Weaker feedforward inhibition accounts for less pronounced thalamocortical response transformation in mouse vs. rat barrels

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Kwegyir-Afful EE, Kyriazi HT, Simons DJ. Weaker feedforward inhibition accounts for less pronounced thalamocortical response transformation in mouse vs. rat barrels. J Neurophysiol 110: 2378–2392, 2013. First published August 21, 2013; doi:10.1152/jn.00574.2012.—Feedforward inhibition is a common motif of thalamocortical circuits. Strong engagement of inhibitory neurons by thalamic inputs enhances response differentials between preferred and nonpreferred stimuli. In rat whisker-barrel cortex, robustly driven inhibitory barrel neurons establish a brief epoch during which synchronous or near-synchronous thalamic firing produces larger responses to preferred stimuli, such as high-velocity deflections of the principal whisker in a preferred direction. Present experiments in mice show that barrel neuron responses to preferred vs. nonpreferred stimuli differ less than in rats. In addition, fast-spike units, thought to be inhibitory barrel neurons, fire less robustly to whisker stimuli in mice than in rats. Analyses of real and simulated data indicate that mouse barrel circuitry integrates thalamic inputs over a broad temporal window, and that, as a consequence, responses of barrel neurons are largely similar to those of thalamic neurons. Results are consistent with weaker feedforward inhibition in mouse barrels. Differences in thalamocortical circuitry between mice and rats may reflect mechanical properties of the whiskers themselves.

cortical circuits; thalamus; whiskers

SENSORY AREAS OF THE CEREBRAL cortex are strongly driven by thalamic inputs. Studies of visual and somatosensory systems offer compelling evidence for such feedforward models. Accumulating evidence suggests a common circuit motif of thalamocortical input to both excitatory and inhibitory neurons whose interactions alter or transform incoming sensory signals (Alonso and Swadlow 2005; Bruno 2011). Feedforward inputs establish initial cortical response tuning, whereas engagement of inhibitory neurons by thalamocortical inputs acts in conjunction with neuronal and circuit nonlinearities (Pesavento et al. 2010) to enhance response differentials between preferred and nonpreferred stimuli (Miller 2003; Miller et al. 2001). Thalamic inputs evoke short-latency excitation followed by inhibition, creating a limited temporal window for afferent signals to produce cortical spiking (Gabernet et al. 2005; Wehr and Zador 2003). Indeed, diverse evidence indicates that response tuning in thalamocortical circuits is strongly affected by thalamic response timing and firing synchrony (Blomquist et al. 2009; Bruno and Sakmann 2006; Cardin et al. 2010). It is likely that, within this overall operational framework, details of local circuitry reflect evolutionary differences in brain structure and function, as well as constraints imposed by the nature of afferent signals arising from different sensory systems in different species.

Thalamocortical processing in the rat whisker/barrel system is highly sensitive to thalamic population input timing (Pinto et al. 2003; Wang et al. 2010). Strong feedforward inhibition and local circuit dynamics create a brief time epoch, called a “window of opportunity” by Pinto et al. (see also Alonso and Swadlow 2005), for synchronous or near-synchronous thalamic firing to engage local networks of excitatory layer 4 barrel neurons before activity is damped by powerful inhibition. Such thalamic input signals, transmitted via populations of convergent thalamocortical neurons, are produced by whisker deflections that evoke the most robust firing of excitatory barrel neurons. As a result, cortical neurons are differentially sensitive to deflections of the principal (PW) vs. adjacent whiskers (AWs), deflection onsets vs. offsets, and high- vs. low-velocity movements. Developmental changes in thalamocortical response transformation in normally reared rat pups can be explained by a progressive elaboration of mechanisms that render barrel circuitry increasingly sensitive to thalamic response timing (Shoykhet and Simons 2008).

Whisker-related barrels are present in many species, being notably prominent in rodents (Woolsey et al. 1975). The whisker-to-barrel pathway thus provides a highly advantageous model system for establishing commonalities of thalamocortical processing. Perhaps even more importantly, comparative studies may identify species-related differences in circuit organization that could potentially serve as a basis for extrapolation to other, nonrodent species or even other sensory systems. Cellular neuroanatomical and neurophysiological data obtained from the two closely related species of mice and rats are quite similar, and, from a circuit perspective, their barrels are typically viewed as equivalent or nearly so. Nevertheless, barrels in rats and mice appear strikingly different (Welker and Woolsey 1974), reflecting differences in brain size and cortical packing density (Lee and Woolsey 1975). It is not known whether such gross morphological differences influence circuit function, or whether other factors, perhaps unrelated or only weakly related to gross morphology, do. For example, even casual inspection of whiskers in mice and rats reveals that they differ substantially in length and especially thickness. A recent study of whisker-evoked responses in mouse trigeminal ganglion neurons (Kwegyir-Afful et al. 2008) revealed substantial similarities with the rat, but also some subtle differences that could potentially affect information transfer in the whisker-to-barrel pathway.

Here we examine information processing in mouse barrels by recording responses of thalamic “barreloid” and cortical...
barrel neurons to the same types of whisker stimuli employed previously in rats. Similar analyses, including computer simulations, are used to characterize the thalamocortical response transformation, allowing for some direct comparisons with findings from rats. Mouse barrels are considerably smaller than rat barrels, perhaps reflecting less circuit complexity in the former (Welker and Woolsey 1974). Thalamocortical processing in the mouse may be similar to that observed in immature rats (Shoykhet and Simons 2008). We find that mouse barrel circuitry integrates thalamic inputs over a broad temporal window, and that responses of mouse barrel neurons more closely reflect those of thalamic neurons than is the case in rats. Results are consistent with less robustly driven inhibitory neurons and hence weaker feedforward inhibition in mouse barrels.

METHODS

Surgical Procedures

Care and use of the mice in the study were approved by the University of Pittsburgh IACUC. Twenty-three adult C57 male mice weighing 20–25 g, were used in this study. Surgical procedures have been previously described (Simons and Carvell 1989). Under isoflurane anesthesia (1.5%), a venous catheter was inserted in the external jugular vein for later administration of fentanyl and pancuronium bromide, and a tracheal cannula was inserted to maintain a clear airway. A second catheter was placed in the left femoral artery to monitor blood pressure.

Experiments for recordings from layer IV of the primary somatosensory cortex (SI) and ventral-posterior medial thalamus (VPm) were performed in different mice. Data were collected for layer IV recordings from 14 animals and from VPm in 9 animals. All surgical procedures were conducted using isoflurane anesthesia. In both cases, the dorsal surface of the skull overlying the right VPm or SI was exposed. For VPm recordings, a small craniotomy was centered 1.5 mm caudal to bregma and 1.5 mm lateral to the midline; for access to the barrel cortex the craniotomy was centered 1.5 mm caudal to bregma and 3.0 mm lateral to the midline. The dura remained intact in both thalamic and cortical experiments.

A steel post was fixed to the skull with dental acrylic for holding the animal’s head without pressure points and for allowing unrestricted access to the left face. Small stainless steel screws were used as reference ground and EEG electrodes. A dam around the craniotomy was constructed with dental acrylic, and saline was applied to the craniotomy to prevent drying of the brain surface. Following all surgical procedures, mice were moved to a vibration-isolated environment and allowed a recovery period of 2–3 h. To monitor blood pressure, heart rate, electrocorticogram and tracheal air-way pressure throughout the experiment. If normal physiological values could not be maintained, which was rare, or at the end of the experiment, the animal was administered a lethal dose of pentobarbital sodium (100 mg/kg iv) and perfused transcardially for cytochrome oxidase histochemistry. The brain was excised for histological analysis of the recording sites. Cortical tissue was examined in 60-μm-thick tangential sections reacted for cytochrome oxidase and counterstained for Nissl. Thalamic recording specimens were similarly stained but sectioned in the coronal plane.

