Processing in layer 4 of the neocortical circuit: new insights from visual and somatosensory cortex

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Recent experimental and theoretical results in cat primary visual cortex and in the whisker-barrel fields of rodent primary somatosensory cortex suggest common organizing principles for layer 4, the primary recipient of sensory input from the thalamus. Response tuning of layer 4 cells is largely determined by a local interplay of feed-forward excitation (directly from the thalamus) and inhibition (from layer 4 inhibitory interneurons driven by the thalamus). Feed-forward inhibition dominates excitation, inherits its tuning from the thalamic input, and sharpens the tuning of excitatory cells. Recurrent excitation enhances responses to effective stimuli.

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Abbreviations
EPSP	excitatory post-synaptic potential
FS	fast-spiking
GABA	γ-aminobutyric acid
IPSP	inhibitory post-synaptic potential
LGN	lateral geniculate nucleus
LTS	low-threshold spiking
RF	receptive field
S1	primary somatosensory cortex
V1	primary visual cortex

Introduction
The cerebral cortex has a stereotyped six-layer structure (reviewed in [1]). 'Feed-forward' inputs to layer 4 of the primary sensory cortex come from the thalamus and represent the sensory periphery. Layer 4 cells project to layers 2/3, which in turn provide feed-forward input to layer 4 of the next higher cortical area and to deep layers. Deep layers then provide feedback to layers 2–4 and the thalamus as well as output to non-thalamic subcortical structures.

In order to understand the computations being performed by the cortex, we need to understand the nature of the processing undertaken by each layer. A natural starting place is layer 4, the layer in which sensory input first arrives. In recent years, studies in cat primary visual cortex (V1) and rodent primary somatosensory cortex (S1) have converged on intriguingly similar pictures of the processing taking place in cortical layer 4. These pictures suggest that, as befits its position, the response tuning of layer 4 cells is largely determined by feed-forward input, including feed-forward inhibition (inhibition from interneurons driven by the thalamus) as well as feed-forward excitation (directly from the thalamus). In both systems, the inhibition dominates, so that a cell can only be excited by stimuli that cause the effects of feed-forward excitation and inhibition to be separated in time; concurrent engagement of the two yields a net inhibition. Neurons providing feed-forward inhibition follow the tuning of thalamic inputs, and tighten the tuning of excitatory cells by eliminating responses to stimuli that evoke concurrent inhibition and excitation. Feed-forward inhibition and recurrent excitation are all evoked locally, from V1 cells preferring nearby orientations and from S1 cells preferring the same whisker. Whereas the feed-forward input establishes initial response tuning, local recurrent excitation and neuronal non-linearities (e.g. spike threshold) enhance responses evoked by preferred versus non-preferred stimuli.

In this article, we review the evidence leading to these converging pictures, along with countervailing evidence that renders these pictures still controversial. We also highlight some remaining differences between the pictures arising from the two systems.

Layer 4 of cat V1
Orientation tuning and its contrast invariance
Cells in layer 4 of cat V1 are predominantly simple cells: cells with receptive fields (RFs) consisting of aligned, alternating ON (light-preferring) and OFF (dark-preferring) subregions [2–4]. Sub-regions share a common axis of elongation, which defines each cell's preferred orientation — the orientation of a light/dark edge that best drives the cell. Afferents from the lateral geniculate nucleus (LGN) form patterns matching the cell's subregion structure: ON-center afferents have RF centers overlying ON subregions, and OFF-center afferents similarly overlie OFF subregions [5,6] (Figure 1a). We will frequently refer to 'thalamic input tuning', by which we mean the net tuning of the patterned set of LGN input received by a simple cell.

The degree to which feed-forward excitation determines a simple cell's response properties has been the subject of great controversy [7,8]. A key insight comes from the invariance of orientation tuning with changes in stimulus contrast (the magnitude of light/dark differences in the stimulus relative to its mean luminance [9,10,11••]; Figure 2). As explained in the Figure 1 legend, this invariance demonstrates that the arrangement of LGN inputs alone is not sufficient to explain simple-cell orientation tuning.

Figure 1

LGN inputs to simple cells and the problem of contrast invariance of orientation tuning. **(a)** Blue lines show an idealized simple cell receptive field: the solid oval in the center represents an ON-subregion, dashed subregions to either side represent OFF-subregions. Green circles represent the receptive field centers of the LGN cells found to connect to the simple cell: solid circles, centers of ON-center inputs; dashed circles, centers of OFF-center inputs. Simple cell receives input from ON-center LGN cells with centers overlying its ON-subregions, and from OFF-center LGN cells with centers overlying its OFF-subregions. Composite data from [6]. **(b)** and **(c)**: the problem of contrast-invariant orientation tuning. (b) A dim vertically-oriented flash covering the ON-subregion (red rectangle) will weakly excite the ON-center inputs with underlying centers. (c) A bright horizontally-oriented flash (red rectangle) will strongly excite the

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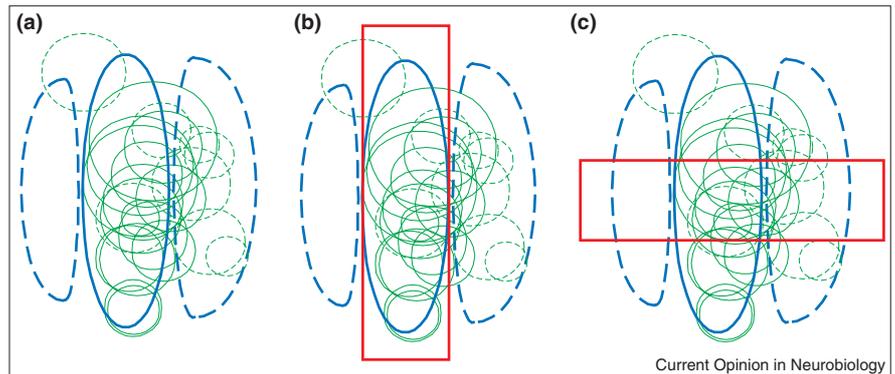
subset of ON-center inputs with underlying centers, and will suppress the OFF-center inputs with underlying centers. Excited cells can greatly increase their firing rates, to 100 Hz or more compared to spontaneous rates of 10–15 Hz, while suppressed cells can only decrease their rates to 0. Accordingly, even if the number of

suppressed OFF-center inputs were equal to the number of excited ON-center inputs, the bright orthogonal bar would yield a net positive LGN input. Thus, the two stimuli can be arranged to give the same total pulse of LGN input. Yet a typical simple cell will respond to the dim vertical flash and not to the bright horizontal flash.

Antiphase inhibition

A recent model [12], however, proposes that consideration of feed-forward inhibition along with feed-forward LGN excitation suffices to explain the contrast–invariance of orientation tuning and a variety of other response properties. To understand this proposal, we need first to define some terms. We refer to two simple cells of the same preferred orientation as having the same phase if, in the region in which their RFs overlap, their ON and OFF subregions overlie. We refer to two such neurons as having opposite phase or being antiphase to one another if, in the region of coincidence, ON-subregions of one intersect OFF-subregions of the other.

