

Angularly Nonspecific Response Suppression in Rat Barrel Cortex

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Response modulation by prior sensory stimulation is a common property of cortical neurons. The degree to which effects are specific to the adapting stimulus provides insights into properties of the underlying circuitry. Here, we examined the effects of an adapting whisker deflection's angle on the angular tuning of layer IV barrel neurons and their major input source, thalamic barreloid neurons. In both barrel regular-spike units (RSUs) and fast-spike units (FSUs), presumed excitatory and inhibitory neurons, prior whisker deflections suppressed subsequent test deflections in a largely angularly nonspecific manner, that is, adaptation in one direction reduced responses for test deflections of all angles. FSUs were poorly tuned for deflection angle and remained so after adaptation. In adapted RSUs, responses to suboptimal directions were suppressed most and angular preferences remained constant; tuning therefore became sharper. Adaptation effects in RSUs and FSUs do not appear to reflect corresponding changes in thalamic neurons. The angularly nonspecific suppression of barrel neurons is likely mediated by local intrabarrel suppressive interactions, such as broadly tuned inhibition and/or short-term synaptic depression of excitatory connections. The dominance of angularly nonspecific suppression suggests that barrel neurons interact largely in an angularly nonspecific manner to reinforce stimulus preferences encoded by their synchronously firing thalamic inputs.

Keywords: adaptation, barrel cortex, inhibitory neuron, rat, thalamocortical, whisker

Introduction

A ubiquitous property of perception is that it can be altered by adaptation with repetitive sensory stimulation. The neural basis of perception indicates that the responses of sensory neurons are indeed modifiable. This is the case for the stimulus-evoked responses of cortical neurons after adaptation, which often are significantly suppressed and their tuning curves altered. Responses to specific stimuli can be suppressed or facilitated depending on the particular modality and characteristics of the adapting stimuli. A striking example is found in some macaque area V4 neurons, which prior to adaptation are not direction selective for the motion of visual stimuli. Adaptation to a grating moving in one direction causes these neurons to become preferentially responsive to the opposite direction of motion (Tolias and others 2005). The modification of tuning properties may be due to the effect of repetitive stimulation on the dynamics of cortical circuits. Adaptation could change the cortical circuit's overall level of excitability and its dependence on feed-forward (e.g., thalamic for primary sensory cortices) versus intracortical inputs.

Barrels are an ideal site to examine the effects of adaptation because they are well-defined cortical circuits. Barrels are

anatomically and functionally defined modules in layer IV of the rat primary somatosensory cortex that contains excitatory and inhibitory neurons having distinctly different receptive field properties. The characteristic responses of excitatory and inhibitory neurons are a product of their intrinsic properties as well as their receiving different inputs. Fast-spike units (FSUs or putative inhibitory cells) are more responsive and broadly tuned for the angle of whisker deflections than regular-spike units (RSUs or putative excitatory cells) (Simons and Carvell 1989; Swadlow and Gusev 2000; Kida and others 2005). The difference in the angular tuning properties of FSUs versus RSUs is established by thalamic inputs (Bruno and Simons 2002); individual FSUs receive convergent inputs from numerous thalamic neurons having a wide range of preferences (see also Swadlow and Gusev 2000), whereas individual RSUs receive input from a smaller number of thalamic cells having more similar, though not always identical, angular preferences. Thalamic neurons having similar preferences fire more short-latency spikes in response to preferred direction deflections, producing a population response that increases robustly and quickly (Temeranca and Simons 2003; see also below). Barrel circuitry renders RSUs preferentially responsive to this initial synchronous firing, presumably enabling RSUs to fire in an angularly selective fashion despite substantial convergence of thalamic inputs (for a different view, see Wilent and Contreras 2005 and Discussion).

Individual barrels contain functional subdivisions based on angular tuning (Bruno and others 2003). Within a vertical electrode penetration through a layer IV barrel, excitatory cells have similar angular preferences and form "angular tuning domains," but horizontally adjacent sites (only 75 μm away) may contain neurons with similar or different angular preferences (Bruno and others 2003). Because spiny cell dendrites likely extend through many domains, a given RSU may receive intracortical inputs from other excitatory cells having the same or different angular preferences. The specificity of connections among cells within different angular tuning domains is unknown. Insights may be gained by determining how the angle of adapting whisker deflections affects the response properties of barrel neurons.

Recently, we demonstrated that FSUs and RSUs display parallel changes in responsiveness during repetitive whisker stimulation (Khatri and others 2004). In both neuronal types, adapted responses were smaller in magnitude and briefer in duration. The findings indicate that FSUs and RSUs maintain their distinctive response signatures after adaptation. Here, we investigate this further by determining the effects of repetitive whisker stimulation in different directions. Of particular interest is whether RSUs and FSUs retain their distinctive angular tuning properties after adaptation. For comparison, angularly

dependent adaptation effects were also examined in thalamic barreloid neurons.

We recorded the responses of RSUs and FSUs in layer IV barrels and those of thalamocortical units (TCUs) in the ventral posterior medial (VPM) nucleus, their primary source of afferent input. Whisker stimuli were systematically varied in deflection angle, preceded by adapting deflections in the same or different directions. In some experiments, layer IV circuitry was rendered unresponsive during sensory adaptation by concurrent electrical stimulation in overlying layer III. These approaches enabled us to determine whether the responses of individual neurons evoked by particular angles of whisker deflection are suppressed most when preceded by deflections in the same direction and whether effects observed in the cortex were of cortical origin. Findings suggest that intrabarrel circuits are dominated by angularly nonspecific interactions and that angular specificity is provided by tuned thalamic inputs. We propose that during repetitive and ongoing whisker stimulation, as observed during tactile discrimination (Carvell and Simons 1990; Harvey and others 2001), circuit dynamics enhance the angular tuning of excitatory barrel neurons by evoking pervasive, angularly non-selective suppressive influences, such as intrabarrel inhibition and/or short-term depression of excitatory synapses.

Methods

Animals and Surgical Preparation

Surgical preparation and maintenance of the rats during electrophysiological recording were identical to methods described previously (Simons and Carvell 1989; Khatri and others 2004). Adult Sprague-Dawley female rats (200–300 g) were obtained from a commercial supplier. All surgical preparations were performed under halothane anesthesia. A silastic catheter was inserted into the right jugular vein and led out from the nape of the neck for later drug delivery. A short length (~40 mm) of polyethylene tubing was inserted into the trachea for later artificial respiration, and the left femoral artery was cannulated using an angiocath catheter in order to measure blood pressure. After exposing the skull, small stainless steel screws were placed over the left occipital and frontal cortex for electroencephalography (EEG) recordings, and a ground screw was placed over the right frontal cortex. Dental acrylic was used to attach a steel post to the skull. The post, which was used to hold the animal's head without pressure points during the rest of the experiment, permitted unimpeded access to the facial vibrissae. In cortical experiments, the bone overlying the right barrel cortex was thinned and a small (<1 mm²) craniectomy was made. For thalamic experiments, a craniectomy was made overlying VPM nucleus. The dura was incised to prevent the brain from dimpling and thus suffering compression damage due to electrode insertion. Lastly, an acrylic dam was constructed around the cranial openings and filled with saline.

Body temperature was maintained at 37 °C by a servo-controlled heating blanket (Harvard Apparatus, Holliston, MA). For neural recordings, halothane was discontinued and the rat was maintained in a lightly narcotized, sedated state by intravenous (i.v.) infusion of fentanyl (Sublimaze, ~10 µg/kg h; Janssen Biochimica, Berse, Belgium). To prevent spontaneous movement of the vibrissae, which might interfere with stimuli produced by electromechanical stimulators (below), neuromuscular blockade was induced with pancuronium bromide (1.6 mg/kg h), and the animal was respired (90–100 breaths/min) using a positive pressure ventilator. A computer continuously monitored the rat's EEG, mean arterial pressure, arterial pulse rate, and tracheal airway pressure waveform. Experiments were terminated (see below) if any of the above indicators could not be maintained within normal physiological ranges; this occurred rarely.

