Mechanisms of Orientation Selectivity in the Primary Visual Cortex

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Abstract

The mechanisms underlying the emergence of orientation selectivity in the visual cortex have been, and continue to be, the subjects of intense scrutiny. Orientation selectivity reflects a dramatic change in the representation of the visual world: Whereas afferent thalamic neurons are generally orientation insensitive, neurons in the primary visual cortex (V1) are extremely sensitive to stimulus orientation. This profound change in the receptive field structure along the visual pathway has positioned V1 as a model system for studying the circuitry that underlies neural computations across the neocortex. The neocortex is characterized anatomically by the relative uniformity of its circuitry despite its role in processing distinct signals from region to region. A combination of physiological, anatomical, and theoretical studies has shed some light on the circuitry components necessary for generating orientation selectivity in V1. This targeted effort has led to critical insights, as well as controversies, concerning how neural circuits in the neocortex perform computations.

The road is always better than the inn.

—Miguel de Cervantes, *Don Quixote de la Mancha*

INTRODUCTION

A central objective of systems neuroscience has been and remains to understand how the sensory inputs we receive are integrated with our expectations about the world around us to generate behavior. As visual sensory information travels through our nervous system, it undergoes systematic transformations in its representation. A signature of this process is the progression of receptive field properties in neurons along the visual pathways of the brain. The concept of a receptive field was originally developed in the context of the visual system, where it has been defined as an intricate and specific visual stimulus space that modulates responses of neurons across the visual pathway from the retina, via the thalamus, to the cortex (Hartline 1949). Over the past half century, the definition and study of the receptive field construct has been extended to all sensory pathways: In the auditory system, it corresponds to the combination of sounds that modulate neural responses; in the somatosensory system, it corresponds to the location and types of pressure felt across the body that modulate neural responses. Indeed, neuronal receptive fields—across all sensory modalities—represent how information about the world is transformed and processed as it moves from the site of initial neural transduction to the neocortex. Importantly, the receptive field construct has provided us with a specialized tool to probe the neural computations that underlie cortical processing and, ultimately, behavior.

Following its transduction by photoreceptors, incoming visual information undergoes a number of transformations within the series of retinal neurons, ultimately progressing to the retinal ganglion cells, characterized by circularly symmetric receptive fields with an antagonistic center/surround organization in primates and carnivores (Kuffler 1953). In mammals, retinal ganglion cells project to many central processing centers, but the bulk of these afferents innervate the superior colliculus and the lateral geniculate nucleus (LGN) of the thalamus. The LGN, which receives 90% of the output of the retina in primates (Perry et al. 1984), relays visual information to the first neocortical visual area, the primary visual cortex (V1).

V1 is the site of dramatic transformations in the neural representation of the visual world. Whereas both retinal ganglion cells and their target LGN relay cells in primates and carnivores are characterized by circularly symmetric receptive fields and respond to almost any stimulus presented within their receptive fields, V1 neurons are sensitive to several complex visual stimulus attributes, including orientation, direction of motion, size, and binocular disparity of visual stimulus contours (Hubel & Wiesel 1962). In many cases, this selectivity is exquisitely sensitive: V1 neurons may provide zero response to visual stimulation unless a stimulus's features specifically match the neuron's preferences, as defined by its receptive field.

These profound changes in the character of the receptive field along the visual pathway have positioned V1 as a model system for studying the circuitry that underlies neural computations in the neocortex. Relative anatomical uniformity characterizes the circuitry of the neocortex, even though it processes distinct signals from region to region. For example, despite the distinct structure of visual and auditory signals, much of the circuitry found in auditory and visual areas of the neocortex is quite similar (Somogyi et al. 1998; but see Smith & Populin 2001). Frontal areas of the neocortex are thought to be the neural substrate for our cognitive abilities, awareness, and planning. Yet, how neocortical circuitry allows us to recognize complex stimuli, to make decisions, and to generate intricate plans is unclear, and the methods to uncover the neural basis for those computations on a circuit level are just being developed. By comparison, the transformations

performed by V1 on the inputs it receives from the LGN—the emergence of orientation selectivity, for example—are complex enough to be interesting, but simple enough to be tractable. A critical advantage of studying transformations in V1 is that it is possible to build quantitative models that can account for or make predictions of the responses of V1 neurons. These predictions have led experimentalists to perform specific and complex experiments, creating a fruitful interaction that has driven intense scrutiny and debate, while advancing our understanding of the processing conducted by the circuitry of the neocortex (Sompolinsky & Shapley 1997, Ferster & Miller 2000).