Single-unit Recordings

Extracellular unit recordings were obtained with tungsten microelectrodes (3–7 MΩ at 1,000 Hz; Frederick Haer). Electrodes were advanced perpendicular to the cortical surface using a hydraulic microdrive. Whiskers on the contralateral face were manually deflected during electrode advancement to detect units with low or no spontaneous activity. Cortical recordings were obtained from identified layer IV barrels using microdrive readings and examination of tangential sections through the barrel field. Thalamic penetrations were examined to confirm that recording sites were within VPm, but recording sites were not reconstructed with respect to individual barrel-rows.

Waveforms from well-isolated and stable units were parsed from the analog record using an analog-to-digital converter at a sampling rate of 32 kHz and saved to disk using LabView. Unit waveforms were sorted off-line using custom-written software to verify that data from only one clearly identifiable unit were taken at a recording site. The software, also written in LabView, allowed for visualization of unit waveforms during the sorting procedure. Single units were identified using analyses based on the first two principal components of the spike waveform and on an interspike interval criterion. For cortical recordings, we obtained data only from units with initially negative waveforms. Units were classified by the time course of their waveforms into two groups (Bruno and Simons 2002; Simons 1978), regular-spike units (RSUs) and fast-spike units (FSUs). Cells were deemed to be FSUs if they had initially negative phases <0.175 ms total spike duration. Simple stimuli were used to study vibrissa responsive units in the rat and in the mouse trigeminal ganglion (see Discussion).

Stimulus Protocols

Standard protocol. Hand-held probes were used to identify each cell’s PW, defined as the whisker evoking the most robust response. For characterizing basic response properties of the cells, we positioned a multigate piezoelectric-based stimulator (Simons 1983) on the PW or one or more of the immediately AWs in the same row or arc. The stimulator was attached to the whisker 7 mm from the skin surface by inserting its distal 2–3 mm into a 30-gauge tube. The whisker was thus free to slide in and out of the tube as the whisker was deflected; the slight curvature of the whisker coupled with the relatively large deflection amplitudes ensured reliable movement of the hair. Ramp-and-hold deflections of 0.7-mm amplitude and having onset and offset velocities of ~125 mm/s and an intervening plateau duration of 200 ms were applied at interstimulus intervals of 1.5 s. Individual whiskers were deflected in eight directions (in 45° increments relative to the horizontal alignment of the whisker row). The 8 different stimuli were delivered in pseudorandom fashion, and 10 such blocks were used for a total of 80 stimuli. Similar stimuli were used previously to study vibrissa responsive cells in the rat and in the mouse trigeminal ganglion (see Discussion).

Velocity/amplitude protocol. Velocity and amplitude sensitivities of neurons were investigated by deflecting the PW using 600-, 300-, and 150-μm ramp-and-hold stimuli, having average onset (and offset) velocities of 10, 50, 100, 150, and 200 mm/s. For these stimuli, a shorter stimulator was used that could produce higher velocity deflections. The stimulator was attached ~5 mm from the skin surface. The
motion of the stimulator was calibrated with a photodiode device. Average onset velocity was measured over the entire movement phase of the deflection ramp. To overcome inertia of the stimulator and achieve the same average velocity for all stimulus amplitudes, the acceleration of the initial part of the smaller amplitude stimuli (300 and 150 μm) was slightly increased. Mechanical ringing was minimized using a Bessel-filter to smooth the trapezoidal ramp-and-hold waveforms. Deflections were delivered to the PW in each cell’s preferred direction, determined first using the multiangule stimuli described above. Stimuli were also delivered separately in the caudal direction for all cells. The 15 stimuli (5 velocities at 3 different amplitudes) were delivered pseudorandomly at an interstimulus interval of 1.5 s with 10 repetitions for each amplitude-velocity combination.

For the velocity/amplitude stimuli, we positioned the whisker in the stimulator so that it was immediately engaged by stimulus onset, even in the case of the lowest amplitude deflections. Because such engagement could not be ensured with return movements, particularly with low-amplitude deflections, we analyzed velocity/amplitude data only for stimulus onsets.

Data Analysis

Spike times were accumulated into peristimulus time histograms (PSTHs). Unless otherwise specified, all analyses were based on 1-ms binned spike times. Responses were quantified by taking spike counts within selected time intervals corresponding to prestimulus (spontaneous) activity and responses to deflection onset (ON response), plateau, and offset (OFF response). With the standard protocol stimuli, ON and OFF responses were highly transient, and a 25-ms response window was used for analyzing TCU, RSU, and FSU data. Plateau responses were calculated during a 100-ms period near the end of the steady-state deflection. For the velocity/amplitude stimuli, response durations varied considerably, particularly for TCUs, many of which fired throughout the duration of slow deflections. We therefore selected response windows separately for each stimulus by examining population PSTHs. Responses to the two slowest velocities (10 and 50 mm/s) lasted as long as 100 and 50 ms, respectively (for 600-μm deflections), whereas higher velocities evoked shorter responses (25–35 ms).

Statistical analyses were performed using Microsoft Excel and SPSS or the Excel add-in Analyse-It. Group comparisons among TCUs, RSUs, and FSUs were assessed with one-way analysis of variance (ANOVA) with the Bonferroni correction for multiple comparisons. We used Mann-Whitney U-tests for two-group comparisons, e.g., TCUs vs. RSUs. For assessing interaction between amplitude and velocity, we used two-factor ANOVA (SPSS). We used linear regression analysis to determine the correlation between stimulus velocity and response magnitude. In the text, data are reported as means and standard deviations; unless otherwise noted, graphical data are presented as median boxes denoting 25th and 75th quartiles and lines denoting maximum and minimum values.

Significant stimulus-evoked responses were defined as those having response magnitudes significantly exceeding prestimulus activity levels, computed from a 100-ms period preceding each stimulus. Cells were classified as either slowly adapting or rapidly adapting following criteria described in Simons and Carvell (1989). Briefly, cells were considered slowly adapting if they had firing rates during the latter 100 ms of the stimulus plateau that were statistically greater than spontaneous firing rates (t-test, P < 0.05, 1-tail). All other cells by default were classified as rapidly adapting.

Angular tuning properties of the cells were characterized by constructing polar plots from ON responses in the eight different stimulus directions. To quantify tuning, we computed a tuning index, calculated as the ratio of the spike count at the maximally effective angle to the spike count averaged over all eight directions. A cell that responds equally in all directions will have a tuning index of 1.0, whereas a neuron responding to deflection unequally in various directions will have an index >1.0 with a maximum of 8.0. For example, a cell that fired an average of 1.0 spike at only one angle has a response of 0.125 averaged across all eight angles and hence a tuning ratio of 1/0.125 = 8.0.

We separately classified individual cells into one of eight angular tuning categories using Dunnett’s test for multiple comparisons wherein we compared the mean response at the maximally effective deflection angle with each of the other seven angles. A highly tuned cell, in which the maximally effective angle was statistically larger than all other angles, has a tuning category of 7, and a nontuned cell, in which all responses are statistically equivalent, is a category 0 cell. This statistically based categorization avoids potential confounds related to the unit’s firing rate. The tuning index and tuning category measures are highly correlated (see RESULTS).