Recordings

Data were obtained at a sampling rate of 32 kHz from cortical barrels and thalamic barreloids in the VPM nucleus using high-impedance

(5–10 MΩ) stainless steel microelectrodes (Frederick Haer, Brunswick, ME). Signals were amplified and band-pass filtered at 300–10 kHz. In order to determine the principal whisker (PW), defined as the whisker evoking the strongest response, whiskers on the contralateral mystacial pad were stimulated manually during electrode advancement. Extracellularly recorded neurons were identified by spike amplitude and waveform criteria using a virtual oscilloscope with a triggered delay and amplitude discriminator produced by custom software written in Labview version (National Instruments, Austin, TX). Parsed waveforms were saved to the disk. When multiple units were present, only the one having the largest amplitude was discriminated. Units were further isolated off-line using the cluster-cutting program mclust version 2.0 (A. David Redish, University of Minnesota, Minneapolis, MN). In the cortex, we distinguished 2 types of neurons based on spike waveform: RSUs and FSUs (Simons 1978; Bruno and Simons 2002). These are thought to represent the discharges of excitatory and inhibitory barrel neurons, respectively. In this study, we compared the response properties of RSUs and FSUs with identically studied TCUs.

Histology and Recording Locations

At the termination of an experiment, the rat was deeply anesthetized with pentobarbital sodium (100 mg/kg i.v.) and perfused transcardially for cytochrome oxidase (CO) histochemistry. The cortex was cut tangentially, and the thalamus was sectioned coronally. Tissue sections were reacted for CO, and all sections were counterstained with thionine. Using microdrive readings, signs of tissue disruption, and/or electrolytic lesions made with metal microelectrodes, recording sites were localized with respect to individual barrels; data are presented only for units recorded in CO-rich barrel centers. Detailed procedures for determining the locations of recorded units are provided in a previous publication from this laboratory (Kyriazi and others 1998). Because of the complex geometry of thalamic barreloids, no attempt was made to identify thalamic recording sites with respect to individual barreloids, but all recording sites were confirmed as being located within the VPM thalamic nucleus.

Whisker Stimulation Protocols

For each unit, we first used handheld probes to identify the PW, defined as the whisker evoking the most vigorous response. The PW was trimmed to 12–15 mm in length, and a multiangle piezoelectric stimulator was advanced over the terminal 2–5 mm of the cut end of the whisker (Simons 1983).

As previously described (Simons and Carvell 1989), a smoothed ramp-and-hold stimulus (peak velocity ≈125 mm/s, peak amplitude = 1 mm, duration = 200 ms) was applied to the PW randomly in each of the 8 angles spanning 0–360° in increments of 45°. Within a trial, the ramp-and-hold was presented at the same angle before and after an adapting stimulus (see Fig. 1). The adapting stimulus began with a ramp of velocity and amplitude identical to the ramp of the preceding ramp-and-hold. The adapting stimulus onset ramp was followed by a positively rectified 20-Hz sinusoid in 1 of the 4 cardinal directions (0°, 90°, 180°, or 270°) for 100 ms (2.5 cycles). Four directions of adapting deflections were used rather than all 8 in order to reduce the length of the time required to deliver the entire stimulus battery. Twenty-hertz sinusoidal

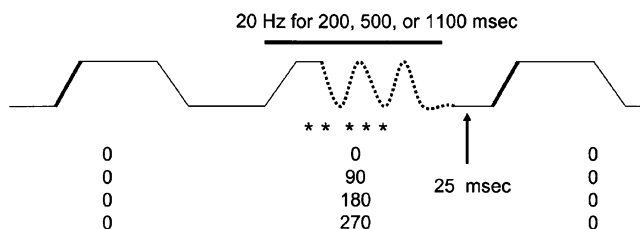


Figure 1. The adaptation paradigm. A nonadapting ramp-and-hold is presented in 1 of the 8 directions (0–315°, increments of 45°). Five hundred milliseconds later, a 20-Hz adapting stimulus is presented in 1 of the 4 cardinal directions. After a delay of 25 ms, another ramp-and-hold is delivered. ON responses evoked by the onset ramps were analyzed before and after adaptation (thick line). Asterisks indicate when the cortex was electrically stimulated in a subset of experiments.

adapting deflections were chosen because these stimuli produce more response suppression in RSUs and FSUs than in TCUs (Khatri and others 2004). The stimulus design allowed the comparison of responses with a ramp-and-hold deflection angle (e.g., 0°) before and after adapting stimuli of the same or different angles. The postadaptation ramp-and-hold followed the adapting stimulus by either 25 or 50 ms. These 2 time delays were used with the intent of further differentiating the effects of adaptation on cortical and thalamic neurons. For a given delay, there were a total of 32 conditions (8 pre- and postadaptation ramp-and-holds × 4 cardinal adapting directions). A block consisted of the 32 stimuli presented in pseudorandom order, and 10 such blocks were delivered.

Cortical Inactivation by Electrical Microshocks

In some experiments, adapting whisker deflections were paired with electrically evoked cortical suppression. Electrical stimulation was applied with a single microelectrode (<2 MΩ impedance at 1000 Hz) that was made from pulled and beveled glass pipettes loaded with carbon fibers or from quartz-insulated platinum-tungsten (90–10%) core fibers (Uwe Thomas Recording, Giessen, Germany). The stimulation microelectrode was lowered approximately 600 μm below the pial surface into layer II/III overlying the barrel that was targeted for neural recordings; layer IV corresponded to depths of 725–950 μm. The depth of 600 μm was chosen for electrical stimulation to minimize the likelihood of activating thalamic afferents as suggested by Chung and Ferster (1998). Prior to applying shocks with adapting whisker deflections, the effectiveness of the shocks alone was determined. The stimulation parameters, taken from Chung and Ferster (1998), effectively reduced cortical responses to whisker stimulation in layers II through VI (see Figs 2 and 3). Shocks were delivered 20 ms prior to the estimated arrival time for whisker-evoked thalamocortical inputs. A 20-ms delay was used so that whisker-evoked thalamocortical activity reached the barrel when cortical circuitry was maximally suppressed. An 8-Hz periodic pulsatile stimulus was applied to the whisker, and a single 200-μs shock of either 150 or 600 μA was delivered to the cortex. In Figure 2, the responses of a cell recorded at ~1550 μm in depth are displayed. Comparison of the 150- and 600-μA conditions indicates that the latter produces a larger response reduction. The reduction after the 600-μA shocks was quantified across the sampled

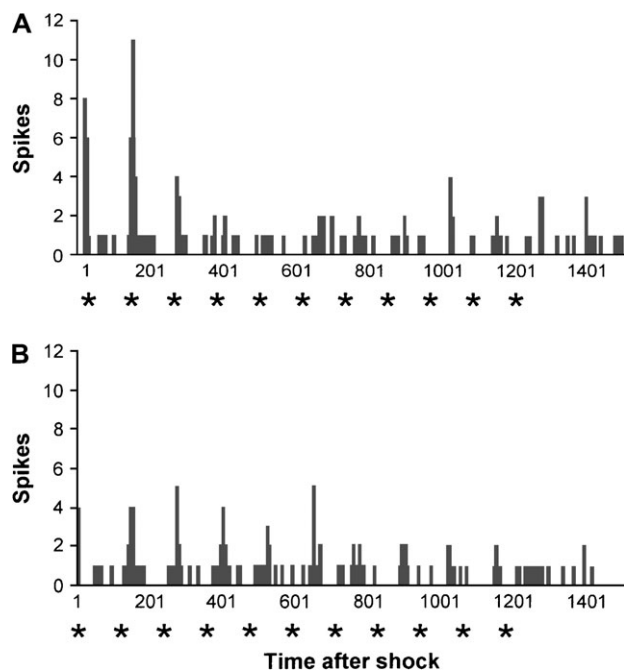


Figure 2. Example of response suppression produced by different amounts of electrical stimulation: (A) 150 μA, (B) 600 μA. The shocks and an 8-Hz periodic whisker stimulus were simultaneously delivered at time 0. Asterisks indicate the time of each whisker deflection.

cells ($n = 13$) as a function of depth by dividing the average firing rate in the 280-ms period after the shock by the average firing rate during the same time period in control trials having no shock. Figure 3 shows that equivalent effects of the shock were observed at different cortical depths; the average reduction was ~35%. Inspection of histologically prepared specimens indicated that electrical stimulation did not produce visible damage to the cortical tissue (e.g., lesions).

