Cortical Columnar Processing in the Rat Whisker-to-Barrel System

JOSHUA C. BRUMBERG,[1] DAVID J PINTO,[2] AND DANIEL J. SIMONS[1]
[1]*Department of Neurobiology and* [2]*Department of Mathematics, University of Pittsburgh, Pittsburgh, Pennsylvania 15261*

Brumberg, Joshua C., David J Pinto, and Daniel J. Simons. Cortical columnar processing in the rat whisker-to-barrel system. *J. Neurophysiol.* 82: 1808–1817, 1999. Controlled whisker stimulation and single-unit recordings were used to elucidate response transformations that occur during the processing of tactile information from ventral posterior medial thalamus (VPM) through cortical columns in the rat whisker/barrel cortex. Whiskers were either deflected alone, using punctate ramp-and-hold stimuli, or in combination with a random noise vibration applied simultaneously to two or more neighboring whiskers. Quantitative data were obtained from five anatomically defined groups of neurons based on their being located in: VPM, layer IV barrels, layer IV septa, supragranular laminae, and infragranular laminae. Neurons in each of these populations displayed characteristic properties related to their response latency and time course, relative magnitudes of responses evoked by stimulus onset versus offset, strength of excitatory responses evoked by the noise stimulus, and/or the degree to which the noise stimulus, when applied to neighboring whiskers, suppressed or facilitated responses evoked by the columnar whisker. Results indicate that within layer IV itself there are at least two anatomically distinct networks, barrel and septum, that independently process afferent information, transforming thalamic input in similar but quantitatively distinguishable ways. Transformed signals are passed on to circuits in supragranular and infragranular laminae. In the case of supragranular neurons, evidence suggests that circuits there function in a qualitatively different fashion from those in layer IV, diminishing response differentials between weak and strong inputs, rather than enhancing them. Compared to layer IV, the greater heterogeneity of receptive field properties in nongranular layers suggests the existence of multiple, operationally distinct local circuits in the output layers of the cortical column.

INTRODUCTION

Since Mountcastle's seminal descriptions of cortical columnar organization (Mountcastle 1957; Mountcastle and Powell 1959), numerous investigations, especially of sensory cortices, have sought to determine how information is processed within and among these columns (see Mountcastle 1979). Because of the unique relationship between individual tactile organs (the facial whiskers) and identifiable groupings of layer IV neurons, called barrels, the rodent somatosensory cortex has been particularly useful as a model system. Early physiological studies provided compelling evidence for serial processing within the cortical column. Notably, receptive fields of individual neurons were found to be smallest in layer IV, where many neurons respond strongly only to the columnar whisker, called the principal whisker (PW), and considerably larger in supra- and infragranular layers (Chapin 1986; Simons 1978). Also, the organization of inhibitory receptive field properties appears to be more varied and complex in nongranular laminae (Simons 1985). Support for laminar-dependent processing was provided by measures of response timing and latency that showed layer IV neurons to be activated earliest by whisker stimulation (Armstrong-James et al. 1992; Carvell and Simons 1988; Moore and Nelson 1998). Also, adjacent whisker excitatory responses in supragranular neurons are diminished by ablation of the associated layer IV barrel in the adjacent column (Goldreich et al. 1999).

To date, investigations of laminar-dependent processing have focused largely on the issue of receptive field size and response timing, and on possible anatomic substrates that could underlie the synthesis of large receptive fields of nongranular neurons from the relatively small ones observed in the barrels. Multiwhisker receptive field organization in the nongranular layers is unlikely to reflect a simple summation of single-whisker inputs passively transmitted from the barrels. Even in the case of barrels, where cortical cytoarchitecture corresponds in one-to-one fashion with the topographic representation of individual whiskers, the spatially focused (e.g., single-whisker) receptive fields of barrel neurons are actively synthesized from multiwhisker thalamic inputs. The circuit operations that effect this transformation in receptive field *size* are also responsible for producing a variety of other differences in the response properties of cortical barrel versus thalamic barreloid neurons. Indeed, it was analyses of these other properties, such as the relative magnitudes of responses to stimulus onsets and offsets (Kyriazi et al. 1994), that led to an understanding of the circuit dynamics responsible for focusing the receptive field of barrel neurons onto the principal whisker (Pinto et al. 1996).

Quantitative receptive field studies of the barrel cortex have typically employed punctate whisker deflections, which synchronously activate neurons throughout the whisker to barrel pathway. In a previous study of thalamic barreloid and cortical barrel neurons (Brumberg et al. 1996), we employed a random vibration stimulus, alone and in combination with ramp-and-hold deflections, to probe inhibitory interactions among inputs from neighboring vibrissae. This allowed simultaneous stimulation of a number of neighboring vibrissae without reaching asymptotic levels of inhibition, enabling us to determine that the inhibitory effects of adjacent whisker conditioning stimuli summate in layer IV barrel neurons. In the present experiments, we wished to extend this approach to the study of supra- and infragranular neurons and of neurons in the layer IV septa, with the intention of revealing the nature of interlaminar response transformations other than those related to receptive field size per se. Results indicate that layer IV is comprised of two anatomically distinguishable circuits (barrel and septum) that effect quantitatively different transformations of their thalamic inputs. Supra- and infragranular laminae contain a vari-

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

ety of circuits, which unlike the case in layer IV, are spatially intermingled. The dynamics and response transformations in some of these circuits may be qualitatively different from those in layer IV.

METHODS

Preparation

Twenty-five adult female rats weighing 246–370 g (mean = 312 g, Sprague-Dawley strain, Zivic Miller, Zelienople, PA and Hilltop Lab Animals, Scottdale, PA) were used for these experiments. The surgical preparation has been described previously (Brumberg et al. 1996; Simons and Carvell 1989). Briefly, the rats were initially sedated with metofane (methoxyflurane, Pitman-Moore, Mundelein, IL), and all subsequent surgery was performed using halothane anesthesia. A 0.020-in. silastic catheter was inserted into the right jugular vein (Harms and Ojeda 1974) and tunneled subcutaneously to an opening at the nape of the neck. A tracheotomy was performed with insertion of a 40-mm length of polyethylene tube (1.67 mm ID). To monitor arterial pressure, the femoral artery was catheterized with a 22-gauge angiocath and attached to a pressure transducer (World Precision Instruments, Sarasota, FL). Stainless steel screws were placed over the left temporal and occipital cortex for electroencephalographic recordings, and a stainless steel ground screw was inserted over the right frontal cortex. A steel post was affixed to the left side of the skull with dental acrylic to hold the rat's head without pressure points and to allow unobstructed access to the mystacial pad.

Recordings were made in both the ventral posterior medial nucleus of the thalamus (VPM) and the rat barrel cortex. For thalamic recordings a craniectomy was made in the skull overlying VPM using skull sutures as landmarks, according to the atlas of Paxinos and Watson (1982). For cortical recordings the bone overlying the barrel field was thinned, and mulitunit mapping procedures with a tungsten microelectrode were used to locate a column of interest (see Simons and Carvell 1989). For most cortical experiments, columns for detailed study were selected near the center of the barrel field, where the principal whisker, e.g., C3, was surrounded by at least two rows or arcs of neighboring whiskers. Subsequently, the dura overlying the barrel of interest was resected to allow for the later insertion of a glass micropipette for electrophysiological recordings. Following the completion of surgery, a well of dental acrylic was constructed around the craniectomy and filled with saline to prevent the pial surface from drying. All wound margins were sutured closed, and ophthalmic ointment was applied to prevent drying of the corneas.

At the conclusion of the surgical preparation, the rat was placed on a vibration isolation table, and its core body temperature was maintained at 37°C by a servo-controlled heating blanket (Harvard Apparatus, Cambridge, MA). Subsequently, the halothane was discontinued, and the rat was maintained throughout the recording session in a lightly narcotized state by means of a constant intravenous infusion of fentanyl [Sublimaze, Jansen Pharmaceuticals; 5–10 mg $\times$ (kg $\times$ h)$^{-1}$]. To prevent spontaneous movements of the whiskers, the rat was immobilized with pancuronium bromide [1.6 mg $\times$ (kg $\times$ h)$^{-1}$] and artificially respired with a positive pressure respirator. The physiological condition of the rat was monitored throughout the experiment by assessing the electroencephalogram, mean arterial pressure, arterial pulse rate, pupillary reflexes, perfusion of glabrous skin, and tracheal airway pressure waveform. Experiments were terminated with a lethal intravenous injection of barbiturate if any of the above indicators could not be maintained within physiological ranges.