After Pinto et al. (2000), we computed a temporal contrast (TC) measure for thalamic population ON responses. This index uses the population PSTH to quantify initial population firing synchrony. TC is measured as the amount of time required for the sampled population to generate a fixed percentage of the total response magnitude (spike count). For example, TC10 is defined as the number of spikes contained in the first 10% of the total response divided by the amount of time (measured in 100-μs bins) required to generate those spikes. A rapidly developing population PSTH will have a higher TC value compared with a response that develops more slowly. Intuitively, the TC value approximates a measure of the initial slope of the PSTH.

Computer Simulations

We used computer simulations to compare thalamocortical response transformations in mice vs. rats. The neuronal network model was essentially that described in detail for TC transformations in rat barrels (Kyriazi and Simons 1993). It consists of 100 interconnected layer 4 cells: 30 inhibitory and 70 excitatory. Network activity is computed in 1-ms increments. Input consists of trains of action potentials prerecorded from many thalamocortical neurons individually, in many separate experiments, in response to whisker deflection stimuli. Simulated responses were based on this thalamocortical and feedback (within-barrel) excitation and on inhibition from the network’s simulated cells. The strengths of individual connections are set stochastically about mean and range values that differ for the various types of connections, e.g., TC to excitatory cells, excitation to excitation cells, inhibitory to excitatory cells, etc. If a presynaptic cell fired, it affected the voltage of all cells postsynaptic to it by amounts determined by each connection’s synaptic weight. An individual cell’s total input depended on its convergent inputs, and it, in turn, affected cells that it contacted, set by its divergence factor. Connectivity parameters for the rat and mouse models are listed in Table 1.

Each neuron integrates its inputs over time, where postsynaptic potential (PSP) decay rates were set differently for excitatory and inhibitory synapses, and the resulting intracellular voltages are passed through a sigmoid probability function whose slope is set by a “temperature” parameter for which a higher temperature yields a more gradual slope. A random number generator determines whether or not an action potential occurs. The model generates simulated spike responses that can be compared quantitatively with those from real neurons studied with the same whisker deflection stimuli. In the earlier version of the model, simulated responses of cortical neurons were brief and overly transient. Some of the parameters of the original rat model were adjusted to achieve more realistic ON and OFF response time courses than obtained previously. This involved 40% increases in the PSP decay constants combined with compensatory decreases in excitatory and inhibitory synaptic strengths, or weights. The changes implemented here had the effect of extending response times, while keeping overall response magnitude the same, thus creating more realistic population PSTHs. In addition, TC convergence and synaptic weight to smooth cells were changed so that we
Table 1. Model parameter values

<table>
<thead>
<tr>
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<th>Rat</th>
<th>Mouse</th>
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<tr>
<td><strong>Connectivity parameters</strong></td>
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<tr>
<td>Spiny cell number</td>
<td>70</td>
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</tr>
<tr>
<td>Smooth cell number</td>
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<tr>
<td>TC convergence to spiny</td>
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<td>12 ± 6</td>
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<tr>
<td>TC convergence to smooth</td>
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<tr>
<td>Divergence from spiny</td>
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<td>60 ± 30</td>
</tr>
<tr>
<td>Divergence from smooth</td>
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<td>40 ± 20</td>
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<tr>
<td>Spiny cell synaptic weight to spiny cells, mV</td>
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<tr>
<td>Spiny cell synaptic weight to smooth cells, mV</td>
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</tr>
<tr>
<td>Smooth cell synaptic weight to spiny cells, mV</td>
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</tr>
<tr>
<td>Smooth cell synaptic weight to smooth cells, mV</td>
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<td>−2.88</td>
</tr>
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| **Cell activity parameters** |        |         |
| Refractory period, spiny cells, ms | 4       | 4       |
| Refractory period, smooth cells, ms | 3       | 3       |
| Resting membrane potential (spiny, smooth), mV | −60.0   | −60.0   |
| Firing threshold (spiny and smooth), mV | −45.0   | −45.0   |
| Tau of PSPs evoked by TCUs, ms | 7       | 7       |
| Tau of PSPs evoked by spiny, ms | 7       | 7       |
| Tau of PSPs evoked by smooth, ms | 21      | 21      |
| Threshold function temperature spiny | 2.5     | 2.5     |
| Threshold function temperature smooth | 4.0     | 4.0     |
| Axon conduction times plus synaptic delays, ms | 2       | 2       |
| TCUs                   | 147    | 147     |
| Spiny, Smooth          | 147    | 147     |

TC, temporal contrast; PSP, postsynaptic potential; TCUs, thalamocortical units.

RESULTS

We recorded from a total of 85 neurons in VPm (TCUs) and 147 neurons in SI. Of the barrel units, 122 were classified as RSUs; the remainder as FSUs. In some experiments, we purposely tried to record FSUs; hence the relative proportion of RSUs and FSUs does not reflect the frequency of encountering them in unbiased recordings. Responses to the standard 8-direction protocol were examined in 46 TCUs, 63 RSUs, and 25 FSUs. Thirty-nine TCUs and 59 RSUs were studied using whisker deflections at 3 amplitudes and 5 velocities.

Barreloid and barrel neurons were well driven by small deflections of whiskers. When tested with manually held probes, responses in most cases were clearly transient and could be readily identified with an individual whisker that evoked the most robust responses. When necessary, we deflected an AW using the mechanical stimulator. The whisker evoking the strongest response (determined manually or with a stimulator) was identified as the PW. Histological reconstructions of cortical recording sites indicated that the so-defined PW almost invariably matched its corresponding anatomical barrel in the cortex. Ambiguities were associated with recordings near barrel boundaries. Mouse barrel fields contain only narrow septa, and it was not possible to distinguish between barrel and septal locations with our extracellular recordings. Thalamic recordings were not analyzed with respect to anatomically defined barreloids. However, the functionally defined topographical organization of PWs in VPm was virtually identical to that in rats and to the anatomy of the barreloids in both species.

We examined responses evoked by each cell’s PW and up to four of its immediately AWs using the standard deflection protocol. Figure 1, A, B, and C, shows population PSTHs of TCUs, RSUs, and FSUs to ramp-and-hold deflections. Higher resolution PSTHs for ON responses are shown in Fig. 2.

In all three populations, ON and OFF responses are abrupt and transient, with the TCU response decaying more slowly. TCUs are also notable for their high prestimulus (spontaneous) and PW-evoked firing rates, including elevated firing during the deflection plateau. With AW deflections, following a brief period of decreased firing after the ON response, plateau activity continues to increase until deflection offset. RSUs are less active and show minimal plateau activity, although, interestingly, in the case of AW deflections, plateau firing parallels the slow increase in TCU activity prior to response offset. FSUs, too, are noticeably less responsive than TCUs, unlike in the rat where FSUs are the most active of the three cell classes (Fig. 2). AW-evoked responses (Fig. 1, right) are considerably smaller in all three groups, and their earliest detectable population onset times are similar to those of PWs.