After the preliminary stimulation experiments, in different rats, 5 biphasic electrical shocks (200 μs at 600 μA) were applied during the adapting whisker stimulus (see asterisks in Fig. 1). To minimize further unintended damage to cortical tissue, only 1 or 2 recording penetrations were made through a single barrel in each rat ($n = 23$ recordings from 5 rats, range = 3–6 recordings per rat). Also, for these experiments, cortical recordings consisted of more readily obtained multiunit activity comprising, in our estimates, 3–5 units. Even in the multiunit recordings, the sites displayed angular tuning (see also Bruno and others 2003). Polar plots (described below) were used to determine a site's preferred direction for whisker stimulation. Subsequently, the preferred direction was used for all test deflections. Adapting whisker deflections were delivered in either the preferred or antipreferred directions.

Data Analysis

Unit responses were quantified by initially binning spikes with a 1-ms resolution. The ON response magnitude evoked by the rising phase of a ramp (denoted by stars in Fig. 5) was computed by taking the average number of spikes per stimulus occurring during a 20-ms period beginning 5 ms after the ramp's onset. Effects of adaptation were assessed by comparing pre- and postadaptation ON responses.

Quantification of Angular Tuning

ON responses were represented as polar plots (see Fig. 4), and the shape of the polar plot was quantified using a vector analysis. First, the response magnitude for each angle (normalized to the mean response across all 8 angles) was converted to a vector of polar coordinates. R_0 is the number of spikes contained within the ON response summed across trials.

$$x = R_0 \cos \theta_0$$

$$y = R_0 \sin \theta_0$$

All the 8 angles' vectors are summed, and the magnitude of the resulting vector is computed by

$$VS = (x^2 + y^2)^{1/2}$$

Vector strength (VS) provides a measure of how sharply tuned a neuron is for whisker deflection angle; a large VS corresponds to

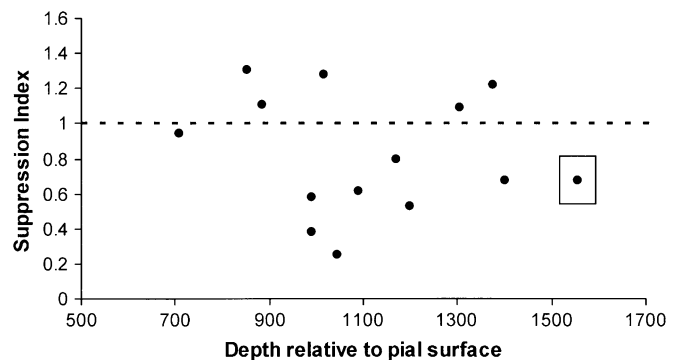


Figure 3. Effects of cortical microstimulation on evoked suppression of multiunit responses as a function of recording depth. Boxed point is the same cell from Figure 2. Suppressive index denotes proportional changes in unit firing; a value <1 indicates a smaller response relative to control.

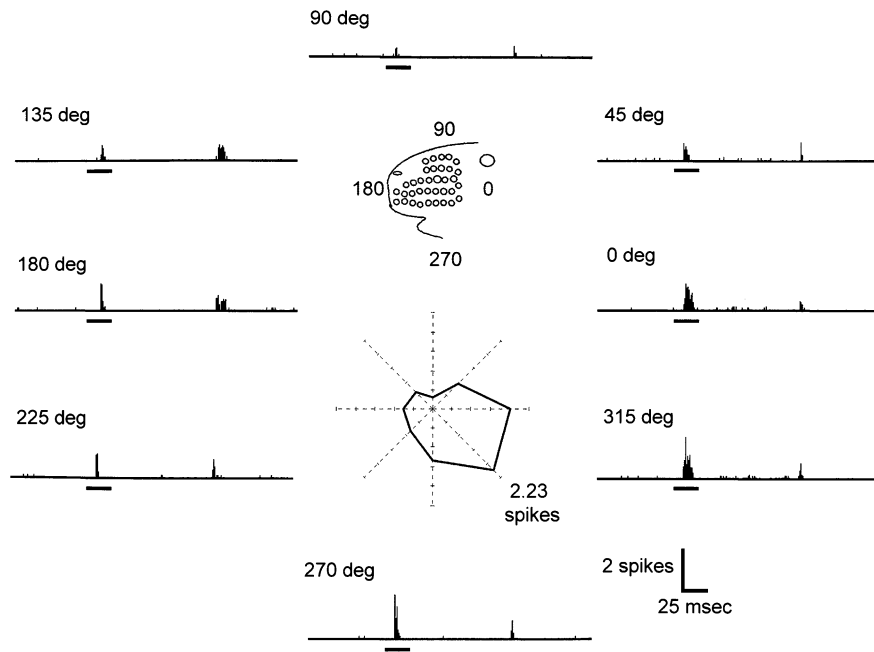


Figure 4. Angular tuning of a putative excitatory cell. PSTHs for each of the 8 directions of ramp-and-hold whisker movements are displayed. The cell's ON response is indicated by the line under each PSTH. The preferred direction is 315°, which evoked 2.23 spikes per deflection.

a more sharply tuned polar plot. The preferred angle is equal to $\arctan(\theta) = \text{sum}(y)/\text{sum}(x)$.

Similarity Index

We used a correlation coefficient to quantify the degree to which 2 polar plots are similar. Similarity index (SI) was calculated by correlating mean ON responses on an angle-by-angle basis. A value of 1.0 indicates that the polar plots are identical in shape, whereas -1.0 indicates they are oppositely shaped.

Due to deviations from normality in the distributions of data, statistical significance is evaluated with nonparametric statistical tests (Mann-Whitney test, Wilcoxon signed-rank test, and Kruskal-Wallis test). Response distributions are graphically displayed as box plots. Upper and lower quartiles are represented by the edges of the box. The lines connecting the upper and lower edges of the box indicate the edges of the distribution minus the outliers.

Results

Data are reported from 30 TCUs, 39 RSUs, and 9 FSUs recorded from 20 rats. All RSUs and FSUs were located within cytochrome-rich barrel centers. Approximately, two-thirds of the RSUs and TCUs were studied using both 25- and 50-ms delay periods following the adapting stimulus; FSUs were examined only with the 25-ms delay. The 3 populations of sampled units were comparable with those reported previously (e.g., Simons and Carvell 1989; Kyriazi and others 1994). As populations, all 3 cell types displayed time-locked responses to the rising and falling phases of the preadaptation ramp-and-hold, that is, ON and OFF responses. As in previous studies, FSUs were the most responsive and had the largest OFF-to-ON ratios (Kyriazi and others 1994), whereas barrel RSUs were the least responsive and had the smallest OFF-to-ON ratios. Also as reported previously, FSUs displayed the poorest angular tuning, responding well to all 8 deflection angles. Nonadapted angular tuning of the ON response as measured with VS was smaller in FSUs (0.56 ± 0.13 , median = 0.52) than in TCUs (3.21 ± 0.33 , median = 3.11)

and RSUs (3.36 ± 0.30 , median = 3.27) (Kruskal-Wallis test, $P < 0.001$) (Fig. 6E). Angular preferences are somewhat biased for caudal whisker deflections in the population of RSUs and TCUs but not in FSUs (Fig. 6A-C). A bias for caudal directions had also been observed previously in RSUs (Bruno and others 2003).