Electrophysiological recordings

Extracellular single-unit recordings from thalamic and cortical neurons were obtained using double-barrel glass micropipettes. One barrel contained 3 M NaCl for unit recordings, and the other contained 10% wt/vol horseradish peroxidase (HRP) for marking selected recording sites. For cortical experiments, units were sampled throughout the depth of the column to gather information about neurons within the supragranular and infragranular layers in addition to layer IV neurons. All cortical neurons in the present sample were found to be "regular-spike" units (RSUs) (Kyriazi et al. 1996; Simons 1978).

At the conclusion of the recording session, the rat was deeply anesthetized with pentobarbital sodium (>100 mg/kg iv) and perfused for HRP and cytochrome oxidase (CO) histochemistry (Simons and Land 1987). Brains were cut in 60-μm sections in the tangential plane, reacted for CO, and counterstained with thionin. Electrode tracks were reconstructed by their direct visualization in the tissue combined with microdrive recordings and HRP marks. Because the brain was cut in a tangential not coronal plane, no attempt was made to determine the precise laminar location of the units, i.e., layer II versus layer III. Neurons encountered in sections superficial to the CO-stained barrel were considered to be supragranular neurons, and those encountered in sections deep to the barrel were considered to be infragranular neurons. Because identification of the superficial boundary of the barrel was based primarily on the CO staining, some neurons located in lower layer III, which are found within the CO-rich area, may have been designated as barrel neurons. Due to the fact that in any individual vertical penetration recordings were obtained from only two, or at most three, barrel neurons, we pooled, where possible, the present sample of barrel neurons with those from our previous study (Brumberg et al. 1996).

Several experiments explicitly targeted septal neurons. In these cases, the probable location of a septum was determined at the outset of the experiment by initial mapping, as above. The electrode was considered to be in the septum if it was positioned in layer IV and if unit responses could be reliably elicited by manual stimulation of several whiskers in multiple rows or arcs. For data analyses, neurons were assigned to the septum category only if their location in the CO-sparse zone between barrel centers was confirmed by subsequent histological examination of the tissue. This assignment may therefore have included neurons located in the barrel side. Because septa between barrel rows are larger than within-row septa, there was a bias toward studying neurons there.

Stimulus protocols

A condition-test paradigm was employed to determine how a neuron's response to deflection of its principal whisker was affected by simultaneous vibration of one or more of its neighboring whiskers. A previous report described the influence of immediately adjacent whiskers on barrel neurons (Brumberg et al. 1996). Here we examine additionally the influence, on neurons at all cortical depths, of vibrissae displaced from the PW by two rows or arcs (FAR whiskers, e.g., row E whiskers for recordings obtained in a row C barrel). Once a suitable PW was determined (see *Electrophysiological recordings*), conventional stimulators, which deflected whiskers singly (see Simons 1983), were placed on the PW and on the caudal and rostral whiskers immediately adjacent to the PW (ADJ whiskers) in the same horizontal row. Modified stimulators were used to deflect simultaneously an entire row or arc of FAR whiskers.

The stimuli have been described previously (Brumberg et al. 1996; Simons 1983). The test alone stimulus consists of a punctate ramp-and-hold deflection (1-mm displacement at ~125 mm/s, held for 200 ms), which was applied in eight different directions (in 45° increments relative to the horizontal alignment of the whisker rows). The conditioning stimulus was a low-amplitude random vibration of the ADJ and/or FAR whiskers. It was generated by amplifying the output of a random-noise generator and filtering the signal to produce a "pink" noise waveform with frequency components in the range of 10–200 Hz. The noise stimulus was superimposed on a 500-ms, 0.5-mm ramp-and-hold displacement and had a maximum peak-to-peak amplitude of 1.0 mm. During condition-test trials, test stimuli were

presented during the central 200 ms of the noise stimulus. Test and condition-test stimuli were randomly interleaved. Due to the large potential parameter space, the conditioning stimuli were applied in only one direction (dorsal) and was identical for all whiskers. For each combination of conditioning whiskers, test and condition-test stimuli were repeated 10 times for a total of 160 presentations (8 directions × 2 conditions × 10).

Interbarrel septa were initially identified by the multiwhisker nature of their receptive fields, determined with manual stimulation. To determine quantitatively the PW for a given septal unit, standard stimulators were placed on the three whiskers that elicited the strongest responses based on hand tapping. The PW was then identified as the whisker that evoked the strongest average onset response to the eight deflection angles. The other two whiskers were designated ADJ, even if they were not immediately caudal or rostral to the PW, i.e., one or both may have been dorsally or ventrally adjacent.

Data were collected during the 500-msec bracketing the ramp-and-hold stimulus. Spike occurrences were digitized with a window discriminator, and interspike intervals were measured with a resolution of 100 msec. Stimuli and data collection were controlled by a DEC LSI 11/73 computer.

Data analysis

The purpose of the data analysis was to determine whether excitatory and/or inhibitory receptive field components differed between thalamic and cortical neurons and, among the latter, according to laminar and cytoarchitectonic (barrel vs. septum) boundaries. To this end, a number of different quantitative indices of the units' functional properties were derived from the spike train data. The initial step in the analysis was the conversion of sequential interspike intervals into peristimulus time histograms (PSTHs) having 1-ms bins. Means ± SD of spike discharges were computed for selected time epochs. Responses to stimulus onset and offset were measured during 30-ms windows following the initial movement of the hair from its neutral position and from its deflected state back to rest. This response window is longer than that used previously (20 ms) in our study of barrel neurons (Brumberg et al. 1996), because we found that the responses of many supragranular neurons, although transient, extended over this longer duration. In the present study responses to stimulus onset and offset were averaged over all eight deflection angles and are denoted as ON and OFF responses, respectively. Previous studies have shown that thalamic and cortical (barrel) neurons differ in terms of the relative magnitudes of responses evoked by stimulus onsets and offsets. As done previously (Kyriazi et al. 1996), this was quantified by computing OFF/ON ratios using responses to stimulus onsets and offsets, averaged over all deflection angles.

Response latencies to stimulus onsets were computed as done previously (Kyriazi et al. 1994). For each neuron and each stimulus presentation, we measured the time, in 100-ms bins, to compare data obtained in the present study with that of our previous studies we choose a 20-ms response window to the occurrence of the first spike, if any, and results were averaged for that neuron. Response windows, which were set separately for each population (e.g., thalamus, barrel) were chosen to begin 1 ms before the earliest detectable stimulus-evoked activity in a population PSTH generated from all responses from the given neuronal population (see, for example, Fig. 7). This minimized inclusion of contaminating spikes due to background activity. Subsequently, latencies for each of the neuronal populations (barrel, spetal, thalamic, infragranular, and supragranular neurons) were determined by averaging the latencies of the individual neurons.

Examination of PSTHs revealed that the responses in the supragranular layers were not as sharply focused temporally as those in the barrel (see Fig. 1). To quantify this phenomenon for each neuron, we computed a measure of response temporal dispersion by constructing ON response PSTHs using 100-ms bins and determining the time required for 50% of the spikes to occur.

