

Temporal Modulation of Spatial Borders in Rat Barrel Cortex

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Temporal modulation of spatial borders in rat barrel cortex. *J. Neurophysiol.* 79: 464–470, 1998. We examined the effects of varying vibrissa stimulation frequency on intrinsic signal and neuronal responses in rat barrel cortex. Optical imaging of intrinsic signals demonstrated that the region of cortex activated by deflection of a single vibrissa at 1 Hz is more diffuse and more widespread than the territory activated at 5 or 10 Hz. With the use of two different paradigms, constant time of stimulation and constant number of vibrissa deflections, we showed that the optically imaged spread of activity is more discrete at higher stimulation frequencies. We combined optical imaging with multiple electrode recording and confirmed that the neuronal response to individual vibrissa stimulation at the optically imaged center of activity is greater than the response away from the imaged center. Consistent with the imaging data, these recordings also showed no response to a second vibrissa deflection at 5 Hz at a peripheral recording site, though there was a significant response to a second vibrissa deflection at 1 Hz at the same peripheral site. These findings demonstrate that vibrissa stimulation at higher frequencies leads to more focused physiological responses in cortex. Thus the spread of activation in rat barrel cortex is modulated in a dynamic fashion by the frequency of vibrissa stimulation.

INTRODUCTION

Layer IV of rodent somatosensory cortex contains discrete clusters of cells commonly referred to as “barrels” (Woolsey and Van der Loos 1970). Within the posterior medial barrel subfield (PMBS) of rat somatosensory cortex, neurons in a given barrel column are most responsive to deflection of a single vibrissa on the rat’s snout, although neurons in each barrel are also responsive to stimulation of other vibrissae (Armstrong-James and Fox 1987; Simons 1978, 1985), with neurons in neighboring barrels maximally responsive to adjacent vibrissae on the rat’s snout. This somatotopy, revealed by conventional electrophysiological techniques (Welker 1971, 1976), renders optical imaging an ideal tool for investigating questions regarding the functional properties of neuronal ensembles in rat barrel cortex. This technique allows us to observe metabolic activity over a large expanse of cortical territory (several millimeters encompassing PMBS) and to thereby observe changes in the spatial pattern of functional activity of a population of neurons.

Recent studies have shown that rats whisk their vibrissae at a dominant frequency of about 8 Hz (Carvell and Simons 1990). Similarly other studies have found that rats exploring their environment sweep their vibrissae at 6–9 cycles/s. (Welker 1964; see also Wineski 1983; Woolsey et al. 1981). An important question is whether or not and how the pattern of cortical activity changes with vibrissa movement in this range of behaviorally relevant frequencies.

A possible basis for frequency-dependent cortical re-

sponses might be the significant differences in response characteristics of the two thalamic nuclei (the ventral posterior medial (VPM) nucleus and the posterior medial (POM) nucleus) that project to rat barrel cortex and their anatomic projections to PMBS (see DISCUSSION). The anatomic and physiological segregation of these two thalamocortical pathways suggests that the input to regions surrounding the barrels in layer IV might be attenuated at higher frequencies and hence that there might be a corresponding drop-off in the strength of optical signal in these surrounding regions.

Finally, it is important to define stimulus parameters for PMBS cortex that activate either 1) predominantly a barrel/column by evoking a spatially discrete and localized cortical response or 2) neurons in interbarrel regions and in other neighboring barrels as well by evoking a more spatially diffuse cortical response. Knowledge of stimulus parameters, such as frequency of vibrissa stimulation (Blood et al. 1995), that elicit a robust and reproducible optical response in rat barrel cortex is of obvious importance for future studies of this system.

To investigate these issues, we used intrinsic signal optical imaging (Grinvald et al. 1986; Masino and Frostig 1996; Masino et al. 1993; Narayan et al. 1994) in rat barrel cortex to study the effects of stimulus frequency on cortical response. Data from both somatosensory (Masino et al. 1993) and visual (Das and Gilbert 1995; Toth et al. 1996) cortices suggest that the optical signal correlates with the activity (extracellular plus intracellular; Moore et al. 1996) of local neuronal populations. We also correlated the optically imaged map with simultaneous recording of neuronal responses at multiple sites in the map.