High-resolution PSTHs in Fig. 2 also include data obtained previously in our laboratory from rats. ON responses of mouse thalamic and cortical neurons begin earlier than those in rats. This likely reflects the smaller head and hence the shorter distance from the face to the thalamus in mice. Relative...
differences in response onset times of RSUs and FSUs vs. TCUs are slightly smaller in rats. Although the distance from thalamus to cortex is greater in rats, TC axons are probably of larger caliber, rendering overall TC conduction times faster in the rat. TCU, RSU, and FSU population responses in mice decay more slowly than those in rats, possibly reflecting less robust intrathalamic and intrabarrel inhibition (see below). Mouse RSU and FSU response profiles have two peaks. The earliest peak appears to correspond to an early peak in the TCU population PSTH. It is unclear what produces later RSU and FSU response peaks, although their presence in mice, but not in rats, may reflect weaker damping of late components of the mouse response (see below). Analysis of individual cells indicated that the mouse RSU profile reflects a heterogeneity of responses rather than a common two-peak response or separate populations having short- or long-latency responses. This was assessed by tabulating early- vs. late-response windows centered around the peaks in the population PSTH and plotting a histogram of the ratios of the spike counts. Ratios were normally distributed, indicating a mix of cells having peak responses at varying times. Similar analyses of early vs. late response components in rat RSUs revealed them to be considerably more homogeneous (see also Simons and Carvell 1989).

**PW Response Magnitudes**

TCUs were the most active of the three cell groups. Spontaneous activities, computed over a 100-ms epoch preceding stimulus presentation, were significantly larger for TCUs than RSUs (7.2 ± 4.7 Hz vs. 2.5 ± 3.8 Hz; \( P < 0.001 \)) and FSUs (4.5 ± 5.9, \( P = 0.004 \)). Spontaneous firing rates of FSUs were higher than those of RSUs, although statistically only at trend level (\( P = 0.07 \)). Figure 3A plots ON and OFF response magnitudes. ON responses, computed over 25-ms windows (see METHODS), were calculated separately for the preferred (maximally effective) direction and for the mean response averaged over all eight deflection angles. Maximum angle ON responses differed among the three cells types (ANOVA, \( P = 0.005 \)). TCU responses (2.6 ± 1.5 spikes/stimulus) were significantly larger than those of RSUs (2.0 ± 1.2 spikes/stimulus; \( P = 0.008 \)) and FSUs (1.7 ± 1.2 spikes/stimulus, \( P = 0.005 \)). FSU firing rates are smaller than those of TCUs. Strikingly, in contrast to findings in rats (Bruno and Simons 2002; Simons and Carvell 1989), RSU and FSU values did not differ (\( P = 0.19 \)). Similar results for the three cell groups were obtained for response magnitudes computed over all angles. Evoked firing rates of TCUs and RSUs are larger than those in rats. The finding that FSUs and RSUs have equivalent ON responses was unexpected. To avoid possible confounds due to dichotomizing units on the basis of waveform time course, we regressed evoked firing rate with duration of the initial phase of the action potential waveform, i.e., the negative component. Regression analyses showed that neither maximal angle ON responses (\( R^2 = 0.003, P = 0.60 \)) nor mean responses over all eight angles (\( R^2 = 0.01, P = 0.30 \)) were significantly related to
spike duration. Spontaneous firing rates were, on the other hand, inversely related such that units with shorter-duration potentials had higher prestimulus activity ($R^2 = 0.13, P < 0.001$), consistent with the background firing rates of units classified as FS being somewhat larger than those classified as RS. This latter relationship was unlikely to be due to cell damage and attendant increases in background firing, because damaged cells typically display increases in spike widths. In addition, we recorded only from units having initially negative waveforms, suggesting that the electrode tip was distant from the recorded neuron.

We computed plateau activity as the firing rate during 100 ms of the plateau phase of the stimulus (Fig. 3B). Plateau responses were calculated at each cell’s preferred angle, and a cell was considered to be slowly adapting if the evoked firing rate exceeded spontaneous levels (see METHODS). Fifty-six percent of TCUs, 22% of RSUs, and 44% of FSUs were classified as slowly adapting (Fig. 3B, right). The percentages of slowly adapting TCUs and RSUs are somewhat larger than those in rats (37 and 15%, respectively; Simons and Carvell 1989). The percentage of slowly adapting FSUs is similar between species. Plateau firing rates of the slowly adapting cells were adjusted by subtracting spontaneous firing (Fig. 3B, left). TCUs were the most responsive ($49.1 \pm 41.1 \text{ Hz}$), followed by RSUs ($22.3 \pm 18.2 \text{ Hz}$), and FSUs ($14.3 \pm 6.8 \text{ Hz}$). Although a higher

Fig. 2. Expanded (0.1-ms bin) ON-response population PSTHs. A: TCUs. B: RSUs. C: FSUs. Mouse PSTHs are from the PW data of Fig. 1. Rat PSTHs are taken from Simons and Carvell (1989). Ramp onset begins at the 5th ms for both mouse and rat data. The earlier response onset times in mouse probably reflect the shorter distance between face and cortex. PSTHs are not smoothed.

Fig. 3. PW-evoked responses magnitudes of mouse TCUs, RSUs, and FSUs. A: ON and OFF responses in spikes/stimulus evoked by the maximally effective (or best) deflection angle (max) and responses averaged over all 8 deflection angles (mean). Boxes show median and 25th and 75th percentiles, and lines show extreme values. B, left: plots firing rates (corrected by subtraction of spontaneous activity) during the plateau phase of the ramp-and-hold deflection for cells classified as slowly adapting. Right: bar chart shows percentages of slowly adapting cells.
percentage of FSUs was slowly adapting relative to RSUs, the lower net plateau responses are smaller due to the higher spontaneous firing rates of the FSUs (see above). In rats, FSU plateau firing rates are slightly higher than TCUs and approximately threefold larger than those of RSUs (Simons and Carvell 1989).

Maximum angle OFF responses differed among the cell types (ANOVA, \( P < 0.002 \)). TCU OFF response magnitudes (2.26 ± 1.21 spikes/stimulus) were significantly larger than those of RSUs (1.46 ± 1.00 spikes/stimulus, \( P = 0.003 \)) and FSUs (1.31 ± 1.04 spikes/stimulus, \( P = 0.001 \)). Similar findings were obtained for OFF responses taken over all eight angles. Previous studies in rat show that the relative sizes of ON and OFF responses differ among TCUs, RSUs, and FSUs (Kyriazi et al. 1994). Therefore, for each cell, we separately calculated OFF/ON ratios based on maximal angle responses and mean responses taken over all eight angles. Unlike in rats where OFF/ON ratios of RSUs are smaller (mean for all 8 angles = 0.65) than those of both TCUs (0.94) and FSUs (0.83), in mice mean values calculated across eight deflection angles are ~1.0 in all cell groups (Fig. 4A, ANOVA, maximum angle, \( P = 0.23 \); all 8 angles, \( P = 0.42 \)).

Spatial Receptive Fields

At least one AW was deflected for 38 TCUs (\( n = 114 \) AWs tested) and 55 RSUs (\( n = 186 \) AWs tested); AW data were obtained for only 3 FSUs (\( n = 9 \) AWs), and therefore FSU data are not considered in the following analyses. AW and PW responses were averaged over all eight angles. For comparison with a similar metric in rats, all AWs were included. We calculated a measure of receptive field focus by normalizing each AW response to that of its corresponding PW (Fig. 4B); a smaller value indicates a receptive field more tightly focused on the PW. AW/PW ratios were similar for TCUs and RSUs (0.23 ± 0.24 vs. 0.21 ± 0.23, \( P = 0.19 \)). In rats mean TCU values (~0.40) are larger and RSU values (~0.10) are smaller, yielding an approximate 4:1 TCU/RSU ratio (Shoykhet and Simons 2008; see also Bruno and Simons 2002).