Troyer *et al.* [12] were inspired by intracellular recordings demonstrating: the inhibition and excitation received by a simple cell have similar tuning, with both maximal at the preferred orientation ([13,14••]; LM Martinez *et al.*, *Soc Neuro Abstr* 1998, **24**:766; LM Martinez *et al.*, unpublished data); but that inhibition and excitation are evoked by stimuli of opposite light/dark polarity [14–16, but see 17], that is, in an ON-subregion, light evokes excitation and dark evokes inhibition, while in an OFF-subregion dark evokes excitation and light evokes inhibition. In short, the RF of the inhibition is antiphase to the RF of the excitation. Together these findings inspired a circuit model [12] in which inhibitory cells project to cells of similar-preferred orientation but opposite phase, whereas excitatory cells project to cells of similar-preferred orientation and phase (Figure 3). A key feature is that the feed-forward (from interneurons driven by the LGN) antiphase inhibition is stronger than the feed-forward LGN excitation; this is consistent with the finding that an electric shock to the LGN, which indiscriminately activates both feed-forward excitation and inhibition, yields a net strong inhibition in the cortex [18].

This strong antiphase inhibition solves the problem posed in Figure 1. A bright bar orthogonal to the preferred orientation will equally excite both the excitatory LGN input to a cell and its antiphase feed-forward inhibition. Because the inhibition dominates, the cell will not fire. More generally, antiphase inhibition achieves contrast-invariant

Figure 2

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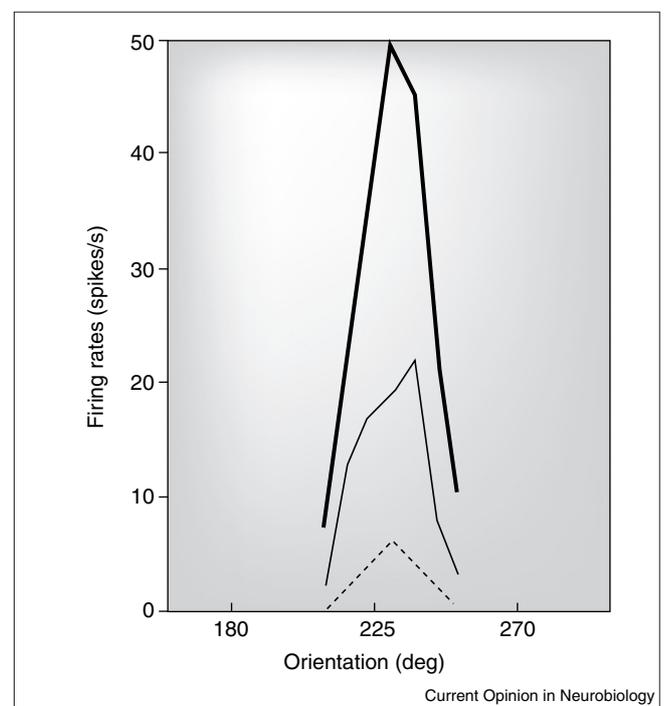
An example of contrast-invariant orientation tuning. Orientation tuning curves of a simple cell obtained with drifting sinusoidal gratings of three different contrasts (5% contrast, dashed line; 20% contrast, thin solid line; 80% contrast, thick solid line). Adapted with permission from [9].

Figure 3
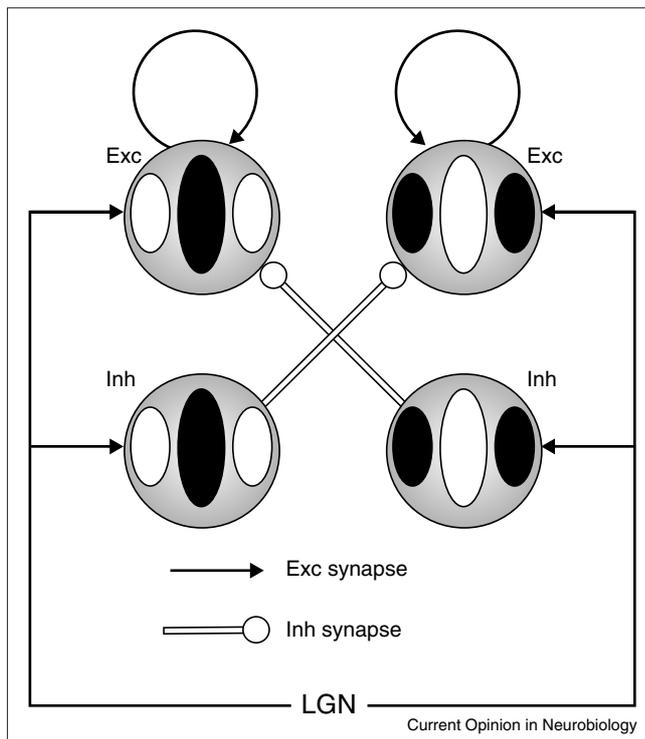
Cartoon of the model circuit for simple cells in V1 layer 4 proposed in [12]. Gray circles represent RFs of two excitatory (exc) neurons and two inhibitory (inh) neurons; white represents ON-subregions, black represents OFF-subregions. The four RFs are meant to be centered at the same retinotopic point. Excitatory cells receive both feed-forward LGN excitation corresponding to their RFs and antiphase feed-forward inhibition. Excitatory cells also provide recurrent excitation to other cells of similar preferred orientation and phase. In addition, excitatory-to-inhibitory and inhibitory-to-inhibitory connections may exist, following the scheme that excitatory cells tend to connect to cells with similar preferred orientation and similar phase while inhibitory cells tend to connect to cells of similar preferred orientation but opposite phase.

orientation tuning [12]. For a stimulus to excite a cell, it must excite the cell's LGN inputs much more strongly than it excites antiphase inhibition. This can only be achieved by a narrow range of orientations around the preferred, and this range stays invariant under changes of stimulus contrast. Note that this model requires that antiphase inhibition be evoked even by stimuli orthogonal to the preferred. That is, the feed-forward inhibition has tuning similar to that of the total thalamic input to a simple cell: it responds to all orientations, although it is driven best by the preferred orientation. Feed-forward inhibition mirrors thalamic input tuning and sharpens tuning of excitatory cells. This model circuit also includes recurrent excitation among cells of similar orientation and phase preference. This serves to amplify responses to effective stimuli without altering tuning.

Feed-forward inhibition can also account for the temporal frequency tuning of cortical cells [19•], which cuts off at lower frequencies than LGN tuning. Furthermore, it

explains a number of contrast-dependent nonlinearities ([20•]; Lauritzen TZ, Krukowski AE, Miller KD, *Soc Neuro Abstr* 2000, **26**:1967; Lauritzen *et al.*, unpublished data) that had previously been proposed to require 'normalizing' inhibition derived equally from cells of all stimulus preferences [21]. One such nonlinearity is cross-orientation inhibition, the reduction of a response to a preferred-orientation stimulus by simultaneous presentation of an orthogonal stimulus. This arises from antiphase inhibition evoked by the orthogonal stimulus in the local circuit; there is no need to invoke inhibition from different cells preferring the orthogonal orientation. In sum, feed-forward inhibition promises to provide a unified account of classical RF properties of simple cells, although many response properties such as direction selectivity, end-stopping, and beyond-the-classical-RF effects remain to be addressed.