METHODS

Sprague-Dawley rats (8 animals) ranging in weight from 175 to 325 g were anesthetized with urethan (1.25 g/kg ip) and the depth of anesthesia was continually monitored so that the animal remained areflexive to hindpaw pinch and the breathing rate remained between 80–120 breaths/min (Armstrong-James and Fox 1987). If the hindpaw reflex was observed or if the breathing rate exceeded 120 breaths/min, a supplemental dose of urethan (10% ip initial dose) was delivered.

Stimulation

The optical response to displacement of individual vibrissae at different frequencies was measured. The vibrissa stimulator consisted of a glass capillary attached to a piezoelectric ceramic wafer (1.5 × 0.5 in., Piezo Systems 2). The vibrissae on the left side of the rat’s face were clipped to a length of 1 cm. The tip of the glass capillary was then placed either over the shaft of the vibrissa or beneath it, so that the point of deflection was 5 mm from the base of the vibrissa (Armstrong-James et al. 1994). A computer-controlled pulse triggered a stimulus generator to send a voltage

step to the piezoelectric wafer, causing a 1 mm up-down, 70 mm/s deflection of the capillary tip. These stimulus parameters have been found to consistently evoke extracellular and intracellular responses from PMBS neurons in urethan-anesthetized rats in our laboratory (Moore and Nelson 1994). No differences in mechanical amplitude of the piezo-electric triggered deflection were found with change in stimulus frequency.

Optical recording

The skull above PMBS (4–7 mm lateral to the midline and 1–4 mm posterior to bregma) (cf. Chapin and Lin 1984) was thinned to a thickness of 100–150 μm . When wet with silicone oil (Accumetric), the thinned skull was rendered translucent, allowing a clear view of the cortical surface (Frostig et al. 1990; Masino et al. 1993).

A video camera-based system (Optical Imaging, New York) was used in the experiments described here (for details see Toth et al. 1996). The camera was focused 450 μm below the surface of the cortex, to approximately the depth of layer IV in PMBS (Welker 1976; Welker and Woolsey 1974). As a result, the optical signal we recorded was a combination of responses from layers II–IV. We imaged a 4.25×3.5 mm horizontal plane of cortex. Light filtered through a 632.8 ± 10 (SE) nm filter was used to illuminate the cortex during data collection. Individual vibrissa stimulation was begun at the onset of a 4.5-s data collection period and maintained for a specific duration (see below) while data were acquired continuously. This vibrissa stimulation condition was interleaved with another 4.5-s time period of data collection during which no vibrissa stimulation took place. These two conditions were randomly interleaved with a 10-s intercondition interval to allow the optical signal to return to baseline. The data acquired during each 4.5-s collection phase were divided into nine frames, each of 500-ms duration.

Analysis

To generate a somatotopic map of activity in the PMBS, several vibrissae (5–10/rat) were individually stimulated and the cortical area imaged. A standard vibrissa stimulus paradigm consisted of 10 vibrissa deflections at 5 Hz for a duration of 2 s each (Masino et al. 1993). For each vibrissa that was individually activated, the stimulation pattern described above and the nonstimulated condition (i.e., imaging the same cortex without vibrissa stimulation) were repeated 30 times and the optical images of barrel cortex summed and averaged. Because of the characteristic rise and fall times of the optical signal (Masino et al. 1993), we usually analyzed the time period 500–2,000 ms after the onset of stimulation (i.e., frames 2–4). An analysis program that locates the $280 \times 280 \mu\text{m}^2$ (21×21 pixel) region of highest activation across the entire imaged area was then applied to the averaged activation map. The center located by this program was then placed on a reference map of the cerebral vasculature.

After obtaining a map, vibrissae showing activation in the exposed region of cortex were tested at deflection rates of 1, 5, and 10 Hz. Averages of 30 trials were obtained at these frequencies under two different stimulus paradigms. Blocks consisting of 10 trials at each frequency were pseudorandomly interleaved for a given vibrissa to avoid any consistent effect of cortical adaptation. Three blocks were run for each frequency.