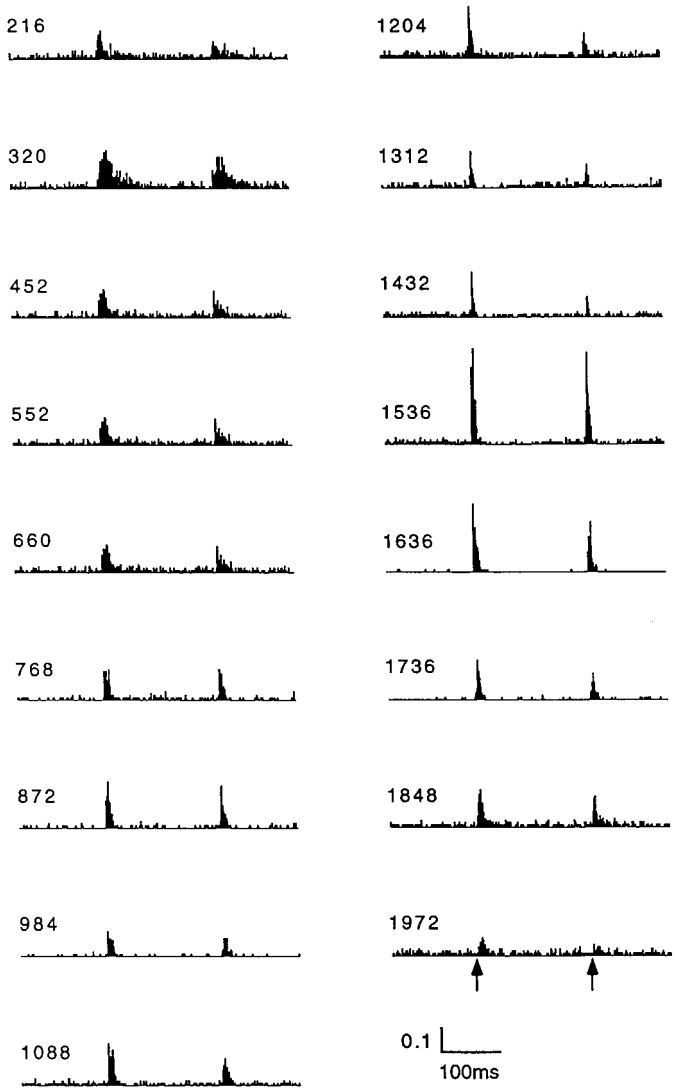

FIG. 1. Peristimulus time histograms (PSTHs) of 17 regular-spike units encountered consecutively in an electrode penetration through the C1 column. Each histogram represents 80 deflections of the principal whisker (PW), summed over 8 directions. Numbers on left indicate approximate depth from pial surface in μm. Each *x*-axis contains 500 1-ms bins. The vertical scale is the same for all the histograms and represents the probability of a spike occurring in each 1-ms bin. Note that the neurons in the supragranular layers ($<$700 μm) have ON and OFF responses that are more temporally dispersed than those at other depths. Arrows indicate the onset and offset of whisker deflection.

Spontaneous and noise-evoked activities were measured by counting the number of spikes that occurred during the 100 ms preceding the test alone response. The change in background activity due to the vibration stimulus was quantified by subtracting the activity count obtained during trials when the conditioning stimulus was present from the count obtained during trials in which the test stimulus was presented alone, i.e., the neuron's spontaneous activity. This metric was used to evaluate the excitatory effects of the conditioning (noise) stimulus.

Suppressive or facilitatory effects of ADJ and FAR whisker vibrations were determined using condition-test ratios. These were computed by dividing the PW's response (for a given response measure, e.g., ON) in the presence of the conditioning stimulus by the PW test alone response. Condition-test responses $<$1.0 are thought to reflect inhibition, ratios $>$1.0 facilitation.

Data were analyzed separately for the five groups of neurons that

were studied: supragranular RSUs, infragranular RSUs, septal RSUs, barrel RSUs, and thalamocortical units (TCUs). Kruskal-Wallis tests of variance (k-w) were used for comparisons among them, and two-tailed Kolmogrov-Smirnov (k-s) or paired *t*-tests were used for two-sample comparisons, e.g., between barrel RSU responses with ADJ versus FAR whisker conditioning stimuli. An alpha level of <0.05 was used as the criteria for statistical significance. Bar graphs are plotted as means, and error bars indicate 1 SE.

RESULTS

Excitatory responses evoked by principal whisker deflections

Figure 1 qualitatively captures similarities and differences among units encountered in a single vertical penetration where we attempted to isolate units at ~100-μm intervals. Focusing on the "shape" of the PSTHs, it is apparent that responses of supragranular neurons (<700 μm) are less temporally coherent than those of middle depth (700–1,000 μm or infragranular neurons ($>1{,}000$ μm).

These aspects of unit responses were quantified for all of the sampled neurons. Figure 2*A* shows the average ON response magnitudes. There were no significant differences in the magnitude of the ON or OFF (data not shown) responses among the various populations studied (k-s tests, $P > 0.05$). Responses of thalamic units were somewhat smaller than those obtained in previous studies using the same stimuli. For each neuronal population, ON responses were significantly larger than OFF responses (paired *t*-tests, $P < 0.001$). OFF/ON ratios (Fig. 2*B*) were computed for each of the different neuronal groups, and it was found that these ratios varied among them (k-w test, $n = 196$, $P < 0.0001$). Consistent with earlier studies, ratios for thalamic neurons were, on average, larger than those for barrel units (0.74 ± 0.06 SE vs. 0.53 ± 0.02; k-s test, $P < 0.003$). Furthermore, OFF/ON ratios of the barrel population are significantly smaller than those of supragranular and infragranular populations (k-s tests, $P < 0.002$), indicating that neurons in the barrel most strongly differentiate between the temporally coherent responses evoked in the thalamus by stimulus onset and the more temporally dispersed responses evoked by stimulus offset (see Kyriazi et al. 1994).

Figure 2*C* presents temporal dispersion data. Responses were most temporally focused within the thalamus (k-s tests, $P < 0.001$) where the 50th percentile spike was reached in

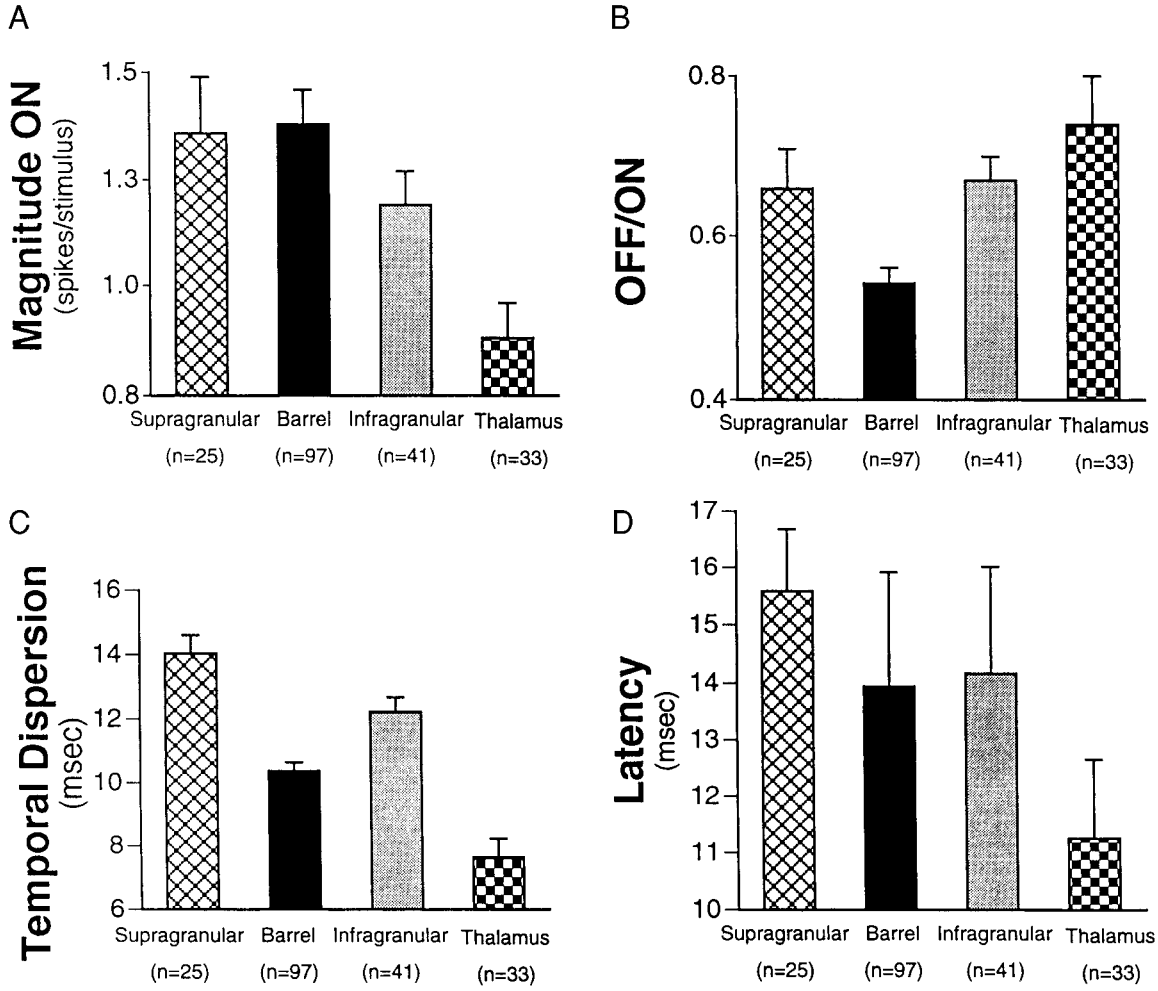

FIG. 2. Excitatory responses from thalamic and 3 groups of cortical neurons evoked by PW deflections. *A*: mean responses to stimulus onset. *B*: size of the OFF response relative to ON. *C* and *D*: 2 measures of response timing, the time of the 50th percentile spike (*C*) and the latency to the 1st spike in the response (*D*). Among cortical neurons, those in the barrel display the most temporally focused responses and most strongly differentiate between responses to stimulus onsets vs. offsets. Error bars indicate 1 SE.