Intracellular evidence for feed-forward processing
A series of intracellular recording experiments from David Ferster's laboratory in recent years have provided compelling evidence that the processing underlying simple cell orientation selectivity is indeed dominantly feed-forward. In one experiment [22], cortical preparations were cooled to block spiking, leaving transmission along and vesicle release from thalamic axons intact (though slowed and diminished). The temporal modulations of voltage in simple cells induced by high-contrast drifting sinusoidal gratings, though smaller in the cooled condition, showed identical orientation tuning in the control and cooled conditions, suggesting that the tuning of a cell's full set of inputs follows the tuning of its total thalamic input. This result is accounted for by the model of Troyer *et al.* [12]: voltage modulations follow the total LGN input, while inhibition and threshold sharpen spike tuning relative to voltage tuning [23,24]. Note that the tuning of voltage modulations induced by thalamic inputs depends on the stimulus: sinusoidal gratings of higher spatial frequencies evoke narrower thalamic input tuning than gratings of lower spatial frequencies [12]. Thus, it is unlikely that this result represents convergent tuning of independent cortical and thalamic circuits, since the tuning of the thalamic input is variable; rather, it appears that full circuit tuning follows that of the total thalamic input.

The cooling did not entirely eradicate cortical spiking; cells in layer 6, farthest from the cooling plate, showed ~15% of their normal spiking responses. Ferster's group therefore assayed the same question by an independent technique, using a shock to the cortex to induce hyperpolarization and thus suppress cortical spiking for a period of >100 msec, and examining the tuning of voltage responses to flashed gratings during the period of suppression [25]. Again, voltage responses showed the same orientation tuning in control and suppressed conditions.

An argument against a feed-forward computation of orientation tuning has been that orientation tuning width is narrower than would be expected from a linear prediction

based on the arrangement of a cell's ON and OFF subregions [26]. However, the feed-forward model predicts that inhibition and threshold sharpen spike tuning relative to voltage tuning; it is voltage tuning that would be expected to follow a linear prediction. Ferster's group tested this by mapping the cell's RF intracellularly with flashed spots, and found that the voltage response to a drifting sinusoidal luminance grating, including its orientation tuning, could be well predicted from the RF map [27••]. However, the linear prediction tended to predict a greater response orthogonal to the preferred orientation than was actually observed, in agreement with earlier results [28].

Finally, Ferster's group examined the intracellular basis of contrast–invariant orientation tuning [11••]. They examined two aspects of the voltage response to drifting sinusoidal gratings of various orientations and contrasts: the amplitude of the temporal modulation of voltage induced by the grating ('voltage modulation'); and the mean depolarization induced by the stimulus ('voltage mean'). They found that both voltage modulation and voltage mean showed similar orientation tuning that simply scaled with changes in stimulus contrast. In combination with their previous findings [22], this suggests that voltage orientation tuning across contrasts follows the tuning of thalamic inputs. Furthermore, voltage noise — the trial-by-trial fluctuations of the average stimulus-induced voltage response for a given stimulus — was critical to smoothing out threshold effects, allowing the contrast-invariant voltage tuning to be transformed into sharper, contrast-invariant spiking tuning.

These results, while not a necessary consequence of the antiphase inhibition model, are consistent with it. The model predicts that the voltage modulation will have orientation tuning that scales with contrast, as observed. The model also predicts that feed-forward inhibition will cancel the mean feed-forward excitation, which is untuned for orientation. The tuned voltage mean may then be induced by the tuned voltage modulations through reversal-potential effects and through induced spiking along with recurrent connections.

Direction selectivity

The results presented thus far have focused on orientation tuning. Simple cells are also directional selective: they prefer stimulus movement in one of the two opposite directions orthogonal to the preferred orientation. This property may also arise in layer 4 from the structure of the feed-forward input along with the effects of spike threshold nonlinearity.

Voltage responses to moving stimuli can be predicted as a simple linear sum of inputs: a moving stimulus can be decomposed into the sum of stationary, temporally modulated stimuli, and voltage responses can correspondingly be predicted from the sum of the voltage responses to stationary stimuli [29]. Furthermore, voltage responses can be seen as arising from sums of only two input components, which resemble non-lagged cells and lagged cells [29], the

two temporal types of LGN inputs. Just as adjacent rows of ON- and OFF-center inputs explain a simple cell's spatial response profile, an appropriate spatial mix of lagged and non-lagged input produces cells whose space–time RFs show preference for one direction. Studies of temporal response profiles of simple cell RFs found timing corresponding to lagged-type input only in cells of layer 4B [30]. Correspondingly, cells in layer 4B show the strongest direction preference in their linear space–time receptive fields [31]. Strobe-rearing greatly reduces direction selectivity in cat V1 cells [32], and eliminates the convergence of non-lagged-like and lagged-like temporal responses in individual simple cells [33]. Adaptation studies suggest that direction-selective simple cells receive inhibition from other simple cells preferring the same direction but with different space–time phases [34]. This suggests a possible generalization from the spatial-phase-specific connectivity discussed here to connectivity specific for space-time phase.

Beyond the antiphase model

Recent findings on inhibitory neurons, promise to complicate the picture presented thus far. Intracellular recordings *in vivo* show two functional types of inhibitory neurons in layer 4 of cat V1: simple cells showing good orientation tuning, and complex cells — responding either to light or dark throughout their RF — with equal responses to all orientations (Hirsch JA *et al.*, *Soc Neuro Abstr* 2000, **26**:1083; Hirsch JA *et al.*, unpublished data). This raises the possibility that the tuning attributed in the antiphase model to simple inhibitory cells — response to all orientations, though tuned for the preferred — might actually be achieved by the combination of two inhibitory populations. Slice recordings reveal two biophysical types of interneurons: fast-spiking (FS) neurons receiving strong feed-forward input from thalamus, and low-threshold-spiking (LTS) neurons with no feed-forward input, thus only providing feedback inhibition ([35••], but see [36••]). Furthermore, there is extensive gap-junction coupling within each type, but not between the two types. There is no simple correspondence between these two biophysical types and the two functional types found in V1 (Hirsch JA, personal communication). The roles of LTS feedback inhibition, gap junction coupling among interneurons, and complex cell interneurons in functional responses remain to be explored.

The major alternative model of V1 circuitry proposes that strong, localized feedback excitation and more widespread feedback inhibition create orientation tuning that is an intrinsic property of cortex, independent of the tuning of the thalamic input [37,38]. In this model, factors that change the tuning of a cell's thalamic input are predicted to have no effect on its orientation tuning. This is contradicted by Ferster's findings and also by data showing that orientation tuning narrows with increasing spatial frequency of a grating stimulus (reviewed in [12]) and with increasing length of a bar stimulus [39]. In both cases, the results are

predicted if a cell's orientation tuning follows its thalamic input tuning.