We separately examined AW responses that were significantly greater than spontaneous firing. Significant AW responses were determined by considering the spontaneous activity of each cell as a Poisson process and calculating whether at least one bin of the ON response PSTH exceeded spontaneous firing using a 95\% confidence interval. A higher proportion of RSU AWs evoked a significant response (RSU: 127/186 = 68\%; TCU: 42/114 = 37\%). Notably, 96\% of RSUs had at least one significant AW response compared with 50\% of TCUs. RSU values are considerably smaller in rats (~35\% of RSUs have at least one significant AW), even though more AWs per PW were tested and broader criteria for defining significant AW responses were used; TCU values are larger in rat (~70\%; Shoykhet and Simons 2008).

For statistically significant AW responses, we examined maximum angle response magnitudes with and without subtractive correction for spontaneous firing. TCU magnitudes were larger than those of RSUs for uncorrected values (1.6 ± 1.2 vs. 0.9 ± 1.0, \( P < 0.001 \)); the latter are similar to those in rats using a similar metric (Simons and Carvell 1989). When corrected for spontaneous firing, TCU and RSU values were equivalent. Together, results indicate that TCU and RSU receptive fields are largely similar to each other in mice, whereas in rats RSU receptive fields are smaller than those of TCUs.

Angular Tuning

We quantified angular tuning for PW responses as the ratio of the maximum angle response to that of the mean response taken over all eight angles. Cells that are better tuned for a specific direction of whisker deflection have larger indexes. There were no significant differences in tuning among the three cell types (TCU: 1.64 ± 0.43, FSU: 1.71 ± 0.63, RSU: 1.65 ± 0.53, \( P = 0.33 \)). Similar results were obtained when we categorized units using a Dunnett’s test to compare the mean maximal angle response with the seven other responses (see Methods). Tuning categories were similar among TCUs, RSUs, and FSUs (Kruskal-Wallis test, \( P = 0.25 \)). Correlation analyses showed that tuning index and tuning categories were highly similar for TCUs, RSUs, and FSUs (all \( P \) values < 0.001).

**Fig. 4.** Three measures derived from PW responses. A: OFF/ON ratios. B: AW/PW ratios based on responses averaged over all 8 deflection angles for all AWs relative to their PWs. C: angular tuning ratios derived from PW ON responses. Conventions as in Fig. 3. RF, receptive field.
Tuning indexes for TCUs and RSUs are similar to those in rats (Shoykhet and Simons 2008). In rats and rabbits FSUs fire robustly at many deflection angles (Simons 1978; Swadlow and Gusev 2002), and rat FSU tuning ratios average ~1.30 (Lee and Simons 2004). Thus FSUs in mice are slightly more angularly tuned than in rats and are similar to RSUs.

**Velocity and Amplitude Sensitivity**

A previous study (Pinto et al. 2000) in rats revealed differences between TCUs and RSUs in their relative amplitude and velocity sensitivities. Here we similarly examined responses of mouse neurons to PW deflections of three amplitudes and five velocities (Fig. 5). Response magnitudes were calculated for each neuron in each cell’s best direction and in the caudal direction. TCUs display amplitude sensitivity (ANOVA; $P = 0.011$, best direction and $P = 0.015$, caudal direction). Larger deflections evoked larger TCU responses, except at the highest velocity. At low velocities, TCUs, as a population, fired throughout the actual whisker movement, consistent with the slowly adapting nature of many of the units (see above) and hence their sensitivity to static whisker displacement. Similar effects are observed in trigeminal ganglion cells (Kwegyir-Afful et al. 2008). The relatively constant number of TCU spikes per stimulus during the 300- and 600-$\mu$m deflections, and the apparent but nonsignificant decrease in response magnitude for the highest velocity, 600-$\mu$m movement, reflect the smaller response windows during which spike counts were summed for the higher velocity movements (see METHODS). Values for the 10- and 50-mm/s movements would be smaller relative to the higher velocities, if one calculated firing rates rather than total spikes.

In contrast to TCUs, RSU spike counts showed a significant effect of velocity at all three amplitudes (best direction: $R^2 = 0.66; P < 0.0001$; caudal: $R^2 = 0.63; P < 0.0001$). RSUs were sensitive to deflection amplitude (ANOVA; $P = 0.012$, best direction and $P = 0.019$, caudal direction), but pairwise comparisons determined that this was due only to a difference in response magnitude evoked by 150-$\mu$m vs. 600-$\mu$m deflections. Thus, when response magnitudes are examined, RSUs were less sensitive to amplitude and more sensitive to velocity than TCUs; this largely reflects the more transient nature of the RSU vs. TCU response, particularly with low-velocity movements.

**Thalamocortical Response Coding**

Responses of thalamic and cortical neurons to ramp-and-hold whisker deflections, such as those used here, are highly transient (e.g., Fig. 1), with the most robust responses being evoked by stimulus ramp onsets and offsets. With the same stimuli used here, responses of primary afferent neurons in the trigeminal ganglion are also short-lived, but detailed analyses reveal that onset deflection velocity and amplitude are encoded by different time periods, beginning as early as the first millisecond of the ON response (Kwegyir-Afful et al. 2008; see also Stüttgen et al. 2006). We therefore examined different time-related components of thalamic ON responses to determine which ones more strongly predict the magnitude of the cortical response. As done previously (Pinto et al. 2002), we...
correlated components of TCU ON responses evoked by 15 different velocity/amplitude deflections with responses elicited from barrel neurons by the same stimuli. The various deflection/amplitude combinations produced a range of TCU and RSU responses.

We first examined total response magnitudes, i.e., the full transient response, regressing the 15 velocity/amplitude response means for TCUs and RSUs from Fig. 5, A and C. RSU responses were weakly predicted by the TCU response (Fig. 6 A, \( R^2 = 0.24, P = 0.06 \)); the relationship is stronger if the outlier point at the lower right of the graph is eliminated (\( R^2 = 0.63, P = 0.0001 \)). Because RSU but not TCU response magnitude was well-correlated with stimulus velocity (Fig. 5), we then explored which aspects of the TCU response were most velocity sensitive and thus likely to provide a more relevant signal for the cortical circuitry. We used a measure of TC devised by Pinto et al. (2000; and see METHODS), calculating a TC index for 10–100% of the TCU population response in 10% increments. For the three different amplitudes, TCU TCs between 10 and 30%, corresponding to the early part of the VPm response, were best correlated with stimulus velocity (Fig. 6 B). TC10 correlates better with velocity than amplitude (Fig. 6 C). For example, for midrange velocities, thalamic TC10 values are actually higher for lower amplitude deflections. Correspondingly, thalamic TC10 also robustly predicts the RSU response (Fig. 6 D; \( R^2 = 0.73, P < 0.001 \)).

Figure 7 A shows the relationship between thalamic initial population firing rates at different velocities and RSU responses in mice and rats. We used TC10 firing rates for mice and TC40 rates for rats, corresponding to the strongest relationships between TC and velocity (see Fig. 6 B). For illustration purposes, only values associated with the lowest and highest velocities are plotted, and the points are simply connected by a straight line. Note that we tested velocities from 10 to 200 mm/s in mouse vs. 75 to 225 mm/s in the rat study by Pinto et al. (2000). A tripling of velocity in the rat produces an approximate doubling of RSU firing, whereas in mice a 20-fold velocity range is required to produce a similar change. A given TC initial firing rate produces a larger RSU response in mice, and these higher RSU firing rates are associated with lower deflection velocities. For equivalent deflection velocities, RSU firing rates derived from TC10 in the mouse are larger than those derived from TC40 in rats. Taken together, the findings indicate a more limited range of velocity sensitivity in mice, because low thalamic initial firing more robustly engages mouse barrel circuitry.