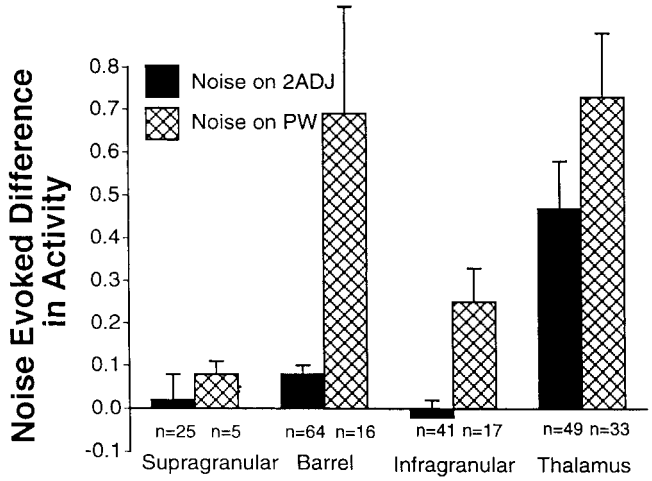

FIG. 3. Net excitatory effects of the noise stimulus when applied to either the PW (▨) or simultaneously to caudal and rostral whiskers immediately adjacent to the PW (ADJ whiskers; ■). On average, there were no significant differences between spontaneous activity and stimulus driven activity in either the supragranular or infragranular layers, although approximately half of the latter displayed statistically significant increases in activity with the noise stimulus on the PW (see text). In contrast the activity of both barrel and thalamic were significantly elevated when the noise stimulus was applied in either condition ($P < 0.05$), but thalamic neurons were considerably more responsive to ADJ stimulation. Plotted are means and 1 SE.

7.63 ± 0.59 ms. Within the cortex responses were most temporally focused in the barrel, least in supragranular neurons, and intermediate in infragranular neurons. Among the three cortical populations, supragranular neurons displayed the greatest temporal dispersion values and the largest OFF/ON ratios. Further analyses indicate that the latter can be accounted for by the later aspect of these neurons' longer duration responses. OFF/ON ratios were computed separately for the first 10 and next 20 ms of the response window. For barrel neurons, OFF/ON ratios were equivalent for the two epochs, but the ratios for supragranular neurons differed substantially. For the early time epoch, OFF/ON ratios of supragranular neurons were smaller and comparable to those of barrel neurons, whereas ratios computed for the 10- to 29-ms window were ~25% larger. All of the above comparisons were statistically significant ($P < 0.05$). OFF/ON ratios of infragranular neurons were similar to those of the supragranular neurons in that the ratio for the short window (10 ms) was more comparable to that of barrel neurons than was the case for the full 30-ms window.

Figure 2*D* presents mean ON response latencies of responses of thalamic and cortical neurons. Appropriately, the difference in timing between thalamic and layer IV barrel neurons was such that the thalamic response preceded the barrel response by 2.69 ms (11.25 ± 1.41 ms vs. 13.94 ± 1.97 ms). The earliest detectable responses in thalamic and barrel population PSTHs (see Fig. 7 for barrel neurons, thalamic data not shown) were 6.93 and 8.25 ms, respectively. Among the cortical populations, barrel neurons showed the shortest mean response latency and supragranular neurons the longest, with infragranular neurons having intermediate values.

Excitatory responses to noise stimulus applied to principal versus adjacent whiskers

Previously, it was shown that vibration of adjacent whiskers exerts substantial inhibitory, but at best only weak excitatory, effects on barrel RSUs (Brumberg et al. 1996). Figure 3 shows noise-evoked excitatory effects at different depths in the barrel column. Stimuli were applied either to the PW or to rostral-caudal adjacent whiskers. For the latter, data are taken from the same supra- and infragranular neurons and a subset of barrel neurons from Fig. 2. The subset of barrel neurons are those for which the noise stimulus was applied to ADJ whiskers. Additional experiments were performed to examine the effect of the noise stimulus when applied to the PW. Thalamic data are taken from an earlier study (Brumberg et al. 1996).

The cross-hatched bars in Fig. 3 plot the change in activity of neurons encountered when the noise stimulus is applied to the PW. Unlike PW deflections evoked by the punctate ramp-and-hold stimulus, which excited neurons throughout the column, the pink noise vibration stimulus selectively activated only barrel neurons. These show a significant increase (paired *t*-test, $P < 0.015$), but effects on infragranular and supragranular neurons were considerably smaller and were not, in fact, significantly different from spontaneous levels (paired *t*-tests, $P > 0.05$). When applied to adjacent whiskers (solid bars), the noise stimulus is much less effective in exciting neurons, even in the barrel (the principal thalamocortical recipient zone). Application of the noise stimulus to the caudal and rostral adjacent whiskers causes a small but statistically significant increase in the firing rate of barrel neurons and a larger increase in thalamic neurons (paired *t*-tests, $P < 0.001$), but not of neurons in the supragranular and infragranular layers (solid bars, Fig. 3). Because of the large variance within the infragranular population, we also analyzed those data on a neuron by neuron basis. Almost half (8 of 17) of the infragranular neurons displayed a statistically significant excitatory response to the noise stimulus (paired *t*-tests, $P < 0.05$). The noise stimulus most strongly excited those neurons in thalamocortical recipient zones, and this finding will be important in interpreting the results of the condition-test experiments described below.

Inhibitory receptive field properties

The noise stimulus, when applied to 2ADJ whiskers, was ineffective in exciting RSUs in the supra- and infragranular layers and evoked only small increases in activity in barrel neurons. Nevertheless, as shown in Fig. 4 application of the conditioning stimulus to two adjacent whiskers (caudal and rostral) diminishes the size of responses evoked by ramp-and-hold PW deflections. Paired *t*-tests comparing test-alone and condition-test responses revealed, on average, suppressive effects of the conditioning stimulus in all cortical layers (all $P < 0.004$). These effects were not, however, equivalent across layers (k-w test, $P < 0.01$). Post hoc Kolmogrov-Smirnov tests revealed that the condition-test ratios for supragranular neurons were significantly larger (indicating less suppression) than those for barrel or infragranular neurons that, in turn, did not differ from each other. Thalamic neurons displayed a lower level of response suppression that was less than that observed in either barrel or infragranular units (k-s tests, $P < 0.05$).