Nonetheless, there remain a number of observations that suggest a role for recurrent connections, cross-orientation inhibition, and/or phase-nonspecific inhibition in generating orientation selectivity (reviewed in [7,8]). When recording from a site preferring one orientation in layer 4 or elsewhere, GABA-induced inactivation of a site 350–700 μm away favoring the orthogonal orientation leads to a broadening of orientation tuning at the recorded site [40,41]. Furthermore, anatomical studies confirm the existence of inhibitory neurons next to inactivation sites that project to the vicinity of the corresponding recording site [42•]. Anatomical labelling combined with optical imaging shows that sites in layer 4 in cat area 18 receive connections from proximal sites that are strongly biased towards similar orientation preferences, as expected from the antiphase model; however, long-range connections over distances up to 2–3 mm are distributed fairly uniformly across orientations [43•]. Adaptation to an orientation to one side of the preferred can induce a shift in orientation tuning towards, and an increase in response to, orientations to the opposite side of the preferred, and this effect shows little dependence on cortical depth, hence it appears likely to hold in layer 4 [44]. Intracellular studies of transient responses to a flashed bar of the preferred orientation show an initial conductance increase with sub- or peri-threshold reversal potential, before the response becomes either excitatory or inhibitory (depending on whether the bar was flashed over an appropriate or inappropriate subregion) [17]; however cells were not identified by layer so the applicability to layer 4 is uncertain. Finally, as already mentioned, a linear model of voltage responses based on responses to flashed spots predicts larger voltage responses to the null orientation than are actually observed [27••,28].

Studies of the dynamics of orientation tuning in response to flashed stimuli have also been argued to support a role for feedback, but at least some of these results may instead be compatible with the results of feed-forward inhibition. A recent intracellular study divided the orientation tuning curve of voltage responses into a tuned component and an untuned component, where the latter is a constant voltage response across orientations. The study found no statistically significant changes with time after stimulus onset in the width of the tuned component, but in many cells the untuned component grew more negative over time (Gillespie DC *et al*., *Soc Neuro Abstr* 2000, **26**:1084; Gillespie DC *et al*., unpublished data). This increasing negativity of the untuned component is expected if feed-forward inhibition follows feed-forward excitation. The overall voltage tuning curve — tuned plus untuned component — would narrow with time, as reported for some cells in another study [45]. An extracellular study in monkey reported that perhaps half of cells studied showed changes in the tuned response component with post-stimulus time, but these effects were not seen in thalamic-recipient

portions of layer 4 [46]. This study used stimuli several times larger than the classical receptive field, so surround suppression effects may have played a role.

In summary, the picture of strong feed-forward antiphase inhibition supplementing the tuning of a cell's thalamic input can explain a large body of diverse data in cat V1 layer 4, but the complexity of the biological circuit remains greater than any single simple model can fully capture.

Layer 4 of rodent S1
Barrel connectivity
Layer 4 of rodent primary somatosensory cortex contains anatomically distinct neuronal networks, called barrels, that correspond in a one-to-one fashion to individual whiskers on the contralateral face [47,48]. Neurons within a barrel are related functionally in that they each respond most robustly to deflection of the same principal whisker. In adult rats, each barrel contains ~8000 neurons [49], of which ~80% are excitatory. Early findings [50], as well as more recent data, consistently suggest substantial connections between neurons in the same barrel, and few, if any, connections between neurons in different barrels [51]. Intracellular recordings of spiny stellate cells *in vitro* from young rats suggest that as many as 20–30% of excitatory barrel neuron pairs are synaptically connected, often reciprocally [52,53••]. Spiny cell axons project robustly to supragranular layers directly above the barrel (i.e. within the same column [54]) but projections back into a barrel from pyramidal neurons in supra- and infra-granular layers are considerably less extensive [51,55,56]. In the tangential plane, spiny cell axons and dendrites are confined largely to the barrel in which the soma is located, and connection probability and strength fall off sharply across the barrel boundary into the intervening septum [57]. Direct connections between barrels are notably sparse [51]. In thalamocortical slices, afferent activity rapidly distributes throughout a barrel with no spread in layer 4 to neighboring barrels [58••]. Activity then propagates vertically within the column before spreading horizontally.

Barreloids
Neurons in somatosensory thalamus are also organized into discrete groups, one for each contralateral whisker, known as 'barreloids'. Recent *in vivo* studies have provided considerable evidence that the RF properties of neurons within an individual barrel reflect their feed-forward input from barreloids along with the local processing occuring within the barrel. Barreloid neurons have multiwhisker excitatory RFs [59,60], although their expression appears to depend strongly on the type and depth of anesthesia [61]. Correspondingly and/or because some barreloid neurons send collateral projections to non-homologous, neighboring barrels [62•,63], barrel neurons, especially inhibitory ones, respond at short latency to both the principal whisker and to whiskers adjacent to them [64,65•]. Adjacent-whisker responses display slightly longer latencies than responses to the principal whisker, but this can

be explained by similar latency differences observed in the corresponding thalamic input neurons [61]. Adjacent whiskers also evoke inhibition of excitatory neurons [59,60], as is discussed below. In lightly narcotized animals, extracellularly recorded adjacent-whisker responses, both excitatory and inhibitory, are unaffected by ablation of the adjacent barrel [66]. Taken with the above, these data suggest that each barrel processes its thalamic inputs largely, or entirely, independently of neighboring barrels, though under some conditions activities in neighboring barrels can influence one another, probably by a poly-synaptic pathway involving non-granular laminae [67].

Feed-forward circuits in barrels

Recent physiological studies have extended early findings indicating that thalamocortical axons strongly and directly engage feed-forward inhibitory circuits within each barrel [68]. FS inhibitory neurons [69,70] respond at monosynaptic latencies to thalamic activation, display relatively linear responses to direct current injections [70] and to synaptic input [71], respond in highly time-locked fashion to afferent signals from the thalamus, and fire synchronously with each other as a result of their receiving common thalamocortical inputs [72,73]. Electrical coupling may also contribute to synchronous firing [35••]. FS units are strongly driven by whisker stimuli and have RF properties that are highly similar to those of thalamic barreloid neurons, including vigorous multiwhisker responses [59,60]. As with barreloid neurons, FS neurons fire about half as many spikes to adjacent whisker deflections as they do to principal whisker deflections [74].

In contrast, these studies have also shown that regular-spike units, many of which are excitatory spiny stellate cells, are less strongly driven by thalamocortical neurons, require more temporal and spatial summation of inputs to reach threshold, and have suprathreshold RFs that are highly focused on the barrel's principal whisker [59]. Adjacent whiskers, on average, evoke only ~20% as many spikes as does the principal whisker in RS neurons, and in many cases evoke no spikes at all [74]. The suppression of responses to adjacent whiskers, in spite of robust thalamic responses, appears to arise from the feed-forward inhibition whose tuning closely follows that of thalamic inputs. The dominance of feed-forward inhibition over excitation is attested to by the finding that in behaving rats, acute trimming of eight surrounding whiskers reduces overall activity in the thalamic barreloid corresponding to the central, intact whisker, but increases overall activity in the corresponding cortical barrel [75••]. The dominance of feed-forward inhibition is also suggested by the findings: that 60% of layer 4 inhibitory interneurons give spiking responses at monosynaptic latencies to thalamic stimulation, whereas <5% of layer 4 excitatory neurons do [36••]; that essentially all layer 4 cells show strong disynaptic IPSPs after thalamic stimulation; and that the monosynaptically-activated inhibitory neurons receive on average five-fold stronger thalamocortical synapses than excitatory neurons.