In mice the absolute change in TC10 firing rates is small over a 20-fold velocity range. Also, as noted above (Fig. 6 A, excepting the outlier), RSU total response magnitudes are well correlated with TCU total response magnitudes. These findings suggest a longer time window of integration in mouse vs. rat barrels. To illustrate this, we plotted RSU responses with TCU firing rates based on the first 5 ms of the thalamic response and on the first 25 ms of the thalamic response. Five milliseconds corresponds to the time required for the mouse VPm response to achieve \( \approx 10\% \) of its full spike count magnitude, i.e., TC10 occurs within the first 3–8 ms, depending on velocity. Twenty-five milliseconds approximates the longest common time epoch wherein both TCUs and RSUs are firing most robustly (see Fig. 2), even at the slowest deflection velocities; the 25-ms window also corresponds to the full response window in rats,

![Fig. 6. TCU-RSU firing and deflection velocity/amplitude. A: RSU spikes/stimulus vs. TCU spikes/stimulus from Fig. 5, A and C; legend in panel B. Note: two points for 300-µm deflections overlap. B: \( R^2 \) values of TCU response magnitudes vs. deflection velocity plotted as a function of TCU temporal contrast (TC) values in 10% increments at 3 deflection amplitudes and averaged over all amplitudes. Data are based on best-direction deflections. Data for rat are taken from Pinto et al. (2000). C: TC10 vs. velocity. D: RSU responses (spikes/stimulus) vs. TC10. Data are taken from 15 velocity/amplitude deflections at best and caudal deflection angles; note that several data points are overlapping.](http://jn.physiology.org/doi/10.1152/jn.00574.2012)
allowing for a direct comparison. Figure 7B illustrates that mouse RSU initial responses are indeed as strongly, or even better, predicted by TCU firing rates calculated over a large time window ($R^2 = 0.95$) as those calculated over just the very earliest component of the thalamic response ($R^2 = 0.73$).

We compared integration times in mice vs. rat barrels by calculating regression values for different time windows, each increasing by 5-ms increments from the onset of the thalamic population response (Fig. 7C). For the rat, analyses were based on data from the study of Pinto et al. (2000). Mouse and rat data are divergent, with stronger predictions with longer time windows in the mouse and weaker predictions in the rat. The analyses suggest that mouse barrel circuitry is less sensitive to the precise timing of thalamic inputs, with temporal summation able to occur over a longer time period.

Simulations

Results from the unit recordings suggest that, unlike rat barrel circuitry, mouse barrels integrate input signals over longer time periods, yielding cortical responses that on average more closely reflect the thalamic input. To explore possible circuit mechanisms that could account for such a difference, we used a previously developed network model of rat barrel circuitry (see METHODS). Input to the model consisted of thalamic spike trains from 45 TCUs studied with the standard deflection protocol; 3,600 stimulus presentations were used (45 cells × 10 blocks of 8 directions). The input generated a high enough density and variation of input spikes that no smoothing was needed.

We began by simply using the existing rat model. When we used mouse thalamic data as input to it, simulated RSU responses were smaller than those of real mouse RSUs (see Fig. 9A). As described in METHODS, we varied only the anatomical parameters of convergences and synaptic strengths. With this restriction, we found that the only way to produce realistic mouse RSU stimulus-evoked response magnitudes and PSTH shapes, as well as spontaneous activity levels, was to reduce the total thalamic synaptic input (number and weight of TC synapses) onto modeled FSUs, along with a slight increase in the effective strength of RSU contacts onto FSUs (Fig. 8). In the rat model the thalamus provides 64% of the total excitatory synaptic input (number and weight of TC synapses) onto modeled FSUs, whereas in the successful mouse model thalamic input provides 32%. In essence, network inhibition was thus shifted from predominantly feedforward to feedback (or recurrent). These changes decreased FSU firing and led to the larger OFF/ON response ratios and more prolonged response time courses found in mouse. The ratio of feedback, intracortical drive to feedforward, thalamic drive is measured by a quantity we call “tension” (see Kyriazi and Simons 1993). Compared with the rat model, the mouse model has four times the inhibitory tension and slightly less excitatory tension. To maintain appropriate levels of network inhibition in the face of decreased FSU firing, the strengths of inhibitory synapses onto excitatory and inhibitory cells were increased.

We compared response magnitudes of simulated ON and OFF responses evoked using the standard deflection protocol and taking the average over all eight deflection angles (Fig. 9). With this stimulus, the initial slopes of thalamic population OFF responses are more gradual than those of ON responses, resulting in disproportionately small RSU OFF vs. ON response magnitudes (see Kyriazi et al. 1994). The mouse and rat models, using corresponding mouse and rat TCU input, faithfully reproduced these response magnitudes. When the mouse model was activated by rat TCU input, simulated RSU ON and OFF responses were larger than normal rat values (data points...
above the unity line in Fig. 9A). OFF responses increased disproportionately more. These changes reflect the wider window of opportunity in mouse. Conversely, when the rat model was activated by mouse TCU input, ON and OFF responses were smaller than normal mouse values, reflecting more rapid closure of the window of opportunity. Again, OFF responses were affected more, but in this case they were disproportionately smaller. The converse effects were observed for modeled FSUs (Fig. 9B), consistent with their receiving weaker feedforward drive in mice.

We tested the model further by comparing real and simulated RSU ON response magnitudes evoked by the 15 velocity/amplitude stimuli. For best angle deflections, real and simulated responses were similar. Simulated responses were slightly smaller than real responses by a mean of 0.141 spikes/stimulus, which corresponds to an 8.0% error. Similar results were obtained with caudal stimuli (0.167 spikes/stimulus, 10.2% error). The smaller simulated vs. real RSU responses likely reflects the limited size of the data set used for thalamic inputs (39 units with only 10 trials at each velocity/amplitude) and hence more irregular input that affects temporal summation in the integrate-and-fire neurons. When we combined best- and caudal-angle deflections, thus almost doubling the number of input units, the error was reduced to 2.0%.

When mouse thalamic data files were used as input to the rat model, simulated responses were considerably smaller relative to the mouse model, with mean differences of 0.845 (best angle) and 1.042 (caudal) spikes per stimulus. As noted in METHODS, attachment of the stimulator to the whisker ensured that the initial movement immediately engaged the hair. With stimulus offset, the whisker could be engaged at various times, depending on its thickness and curvature; with very small stimuli, the whisker might not be directly engaged at all upon stimulus offset, returning to its neutral position only passively. Because each cell was recorded separately, the only synchronizing effect on the thalamic population response is the stimulus. Variations in whisker engagement, especially with small deflections, would have the effect of desynchronizing the thalamic responses. The model is sensitive to such synchrony, especially in the case of OFF responses (Fig. 9). Consistent with this, simulated RSU responses to deflection offsets were nearly uniformly smaller than expected for both best-angle and caudal deflections (mean errors of ~35%).