The emergence of orientation selectivity is one of the most remarkable transformations in V1. In contrast to afferent LGN relay cells, which generally respond equally well to all orientations, V1 neurons are remarkably response to a narrow range of stimulus orientations. V1 neurons can be further described as simple or complex cells (Hubel & Wiesel 1962, Skottun et al. 1991). Simple cells receive direct input from LGN relay cells and thus exhibit a receptive field configuration in which regions that prefer light (ON) or dark (OFF) changes in luminance are segregated. These segregated regions, called subfields, are elongated along the axis of the neuron's preferred orientation (**Figure 1**). The segregation between ON and OFF receptive field subfields allows these neurons to be well described by a single spatiotemporal filter. Complex cells, by contrast, usually receive input from V1 simple cells and have receptive fields in which ON and OFF regions are not spatially segregated, but instead overlap. Because complex cells respond to both increases and decreases in luminance at the same location, they require a receptive field description that includes

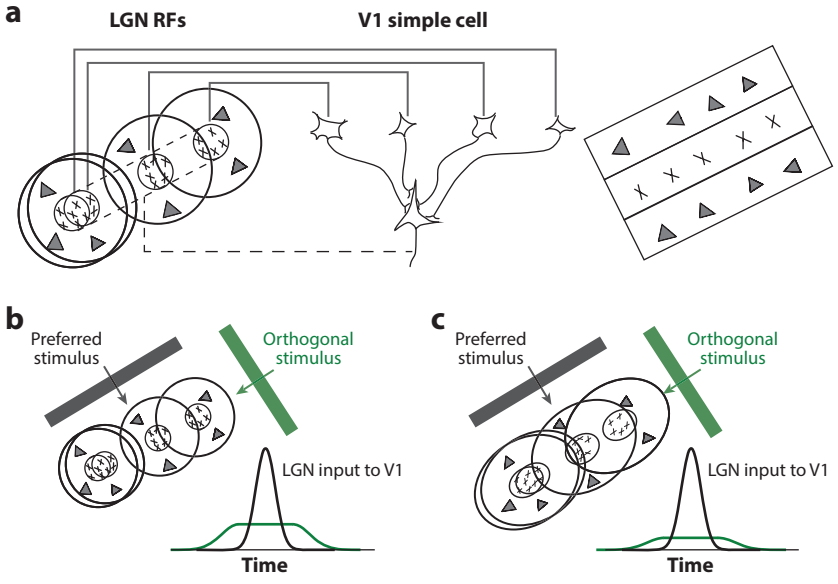

Figure 1

Feedforward model of orientation selectivity in V1. (*a*) Orientation-selective simple cells in V1 have elongated receptive fields with segregated ON regions (*black exes*) and OFF regions (*filled triangles*) (panel adapted from Hubel & Wiesel 1962). (*b*) Target simple cells receive input from thalamic relay cells with circularly symmetric receptive fields that are spatially offset along the axis of the cortical cells orientation preference, but not orientation selective. (*c*) Target simple cells receive input from thalamic relay cells with oblong receptive fields that aid in the emergence of orientation selectivity in V1. Abbreviations: LGN, lateral geniculate nucleus; RF, receptive field; V1, primary visual cortex.

multiple spatiotemporal filters. Although simple and complex cells have often been considered as distinct populations of neurons (Skottun et al. 1991), this dichotomy obscures an underlying organization that is one of degree rather than category (Priebe et al. 2004).