Taken together Figs. 3 and 4 demonstrate that, whereas the noise stimulus evokes excitation of RSUs only within layer IV, it leads to significant response suppression throughout the column. Examination of the data on a cell-by-cell basis indicates, however, considerable laminar-de-

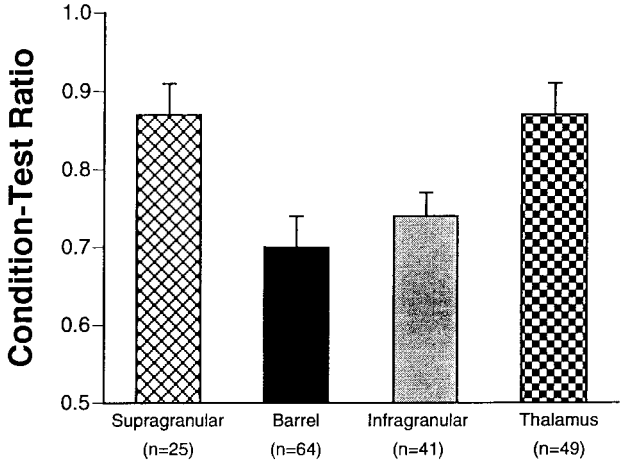

FIG. 4. Effect of adjacent whisker stimulation on PW-evoked responses. Rostral and caudal whiskers were stimulated with the noise stimulus while the PW was deflected with ramp-and-hold deflections. Condition-test ratios <1.0 indicate that the PW response was diminished relative to the response obtained when deflected by itself. Condition test-ratios of the supragranular and thalamic units were significantly less than those observed within the barrel ($P < 0.05$). Plotted are means and 1 SE.

pendent heterogeneity in the effects of different combinations of conditioning stimuli. Figure 5*A* plots condition-test ratios obtained using ADJ and FAR whiskers. For barrel neurons, roughly equivalent levels of inhibition are evoked by either. Data points cluster around a value of 0.75 for both conditioning stimuli, but, because ADJ whiskers evoke somewhat more inhibition than FAR whiskers, there are more points slightly below a regression line corresponding to a hypothetical 1:1 relationship. Values obtained for infragranular neurons are clearly more scattered, whereas the scatter for the supragranular data points is intermediate between barrel and infragranular neurons. This relationship was quantified for each population by computing a Pearson correlation coefficient and subsequently determining the goodness-of-fit of the linear model. R^2 values are plotted in Fig. 5*B*. The largest R^2 value (0.75) was obtained for the population of barrel neurons, whereas the lowest (0.31) was obtained for infragranular neurons; the value for supragranular cells is intermediate (0.48). Thus neurons within the barrel appear to represent a more homogeneous population with respect to the overall organization of their receptive fields. In nongranular layers, effects of neighboring whisker conditioning stimuli are qualitatively and quantitatively more varied. An interesting feature of the infragranular data are that all of the outlying points reflect facilitation by FAR whiskers with some inhibition due to the ADJ whiskers. For supragranular neurons, facilitation is more likely to be produced by adjacent whiskers.

Septal neurons

Here we compare data from 48 septal neurons with those reported above from barrel neurons, the other major population of cortical layer IV neurons examined in the present study. Comparisons are also made with thalamic neurons, because they provide the major afferent input to layer IV. Ramp-and-hold deflections of the PW (see METHODS for identification of the PW in septal neurons) evoked responses that were equivalently robust in septal neurons as in barrel neurons (barrel ON = 1.38 + 0.08 spikes/stimulus, $n = 97$; septal ON = 1.43 + 0.08 spikes/stimulus, $n = 48$). The two populations of layer IV neurons differed substantially, however, in the extent to which they were excited by ADJ stimulation. As shown in Fig. 6*A*, the application of the noise stimulus increased the activities of barrel neurons over spontaneous levels by only 8%, whereas thalamic and septal neurons responded more vigorously (62 and 48% increases, respectively). The increases in activity evoked by the noise stimulus in septal and thalamic neurons differed from those of barrel neurons (k-s tests, $P < 0.05$). Similarly, the relative magnitudes of ON and OFF responses were virtually identical for thalamic and septal neurons, both of which were significantly larger (indicating a relatively larger OFF response) than barrel neurons (Fig. 6*B*; $P < 0.005$). Additionally, the basal firing rates of septal neurons were significantly higher then adjacent barrel neurons (k-s test, $P < 0.001$). With respect to the strength of ADJ-evoked inhibition (Fig. 6*C*), septal neurons (condition-test ratio, 0.82 ± 0.03) were intermediate between barrel (0.70 ± 0.04, k-s test, $P = 0.001$) and thalamic neurons (0.87 ± 0.04, k-s test, $P > 0.05$).

The property for which barrel and septal neurons were indistinguishable from each other, and different from thalamic neurons, was response timing. Figure 7 shows populations PSTHs for barrel and septal neurons. The response properties are highly similar in their onset and overall time course, but the septal response rises more rapidly and decays somewhat more slowly. In these latter two respects, responses of septal neurons are similar to those of thalamocortical neurons (Fig. 2 in

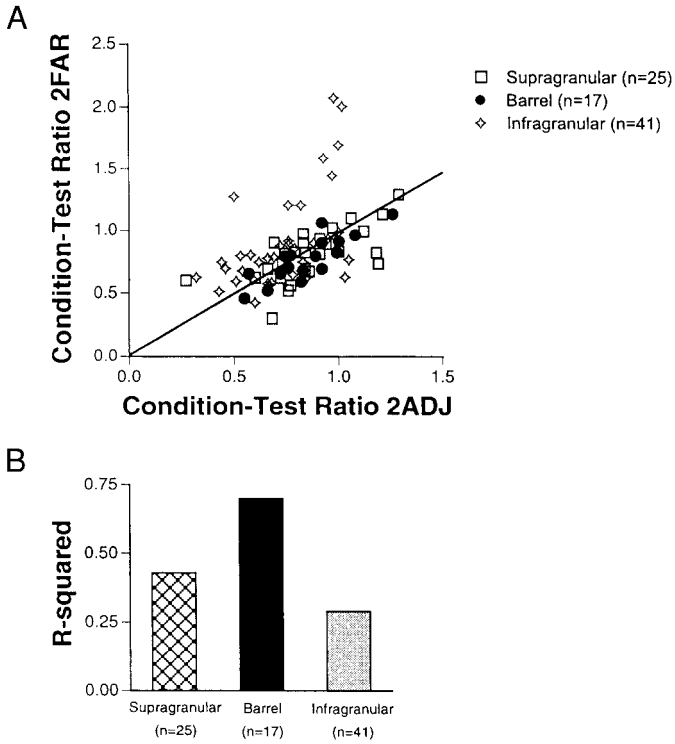

FIG. 5. Effects of adjacent and far whisker stimulation on PW-evoked responses. *A*: scatter plot shows effects on a unit-by-unit basis; solid line denotes a 1:1 relationship. Note that values for barrel neurons cluster around the 1:1 regression line, whereas those in infragranular neurons are more heterogeneous, with some units displaying far whisker facilitation. *B*: R^2 values for the 3 populations and illustrates the greater heterogeneity of receptive fields in the nongranular laminae.

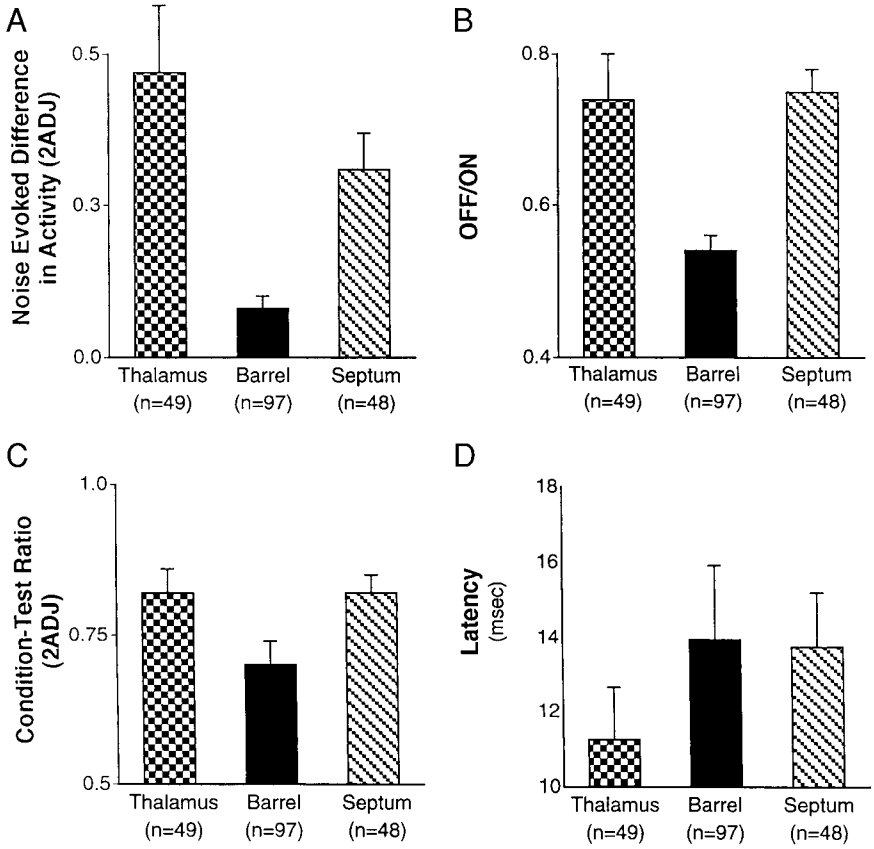

FIG. 6. Quantitative comparisons of thalamic, barrel, and septal unit response properties. Like thalamic neurons, septal neurons show significant elevation of activity in response to caudal and rostral ADJ noise stimulation (*A*), reflective of their multiwhisker receptive fields. Condition-test and OFF/ON ratios of septal neurons are also similar to those of thalamic neurons (*B* and *C*). Latencies of septal and barrel neurons are similar (*D*), suggesting they both receive monosynaptic thalamic input. Thalamic and barrel data are replotted from above. Plotted are means and 1 SE.