The preadaptation ramp-and-hold deflection was varied between 0° and 360° in increments of 45°, followed by a 20-Hz adapting deflection in 1 of the 4 cardinal directions, and then a postadaptation ramp-and-hold stimulus identical to the preadaptation one was delivered (see Fig. 1). The 2.5 cycles of 20-Hz whisker deflection led to reductions in the responses of RSUs to the subsequent ramp-and-hold movement. This is illustrated by the population peristimulus time histograms (PSTH) in Figure 5 that was constructed from the responses of 39 RSUs; here responses are accumulated for 16 combinations of the 4 (0°, 90°, 180°, and 270°) test and adapting deflections. The first ramp-and-hold stimulus evoked a brief response to stimulus onset and a smaller response to stimulus offset. Five hundred milliseconds later, the whisker was deflected with an identical stimulus followed shortly thereafter by 2.5 cycles of a 20-Hz sinusoidal movement; each cycle evoked 2 responses corresponding to movement away from and back to rest, that is, ON and OFF responses. Twenty-five milliseconds after the conclusion of the sinusoid, the whisker was deflected again using the same ramp movement as during the prior 2 stimuli. As illustrated by the population PSTH, RSUs responded less robustly to the third onset ramp than to either the first or the second one. Averaged across all stimulus conditions, RSU responses relative to those evoked by the first ramp decreased by 40% (median adaptation index [AI] = 0.57), and FSU responses decreased by 27% (median AI = 0.75). TCUs displayed less adaptation, responding at near-control levels (median AI = 0.86). Adaptation levels differed (Kruskal-Wallis test, $P \ll 0.001$), with FSUs adapting somewhat less than RSUs (Mann-Whitney test, $P = 0.052$) and both cell types adapting more than TCUs (Fig. 6D). In all 3 cell

populations, the amount of suppression generated by adaptation was least for 270° or downward deflections relative to other directions: RSUs ($P \ll 0.001$), FSUs ($P \ll 0.001$), and TCUs ($P \ll 0.01$). Cells preferring 270° did not differ, however, from those preferring other angles in terms of either nonadapted angular tuning (VS) or spikes per stimulus.

As a measure of overall response reliability, we also examined responses to the first and second onset ramps, matched for stimulus angle. For all 3 populations, first- and second-ramp responses were highly similar to each other in terms of response magnitudes. Angular tuning was quantified with the SI that compares polar plot shapes, in this case, based on the 4 cardinal directions (see Methods). SIs are close to 1.0 for RSUs (0.85 ± 0.02 , median = 0.88), FSUs (0.73 ± 0.09 , median = 0.88), and TCUs (0.85 ± 0.04 , median = 0.95) and are equivalent across cell types (Kruskal-Wallis test, $P = 0.22$) (Fig. 6F). The SIs obtained here contrast with the mean SI of arbitrary pairs of barrel RSUs, which is close to 0 (Bruno and others 2003). The large SIs indicate that responses are reproducible and thus variability will not obscure the effects of adaptation assessed with the third onset ramp.

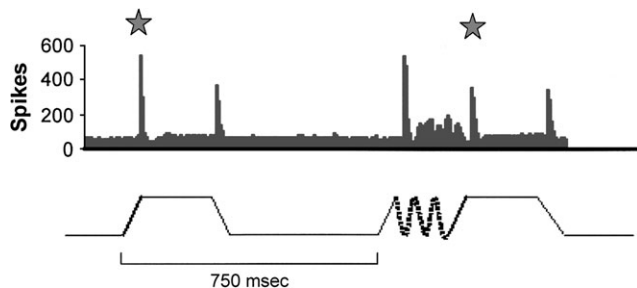


Figure 5. RSU population PSTH. The PSTH is based on 39 cells and 6240 trials (39 cells \times 16 conditions \times 10 repetitions). Stars above PSTH indicate non- and postadapted ON responses, respectively. The 25-ms delay between the adapting and testing stimuli is not apparent in the stimulus trace due to the compressed time scale.

Effects of the Adapting Stimulus Angle

The 20-Hz adapting deflections were equally effective in producing response adaptation regardless of their direction relative to that of the test deflection. Figure 7A shows polar plots obtained from an RSU in the nonadapted condition and following adaptation with the 4 cardinal directions of 20-Hz stimulation. In the nonadapted state, the unit displayed a preference for caudal (0°) deflections. This preference is retained following adaptation at any of the 4 cardinal directions. For example, the RSU's response to 0° is smaller after adaptation with 0° deflections, but responses to all other angles are also suppressed. In each case, the unit's tuning is enhanced as evidenced by the narrowing of the polar plots. The same results hold for the entire RSU population. In Figure 7B, the central panel shows a nonadapted RSU population polar plot in which each individual cell's maximal angle has been rotated to 0°. The surrounding panels contain adapted polar plots for the 0°, 90°, 180°, and 270° adapting deflections; for the individual units, each of the adapted polar plots was rotated by the angular shift used to align the corresponding nonadapted polar plot. The graphs illustrate that regardless of the adapting angle, angular preference remains constant and tuning becomes sharper (see below).

For individual cells of all 3 populations, we compared spike counts evoked by a test deflection when it was preceded by adapting deflections in the same or opposite directions; because responses at some angles were extremely small or 0.0, we did not compute ratios (AI) as in Figure 6D. Adaptation-induced response suppression was largely independent of the directions of the test and adapting stimuli (see Fig. 8). For example, in RSUs, adapting deflections at opposite angles led to a reduction in the average spike count of ~40%. A small angularly specific component of suppression is also evident in that when adapting and test stimuli are of the same direction, adapted responses are even smaller. The distributions of spike counts for the same- and opposite-angle adaptations differed (medians = 0.05 vs. 0.10, Wilcoxon signed-rank test, $P < 0.001$). Similarly, in FSUs, opposite-angle adaptation reduced medians by ~25%, and

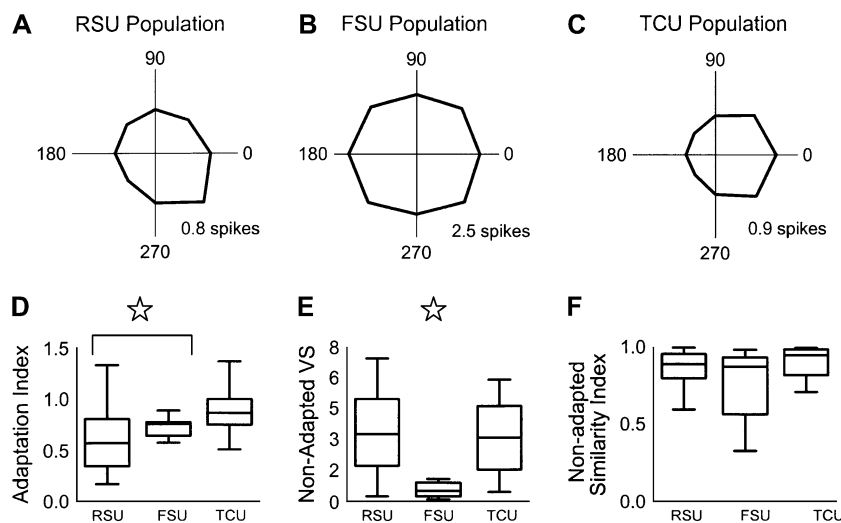


Figure 6. Response properties of RSUs, FSUs, and TCUs. (A) Population polar plot for RSUs. A bias is present for caudal (0° or 315°) deflections. The 315° deflections evoked 0.8 spikes per deflection. (B) Population polar plot for FSUs. No angular preference bias is present. (C) Population polar plot for TCUs. They also display a bias for caudal deflections. (D) AIs (post/preadaptation ON response magnitude). Greater adaptation in RSUs and FSUs relative to TCUs is indicated by the star ($P \ll 0.001$). (E) VS of nonadapted angular tuning. Star indicates that the nonadapted VS is significantly smaller in FSUs ($P \ll 0.001$) than in RSUs and TCUs. (F) Polar plot SIs for response to first and second ramps.