For statistical analyses, two concentric, nonoverlapping annular rings centered on the activity center located by the program were drawn (the center was a circle of 133 μm radius, the outer ring circumscribing the center circle had a 133 μm inner radius and a 506 μm outer radius) (cf. Chapin and Lin 1984 for barrel sizes). For each ring, the activity averaged over all the pixels falling in each ring was calculated (both rings had the same number of pixels). The average activity in the outer ring thus obtained was

then subtracted from the average activity in the center circle. These differences (or slopes of the relative changes in reflectance) obtained for all the stimulated vibrissae were then compared vibrissa-by-vibrissa for all three frequencies. The differences in slope between the three frequencies (1–5 Hz, 5–10 Hz, and 1–10 Hz) were then used to evaluate frequency-dependent fall-off in activity from the putative barrel center (one-tailed, paired student's *t*-test). In an expanded companion analysis, six concentric annular rings were used (center circle of $\sim 133 \mu\text{m}$ diam, surrounding rings of outer diameters 267, 360, 720, 1,080, and 1,440 μm , respectively) and their respective activity averages were calculated and compared. In a similar fashion, fall-off in activity between the center circle and the innermost annular ring (outer diameter 267 μm) was obtained for the set of vibrissae imaged and the two groups of data (1 vs. 5 Hz and 1 vs. 10 Hz) were compared by using a one-way analysis of variance (ANOVA) test to see whether the means were statistically equal.

Histology

At the end of three experiments, animals were euthanized with an overdose of anesthetic and perfused intracardially with saline followed by fixatives. Tangential sections (50 μm) were cut through PMBS in a plane approximately parallel to the plane of optical imaging. Sections were stained for cytochrome oxidase to visualize barrels. In specific cases, a series of cytochrome-oxidase stained tangential sections were superimposed with the aid of lesions made during recording and the barrel pattern reconstructed. These cases were used for correlating the location of imaged barrels with the barrel map within PMBS cortex.

Electrophysiology

To examine the correlation between the optical signal and electrophysiological activity, we recorded somatosensory-evoked local field-potential responses with a pair of electrodes (Uwe Thomas Recording, Marburg, Germany) in cortex that was imaged immediately before electrophysiological recording. Glass insulated platinum-iridium electrodes (3–5 M Ω impedance at 1 kHz) were used in these recordings. The electrical signal was amplified, sampled at 10 kHz, digitized by an A/D board (Data Translation, Marlboro, MA), and recorded and stored on a computer (software supplied by Data Wave Technologies, Longmont, CO). Identical stimuli (piezo-generated vibrissa deflections) were used in the optical and electrical recordings.

RESULTS

For each animal studied, a map of activity centers corresponding to individual vibrissa stimulation (and to putative barrel centers) was generated (Fig. 1, *A* and *B*). The map corresponded to the known somatotopy of vibrissa representation in the PMBS of rat cortex. In agreement with Masino et al. (1993), we found that histologically identified barrel centers and barrel representations measured with optical imaging were localized to the same spot in the cortical sheet (Fig. 1*C*).

To examine the effect of stimulus frequency on representation borders, we first kept the time of stimulation constant (2 s) and then studied the spatial spread of activation at vibrissa stimulation frequencies of 1, 5, and 10 Hz. A more diffuse spatial spread of activity under the 1-Hz stimulus condition compared with the 5- and 10-Hz stimulation conditions (Fig. 2, *A* and *B*) was observed. Although the level of optical signal at the barrel centers for 1- and 5-Hz stimuli was the same ($n = 10$ vibrissae), there was a sharper fall-