Kyriazi et al. 1994). Latency measures (Fig. 6*D*) show that barrel and septal neurons respond at virtually the same time to whisker stimulation (13.94 + 1.97 ms vs. 13.74 + 1.45 ms, k-s test, $P > 0.05$).

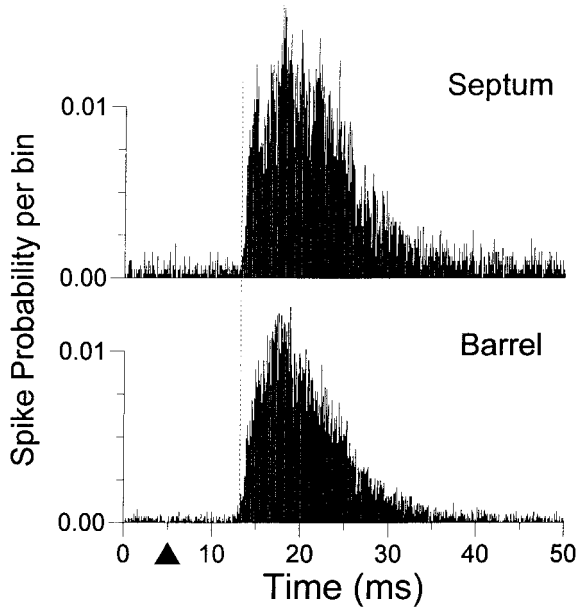

FIG. 7. Population PSTHs for barrel and septal units. PSTHs are accumulated from the responses of all septal ($n = 48$) and barrel ($n = 97$) units in response to deflections of the PW in 8 different directions, repeated 10 times. Data are plotted in 100-μs bins. Arrowhead at 5.0 ms indicates stimulus onset, and the vertical dotted line denotes the earliest response time in the septal population.

DISCUSSION

The present experiments employed a random vibration stimulus to probe interactions among inputs from neighboring vibrissae. Compared with punctate whisker deflections, the "pink noise" stimulus is less likely to be maximally suprathreshold, permitting stimulation of multiple whiskers before saturating effects of conditioning stimuli are reached. Unexpectedly, supra- and infragranular neurons were, at best, only weakly excited by the noise stimulus, even when it was applied to the columnar whisker. The apparent lack of responsiveness of supra- and infragranular neurons to noise stimuli applied to their PWs may reflect our use of mean firing rate per 100-ms epochs as the response measure. The pink noise stimulus probably contains some components, e.g., high-velocity deflections, that activate neurons throughout the cortical column, but the brief changes in unit firing could be lost in the time-averaging measurement. In this regard, the use of "frozen noise," in which the same random stimulus is applied repeatedly, may better reveal the efficacy of small, varying whisker perturbations in engaging the excitatory circuitry of the cortical columns. Nevertheless, the present findings indicate that the noise stimulus was considerably less effective in exciting cortical neurons outside the major thalamocortical recipient zone in layer IV. Similarly, superficial pyramidal neurons in visual cortex respond only weakly to sparse noise stimuli (Hirsch et al. 1997). This and other lines of evidence to be reviewed below are consistent with the concept of laminar-dependent processing of sensory information in barrel-related cortical columns. Moreover, the present findings indicate that within layer IV itself there are at least two operationally distinct

networks, barrel and septum, which independently process afferent information and then pass it on to supragranular and infragranular layers, which each also contain a variety of local circuits.

Laminar-dependent response transformations within the cortical column

A serial model of information processing within whisker/barrel cortex was first proposed by Simons (1978), who argued that the large, relative to layer IV, receptive fields of supra- and infragranular neurons were due to convergence of inputs from single-whisker neurons in multiple layer IV barrels. Similar conclusions have been reached by numerous subsequent anatomic and physiological studies (see Armstrong-James et al. 1992; Chapin 1986; Simons 1985; White 1989). A number of the latter have based this conclusion on various measures of neuronal response timing following punctate whisker deflections. In the present study, it was determined that layer IV neurons fire an average of 2.69 ms after the thalamocortical neurons, whereas responses of infragranular and supragranular neurons occur 0.92 and 1.84 ms later than the layer IV response. These values are comparable with excitatory postsynaptic potential (EPSP) onset times in in vitro (Agmon and Connors 1992), in vivo intracellular studies (Carvell and Simons 1988; Moore and Nelson 1998) and previous extracellular measurements (Kyriazi et al. 1998) of the rat barrel cortex. It is known that layer V pyramidal cells receive direct monosynaptic thalamocortical inputs (Agmon and Connors 1992; see White 1989). Interestingly, some layer V neurons were activated by the noise stimulus, perhaps reflective of strong thalamic input onto these cells.

The noise stimulus failed to excite strongly neurons (RSUs) in nongranular layers, when applied to the adjacent whiskers. As an adjacent whisker conditioning stimulus, however, it was effective in inhibiting PW responses evoked by punctate whisker deflection. Condition-test ratios of supra- and, to a lesser extent, infragranular neurons were, on average, somewhat larger (indicative of less response suppression) than those of layer IV barrel neurons, although in a previous study using punctate conditioning stimuli (Kyriazi et al. 1998), values were equivalent across cortical laminae. We propose that inhibitory receptive field properties observed superficial and deep to the barrel in the present study reflect *preprocessing* by barrel circuitry, with considerably less, or possibly even no, direct contribution from the inhibitory circuitry of the supra- and infragranular laminae themselves. According to this view, under the present stimulus conditions, adjacent whisker inhibition is evoked in barrel RSUs by activation of inhibitory barrel neurons ("fast-spike units," FSUs), which are strongly excited by the adjacent whisker noise stimulus (Brumberg et al. 1996). The "inhibitory" receptive field property of RSUs is then fed forward to nongranular neurons that receive excitatory inputs from the barrel. Relay of inhibitory receptive field properties has also been proposed to account for the finding that microiontophoresis of the $GABA_A$ antagonist bicuculline methiodide produces less condition-test disinhibition in supra- and infragranular layers than in the barrel (Kyriazi et al. 1996). Additionally, the former laminae display less $GABA_A$ receptor and glutamic acid decarboxylase (GAD) immunoreactivity (Land et al. 1995; McCasland and Hibbard 1997). The relay of inhibitory receptive field properties has been proposed as an explanation for end-stopping of neurons within the supragranular layers of cat primary visual cortex (Bolz and Gilbert 1986). Another possibility that cannot be excluded by the present data are that the inhibitory receptive field properties observed in the nongranular layers are due to direct inhibitory projections onto these neurons from the inhibitory neurons that reside within the barrel.

Supragranular neurons displayed the longest response latencies and the weakest responses to the noise stimulus, findings consistent with the idea that they receive their major afferent excitation from the subjacent barrel rather than from thalamocortical afferents. Response properties of supragranular neurons differed, however, from those of barrel neurons in several interesting respects. Responses to ramp-and-hold PW deflections were more temporally dispersed, and this differential was more pronounced for responses to stimulus offset than onset. In addition, supragranular neurons displayed larger OFF/ON ratios (indicative of a relatively larger OFF response) and less adjacent whisker-evoked response suppression.