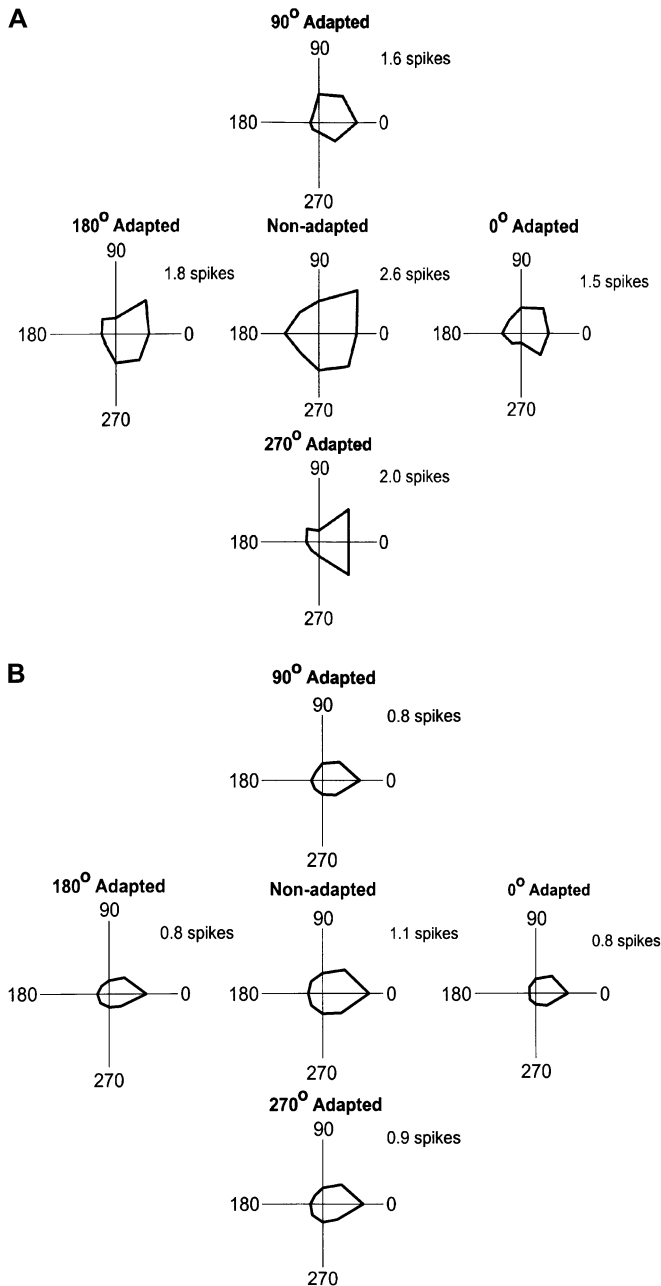


Figure 7. (A) Typical RSU behavior. Center panel is the nonadapted angular tuning. A total of 2.6 spikes were evoked on average for each 45° deflection. The rightmost panel is the angular tuning after 0° adaptation. Note that overall angular orientation is maintained postadaptation and angular tuning is sharper. (B) RSU population. Response for each cell has been rotated such that 0° represents the preferred angle of the nonadapted response; for adapted responses, polar plots were rotated by the angular shift used for the corresponding nonadapted plot.

same-angle adaptation reduced responses by an additional 15% (medians = 0.78 vs. 1.15, Wilcoxon signed-rank test, $P = 0.003$). A possible concern is that the observed direction-specific effect is a consequence of the already described finding that 270° adapting deflections evoked less suppression than other angles. This was not the case, however, because even when 90° and 270° stimuli were removed from the analysis, RSUs and FSUs still displayed a direction-specific effect ($P = 0.001$ and $P = 0.037$, respectively).

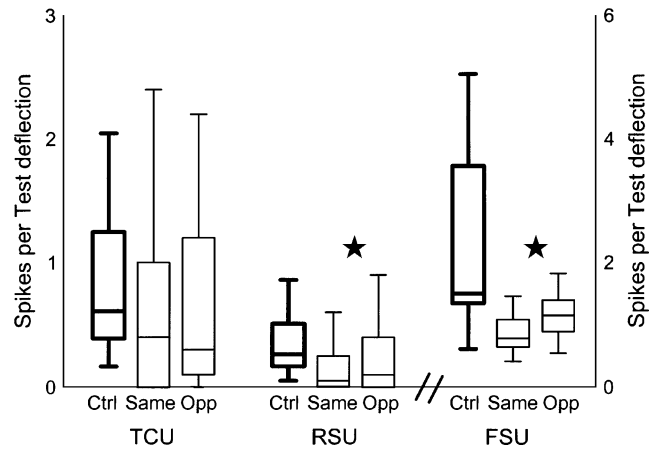


Figure 8. Responses of TCUs, RSUs, and FSUs to same- and opposite-angle adaptation. y axis on the left is for TCUs and RSUs. Right y axis is for FSUs. Stars indicate significant differences ($P < 0.01$) between responses after same- and opposite-angle adaptation. Direction-specific suppression is present in RSUs and FSUs but not in TCUs.

For TCUs, adaptation effects were equivalent for adapting stimuli at the same and opposite directions (Wilcoxon signed-rank test, $P = 0.86$). A direction-specific effect was observed, however, when only the first 5 ms of the thalamic response was examined (same vs. opposite medians = 0.10 vs. 0.20, Wilcoxon signed-rank test, $P = 0.016$). This time epoch has previously been shown to be the critical determinant of cortical responses (see below). This apparent direction-specific effect appears to be a consequence of the fact that, as in the cortex, 270° adapting deflections evoked less suppression than the 90° ones. Unlike in the cortex, however, there was no direction-specific effect if responses after 90° and 270° adapting deflections were removed.

Similar analyses were performed on data from 25 RSUs and 21 TCUs obtained under the condition where the delay between the end of the adapting stimulus and the beginning of the test deflection was extended to 50 ms. In both populations, response suppression was less pronounced, but a small direction-specific effect was still present in RSUs. Again, TCUs displayed no significant direction-specific effect, even if 90° and 270° adapting deflections were not removed.

To determine the robustness of the adaptation effects in RSUs, we examined the effects of 2 longer durations of adapting stimuli (500 and 1100 ms, $n = 20$ and 33 RSUs) using the same 20-Hz sinusoids and a 25-ms delay. Adaptation duration was lengthened by increasing the number of sinusoidal deflections. The longer durations were expected to depress thalamocortical input and intrabarrel circuits even further due to more complete synaptic depression and/or summation of inhibition. As shown in Figure 9, firing rates were somewhat higher after the 1100-ms adaptation period, but this change was not significant for either the same- or opposite-angle adaptation (Kruskal-Wallis test, P values > 0.20). Adaptation effects described previously for the 200-ms period were also observed for the 1100-ms case; strong adaptation was produced by both same- and opposite-angle deflections, and firing rates with the former stimuli were reduced more. A difference between same- and opposite-angle adaptation effects was not observed for the 500-ms period, perhaps due to large variability in the sample.

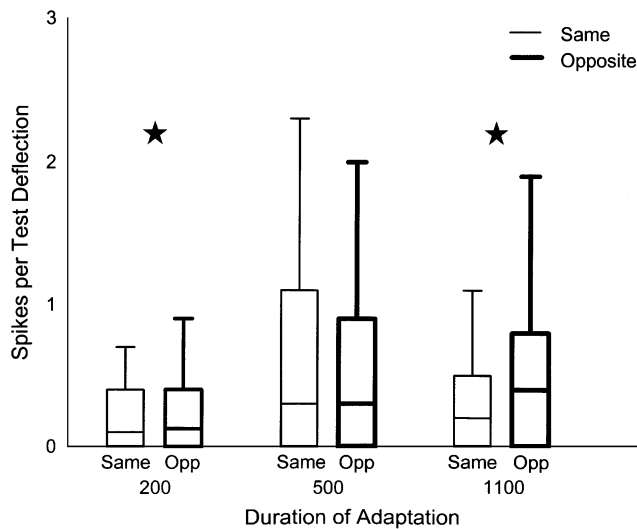


Figure 9. Effect of adaptation duration on direction-specific suppression of RSU responses. The nonadapted preferred direction response is ~ 1.0 spikes per deflection. The amount of direction-specific versus -nonspecific suppression was independent of the duration of adaptation.