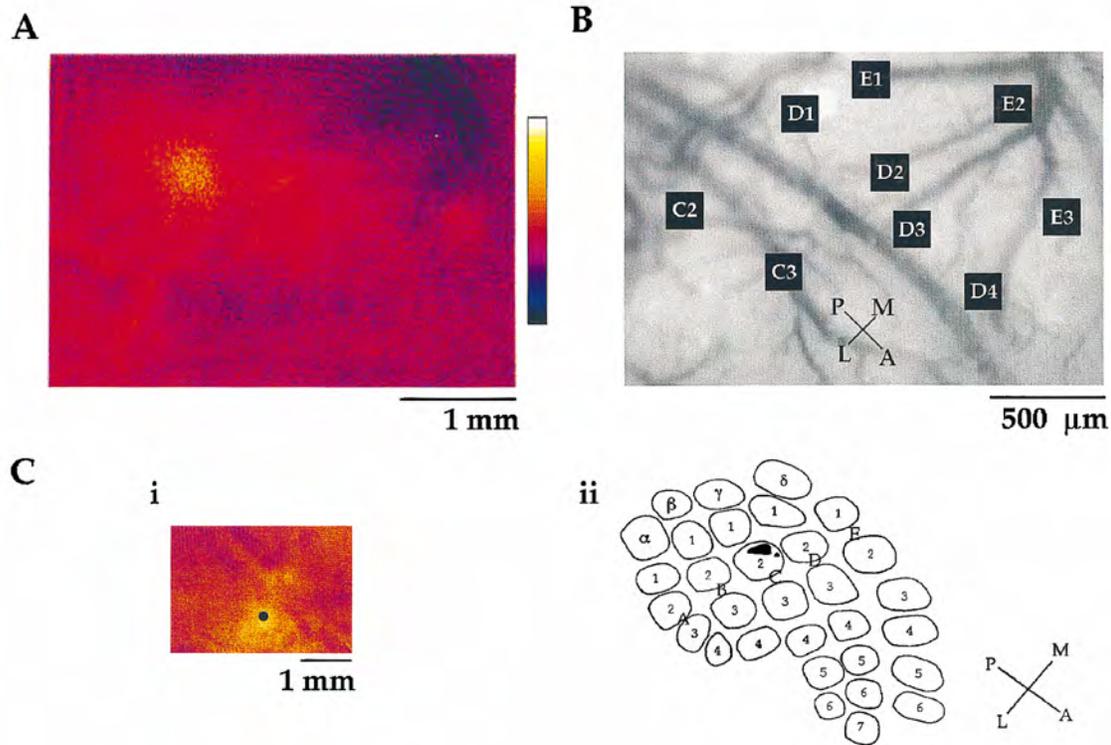


FIG. 1. *A*: localization of cortical activity after vibrissa stimulation. Optical image (average of 30 trials of 1-mm up-down deflection of vibrissa) of barrel cortex after stimulation of an individual vibrissa at 5 Hz for 2 s. Color bars: relative intensity of signal from minimum (black) to maximum (white). *B*: a composite optical map of barrel cortex obtained by stimulating each vibrissa individually (5 Hz, 2 s) and deriving its cortical activity center. *C*: confirmation of barrel imaging. *i*: individual vibrissae were stimulated (5 Hz, 2 s) and cortical area corresponding to PMBS was imaged. After several vibrissae were imaged, an electrolytic lesion was made near center of optically imaged expanse of cortex, at an activity center corresponding to C2 vibrissa stimulation. Black dot indicates location of lesion. *ii*: line drawing showing location of lesion in histologically defined C2 barrel. A–E, barrel rows. A series of angential sections were stained with cytochrome oxidase, superimposed with aid of lesions, and hand drawn.

off in activation away from the activity center for the 5-Hz stimulus (Fig. 2C) than for the 1-Hz stimulus ($P < 0.005$, see METHODS), indicating that the barrel activation was more discrete at 5-Hz stimulation than at 1-Hz stimulation. A more discrete spatial spread of activation was also obtained for the 10-Hz stimulus than for the 1-Hz stimulus ($P < 0.025$, $n = 10$). No statistical difference ($P > 0.05$) was found between activity spread for 5- and 10-Hz stimuli. Statistically significant differences ($P < 0.002$, one-way ANOVA) in the fall-off in activation from the optical activity center were found between 1 and 5 Hz and also between 1 and 10 Hz, even at a radius of 200 μm . Thus higher frequencies yield more focal activation in rat barrel cortex.

The signal strength at the optical activity centers for all three frequencies was indistinguishable ($P = 0.69$, one-way ANOVA). Thus although higher frequencies lead to attenuation in the strength of optical signal in the surround, they do not affect the strength of signal in the center of a vibrissa representation.