In effect, it appears that supragranular circuitry disproportionately *diminishes* differences between strong (ON, PW-alone) and weaker (OFF, conditioned-PW) responses emanating from the layer IV barrel. With respect to OFF/ON ratios, differences between supragranular and barrel neurons were due to the latter 20 ms of the response, which was considerably larger in supragranular neurons. Thus the same mechanism that underlies the greater temporal dispersion of the supragranular neuron response may also contribute to the disproportionate enhancement of the OFF response. This mechanism may also account, at least in part, for the larger condition-test ratios of supragranular neurons. As in the case of OFF/ON ratios, condition-test ratios of supragranular neurons were smaller, and thus more comparable to those of barrel neurons, during the first 10 ms of the response.

Interestingly, the response transformation from barrel to supragranular circuits differs substantively from the transformation from thalamic barreloid to cortical barrel. In that circuit, differences between ON and OFF responses are disproportionately *enhanced*. To what extent this reflects differences in synaptic transmission versus differences in connectivity patterns remains to be determined. Barrel and supragranular circuits are likely to differ also with respect to the relative efficacy of afferent synapses (thalamocortical vs. corticocortical), afferent engagement of inhibitory interneurons, and the strengths of local recurrent excitation (Keller 1995; Kyriazi et al. 1998). These circuit features are known to be critically important for the barreloid to barrel response transformation (Kyriazi and Simons 1993; Pinto et al. 1996; Simons 1997).

Response properties of infragranular neurons differed in several respects from those of supragranular neurons. They displayed stronger adjacent whisker-evoked inhibition, and they were more likely to be facilitated by FAR whisker stimulation. Also, unlike supragranular neurons, at least some units in infragranular layers were excited by the noise stimulus applied to the PW. There are several potential sources of this excitation: infragranular neurons may be excited by barrel neurons in the same cortical column, by barrel neurons from adjacent columns and/or by direct thalamocortical synapses (see Keller 1995; White 1989). Whatever the source, excitatory responses to the noise stimulus could account for the between-

whisker interactions observed here. For example, excitation of infragranular neurons by the noise stimulus could evoke inhibition in infragranular neurons in adjacent columns by means of synaptic connections onto local inhibitory neurons there (see Fig. 5) (Kyriazi et al. 1998). Similarly, net excitatory inputs from more distant columns, via horizontal connections, could account for the observed facilitatory effects of FAR whisker conditioning stimuli.

Barrels and septa: different parallel circuits in layer IV

An interesting and unexpected finding in the present study is that layer IV septal neurons have receptive field properties more similar to those of VPM thalamocortical neurons than to those of RSUs in the neighboring layer IV barrels. Like the former, septal neurons have multiwhisker excitatory receptive fields, display less adjacent-whisker evoked inhibition than barrel neurons, and have OFF/ON ratios of ~1.0, considerably larger than those of barrel neurons. Previously, it was suggested that septal neurons receive their major afferent drive from barrel neurons (for a review see Armstrong-James 1995). This conclusion was based on the finding that the modal latencies of septal neurons are longer than those of barrel neurons and was viewed as being consistent with anatomic studies demonstrating that relatively fewer thalamic afferents from VPM terminate in the septum versus the barrel (Chmielowska et al. 1989; Lu and Lin 1992). Consistent with the findings in the present study, modal latencies of some septal neurons were, however, indistinguishable from barrel neurons (Armstrong-James et al. 1992). Our population PSTHs and latency analyses both indicate that septal neurons respond to whisker stimuli at virtually the same time as barrel neurons, but several milliseconds before supragranular neurons, which are almost certainly postsynaptic to layer IV. In addition, septal neurons, unlike supragranular neurons, are excited by the noise stimulus whether it is applied to principal or adjacent whiskers. Taken together, the findings suggest that septal neurons, like barrel neurons, receive strong afferent drive and, unlike supragranular neurons, may not depend on the neighboring barrels for their activation.

How, then, do septal neurons receive their whisker inputs? Thalamocortical synapses of VPM origin, although smaller in number than in barrel centers, are present in rat septa (Lu and Lin 1983). Moreover, the dendrites of septal neurons extend into the centers of neighboring barrels (Simons and Woolsey 1984), where they could be contacted by thalamocortical VPM axons that terminate densely there. In light of the findings by White and colleagues that a wide variety of postsynaptic targets in the barrels receive VPM synapses (White 1978, 1979; for review see White 1989), it is indeed highly likely that at least the distal dendrites of septal neurons receive them, too. The equivalently short response latencies of barrel and septal neurons are consistent with the anatomic findings. We propose that septal neurons, like their counterparts in the barrel centers, receive monosynaptic inputs from VPM barreloid neurons, but the response properties of septal and barrel neurons differ because of differences in the local circuits in which they are embedded (Kim and Ebner 1999). For example, the higher rates of spontaneous activity within the septa might reflect a network under less tonic inhibitory control. Barrel neurons form a network of recurrently interconnected excitatory and inhibitory neurons, and the dynamics of their interactions produces barrel neuron receptive field properties that differ from those of their VPM inputs (Brumberg et al. 1996; Kyriazi et al. 1994; Simons and Carvell 1989). In modeling studies, reducing the degree to which barrel neurons interact with each other diminishes differences between the receptive field properties of barrel and thalamic neurons, yielding simulated barrel response properties highly similar to those observed here in septal neurons (Kyriazi and Simons 1991; Pinto et al. 1996).

Receptive field heterogeneity reflects multiple local circuits

We found the receptive field properties of nongranular neurons to be more heterogeneous than those of barrel neurons, which presumably provide a major source of excitatory input to them. Similar findings have been made in previous studies of barrel cortex (Simons 1978, 1985). In the latter study, asymmetrically organized receptive fields, wherein one ADJ evoked substantially more inhibition than another, were most commonly observed in infragranular layers. Although this finding is not identical to the present results, it is similar in that facilitation (by FAR whisker stimulation) was observed most prominently in infragranular neurons. Similarly, it is known that infragranular neurons in primary visual cortex have the most heterogeneous receptive field properties (Gilbert 1977). In contrast, barrel neurons (RSUs) have consistently been found to have receptive field properties that are qualitatively similar to each other, despite the fact that thalamic barreloid neurons are markedly more heterogeneous by almost any measure of receptive field property. For example, almost all barrel RSUs have small excitatory receptive fields with relatively symmetrical inhibitory surrounds, and all display monotonically larger responses with increases in whisker deflection velocity; the excitatory and inhibitory receptive fields of barreloid neurons vary widely, and as many as half of the cells display negatively sloped velocity-response relationships (Pinto 1997; Simons and Carvell 1989). Thus the barrel appears to represent a nodal point of homogeneity in the transformation of the afferent signal from varied receptive fields in the thalamus to a multiplicity of nongranular receptive field properties, many of which may be quite complex in their organization.

The present findings from layer IV suggest that septal neurons and barrel neurons operate within parallel networks whose different local circuit dynamics regulate how the neurons integrate their VPM inputs. We propose that similar organizational principles characterize the supra- and infragranular layers, too. Unlike layer IV, however, in which the two types of local circuits (barrel and septal) are anatomically distinguishable, different circuits in nongranular layers may be spatially intermingled, with no obvious cytoarchitectural signatures. Also, unlike circuits in layer IV, which have a limited number of afferent sources and a predominance of local interconnectivities, circuits in supra- and infragranular layers are influenced by a wide variety of local and distant corticocortical inputs (Bernardo et al. 1990a,b; Keller 1995). Moreover, apical dendrites of neighboring infragranular pyramidal neurons are known to receive different proportions of thalamocortical synapses even though the dendrites are embedded within the same neuropil (White 1989). Differences in the source and nature of synaptic inputs to such neurons are likely to render the oper-

ations of their constituent circuits as distinctive as those in layer IV.

We thank Dr. Harold T. Kyriazi for help with the data analysis and for critical comments on the manuscript.

This work was supported by National Institute of Neurological Disorders and Stroke Grant NS-19950 and National Science Foundation Grant IBN 9421380.

Present address and address for reprint requests: J. C. Brumberg, Section of Neurobiology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510.

Received 20 April 1999; accepted in final form 1 July 1999.