Adaptation during Cortical Inactivation

Thalamic input imparts angular tuning to barrel neurons (Bruno and Simons 2002; Bruno and others 2003). Thus, angularly specific suppression in the cortex could reflect greater depression of thalamocortical synapses. To test this, we suppressed cortical activity during the delivery of the adapting whisker deflections. We adopted the method of Chung and Ferster (1998) in which electrical pulses are delivered to a site several hundred microns superficial to the recording electrode in layer IV. Brief trains of electrical pulses are thought to render the cortical network refractory without directly affecting thalamocortical synapses. Cortical activity could not be monitored during electrical stimulation due to the presence of stimulus artifacts, but deflection-evoked activity following the shocks could be measured. After 5 shocks alone (without accompanying whisker deflections), multiunit activity ($n = 23$ sites) evoked by deflections in the preferred direction was suppressed by $57 \pm 7\%$. Responses were smaller after 5 shocks than 1 shock (medians = 0.7 vs. 0.4 spikes per deflection, Wilcoxon signed-rank test, $P \ll 0.001$). Thus, the electrical shocks produced the desired reduction in overall cortical excitability during the period of sensory adaptation.

Figure 10 shows results obtained when the electrical shocks were delivered simultaneously with the adapting whisker deflections. Response suppression was greater when the 20-Hz adapting stimulus was paired with 5 shocks versus 1 shock (responses averaged over both same and opposite adaptation conditions, 0.56 ± 0.11 vs. 1.23 ± 0.20 spikes per stimulus, paired t -test, $P \ll 0.001$). Nevertheless, barrel neurons still displayed angularly specific suppression, and suppressive effects for same-angle adaptation were again greater than those for opposite-angle adaptation in both the 1- and 5-shock conditions (Wilcoxon signed-rank test, $P = 0.002$ and 0.005 , respectively). The greater amount of angularly nonspecific suppression evoked by 5 shocks is due to its producing a greater amount of response suppression than 1 shock. Direction-specific suppression was observed at 15 of the 19 individual recording sites where whisker-evoked responses persisted after

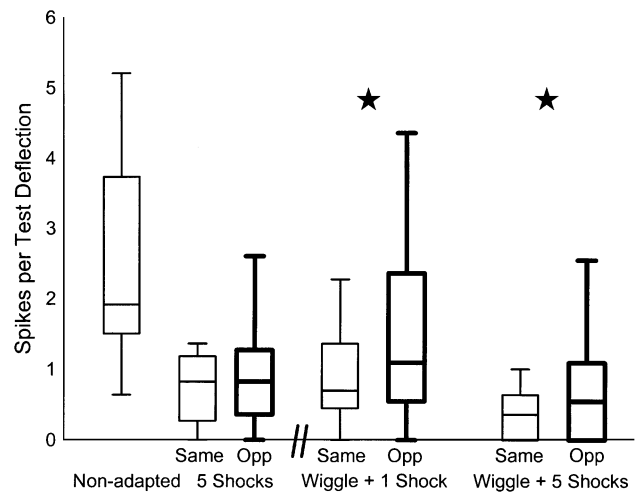


Figure 10. Effect of pairing adaptation whisker deflections with electrical stimulation of the cortex. Direction-specific suppression is present whether 1 or 5 cortical shocks are presented. Note that the large nonadapted response magnitude is due to data in this figure only, being from multiunit recordings. Stars denote significant differences ($P < 0.01$).

the electrical shocks. The above effects were also observed when 90° and 270° adapting and test deflections were removed from the analysis. Together, the findings indicate that angularly specific adaptation can be produced without fully functioning intracortical circuits.

Adaptation-Induced Effects on Angular Tuning

In RSUs, angularly specific suppression is only $\sim 10\%$ stronger than angularly nonspecific suppression. As a result, the shape of a cell's polar plot remains approximately the same before and after adaptation, as illustrated by the RSU in Figure 7A. To quantify this for each cell, the VS measure was used to calculate a phase angle representing each polar plot's overall orientation (see Methods). Vector angles in the nonadapted and adapted conditions were compared by subtraction. Figure 11 shows data for 0° adapting deflections. Following adaptation, vector angles were equivalent to those in the nonadapted condition (Fig. 11A). For 24 of 38 (63%) RSUs, the preferred angle after adaptation remained within 45° of its nonadapted value. For 34 of 38 of those same RSUs, the preferred angle remained within 90° of the nonadapted value. Similar results, not shown, were obtained for the other 3 adapting angles and for the other cell types (FSUs and TCUs).

Observation of individual units, such as the RSU illustrated in Figure 7A, suggested that adaptation enhances angular tuning, that is, it makes the polar plots narrower. Again, we used the measure of VS to quantify angular tuning. There was no effect of the particular adapting angle, and therefore, postadaptation responses were averaged for all 4 angles of adaptation. Comparisons of pre- and postadaptation vector magnitudes showed that for 34 of 40 RSUs ($\sim 83\%$), adaptation increased angular tuning (Fig. 11B). On average, vector magnitudes increased $\sim 30\%$ after adaptation (pre- vs. postmedians = 3.27 vs. 4.29, Wilcoxon signed-rank test, $P < 0.001$). Tuning was not significantly affected in FSUs, which remained as poorly tuned in the adapted state as they were in the nonadapted one. Similar results for RSUs and FSUs were obtained when tuning was assessed by a ratio in which the response to the maximally effective angle is divided by the mean response across all 8 angles.

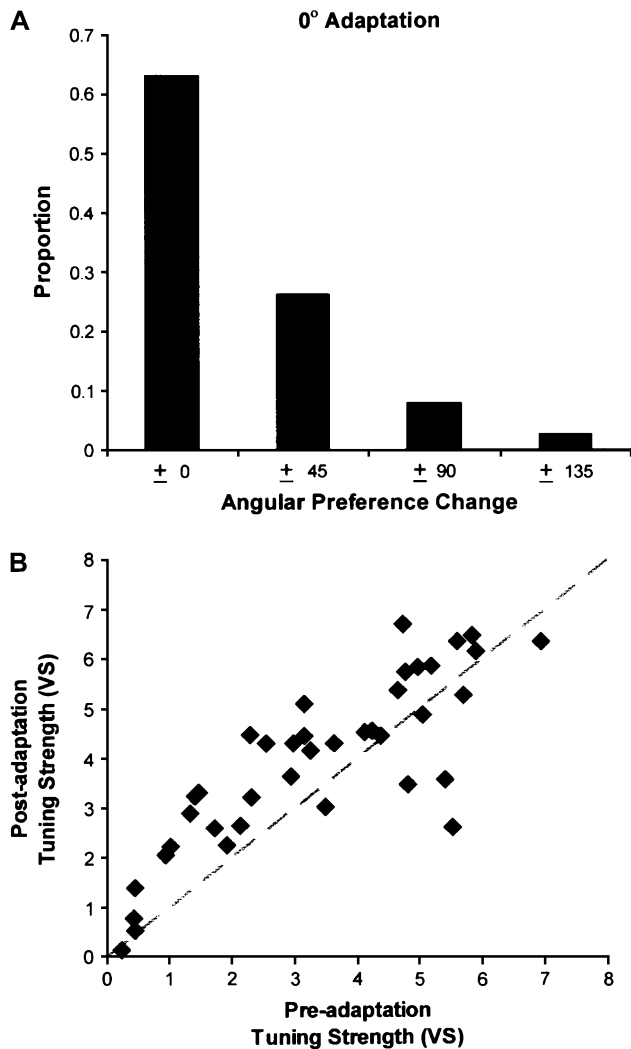


Figure 11. RSU responses after adaptation. (A) Distribution of angular preference changes after 0° adaptation. The angular preference of 63% of the postadapted RSUs remained within 45° of the nonadapted angular preference. (B) Angular tuning before and after 0° adaptation. RSU tuning is sharpened in 33 of 40 cases.