We obtained similar results when the number of deflections was fixed at five for the three frequencies under study, while the time of stimulation was varied. Because the duration of stimulation was different for the three frequencies, it was not possible to compare the signal over the same time frames. Hence we summed and averaged the signal over all time frames for the duration of the stimulation and for 1 s after its offset (frames 1–9 for 1 Hz, frames 1–4 for 5 Hz,

and frames 1–3 for 10 Hz). For 15 of 16 vibrissae studied (5 animals), the spread of activity for the 5-Hz stimulus was less than ($n = 7$) or equal to ($n = 8$) that for the 1-Hz stimulus. For the population, activation was more discrete for the 5-Hz stimulus as compared with the 1-Hz stimulus ($P < 0.025$). Similarly stimulation at 10 Hz yielded more spatially discrete activation than the 1-Hz stimulus ($P < 0.05$).

Because the optical signal represents the activity of populations of neurons, we examined the effect of stimulus frequency on spread of cortical activation by combining optical imaging with electrical recording of local field potentials at two spatially separated electrodes. After the imaging session, one electrode was placed in the center of the optical spot generated by stimulation of a vibrissa (C1, marked “center” in Fig. 3A) and a second electrode was placed at a lateral distance of $\sim 700 \mu\text{m}$ from the optical activity center (marked “periphery” in Fig. 3A). The electrodes were each lowered to a depth of 300–600 μm , corresponding to the depths at which the intrinsic signal was measured. At a lateral distance equivalent to the spacing of the periphery electrode from the center, optical responses to 5-Hz stimulation have returned to baseline (Fig. 2C). Figure 3B shows somatosensory-evoked responses to the first and second vibrissa deflection, carried out at 1 and 5 Hz, at each of the two electrodes. Responses were larger in the electrode located at the center of the optical spot, similar to