Action potentials provided the basis for the original observation of orientation selectivity in V1. These potentials were recorded by placing an insulated metal electrode near individual neurons (Hubel 1957). Action potentials are the result of the depolarization of the neuron by synaptic inputs and intrinsic conductances. Thus, studies of action potentials offer a perspective that reflects the information these potentials are conveying to downstream targets. In this review, I discuss the mechanisms responsible for the emergence of orientation selectivity in cat V1, with particular focus on how intracellular recordings, made by gaining access to the interior of neurons, have shed light on circuits that underlie response selectivity. These recordings allow us to capture both the output of neurons and the aggregate synaptic input that neurons receive. They therefore provide a critical perspective on how transformations in stimulus encoding occur in the neocortex.

FEEDFORWARD MODELS OF ORIENTATION SELECTIVITY

Few models of neuronal computation have the simplicity and longevity of the feedforward model for the first emergence of orientation selectivity in V1 proposed by Hubel & Wiesel (1962). According to their model, V1 simple cells—the neurons that receive direct LGN input—are orientation selective by virtue of excitatory input from LGN relay cells whose receptive fields are aligned along the axis of the simple cell's preferred stimulus orientation (**Figure 1*a***). Because LGN relay cells are largely orientation insensitive owing to their circularly symmetric receptive fields, their individual spiking responses will not vary with stimulus orientation (Hubel & Wiesel 1962). The relative timing of their responses, however, does vary with stimulus orientation: The spiking responses of localized LGN relay cells will be nearly simultaneous when an oriented stimulus is presented at the target V1 neuron's preferred orientation, but the corresponding LGN relay cell responses will be spread out in time for nonpreferred stimulus orientations (see the inset in **Figure 1*b***). Even for nonpreferred stimuli, however, the total excitatory input from LGN relay cells is nonzero. A threshold is therefore required to render the spike output of the cell perfectly orientation selective, with no response at the null (orthogonal) orientation (Troyer et al. 1998, Finn et al. 2007).

One feature of their extracellular spiking records that may have prompted Hubel and Wiesel to propose the feedforward model is the resemblances between ON and OFF centers and surrounds of retinal ganglion cells and LGN relay cells and between ON and OFF regions of V1 simple cells. Yet this observation was not sufficient to confirm the feedforward model. Instead, clear validation of their proposal required that the receptive field properties of the LGN relay cells providing direct input to orientation-selective V1 neurons have the correct polarity (ON and OFF preferences) and spatial selectivity to underlie orientation tuning. This prediction was not so readily testable, however, as it would require the experimental identification of pairs of directly connected LGN relay cells and target V1 neurons. It took 25 years for this prediction to be tested: In a set of landmark studies, two groups (Tanaka 1983, 1985; Reid & Alonso 1995) recorded simultaneously from relay cell–cortical cell pairs and compared their receptive field properties. Both research groups found that the polarity and spatial selectivity of LGN relay cell–V1 neuron pairs have matching polarity and spatial selectivity, supporting the model by Hubel and Wiesel for the emergence of orientation selectivity in V1.

These landmark studies demonstrated that the polarity and spatial selectivity of LGN relay cell–V1 neuron pairs are in register, as required by the feedforward model; another critical feature of the proposal by Hubel and Wiesel was that many LGN relay cells with spatially but specifically

offset receptive fields converge onto a single V1 neuron to generate its orientation selectivity. To uncover whether this functional anatomy existed, Chapman et al. (1991) took advantage of the columnar organization of orientation selectivity within V1 to analyze the spatial offset of the receptive fields of many LGN neurons. These investigators inactivated the cortex—and thus cortical neuron spiking responses—using $GABA_A$ agonist muscimol and measured the selectivity of the still-active LGN relay cell afferents to a single V1 orientation column. They identified LGN relay cells with spatially offset receptive fields, such that their aggregate receptive field was oriented along the orientation of the cortical column under study. Together with the previous paired-cell experiments described above, it became evident that the biological underpinnings speculated by Hubel and Wiesel so many years ago do indeed exist in a manner consistent with the generation of orientation-selective receptive fields in the neurons of V1.