Spike timing

Intracellular recordings from both RS and FS barrel neurons *in vivo* show that principal whisker deflections produce short-latency excitatory post-synaptic potentials (EPSPs) followed a few milliseconds later by inhibitory post-synaptic potentials (IPSPs); EPSP latencies are shortest in layer 4 [76–78]. Whereas longer latency EPSPs and/or IPSPs may be evoked by neighboring whiskers, the principal whisker evokes both the strongest excitatory and inhibitory responses. In extracellular unit recordings from RS cells, inhibitory effects are inferred from suppression of one whisker's excitatory response by prior or simultaneous deflection of nearby whiskers. The suppressive effects of individual whiskers summate [60,79] and are regulated by behavioral state [66]. Consistent with intracellular findings, the principal whisker exerts the strongest suppression but adjacent whiskers also evoke suppression [59,60].

In extracellular recordings, excitatory barrel neurons have smaller RFs than thalamic or inhibitory neurons. Surprisingly, examination of both real and simulated barrel response data suggests that this *spatial* focus results from the barrel circuit's sensitivity to thalamic input *timing*. Whisker stimuli that evoke abrupt and synchronous increases in thalamic firing also evoke strong responses in excitatory barrel neurons, while those that evoke more gradual changes in thalamic firing evoke only weak responses and/or suppression in excitatory barrel neurons. Whisker stimuli that evoke abrupt changes in thalamic firing include deflections of the principal versus adjacent whiskers [59], deflection onsets versus offsets [80], and high versus low velocity deflections [81••]. Deflection amplitude does not affect thalamic response timing, and consequently it does not strongly influence responses of excitatory barrel neurons [81••].

Analyses of simulated barrels [74,82] provide the following explanation for the circuit's sensitivity to input spike timing (Figure 4). Strong synchronous activation of thalamic inputs overcomes the high response thresholds of excitatory neurons, leading them to spike. Consequently, the strong recurrent excitatory circuitry rapidly and nonlinearly reinforces the excitatory response. Although feed-forward inhibition is also evoked by such synchronous activation, it grows more linearly and develops too late to prevent the initiation of an excitatory response. Within a few milliseconds, the excitatory response feeds back onto the inhibitory population. This boosts an inhibitory response that has already been primed by feed-forward mechanisms, leading to a powerful suppression of all spiking activity within the circuit. By comparison, stimuli that evoke less synchronous thalamic inputs evoke excitatory and inhibitory responses with comparable rates of increase so that the dominant feed-forward inhibition is sufficient to prevent an explosive, albeit momentary, increase in excitation. When tonic levels of intrabarrel inhibition increase (e.g. by continuously vibrating an adjacent whisker) the circuit's sensitivity to thalamic response

Figure 4
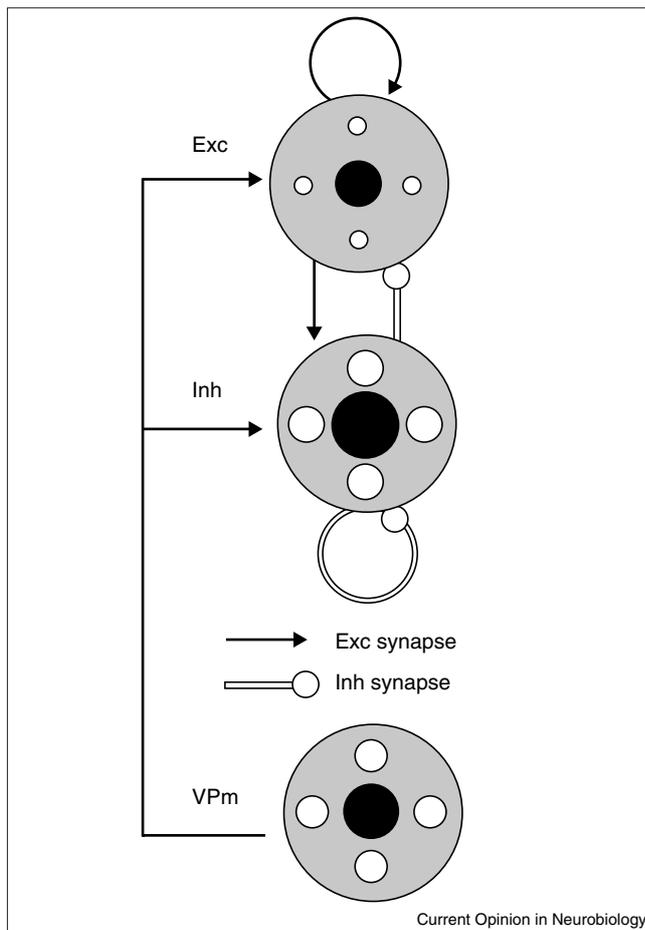
Cartoon of the model circuit for barrel neurons proposed in [74,82]. Gray circles represent RFs of populations of excitatory (exc) and inhibitory (inh) barrel neurons, both of which receive inputs from a population of thalamocortical neurons in the homologous barreloid of the ventral posteromedial nucleus (VPm). Excitatory and inhibitory barrel neurons are recurrently and reciprocally interconnected. Dark circles in the center represent the average number of spikes evoked by the principal whisker, open circles represent responses to the four immediately adjacent whiskers. The size of the circle denotes the approximate strength of the response; inhibitory neurons are the most responsive. Note that the model circuit represents neurons within a single barrel and that there are no connections with other barrels.

synchrony becomes even more pronounced, increasing the spatial focus of receptive fields [60].

Conclusions: common principles of information processing in visual and somatosensory thalamocortical circuits

This review has revealed a number of properties that appear likely to be common to layer 4 of cat visual cortex and rat somatosensory cortex: First, thalamic activation produces strong feed-forward inhibition, mediated by local interneurons in layer 4, as well as feed-forward excitation. Second, feed-forward inhibition dominates feed-forward excitation, so that nonspecific or tonic thalamic activation evokes a net inhibition. Third, feed-forward inhibition shows tuning

similar to that of a cell's thalamic input, so that a preferred stimulus evokes both the strongest inhibition and the strongest excitation. Fourth, feed-forward inhibition sharpens the tuning of an excitatory neuron relative to its thalamic input, suppressing responses to non-preferred whiskers in S1 or to non-preferred orientations in V1. Thus, inhibitory neurons have broader tuning than excitatory neurons. Fifth, an effective stimulus evokes feed-forward excitation that is separated in time from the feed-forward inhibition it evokes. However, this separation is typically on much finer time scales in S1 than in V1. Sixth, local recurrent excitation works in conjunction with neuronal non-linearities (e.g. spike threshold) to enhance responses evoked by preferred versus non-preferred stimuli. Finally, processing within layer 4 is largely local in nature, restricted to a single whisker barrel in S1 or to nearby preferred orientations in V1. In particular, adjacent-whisker inhibition in S1 and cross-orientation inhibition in V1 both may primarily arise locally, from inhibitory neurons that prefer the locally-preferred stimulus but also respond to the adjacent whisker or cross orientation.

However, at least two major differences between the two systems are also apparent. First, the V1 circuit model depends on opponent inhibition. That is, an additional stimulus variable, phase, exists for which the tuning of an inhibitory cell tends to be opposite to that of the cell it inhibits. No analogous variable is known for S1, but it is possible the appropriate stimulus parameters have not yet been examined. Second, the S1 circuit depends on rapid recruitment of recurrent excitation outracing feed-forward inhibition, and so is sensitive to the rate of change rather than the magnitude of thalamic responses. The model V1 circuit does not show such dependence (although one V1 model has proposed a similar timing sensitivity [83,84]). This may be a true difference between the systems, reflecting the specialization of the barrel circuit for sensitivity to transients evoked by whiskering a textured surface. Alternatively, this may simply reflect a difference in the stimuli typically used to study the two systems, so that closer examination of transient responses might reveal an analogous dependence in V1.