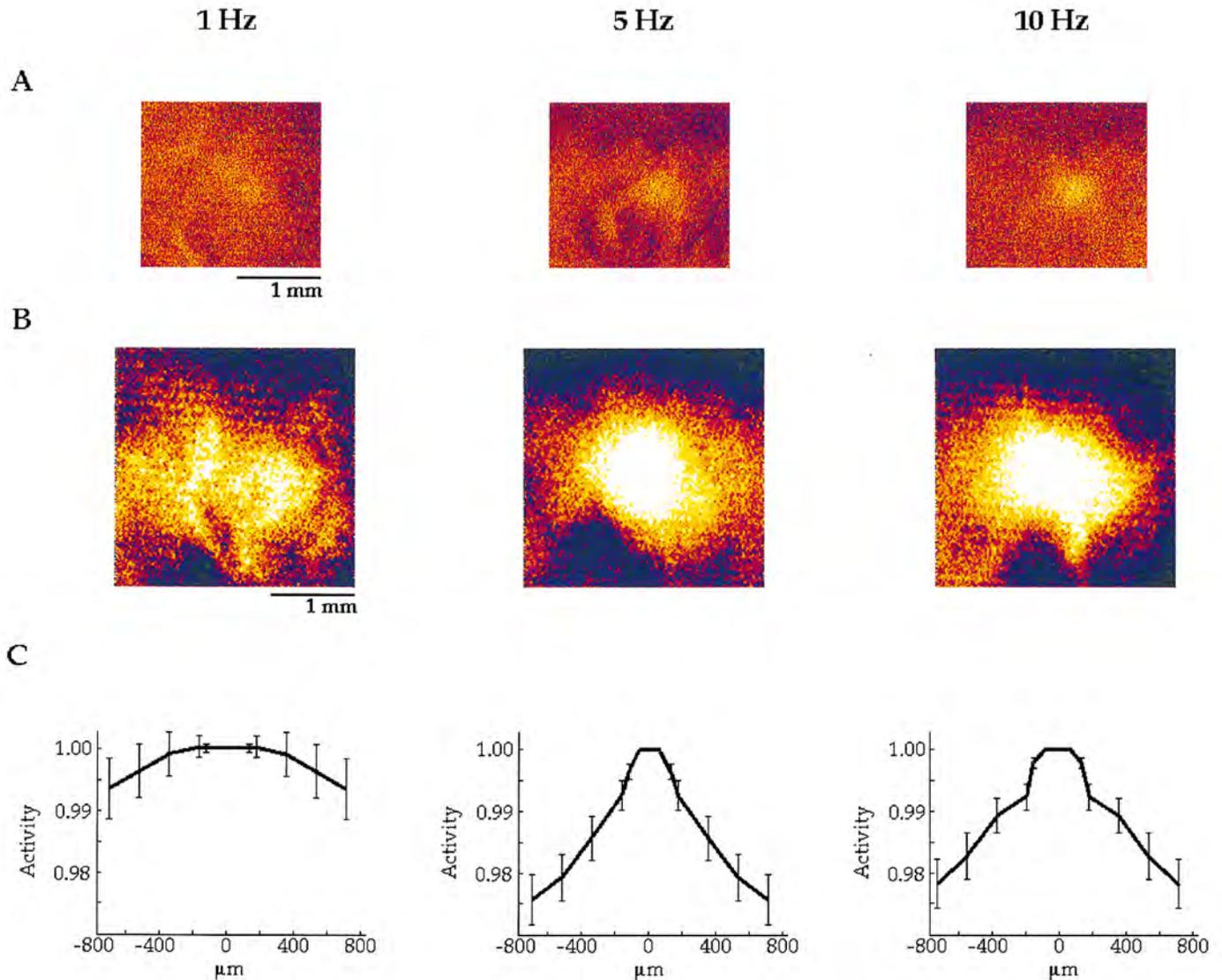


FIG. 2. Effect of stimulation frequency on spread of cortical activity. *A*: optical images of barrel cortex after stimulation of same vibrissa (C1) for 1 Hz (*left*), 5 Hz (*middle*), and 10 Hz (*right*) stimulations are shown. Stimulation time was kept the same for all 3 frequencies at 2 s. *B*: frequency effect averaged across all vibrissae ($n = 10$): D1, D2, D3, D4, C1, C2, B3, E4, δ , and γ vibrissae from 2 animals. An optical image of barrel cortex resulting from stimulation of each of vibrissae individually was determined and activity center or region of highest activation for each vibrissa obtained. Optical images (2.67×2.67 mm) centered at these computed activity centers were superimposed and summed for each stimulation frequency separately to obtain images shown here. *C*: fall-off in activity with distance from vibrissa center, for C1 vibrissa. Ordinate shows changes in reflectance normalized to the activity center. Abscissa, distance in μm from activity center.

the optically imaged intrinsic signal. After stimulation at 1 Hz, the second deflection still evoked a consistent response in both the center and the periphery electrode. In contrast, for 5-Hz stimulation, the response at the periphery electrode after the second deflection of the C1 vibrissa (Fig. 3*B*, *bottom right*) was virtually absent, although a small but clear response was present at the center electrode (Fig. 3*B*, *bottom left*). This differential loss of response in the periphery electrode at 5 Hz replicates the loss of optical signal in the periphery at higher frequencies.

DISCUSSION

This study shows that under two different stimulation conditions (constant time of stimulation and constant number of

deflections), activation in barrel cortex is more spatially discrete when individual rat vibrissae are deflected at 5 or 10 Hz than at 1 Hz. There are several possible explanations for this result. Thalamocortical projections originating in VPM and POM nuclei of the thalamus have different patterns of termination in PMBS (Koralek et al. 1988). VPM projections synapse in the hollows of the barrels in granular layer IV, and in the corresponding parts of upper layer VI, lower layer V, and the lower part of layer III (Chmielowska et al. 1989; Jensen and Killackey 1987; Killackey 1973; Killackey and Leshin 1975; Lu and Lin 1993); POM projections synapse in layer IV of septal regions between the barrels (Chmielowska et al. 1989; Lu and Lin 1993), and in layers I and upper layer V (Lu and Lin 1993). These two nuclei also differ in their ability to fire action potentials in response to increasing frequency of vibrissa