Using the VS measure, adapted responses were $\sim 30\%$ more sharply tuned in TCUs (medians = 3.11 vs. 3.99, Wilcoxon signed-rank test, $P = 0.005$). This measure, which is based on overall response magnitude (spike count) during a 20-ms poststimulus period, may not be the appropriate metric for characterizing the salient features of the thalamic responses, inasmuch as barrel neurons are sensitive to thalamic population firing synchrony during only the first few milliseconds of the thalamic response. It has been previously demonstrated with the 125-mm/s deflection velocity used here; the responses of layer IV barrel neurons are determined almost exclusively by the first 4 ms of a response produced by the population of thalamic neurons (see Pinto and others 2003). VS measures of TCU polar plots based on this time epoch were equivalent before and after adaptation. We also constructed population PSTHs of thalamic responses to preferred and nonpreferred directions defined as those evoking the maximal and minimal spike counts during the first 4 ms (Fig. 12). In the nonadapted condition (panel A), population responses to preferred and opposite-direction stimuli begin and peak at identical times; peak response

magnitude is substantially larger in the former, yielding a faster rate of rise in the population response. For the adapted response (panel B), the difference in the rate of change of the responses during the first 4 ms is somewhat less pronounced, though the preferred angle response still has a steeper initial slope.

In order to differentiate further the responses of TCUs and RSUs, we used a longer delay (50 vs. 25 ms) between the end of the adapting stimulus and the onset of the test deflection. As expected, response suppression was less in RSUs ($n = 25$). Nevertheless, adaptation sharpened RSU tuning by $\sim 30\%$ (medians = 2.87 vs. 4.13, Wilcoxon signed-rank test, $P < 0.001$). With the longer delay, TCU responses were suppressed only minimally, and angular tuning was unaffected when either the 20- or 4-ms response epoch was examined. Thus, sharper tuning in RSUs as a result of adaptation may occur independent of changes in the thalamic response.

Discussion

Previous studies have demonstrated that repetitive whisker deflections lead to reductions in neural firing in barrel cortex (Simons 1978; Faselow and Nicolelis 1999; Ahissar and others 2000; Garabedian and others 2003; Khatri and others 2004). Adaptation effects may differ quantitatively in thalamic barrel and cortical barrel neurons depending on the stimulation frequency, state of arousal, and type/depth of anesthesia (see Faselow and Nicolelis 1999; Castro-Alamancos 2004). Here we examined whether response suppression in the thalamocortical circuit is selective for a specific characteristic of the adapting whisker deflection, its angular direction. We found that the activity of cortical cells within layer IV barrels is diminished following repetitive whisker deflection in any direction. Effects were observed in both RSUs and FSUs, presumed excitatory and inhibitory neurons, respectively. Effects in the cortex appear to be largely independent of changes in the responses of thalamic input neurons.

For any given barrel unit, adapting stimuli diminished responses regardless of the directions of the adapting and test stimuli. Suppression was not uniform, however, in that, for RSUs, responses to stimuli in nonpreferred directions were diminished more. This parallels previous findings that weaker responses are disproportionately affected by intracortical inhibition (Kyriazi and others 1996). Together, the 2 major effects of adaptation—angularly nonspecific response suppression and the disproportionate reduction of initially weaker (nonpreferred) responses—led to a sharpening of angular tuning in barrel RSUs. The angular preference of RSUs was maintained despite marked reductions in overall evoked firing rates, and concomitantly, tuning was enhanced. These findings suggest that the impact of angularly nonspecific suppression outweighs that of angularly specific suppression. Otherwise, polar plots would have become consistently rounder, and/or their preferred angles would have shifted systematically away from the direction of the adapting stimulus. This suggests that during ongoing tactile exploration, the angular tuning properties of barrel neurons are enhanced regardless of the moment-to-moment changes in the angle of whisker deflection.

Mechanisms of Response Suppression

We classified suppression effects as angularly specific and angularly nonspecific on the basis of whether response suppression occurs when adapting and test stimuli are at the same

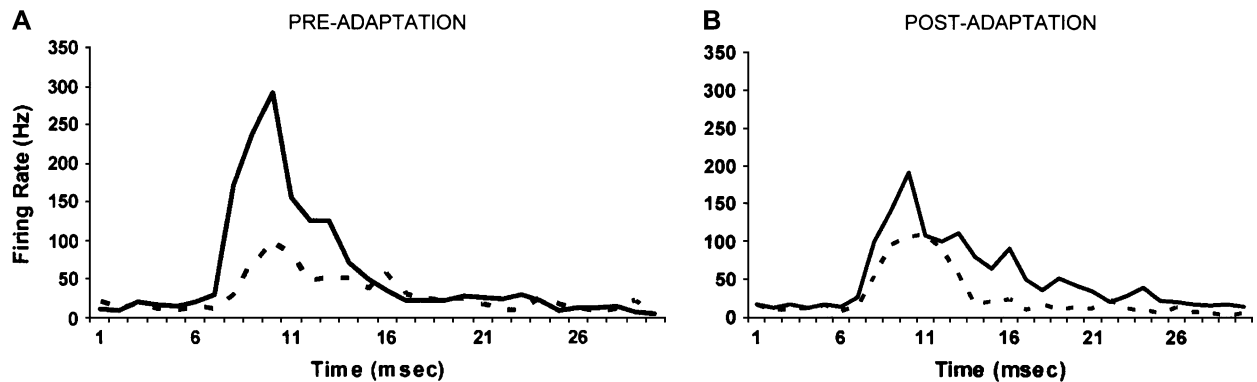


Figure 12. TCU population responses to preferred and antipreferred directions. (A) Preadaptation responses to preferred (solid black) and antipreferred directions (dashed gray). Note the steeper initial slope of the preferred direction response relative to the antipreferred one. (B) Postadaptation responses show response suppression and more similar initial slopes for both movement directions.

or different (e.g., opposite) directions. We propose that both angularly specific and angularly nonspecific effects are mediated largely by local inhibition (see also below), whereas angularly specific suppression reflects an additional contribution of short-term depression at thalamocortical synapses. In the thalamus, adaptation-induced suppression could be mediated by 1) depression at trigeminothalamic synapses (Castro-Alamancos 2002) that, like thalamocortical synapses onto RSUs, appear to be highly angularly specific (see Minnery and Simons 2003) and/or 2) intrathalamic inhibition produced by neurons in the thalamic reticular nucleus (RT). Although RT cells have angular preferences, individual neurons fire robustly at all whisker deflection angles (Hartings and others 2000). The adapting stimuli are of sufficient duration that they could engage corticothalamic feedback mechanisms as well (see Yuan and others 1986). Thalamic effects do not, however, appear to be the principal source of changes observed in the cortex.

A distinctive feature of FSUs in the layer IV barrel is that almost all of them are broadly tuned for deflection angle (see Fig. 2B; Simons 1978; Kida and others 2005); this property reflects highly convergent inputs from multiple thalamocortical neurons having a wide range of preferred deflection angles (Swadlow and Gusev 2000; Bruno and Simons 2002). Recently, we showed that FSUs retain their characteristic high firing rates and temporally focused responses after adaptation with repetitive whisker stimulation similar to that used here (Khatri and others 2004). Present findings indicate, further, that in the adapted state barrel FSUs also retain their broad angular tuning. It is therefore likely that the pervasive, angularly nonspecific adaptation effects observed in the layer IV barrel reflect synaptic inhibition mediated locally by FSUs. Because FSUs are nonselective for deflection angle, the inhibitory network within the barrel is as likely to be engaged when adapting and test angles are similar as when they are different; intracellular recordings have provided evidence that cortical inhibition is evoked at all whisker deflection angles (see Wilent and Contreras 2005). Thus, to the extent that inhibition underlies response suppression observed in cortical neurons, angularly specific effects and angularly nonspecific effects can be mediated by the same mechanism.