In sum, we propose that the S1 barrel circuit is functionally equivalent to the V1 orientation circuit. In S1, the modular circuits are discrete and separated, corresponding to individual whiskers in the periphery. In V1, there is a continuous transition between circuits processing nearby orientations, corresponding to the continuous distribution of orientations in the visual world. Notwithstanding the differences between the two systems, available evidence is consistent with the view that these two well-studied circuits share many similarities in their fundamental operations, which may represent more general properties of neocortical layer 4.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Callaway EM: **Local circuits in primary visual cortex of the macaque monkey.** *Annu Rev Neurosci* 1998, **21**:47-74.

2. Hubel DH, Wiesel TN: **Receptive fields, binocular interaction and functional architecture in the cat's visual cortex.** *J Physiol* 1962, **160**:106-154.

3. Gilbert CD: **Laminar differences in receptive field properties of cells in cat primary visual cortex.** *J Physiol* 1977, **268**:391-421.

4. Bullier J, Henry GH: **Laminar distribution of first-order neurons and afferent terminals in cat striate cortex.** *J Neurophysiol* 1979, **42**:1271-1281.

5. Tanaka K: **Cross-correlation analysis of geniculostriate neuronal relationships in cats.** *J Neurophysiol* 1983, **49**:1303-1318.

6. Reid RC, Alonso JM: **Specificity of monosynaptic connections from thalamus to visual cortex.** *Nature* 1995, **378**:281-284.

7. Ferster D, Miller KD: **Neural mechanisms of orientation selectivity in the visual cortex.** *Ann Rev Neurosci* 2000, **23**:441-471.

8. Sompolinsky H, Shapley R: **New perspectives on the mechanisms for orientation selectivity.** *Curr Opin Neurobiol* 1997, **7**:514-522.

9. Sclar G, Freeman RD: **Orientation selectivity in the cat's striate cortex is invariant with stimulus contrast.** *Exp Brain Res* 1982, **46**:457-461.

10. Skottun BC, Bradley A, Sclar G, Ohzawa I, Freeman RD: **The effects of contrast on visual orientation and spatial frequency discrimination: a comparison of single cells and behavior.** *J Neurophysiol* 1987, **57**:773-786.

11. Anderson JS, Lampl I, Gillespie D, Ferster D: **The contribution of**
•• **noise to contrast invariance of orientation tuning in cat visual cortex.** *Science* 2000, **290**:1968-1972.
The authors studied the intracellular basis for contrast-invariance of orientation tuning in cat V1. They found that a cell's voltage responses showed contrast-invariant tuning − that is, the curve of voltage response versus orientation simply scaled with changes in stimulus contrast. They also found, remarkably, that voltage noise − the trial-by-trial fluctuations from the trial-averaged response to a given stimulus − plays a critical role in transforming contrast-invariant voltage tuning into contrast-invariant spiking tuning.

12. Troyer TW, Krukowski A, Priebe NJ, Miller KD: **Contrast-invariant orientation tuning in cat visual cortex: feed-forward tuning and correlation-based intracortical connectivity.** *J Neurosci* 1998, **18**:5908-5927.

13. Ferster D: **Orientation selectivity of synaptic potentials in neurons of cat primary visual cortex.** *J Neurosci* 1986, **6**:1284-1301.

14. Anderson JS, Carandini M, Ferster D: **Orientation tuning of input**
•• **conductance, excitation, and inhibition in cat primary visual cortex.** *J Neurophysiol* 2000, **84**:909-926.
Here, intracellular recordings were used to assess the orientation tuning of excitatory and inhibitory inputs to a cell (see also [13]) in the steady-state response to drifting sinusoidal gratings. For simple cells, both excitation and inhibition have similar tuning, peaking at the cell's preferred orientation.

15. Ferster D: **Spatially opponent excitation and inhibition in simple cells of the cat visual cortex.** *J Neurosci* 1988, **8**:1172-1180.

16. Hirsch JA, Alonso JM, Reid RC, Martinez LM: **Synaptic integration in striate cortical simple cells.** *J Neurosci* 1998, **18**:9517-9528.

17. Borg-Graham LJ, Monier C, Frégnac Y: **Visual input evokes transient and strong shunting inhibition in visual cortical neurons.** *Nature* 1998, **393**:369-373.

18. Ferster D, Jagadeesh B: **EPSP-IPSP interactions in cat visual cortex studied with *in vivo* whole-cell patch recording.** *J Neurosci* 1992, **12**:1262-1274.

19. Krukowski AE, Miller KD: **Thalamocortical NMDA conductances and**
• **intracortical inhibition can explain cortical temporal tuning.** *Nat Neurosci* 2001, **4**:424-430.
This paper demonstrates that the combination of feed-forward excitation and feed-forward inhibition in the model circuit of [12] can account for the temporal response tuning of cortical cells.

20. Kayser AS, Priebe NJ, Miller KD: **Contrast-dependent nonlinearities**
• **arise locally in a model of contrast-invariant orientation tuning.** *J Neurophysiol* 2001, **85**:2130-2149.
Demonstration that the model circuit of [12] can account for several nonlinear response properties that were previously suggested [21] to require 'normalizing' inhibition from cells of all preferred orientations.

21. Carandini M, Heeger DJ, Movshon JA: **Linearity and gain control in V1 simple cells.** In *Cerebral Cortex,* vol 13. Edited by Jones EG, Peters A. New York: Plenum; 1998.

22. Ferster D, Chung S, Wheat H: **Orientation selectivity of thalamic input to simple cells of cat visual cortex.** *Nature* 1996, **380**:249-252.

23. Carandini M, Ferster D: **Membrane potential and firing rate in cat primary visual cortex.** *J Neurosci* 2000, **20**:470-484.

24. Volgushev M, Pernberg J, Eysel UT: **Comparison of the selectivity of postsynaptic potentials and spike responses in cat visual cortex.** *Eur J Neurosci* 2000, **12**:257-263.

25. Chung S, Ferster D: **Strength and orientation tuning of the thalamic input to simple cells revealed by electrically evoked cortical suppression.** *Neuron* 1998, **20**:1177-1189.

26. Gardner JL, Anzai A, Ohzawa I, Freeman RD: **Linear and nonlinear contributions to orientation tuning of simple cells in the cat's striate cortex.** *Vis Neurosci* 1999, **16**:1115-1121.

27. Lampl I, Anderson J, Gillespie D, Ferster D: **Prediction of orientation**
•• **selectivity from receptive field architecture in simple cells of cat visual cortex.** *Neuron* 2001, **30**:263-274.
Using intracellular recording, Lampl *et al.*, show that voltage responses to drifting sinusoidal gratings can be predicted by the voltage responses to flashed spots across the RF. In particular, a close match of the predicted and observed orientation tuning was observed, as predicted by a model in which orientation tuning is largely determined by feed-forward processing.