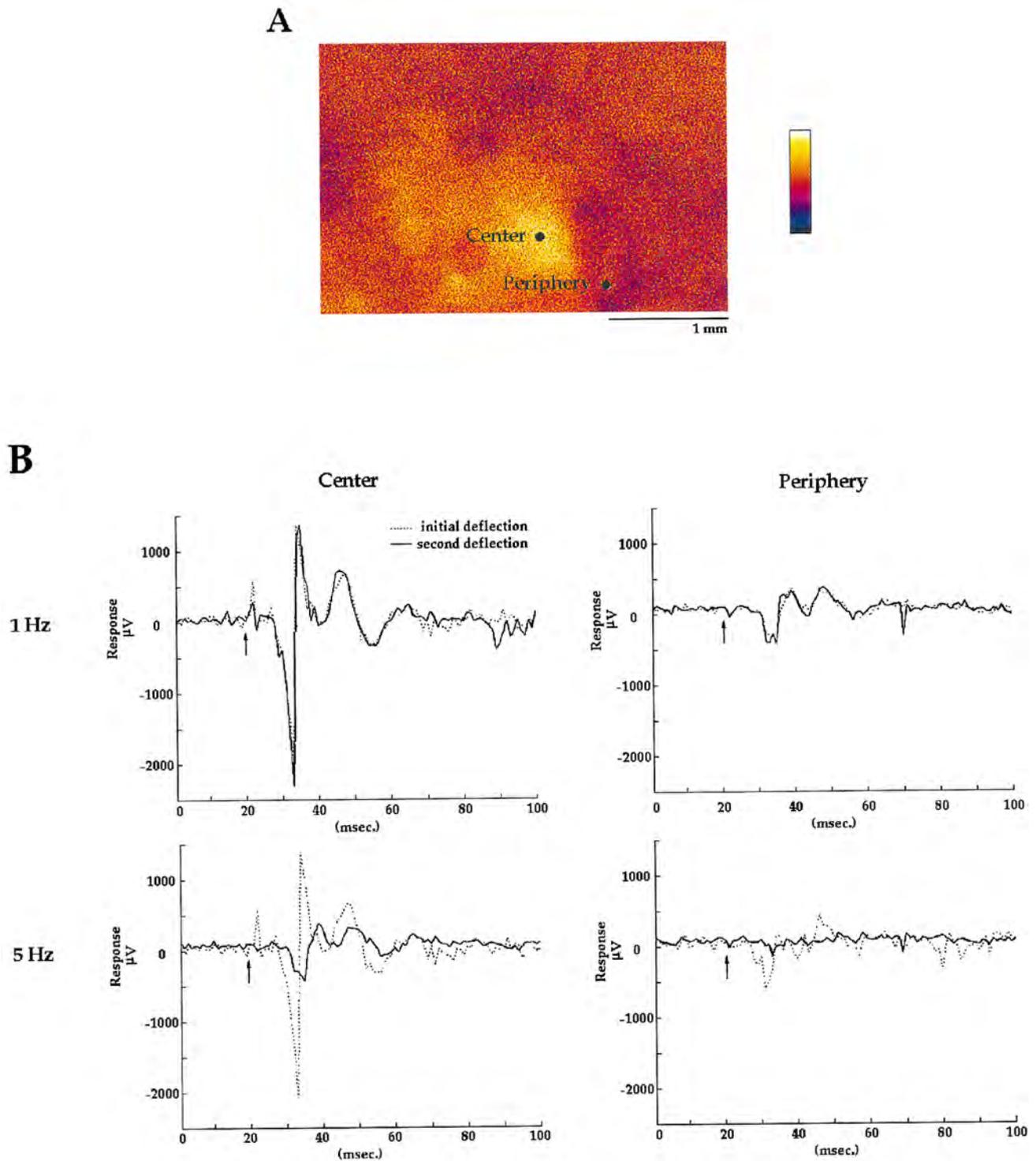


FIG. 3. Electrical recordings showing effect of frequency of vibrissa stimulation on spread of cortical activity. *A*: with standard stimulation conditions (5 Hz, 2 s), an optical map of cortex responding to C1 vibrissa was obtained. Two electrodes were placed at a depth 300–600 μm below cortical surface—one at activity center of imaged area and second $\sim 700 \mu\text{m}$ away. Electrode locations are marked by dots. *B*: responses recorded at activity center and periphery to 1- and 5-Hz C1 vibrissa stimulation. ($\cdot \cdot \cdot$), responses to initial deflection. (—), responses to 2nd vibrissa deflections. Data are shown for a duration of 100 ms, including 80 ms after stimulus onset (\uparrow).