Adaptation-induced reductions in neuronal firing could also be produced by short-term depression of excitatory thalamocortical synapses (Chung and others 2002). If so, such changes should occur independent of the (postsynaptic) cortical net-

work. In order to evaluate possible contributions of thalamocortical synaptic depression, we disrupted the cortical circuitry by applying electrical shocks to layer III at the time the adapting whisker stimuli were delivered. The shock had a magnitude of 600 μ A and a duration of 200 μ s, a charge (1200 nC) more than sufficient to affect cells within a 450- μ m radius (Butovas and Schwartz 2003). We assume therefore that the electrical stimuli nonselectively discharged most neurons in the underlying barrel and that the cortical circuit remained largely refractory during the adapting whisker deflections (see Boudreau and Ferster 2005). Evidence for this is that test responses were strongly reduced in magnitude when the shocks were presented alone, and the reduction was greater with 5 shocks than 1. When paired with adapting deflections, angularly specific response suppression was still observed. Assuming that network effects were largely eliminated by the shocks, the angularly specific suppression originates with the thalamic inputs, either as changes in the responses of the thalamocortical input cells or as a reduction in the efficacy of their synapses. This conclusion is consistent with previous findings that the directional specificity of RSUs appears to be inherited from their thalamic inputs due to selective convergence of TCUs having similar angular preferences (Bruno and Simons 2002).

A possible criticism of our usage of electrical stimulation to inactivate the cortex is that the shocks may also have antidromically activated thalamic neurons. Additionally, the shocks may have orthodromically activated corticothalamic cells, and consequently, thalamocortical neurons could have been affected. The large electrical shocks used may well have activated thalamic neurons, both antidromically and orthodromically. However, if thalamic neurons were affected by electrical stimulation, barreloid neurons of different angular preferences should have been influenced in a directionally nonspecific manner. Such an effect could not explain the direction-specific suppression that was observed in barrel neurons after inactivation.

Our proposal of a contribution of thalamocortical synaptic depression to angularly specific suppression is based on the assumption that under the present experimental conditions those synapses can undergo stimulus-dependent depression (Castro-Alamancos 2004). In the present recording conditions, TCUs fire spontaneously at rates of 10–15 Hz (Simons and Carvell 1989; Kwegyir-Afful and others 2005), presumably placing the thalamocortical synapse in a tonic state of partial

depression. In geniculocortical circuits, under conditions where thalamic cells fire spontaneously >20 Hz, thalamocortical synaptic depression can be produced, though at lower levels than those obtained when spontaneous LGN firing is decreased (Boudreau and Ferster 2005; see also Swadlow and Gusev 2002). Thus, in our experiments, it is likely that the adapting whisker stimuli cause further reductions in thalamocortical synaptic efficacy. Low levels of spontaneous thalamic activity could be associated with somewhat different effects. For example, a preliminary report by Garabedian and others (2003) suggests that angularly specific suppression dominates the responses of barrel neurons in barbiturate-anesthetized animals, resulting in marked alterations of polar plot shape and hence angular preference. Thus, depending on the level and pattern of thalamic background firing, a whisker's initial deflection could render barrel circuitry differentially responsive to subsequent deflections of that whisker in the same or a different direction. Receptive field size, another spatial property of barrel neurons, is also affected by tonic activity levels in the thalamocortical circuit (Castro-Alamancos 2002; see also Kwegyir-Afful and others 2005).

Are Interactions among Angular Tuning Domains Functionally Specific?

A barrel contains angular tuning domains or minicolumns in which RSUs lying in vertical register within layer IV share the same angular preference (Bruno and others 2003). Tuning domains for different angles may be represented at multiple locations within a barrel and appear to be complexly or randomly dispersed throughout it. They are estimated to be ~ 75 μm wide and thus smaller than the dendritic/axonal arbors of barrel spiny stellate cells, which can span ~ 200 μm (Simons and Woolsey 1984; Lubke and others 2000); the dendritic and axonal process of many inhibitory neurons are considerably larger (Erickson and others 2004). These anatomical features of barrel circuitry raise the issue of whether functional angular tuning domains are synaptically interconnected in an angularly specific manner. Individual barrels in rats contain morphologically identifiable subunits (i.e., subbarrels: Land and Erickson 2005), but there is no evidence to date that these—or other subdivisions—of the barrel neuropil are interconnected in a systematic fashion. In vitro studies have shown that any given pair of excitatory barrel neurons located within a 300 - μm radius of each other may be synaptically interconnected, leading to the suggestion that the barrel is a “spatially homogeneous processing unit” (Petersen and Sakmann 2000). We attempted to probe these connections functionally by determining whether adaptation of barrel neurons is angularly specific; the rationale is that angularly specific suppression would be mediated by angularly specific circuits. On average, the RSUs recorded here spontaneously fired spikes at a rate of 2.5 Hz, and in conjunction with the in vitro findings, this suggests that the suppression of RSU-RSU synapses is only $\sim 15\%$ complete (Petersen 2002). Thus, in our recording conditions, intrabarrel excitation should be functionally intact and subject to further short-term depression. We found pervasive angularly nonspecific suppression. This suggests either that excitatory cells in neighboring angular tuning domains interconnect nonspecifically or that the effects of adaptation-induced depression at angularly specific excitatory-to-excitatory cell synapses are weak relative to those of global inhibition (see above).

Feed-forward Inhibition and the Specificity of Sensory Adaptation

The present findings are consistent with feed-forward models of thalamocortical circuits in which stimulus-specific responses of layer IV neurons derive largely from specific patterns of thalamic input onto cortical cells (e.g., Hubel and Wiesel 1962; Simons and Carvell 1989). In terms of angular sensitivity in the whisker system, excitatory barrel neurons (RSUs) are thought to receive synchronously active, convergent inputs from thalamocortical neurons having similar, though not identical, angular preferences. In RSUs, short-latency excitatory conductances of presumed thalamic origin appear to increase more rapidly for preferred versus nonpreferred direction stimuli (see Figs 3 and 4 in Wilent and Contreras 2005). Similarly, faster whisker deflections evoke both greater thalamic initial population firing synchrony and larger RSU responses, and this robust relationship holds regardless of whether the PW is deflected in each cell's preferred direction or in the arbitrarily chosen caudal direction (Pinto and others 2000). Thus, circuit dynamics, mediated by local interconnections among and between excitatory and inhibitory barrel cells, may contribute to angular tuning by enhancing the nonlinear sensitivity of RSUs to the rate of rise of the thalamic input signal, as occurs in the case of velocity sensitivity (Pinto and others 2000; Wilent and Contreras 2004). Additionally or alternatively, angular tuning could be enhanced by the relative proximal/distal distribution onto spiny cell dendrites of thalamic inputs from cells having different preferred directions (Wilent and Contreras 2005). In either case, a critical feature of the local circuit is the strong feed-forward engagement of FSUs that creates a brief “window of opportunity” for preferred thalamic inputs to engage local excitatory neurons before they are overwhelmed by intrabarrel inhibition (Pinto and others 2003; see also Swadlow 2003).

In cat visual cortex, orientation selectivity is thought to depend on feed-forward geniculocortical inputs (Ferster and others 1986), with local excitatory and inhibitory circuitry serving to reinforce or maintain the tuning preference provided by thalamic inputs (Troyer and others 1998). Interestingly, orientation-specific or orientation-nonspecific adaptation effects may predominate depending on a cell's distance from a pinwheel center (Dragoi and others 2001). In auditory cortex too, strong frequency-specific adaptation effects can be observed (Ulanovsky and others 2003). One difference in local circuit function that may underlie the strikingly dissimilar effects of adaptation in these systems versus the somatosensory system is the degree to which feed-forward inhibition is stimulus specific. In barrels, FSUs are typically broadly tuned for deflection angle, whereas available evidence suggests that inhibitory neurons in cat primary visual cortex are sharply tuned for orientation (Azouz and others 1997; Anderson and others 2000; Martinez and others 2002). The degree of correspondence between the stimulus specificity of local inhibitory interneurons and that of the excitatory neurons upon which they synapse may be an important factor in determining how ongoing sensory information affects the moment-to-moment activity of cortical circuits.

Notes

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