The modeling analyses demonstrate that, as a result of different strengths of feedforward inhibition, simulated rat and mouse barrels have different sensitivities to slowly rising inputs, e.g., OFF responses, such that mouse barrels are more likely to continue to respond to late arriving inputs. Indeed, the real data of Fig. 7C indicate that, unlike in rats, later components of the thalamic input signal contribute to the RSU
response. We explored this further using the Pinto et al. (2000) reduced model. Parameter values for the rat model are based directly on the integrate-and-fire model (above). We made exactly the same changes to the mouse reduced model that we had made for the large-scale spiking model, e.g., reducing TC synaptic strengths to simulated FSUs. We then examined both models’ responses to input “triangles” in which the height (amplitude) and base (duration) remained constant, varying only the onset and offset slopes (Fig. 10). Values for the input waveforms correspond to average TCU responses in spikes per 1-ms bin and were chosen to approximate firing rates of real TCUs to fast stimulus onsets (Fig. 1).

As reported previously (Pinto et al. 1996) with rapidly rising inputs (Fig. 10A), both excitatory and inhibitory cell populations in the rat model respond robustly to ramp onset followed by rapid declines in firing; the strongly damped nature of the response reflects activity in the inhibitory population. With slowly rising inputs (Fig. 10B), network activity is clearly dominated by the inhibitory population. As the inhibitory response mirrors the onset ramp, the excitatory population becomes progressively less active. By contrast, in the mouse model, excitatory and inhibitory populations fire more similarly to each other for both the steep and shallow input triangles (Figs. 10, C and D). With the former, the firing of both populations is truncated shortly after ramp onset, reflecting the effects of the modeled inhibitory population. However, with the slowly rising ramp, the mouse excitatory population responds comparatively well. Indeed, firing in both simulated cell populations continues and actually increases during the onset ramp. Interestingly, a similarly slow rising population response occurs in TCUs during the plateau phase of AW deflections and the RSU population reflects it (Fig. 1). That model neurons remain responsive to late arriving inputs indicates further that firing in networks having relatively weak feedforward inhibition is determined by input response magnitudes calculated over long time epochs (Figs. 7, B and C).

DISCUSSION

Here we investigated thalamocortical response transformations in the mouse whisker-to-barrel system by examining a number of response properties of thalamic VPm neurons and cortical barrel neurons. We used similar approaches, including nearly identical whisker deflection protocols, that we have used previously in rats to define important operational features of thalamocortical circuitry. Spontaneous and evoked responses of mouse RSUs were on average more robust than in the rat. Although extracellular recordings are biased to responsive cells, we used unit sampling and recording procedures virtually identical to those in our rat studies. Importantly, differences in response magnitudes between mice and rats are paralleled by a number of other findings related to response timing that are unlikely simply to reflect unit sampling procedures.

Quantitative assessments revealed that RSU receptive fields in the mouse are largely similar to those of TCUs. This contrasts

Fig. 10. Simulated responses of excitatory and inhibitory cell populations to artificial thalamic inputs consisting of equal amplitude and duration triangles having different onset slopes. A and B: rat model. C and D: mouse model. E and F: input. Parameters for the steep-sloped ramp in E were chosen to evoke peak excitatory population firing rates that approximate those observed in real RSUs. Insets in A and C show magnified onset responses. Simulations performed using the reduced Pinto model (see text).
with findings in adults where receptive fields of barrel RSUs are smaller than those of their thalamic inputs, even in functionally connected TCU-RSU pairs (Bruno and Simons 2002). AW/PW ratios in mice are more similar to those in young, e.g., 2-wk-old, rats (Shoykhet and Simons 2008). In mouse barrels, responses evoked by AW deflections were, at the population level, similar in onset time to PW responses, suggesting that, as in rats, at least the early component of AW responses in mouse barrels reflects direct thalamic inputs (Bruno and Simons 2002; Kwegyir-Afful et al. 2005; Roy et al. 2011).

In VPm, both whisker-evoked ON and OFF responses are more robust in mice than rats. TCU ON responses are initially smaller than those in rats, but they persist for a longer time, yielding larger overall response magnitudes (Fig. 2A). Firing rates during a sustained deflection, e.g., the stimulus plateau, are also higher in mice; a larger proportion of mouse TCUs are slowly adapting than in rat. As a consequence of their greater static position sensitivity, TCUs, as a population, fire throughout slow-velocity deflections. It is unlikely that the greater overall responsiveness of mouse TCUs simply reflects inputs from primary afferent neurons that fire more robustly than those in rats. Percentages of slowly adapting trigeminal ganglion cells are equivalent between the two species as are response magnitudes of slowly adapting cells (Kwegyir-Afful et al. 2008). Responses of rapidly adapting cells are smaller and shorter in duration than those in rats; this could account for the slightly smaller initial response of mouse VPm neurons to deflection onset (Fig. 2A). One possibility is that intrathalamic inhibition, mediated by the thalamic reticular nucleus, is weaker in mice vs. rats. In this regard, it may be significant that, in contrast to mice and rats (see Harris and Hendrickson 1987), higher-order species like cats and primates have local inhibitory interneurons within the ventral posterior thalamus (Ralston 1983), suggesting a possible phylogenetic trend toward greater thalamic inhibition in species having larger and more complexly organized brains. Detailed comparative mouse vs. rat studies of neurons in nucleus reticularis thalami (Cox et al. 1997; Hartings et al. 2000) and also of afferent cells in the brainstem principal sensory nucleus (Minnery et al. 2003; Minnery and Simons 2003) might provide interesting insights into the evolution of thalamic processing circuits.

A striking and unexpected finding is that, in the mouse, FSUs (presumed inhibitory barrel cells) have stimulus-evoked responses that are much smaller than those in the rat. Stimulus-evoked FSU firing rates are equivalent in magnitude to or smaller than those of presumed excitatory neurons (RSUs) and considerably less robust than those of TCUs; in rats, FSUs have higher evoked firing rates than both RSUs and TCUs. In rats, FSUs are broadly tuned for deflection angle, and their AW responses are larger than those of RSUs. FSUs in mice are more angularly tuned than FSUs in rats, and in this respect they are more similar to mouse RSUs. We did not assess AW responses of FSUs in the present study, but a straightforward prediction is that their receptive fields are more focused on the PW than is the case in rats. A second prediction is that between-whisker inhibition (e.g., Simons and Carvell 1989) should be less robust in mouse barrel neurons, and, because of less robust thalamic inhibition, perhaps in mouse barrelloid neurons as well (see above).

In thalamocortical circuits, high FSU firing rates are thought to reflect intrinsic properties of FS interneurons, as well as their receipt of convergent synaptic inputs from large numbers of strongly active TCUs (Bruno and Sakmann 2006; Cruikshank et al. 2007). In rat barrels in vivo, functional connections are more likely to be observed between TCUs and FSUs than between TCUs and RSUs (Bruno and Simons 2002), and in vitro, thalamic stimulation is more likely to evoke spikes from FSUs than RSUs (Porter et al. 2001). It is possible that parvalbumin-positive barrel neurons (FS cells) are biophysically dissimilar in mice and rats and/or that strengths of individual thalamic synapses onto them differ. For example, weaker electrical coupling or lower input resistances could diminish whisker-evoked FSU responses and hence their damping effects in the barrel network (Gibson et al. 1999; Pesavento et al. 2010). Such properties are represented in our models by cell-type-specific firing functions, which we explicitly chose to hold constant when comparing simulated mouse and rat data.