28. Volgushev M, Vidyasagar TR, Pei X: **A linear model fails to predict orientation selectivity of cells in the cat visual cortex.** *J Physiol* 1996, **496**:597-606.

29. Jagadeesh B, Wheat HS, Kontsevich LL, Tyler CW, Ferster D: **Direction selectivity of synaptic potentials in simple cells of the cat visual cortex.** *J Neurophysiol* 1997, **78**:2772-2789.

30. Saul AB, Humphrey AL: **Evidence of input from lagged cells in the lateral geniculate nucleus to simple cells in cortical area 17 of the cat.** *J Neurophysiol* 1992, **68**:1190-1208.

31. Murthy A, Humphrey AL, Saul AB, Feidler JC: **Laminar differences in the spatiotemporal structure of simple cell receptive fields in cat area 17.** *Vis Neurosci* 1998, **15**:239-256.

32. Humphrey AL, Saul AB: **Strobe rearing reduces direction selectivity in area 17 by altering spatiotemporal receptive-field structure.** *J Neurophysiol* 1998, **80**:2991-3004.

33. Humphrey AL, Saul AB, Feidler JC: **Strobe rearing prevents the convergence of inputs with different response timings onto area 17 simple cells.** *J Neurophysiol* 1998, **80**:3005-3020.

34. Saul AB: **Visual cortical simple cells: who inhibits whom.** *Vis Neurosci* 1999, **16**:667-673.

35. Gibson JR, Beierlein M, Connors BW: **Two networks of electrically**
•• **coupled inhibitory neurons in neocortex.** *Nature* 1999, **462**:75-79.
In paired cell recordings, electrical coupling between two types of inhibitory neurons in layer 4 of S1 cortex is demonstrated here. FS neurons, which receive thalamic input, are coupled to other fast-spike neurons. Low-threshold neurons, which do not receive thalamic input, are coupled to other low-threshold neurons (but see [36]).

36. Porter JT, Johnson CK, Agmon A: **Diverse types of interneurons**
•• **generate thalamus-evoked feed-forward inhibition in the mouse barrel cortex.** *J Neurosci* 2001, **21**:2699-2710.
This study demonstrates powerful feed-forward inhibition in layer 4 of S1, with ~60% of inhibitory neurons driven by thalamic stimulation. These inhibitory neurons receive thalamic synapses ~five times larger than those onto excitatory neurons. In contrast to [35], adapting and non-adapting interneurons are equally likely to be thalamically driven.

37. Somers D, Nelson SB, Sur M: **An emergent model of orientation selectivity in cat visual cortical simple cells.** *J Neurosci* 1995, **15**:5448-5465.

38. Ben-Yishai R, Bar-Or RL, Sompolinsky H: **Theory of orientation tuning in visual cortex.** *Proc Natl Acad Sci USA* 1995, **92**:3844-3848.

39. Orban GA: **Quantitative electrophysiology of visual cortical neurones.** In *Vision and Visual Dysfunction. The Neural Basis of Visual Function.* Edited by Cronly-Dillon AG, Leventhal J. London: Macmillan Press; 1991:173-222.

40. Crook JM, Kisvardy ZF, Eysel UT: **GABA-induced inactivation of functionally characterized sites in cat visual cortex (area 18): Effects on direction selectivity.** *J Neurophysiol* 1996, **75**:2071-2088.

41. Crook JM, Kisvardy ZF, Eysel UT: **GABA-induced inactivation of functionally characterized sites in cat striate cortex: effects on orientation and direction selectivity.** *Vis Neurosci* 1997, **14**:141-158.

42. Crook JM, Kisvardy ZF, Eysel UT: **Evidence for a contribution of**
• **lateral inhibition to orientation tuning and direction selectivity in cat visual cortex: reversible inactivation of functionally characterized sites combined with neuroanatomical tracing techniques.** *Eur J Neurosci* 2000, **10**:2056-2075.
Following on from previous experiments suggesting that cross-orientation inhibition from GABA-inactivated sites in V1 contributes to orientation tuning [41], this paper anatomically demonstrates that inhibitory neurons project from the GABA site to the vicinity of the site preferring the orthogonal orientation.

43. Yousef T, Bonhoeffer T, Kim DS, Eysel UT, Toth E, Kisvarday ZF:
• **Orientation topography of layer 4 lateral networks revealed by optical imaging in cat visual cortex (area 18).** *Eur J Neurosci* 1999, **11**:4291-4308.
Showed that shorter-range connections (within about 500 μm) in layer 4 of cat area 18 are strongly biased to connect cells of similar orientation preference, but longer-range connections are spread fairly equally over cells of all orientation preferences, consistent with [41].

44. Dragoi V, Sharma J, Sur M: **Adaptation-induced plasticity of orientation tuning in adult visual cortex.** *Neuron* 2000, **28**:287-298.

45. Volgushev M, Vidyasagar TR, Pei X: **Dynamics of the orientation tuning of postsynaptic potentials in the cat visual cortex.** *Vis Neurosci* 1995, **12**:621-628.

46. Ringach DL, Hawken MJ, Shapley R: **Dynamics of orientation tuning in macaque primary visual cortex.** *Nature* 1997, **387**:281-284.

47. Woolsey TA, Van der Loos H: **The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex.** *Brain Res* 1970, **17**:205-242.

48. Welker C: **Receptive fields of barrels in the somatosensory neocortex of the rat.** *J Comp Neurol* 1976, **166**:173-189.

49. Keller A, Carlson GC: **Neonatal whisker clipping alters intracortical, but not thalamocortical projections, in rat barrel cortex.** *J Comp Neurol* 1999, **412**:83-94.

50. Woolsey TA, Dierker ML, Wann DF: **Mouse SmI cortex: qualitative and quantitative classification of *Golgi*-impregnated barrel neurons.** *Proc Natl Acad Sci USA* 1975, **72**:2165-2169.

51. Kim U, Ebner FF: **Barrels and septa: separate circuits in rat barrel cortex.** *J Comp Neurol* 1999, **408**:489-505.

52. Egger V, Feldmeyer D, Sakmann B: **Coincidence detection and changes of synaptic efficacy in spiny stellate neurons in rat barrel cortex.** *Nat Neurosci* 1999, **2**:1098-1105.

53. Feldmeyer D, Egger V, Lübke J, Sakmann B: **Reliable synaptic**
•• **connections between pairs of excitatory layer 4 neurones within a single 'barrel' of developing rat somatosensory cortex.** *J Physiol* 1999, **521**:169-190.
Dual recording between excitatory barrel neurons reveals highly reliable connections restricted to the confines of a single barrel. Together with [52,54,57], this study provides unique quantitative data about local, recurrent excitatory circuitry within individual barrels.

54. Lübke J, Egger V, Sakmann B, Feldmeyer D: **Columnar organization of dendrites and axons of single and synaptically coupled excitatory spiny neurons in layer 4 of the rat barrel cortex.** *J Neurosci* 2000, **20**:5300-5311.

55. Gottlieb JP, Keller A: **Intrinsic circuitry and physiological properties of pyramidal neurons in rat barrel cortex.** *Exp Brain Res* 1997, **115**:47-60.

56. Staiger JF, Kötter R, Zilles K, Luhmann HJ: **Laminar characteristics of functional connectivity in rat barrel cortex revealed by stimulation with caged-glutamate.** *Neurosci Res* 2000, **37**:49-58.