deflection. VPM neurons respond without attenuation to deflection rates of up to 5 Hz, with only moderate ($\sim 30\%$) attenuation at 10 Hz. POM neurons, conversely, moderately attenuate their firing at 5 Hz and are almost completely unresponsive to

maintained deflection rates of ≥ 10 Hz (Diamond et al. 1992). With respect to our data, one possibility is that at lower frequencies (i.e., 1 Hz) of vibrissa stimulation, deflection of a single vibrissa activates the barrel-specific VPM input as well as the

more diffuse POM input. As a result, the appropriate layer IV barrel will become active along with a diffuse cortical region surrounding it. However, at 5 Hz or higher frequencies of vibrissa stimulation, POM neurons will not be significantly activated and only the barrel-specific VPM projection will carry a thalamocortical signal, creating a discrete region of cortical activity inside the corresponding barrel. We recorded optical signals at a depth corresponding to layer IV in the rat barrel cortex. Our results, therefore, may reflect these anatomic and physiological differences between VPM and POM neurons in PMBS in layer IV.

A second possible explanation is that higher frequencies of stimulation lead to an increased prominence of the input from a vibrissa to its anatomically corresponding barrel, as previously suggested by Simons (1996) and Brumberg et al., (1996). They have made this suggestion in part on the basis of results showing that a high-frequency (10–200 Hz) white-noise stimulus applied to an adjacent vibrissa preferentially inhibits weaker inputs (Brumberg et al. 1996). Similarly blockade of GABA_A inhibitory currents with bicuculline methiodide preferentially enhances the responses of weaker inputs (Kryazi et al. 1996). This frequency-dependent inhibition, which may be the result of a nonlinearity in the sensitivity of inhibitory interneurons to higher frequencies of stimulation (see Simons 1996), should limit the intracortical flow of information out of a barrel and effectively inhibit surround receptive field inputs, causing a more discrete representation of a vibrissa within the cortical map.

A third mechanism that could explain these results is a decreased lateral spread of intracortical activity resulting from preferential intracortical adaptation of horizontal connections. By using a thalamocortical slice preparation through the barrel cortex, Gil et al. (1996) have shown that paired pulse stimulation of thalamocortical pathways at a range of stimulus frequencies (0.5–100 Hz) leads to significantly greater attenuation of the response compared with stimulation of layer 3 intracortical pathways at the same frequencies (see also Agmon and Connors 1991; Deisz and Prince 1989). This dissociation suggests that stimulation of vibrissae at higher frequencies should lead either to no change or to a broadening of the spread of signal because the lateral spread of information is better preserved. We observe the opposite effect, suggesting that selective adaptation of cortical activation through horizontal connections cannot explain our results.

The choice of anesthetic in the present study is unlikely to account for these results. In contrast to the awake condition, urethan-anesthetized animals have a large late component in their stimulus-evoked neuronal responses in cortex; however, no significant differential effects of urethan anesthesia have been found on neuronal responses in the barrels versus the interbarrel areas of PMBS (Simons et al. 1992). To date the susceptibility of VPM versus POM neurons to urethan anesthesia has not been investigated.

The somatosensory pathway in rats had long been considered to be a labeled-line pathway (Welker, 1971, 1976; Woolsey and Van der Loos 1970), although several kinds of evidence are challenging that view. Our data show that by changing stimulation frequency alone, it is possible to differentially activate different pools of neurons, thus achieving a dynamic grouping and ungrouping of neurons within somatosensory cortex. These results argue against the prior

view that stimulation of a single vibrissa at low frequencies of stimulation causes only the activation of a single column or barrel (see also Nicolelis and Chapin 1994) and suggest instead a more labile and complex functional mapping that extends beyond the cytochrome-oxidase based anatomic maps in rat PMBS.

Finally, despite the temporal limitations of optical recording of intrinsic signals, we have used this method to study a temporal phenomenon by studying the spatial signature that it leaves behind in cortex. It should be possible to use this technique to study other temporal phenomena that cause spatial changes in cortical organization, e.g., plasticity after vibrissa pairing (Armstrong-James et al. 1994; Diamond et al. 1994; Moore et al. 1995; Simons 1985).

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