REFERENCES

AGMON, A. AND CONNORS, B. W. Correlation between intrinsic firing patterns and thalamocortical synaptic responses in mouse barrel cortex. *J. Neurosci.* 12: 319–329, 1992.

ARMSTRONG-JAMES, M. The nature and plasticity of sensory processing within adult rat barrel cortex. In: *Cerebral Cortex*, edited by E. G. Jones and I. T. Diamond. New York: Plenum, 1995, vol. 11, p. 333–373.

ARMSTRONG-JAMES, M., FOX, K., AND DAS-GUPTA, A. Flow of excitation within rat barrel cortex on striking a single vibrissa. *J. Neurophysiol.* 68: 1345–1358, 1992.

BERNARDO, K. L., MCCASLAND, J. S., AND WOOLSEY, T. A. Local axonal trajectories in mouse barrel cortex. *Exp. Brain Res.* 82: 247–253, 1990a.

BERNARDO, K. L., MCCASLAND, J. S., WOOLSEY, T. A., AND STROMINGER, R. N. Local intra- and interlaminar connections in mouse barrel cortex. *J. Comp. Neurol.* 291: 231–255, 1990b.

BOLZ, J. AND GILBERT, C. D. Generation of end-inhibition in the visual cortex via interlaminar connections. *Nature* 320: 362–365, 1986.

BRUMBERG, J. C., PINTO, D. J, AND SIMONS, D. J. Spatial gradients and inhibitory summation in the rat whisker barrel system. *J. Neurophysiol.* 76: 130–140, 1996.

CARVELL, G. E. AND SIMONS, D. J. Membrane potential changes in rat SmI cortical neurons evoked by controlled stimulation of mystacial vibrissae. *Brain Res.* 448: 186–191, 1988.

CHAPIN, J. K. Laminar differences in sizes, shapes and response profiles of cutaneous receptive fields in the rat S1 cortex. *Exp. Brain Res.* 62: 549–559, 1986.

CHMIELOWSKA, J., CARVELL, G. E., AND SIMONS, D. J. Spatial organization of thalamocortical and corticothalamic projection systems in the rat SmI barrel cortex. *J. Comp. Neurol.* 285: 325–338, 1989.

GILBERT, C. D. Laminar differences in receptive field properties of cells in cat primary visual cortex. *J. Physiol. (Lond.)* 268: 391–421, 1977.

GOLDREICH, D., KYRIAZI, H. T., AND SIMONS, D. J. Functional independence of layer IV barrels in rodent somatosensory cortex. *J. Neurophysiol.* 82: 1311–1316, 1999.

HARMS, P. G. AND OJEDA, S. R. A rapid and simple procedure for chronic cannulation of the rat jugular vein. *J. Appl. Physiol.* 36: 391–392, 1974.

HIRSCH, J. A., ALONSO, J. M., REID, R. C., AND MARTINEZ, L. M. Differences between the synaptic responses of first and second order complex cells in cat striate cortex. *Soc. Neurosci. Abstr.* 23: 1668, 1997.

KELLER, A. Synaptic organization of the barrel cortex. In: *Cerebral Cortex*, edited by E. G. Jones and I. T. Diamond. New York: Plenum, 1995, vol. 11, p. 221–262.

KIM, U. AND EBNER, F. F. Barrels and septa: separate circuits in rat barrel field cortex. *J. Comp. Neurol.* 408: 489–505, 1999.

KYRIAZI, H. T., CARVELL, G. E., BRUMBERG, J. C., AND SIMONS, D. J. Quantitative effects of GABA and bicuculline methiodide on receptive field properties of neurons in real and simulated rat whisker barrels. *J. Neurophysiol.* 75: 325–328, 1996.

KYRIAZI, H. T., CARVELL, G. E., BRUMBERG, J. C., AND SIMONS, D. J. Laminar differences in bicuculline methiodide's effects on cortical neurons in the rat whisker/barrel system. *Somatosens. Mot. Res.* 15: 146–156, 1998.

KYRIAZI, H. T., CARVELL, G. E., AND SIMONS, D. J. Off response transformation in the whisker/barrel system. *J. Neurophysiol.* 72: 392–401, 1994.

KYRIAZI, H. T. AND SIMONS, D. J. Thalamocortical response transformations in simulated whisker barrels. *J. Neurosci.* 13: 1601–1615, 1993.

LAND, P. W., DE BLAS, A. L., AND REDDY, N. Immunocytochemical localization of $GABA_A$ receptors in rat somatosensory cortex and effects of tactile deprivation. *Somatosens. Mot. Res.* 12: 127–141, 1995.

LU, S. M. AND LIN, R.C.S. Thalamic afferents of the rat barrel cortex: A light- and electron-microscopic study using *phaseolous vulgaris* leucoagglutinin as an anterograde tracer. *Somatosens. Mot. Res.* 10: 1–16, 1992.

MCCASLAND, J. S. AND HIBBARD, L. S. GABAergic neurons in barrel cortex show strong, whisker dependent metabolic activation during normal behavior. *J. Neurosci.* 17: 5509–5527, 1997.

MOORE, C. I. AND NELSON, S. B. Spatio-temporal subthreshold receptivive fields in the vibrissa representation of rat primary somatosensory cortex. *J. Neurophysiol.* 80: 2882–2892, 1998.

MOUNTCASTLE, V. B. Modality and topographic properties of single neurons of cat's somatic sensory cortex. *J. Neurophysiol.* 20: 408–434, 1957.

MOUNTCASTLE, V. B. An organizing principle for cerebral function: the unit module and the distributed system. In: *The Neurosciences, Fourth Study Program*, edited by F. O. Schmitt and F. G. Worden. Cambridge, MA: MIT Press, 1979, p. 21–42.

MOUNTCASTLE, V. B. AND POWELL, T.P.S. Neural mechanisms subserving cutaneous sensibility, with special reference to the role of afferent inhibition in sensory perception and discrimination. *Bull. Johns Hopkins Hosp.* 105: 201–232, 1959.

PAXINOS, G. AND WATSON, C. *The Rat Brain in Stereotaxic Coordinates.* Sydney, Australia: Academic, 1982.

PINTO, D. J. *Computational, Experimental, and Analytic Explorations of Neuronal Circuits in the Cerebral Cortex* (PhD thesis). Pittsburgh, PA: Univ. of Pittsburgh, 1997.

PINTO, D. J., BRUMBERG, J. C., SIMONS, D. J., AND ERMENTROUT, G. B. A quantitative population model of whisker barrels: re-examining the Wilson-Cowan equations. *J. Comput. Neurosci.* 3: 247–264, 1996.

SIMONS, D. J. Response properties of vibrissa units in rat SI somatosensory neocortex. *J. Neurophysiol.* 41: 798–820, 1978.

SIMONS, D. J. Multi-whisker stimulation and its effects on vibrissa units in rat SmI barrel cortex. *Brain Res.* 276: 178–182, 1983.

SIMONS, D. J. Temporal and spatial integration in the rat SI vibrissa cortex. *J. Neurophysiol.* 54: 615–635, 1985.

SIMONS, D. J. Rodent whisker barrels: windows into cerebral cortical function. *News Physiol. Sci.* 12: 268–273, 1997.

SIMONS, D. J. AND CARVELL, G. E. Thalamocortical response transformation in the rat vibrissa/barrel system. *J. Neurophysiol.* 61: 311–330, 1989.

SIMONS, D. J. AND LAND, P. W. A reliable technique for marking the location of extracellular recording sites using glass micropipettes. *Neurosci. Lett.* 81: 100–104, 1987.

SIMONS, D. J. AND WOOLSEY, T. A. Morphology of Golgi-cox-impregnated barrel neurons in rat SmI cortex. *J. Comp. Neurol.* 230: 119–132, 1984.

WHITE, E. L. Identified neurons in mouse SmI cortex which are postsynaptic to thalamocortical axon terminals: a combined golgi-electron microscopic and degeneration study. *J. Comp. Neurol.* 181: 627–661, 1978.

WHITE, E. L. Thalamocortical relations. A review with emphasis on projections of specific thalamic nuclei to the primary sensory areas of the neocortex. *Brain Res. Rev.* 1: 275–311, 1979.

WHITE, E. L. *Cortical Circuits: Synaptic Organization of the Cerebral Cortex. Structure, Function, and Theory.* Boston, MA: Birkhauser, 1989.