57. Petersen CH, Sakmann B: **The excitatory neuronal network of rat layer 4 barrel cortex.** *J Neurosci* 2000, **20**:7579-7586.

58. Laaris N, Carlson G, Keller A: **Thalamic-evoked synaptic**
•• **interactions in barrel cortex revealed by optical imaging.** *J Neurosci* 2000, **20**:1529-1537.
Optical imaging of voltage-sensitive dye signals in thalamocortical slices demonstrates that afferent stimulation evokes activity initially within the confines of an individual barrel, which then propagates vertically within the cortical column.

59. Simons DJ, Carvell GE: **Thalamocortical response transformation in the rat vibrissa/barrel system.** *J Neurophysiol* 1989, **61**:311-330.

60. Brumberg JC, Pinto DJ, Simons DJ: **Spatial gradients and inhibitory summation in the rat whisker barrel system.** *J Neurophysiol* 1996, **76**:130-140.

61. Friedberg MH, Lee SM, Ebner FF: **Modulation of receptive field properties of thalamic somatosensory neurons by the depth of anesthesia.** *J Neurophysiol* 1999, **81**:2243-2252.

62. Arnold PB, Li CX, Waters RS: **Thalamocortical arbors extend**
• **beyond single cortical barrels: an *in vivo* intracellular tracing study in rat.** *Exp Brain Res* 2000, **136**:152-168.
Examination of the arbors of intracellularly stained and physiologically characterized thalamocortical neurons demonstrates that they differ in their projections to layer 4 versus other laminae, and in their confinement to barrels.

63. Land PW, Buffer SA Jr, Yaskosky JD: **Barreloids in adult rat thalamus: three dimensional architecture and relationship to somatosensory cortical barrels.** *J Comp Neurol* 1995, **355**:573-588.

64. Brumberg JC, Pinto DJ, Simons DJ: **Cortical columnar processing in the rat whisker-to-barrel system.** *J Neurophysiol* 1999, **82**:1808-1817.

65. Petersen RS, Diamond ME: **Spatial-temporal distribution of**
• **whisker-evoked activity in the rat somatosensory cortex and the coding of stimulus location.** *J Neurosci* 2000, **20**:6135-6143.
Investigation into the representation of single-vibrissa deflections by populations of cortical barrel neurons using a spatial array of electrodes. The total territory of activation encompassed from 2–11 barrels over 30–60 ms. However, the discrimination of one whisker from another peaked at 16 ms and was 90% accounted for by the activity in a single barrel.

66. Goldreich D, Kyriazi HT, Simons DJ: **Functional independence of layer IV barrels in rodent somatosensory cortex.** *J Neurophysiol* 1999, **82**:1311-1316.

67. Armstrong-James M, Callahan CA, Friedman MA: **Thalamo-cortical processing of vibrissal information in the rat. I. Intracortical origins of surround but not center-receptive fields of layer IV neurons in the rat S1 barrel field cortex.** *J Comp Neurol* 1991, **303**:193-210.

68. White EL: **Identified neurons in mouse SmI cortex which are postsynaptic to thalamocortical axon terminals: a combined *Golgi*-electron microscopic and degeneration study.** *J Comp Neurol* 1978, **181**:627-661.

69. Simons DJ: **Response properties of vibrissa units in the rat SI somatosensory neocortex.** *J Neurophysiol* 1978, **41**:798-820.

70. McCormick DA, Connors BW, Lighthall JW, Prince DA: **Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex.** *J Neurophysiol* 1985, **54**:782-805.

71. Angulo MC, Rossier J, Audinat E: **Postsynaptic glutamate receptors and integrative properties of fast-spiking interneurons in the rat neocortex.** *J Neurophysiol* 1999, **82**:1295-1302.

72. Swadlow HA: **Influence of VPM thalamic afferents on putative inhibitory interneurons in S1 of the awake rabbit: evidence from cross-correlation, microstimulation and latencies to peripheral sensory stimulation.** *J Neurophysiol* 1995, **73**:1584-1599.

73. Swadlow HA, Beloozerova IN, Sirota MG: **Sharp, local synchrony among putative feed-forward inhibitory interneurons of rabbit somatosensory cortex.** *J Neurophysiol* 1998, **79**:567-582.

74. Kyriazi HT, Simons DJ: **Thalamocortical response transformations in simulated whisker barrels.** *J Neurosci* 1993, **13**:1601-1615.

75. Kelly MK, Carvell GE, Jobling J, Simons DJ: **Sensory loss by**
•• **selected whisker removal produces immediate disinhibition in the somatosensory cortex of behaving rats.** *J Neurosci* 1999, **19**:9117-9125.
Single-unit recordings in behaving rats demonstrate that adjacent whiskers have a net excitatory effect in the thalamus and a net inhibitory effect in the cortex. The results are consistent with the hypothesis that each barrel uses multi-whisker thalamic inputs as well as local inhibitory circuitry to sharpen the RF properties of barrel neurons.

76. Carvell GE, Simons DJ: **Membrane potential changes in rat SmI cortical neurons evoked by controlled stimulation of mystacial vibrissae.** *Brain Res* 1988, **448**:186-191.

77. Moore CI, Nelson SB: **Spatio-temporal subthreshold receptive fields in the vibrissa representation of rat primary somatosensory cortex.** *J Neurophysiol* 1998, **80**:2882-2892.

78. Zhu JJ, Connors BW: **Intrinsic firing patterns and whisker-evoked synaptic responses of neurons in rat barrel cortex.** *J Neurophysiol* 1999, **81**:1171-1183.

79. Mirabella G, Battiston S, Diamond ME: **Integration of multiple-whisker inputs in rat somatosensory cortex.** *Cereb Cortex* 2001, **11**:164-170.

80. Kyriazi HT, Carvell GE, Simons DJ: **OFF response transformations in the whisker/barrel system.** *J Neurophysiol* 1994, **72**:392-401.

81. Pinto DJ, Brumberg JC, Simons DJ: **Circuit dynamics and coding
•• strategies in rodent somatosensory cortex.** *J Neurophysiol* 2000, **83**:1158-1166.
This *in vivo* single unit recording study tested and confirmed predictions from previous modeling work that barrel circuitry is preferentially sensitive to synchronous firing among populations of thalamocortical neurons.

82. Pinto DJ, Brumberg JC, Simons DJ, Ermentrout GB: **A quantitative population model of whisker barrels: re-examining the Wilson-Cowan equations.** *J Comput Neurosci* 1996, **3**:247-264.

83. Douglas RJ, Koch C, Mahowald M, Martin KA, Suarez HH: **Recurrent excitation in neocortical circuits.** *Science* 1995, **269**:981-985.

84. Suarez H, Koch C, Douglas R: **Modeling direction selectivity of simple cells in striate visual cortex within the framework of the canonical microcircuit.** *J Neurosci* 1995, **15**:6700-6719.

Now in press

The work referred to in the text as (Lauritzen *et al.*, *Soc Neuro Abstr* 2000, **26**:1967; Lauritzen *et al.*, unpublished data) is now in press:

85. Lauritzen TZ, Krukowski AE, Miller KD: **Local correlation-based circuitry can account for responses to multi-grating stimuli in a model of cat V1.** *J Neurophysiol* 2001, in press.