Absent detailed cross-species comparisons at the cellular level, however, it is useful to consider that differences in thalamocortical response transformations in mice vs. rats may be related to differences in connectional anatomy. This would not be surprising in light of pronounced differences in the sizes and cellular densities of barrels in the two species. In this regard, present results are consistent with the idea that FS neurons in mouse barrels receive fewer TC synaptic inputs converging from different TCUs or from multiple contacts from individual TCUs; fewer TC inputs would render mouse FSUs comparatively less responsive to their thalamic inputs (Bagnall et al. 2011). If so, it is unlikely that less thalamic input onto individual FS neurons would be due to a substantially smaller average size of dendritic spread in mouse vs. rat FS neurons. Notably, morphometric comparisons suggest that an average smooth-den- drite barrel cell (presumed inhibitory neuron) in the mouse has a dendritic territory that actually encompasses a larger proportion of a barrel and hence of the total thalamocortical termination zone within it (Simons and Woolsey 1984). Despite the larger coverage, inhibitory neurons in mouse barrels may receive fewer total thalamocortical synapses.

In rats, strong feedforward inhibition renders excitatory barrel neurons sensitive to high- vs. low-velocity whisker deflections (Pinto et al. 2000; Wilent and Contreras 2005). Such stimuli evoke high initial firing synchrony or near-synchrony among VPm neurons (Temereanca et al. 2008; Temereanca and Simons 2003; Wang et al. 2010). As a consequence, rat RSU responses are better predicted by VPm population firing rates within the first few milliseconds of the thalamic response than the total number of spikes comprising the full thalamic response. Decreases in thalamic firing synchrony due to stimulus adaptation is accompanied by a disproportionate decrease in the cortical response to low-velocity deflections and hence increased velocity discriminability (Wang et al. 2010). Because in rats deflection velocity is strongly related to thalamic initial population firing rates, whereas deflection amplitude is better represented by thalamic total response magnitude, ON responses of rat RSUs are determined by deflection velocity, not amplitude. Feedforward inhibition also renders rat barrel neuron responses more transient than those of their thalamic inputs, e.g., Fig. 2. Response transformations are qualitatively similar in mice. RSU response magnitudes are more dependent on deflection velocity

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than amplitude, and ON and OFF responses are more transient than those of TCU s. However, in mice, RSU responses are longer lasting, and for a given thalamic initial population firing rate responses of mouse barrel RSUs are larger. Overall, responses of mouse barrel neurons look quite similar to thalamic input.

Our findings are consistent with weaker thalamocortical feedforward inhibition in mice. Numerous studies have indicated that feedforward inhibition is a critical feature of thalamocortical circuitry in the whisker system in several species (Bruno 2011; Swadlow 2002). In vitro studies indicate key similarities in rats and mice (Cruikshank et al. 2007, Gabernet et al. 2005; Sun 2009), although it is unclear how circuit features such as feedforward inhibition compare quantitatively. Our extracellular recordings do not provide any indication of the relative proportions of FS and RS barrel neurons. Moreover, it is unclear whether mouse and rat barrels differ substantially with respect to the relative numbers of excitatory and inhibitory cells and the extent of their interconnectivities. Our modeling, in which we held constant the relative proportions of excitatory and inhibitory neurons, is consistent with the hypothesis that the wider window of opportunity in mice reflects their having less strongly driven FSUs.

Previous modeling studies have shown that networks with strong thalamocortical activation of inhibitory neurons capture, and predict, firing rates of RSUs and FSUs to a variety of whisker stimuli in rats (Kyriazi and Simons 1993; Pinto et al. 1996). In the present study, we found that such a network could capture mouse RSU and FSU response magnitudes only when feedforward inhibition was reduced. We focused on the transformation of ON and OFF responses, because they are easily assessed and their relative sizes differ for thalamic and barrel neurons. VPm OFF responses in mice as in rats have lower initial population firing rates than ON responses. The mouse model, which was tuned to capture mouse RSU firing, poorly reproduced OFF responses evoked by rat TCU s. With rat inputs to the mouse model, simulated RSU responses were too large, especially those of OFF responses. Conversely, with mouse inputs to the rat model, OFF responses were disproportionately small. Moreover, simulated mouse RSUs fired much more robustly to slowly increasing and hence more later arriving inputs. These findings indicate that cortical responses evoked by slowly developing thalamic responses are less strongly suppressed or damped in the mouse vs. the rat network. Taken together, real and simulated data indicate that the window of opportunity for thalamic signals to engage excitatory barrel circuitry is wider in mice. As a result, response transformations are less robust, with responses of mouse RSUs being more similar to those of their TCU inputs.

In mice, as in rats, thalamic TC, a measure of population initial firing rates, reflects deflection velocity better than the total number of spikes in the variable length thalamic response. Although thalamic cells tend to have larger total response magnitudes with larger whisker deflections, TC is unrelated to deflection amplitude. Because barrel circuitry in both species is sensitive to thalamic firing synchrony or near-synchrony (see also Roy and Alloway 2001), albeit less so in mice, RSU responses are dependent on deflection velocity. Interestingly, mouse barrel circuitry appears to have a more limited operational range. Over similar deflection velocities, average RSU responses in mice range from −1.25 spike/stimulus to 2.20 spikes/stimulus, whereas those in rats range from −0.2 to >2.0 spikes/stimulus (Lee and Simons 2004). With slow deflection velocities comparable to those used here in mice, e.g., 10–75 mm/s, in rats the slope relating TC (and velocity) to RSU firing becomes considerably steeper (Pinto et al. 2003). Findings suggest that barrel circuit operations may be more linear in mice.

Velocity sensitivities of primary afferent neurons differ between mice and rats. For comparable ranges of deflection velocity, firing rates of trigeminal neurons vary over a narrower range in mouse vs. rat. This difference likely reflects mechanical properties of the whiskers and facial tissue (Kwegyir-Afful et al. 2008). For example, in mice both the whisker hairs themselves, which are considerably thinner than those in rats, and mystacial-pad facial tissues may be more compliant and less able to transfer small differences in force to sensory receptors within the follicle.

Our analyses of thalamocortical response transformations are based on comparisons of thalamic and cortical responses to identical whisker deflections. Thus our findings cannot simply reflect species-related differences in the firing of trigeminal ganglion cells. Nevertheless, when comparing mice and rats, it is intriguing that lower velocity sensitivity of the sensory periphery in the mouse parallels reduced velocity sensitivity of the thalamocortical circuit of the whisker-to-barrel pathway. This correspondence is consistent with the view that phenotype robustly determines the organization of central somatosensory circuits. Anatomically, cortical somatotopic maps reflect the spatial pattern and density of peripheral nerve innervation of a particular region of skin (Woolsey 1978). Present findings suggest that for a given species the functional characteristics of the sensory periphery strongly determines central circuits and the operations they perform on sensory input. In this regard, the development of feedforward inhibitory circuitry, including intrinsic FS cell properties, depends on whisker experience (Chittajallu and Isaac 2010; Sun 2009), indicating that this circuit is plastic and, although conserved evolutionarily, may vary quantitatively among species and cortical areas. The peripheral-central relationship likely affects behavior in a species-related fashion as well. Recent behavioral evidence demonstrates that movement velocity is the critical stimulus feature underlying the ability of rats to distinguish among vibratory stimuli (Adibi et al. 2012, see also Wang et al. 2010), and it is likely that velocity sensitivity underlies texture discrimination as well (Hipp et al. 2006). Using comparable behavioral paradigms, it should be possible to test the hypothesis that mice are less able than rats to discriminate differences in whisker stimuli having features that are strongly related to deflection velocity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
AUTHOR CONTRIBUTIONS


REFERENCES