavior and the neural response properties we have identified as band-pass suggests the rat may modulate its whisking rate to take advantage of the inherent time constants of cortical dynamics and thalamocortical circuitry. Our findings closely parallel those observed in the primary auditory cortex of the ketamine anesthetized cat, where normalized spike amplitude showed similar low-pass behavior and VS and SR showed band-pass responses to repetitive stimuli, with a peak at ~8 Hz (Eggermont 1991, 1999). Further, intracellular studies of cat SI have demonstrated that 8- to 12-Hz periodic subthreshold responses emerge during stimulation of the infraorbital nerve at rates ~150 Hz (Hellweg et al. 1977). This similarity in activity patterns across species, anesthesia type, and sensory modality, suggests that the band-pass responses we observed emerge from intrinsic dynamics of these sensory systems. Behavioral data showing that rats change their whisking frequencies in the context of different behavioral tasks (Carvell and Simons 1995) and that the frequency power of whisking changes as a rat improves performance of a discrimination task (Harvey et al. 2001) further suggest that whisking frequency is intentionally modulated to optimize the engagement of temporal cortical dynamics, while these dynamics themselves are stable. Interestingly, mice whisk their vibrissae at higher rates (in the range of 10–15 Hz) than rats (Woolsey et al. 1981). If the properties we have observed are related to the rate at which rats whisk over the course of life experience or to evolutionary selection, then we would predict a subtle, parallel shift in the encoding properties of mouse SI neurons toward higher frequencies.

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