Although consistent with the model by Hubel and Wiesel for the generation of oriented receptive fields in V1, these results were not sufficient to exclude other cortical influences on the generation of V1 orientation selectivity. In the mid to late 1990s, inactivation studies were performed to uncover whether LGN relay cell inputs to V1 are sufficient to support orientation tuning or whether additional cortical network activity would be required. To determine the degree that cortical inputs shaped orientation selectivity, Ferster and colleagues inactivated the cortex—first via cooling and later via electrical shock—and measured its impact on V1 orientation tuning (Ferster et al. 1996, Chung & Ferster 1998). Experimentally, inactivating the cortical circuitry posed a problem, as inactivation would also remove the spiking responses of cortical neurons, typically utilized for measuring orientation selectivity. To circumvent this problem, Ferster et al. (1996) performed technically challenging experiments using intracellular recordings in vivo, allowing for the recording of subthreshold responses of V1 neurons to measure orientation tuning in both the presence and absence of cortical activity. They found that V1 neuron orientation selectivity is largely unaffected by cortical inactivation, providing evidence that the aggregate receptive field properties of LGN relay cells providing input to individual V1 neurons are sufficient to underlie V1 orientation selectivity and that active cortical circuitry is not required to refine said orientation selectivity.

The inactivation experiments performed by Ferster and colleagues indicate that orientation selectivity exists in the inputs to individual cortical neurons, but that selectivity could emerge either from the convergence of LGN neurons with spatially offset receptive fields, as Hubel and Wiesel originally proposed, or from the orientation selectivity of LGN relay cells. Evidence for subcortical orientation selectivity has been observed in carnivores, where orientation biases have been associated with systematic asymmetries of retinal ganglion cell arbors (Boycott & Wassle 1974, Cleland & Levick 1974, Hammond 1974, Levick & Thibos 1980, Leventhal & Schall 1983, Shou et al. 1995). Vidyasagar and colleagues (1996) proposed a simple model in which these asymmetries add to the original framework by Hubel and Wiesel to generate orientation tuning (Pei et al. 1994). In their model, the weak selectivity in thalamocortical inputs is combined with LGN receptive-field spatial overlap (**Figure 1*c***). As long as radial biases are parallel to the spatial organization of LGN receptive fields, then stimuli oriented along that axis should generate a larger synaptic input onto cortical neurons. This selectivity would be further enhanced either by dendritic nonlinearities such as voltage-gated ion channels (Smith et al. 2013) or through the transformation of the membrane potential to action potentials in cortical simple cells (Pei et al. 1994, Vidyasagar et al. 1996, Volgushev et al. 1996).

Although research on orientation selectivity has focused on its emergence in carnivores and primates, recent studies have focused on uncovering the mechanisms underlying orientation selectivity in rodents. The mouse provides an opportunity to exploit recent advances in genetic labeling of specific neuronal subsets, in optogenetics, and in imaging. These techniques promise

an even more detailed and fine-grained understanding of the contribution cortical circuitry makes to the emergence of orientation selectivity than has so far been possible in carnivores and primates. As in carnivores, a critical first step to studying the emergence of orientation selectivity was to determine the degree of selectivity in the convergent input from the LGN onto V1. Lien & Scanziani (2013) isolated the orientation selectivity of synaptic inputs by expressing ChR2 in inhibitory neurons expressing parvalbumin (Lien & Scanziani 2013). Activating those inhibitory neurons suppresses cortical neurons but spares the afferent input from the thalamus, which was measured using intracellular recording. Similar to the inactivation studies performed by Ferster and colleagues, orientation selectivity is evident in the thalamic inputs, suggesting that the basis for orientation selectivity is common across mammals.

Despite the evidence showing similarities between mammals for how orientation selectivity emerges, there are also systematic differences in the functional organization across mammals. Mouse receptive fields as well as preferred stimulus size are almost ten times larger than those in the cat. Whereas the visual cortex of carnivores and primates is characterized by columns of neurons with similar orientation selectivity, mouse visual cortex is characterized by a relative lack of functional organization, termed salt-and-pepper in which neurons with distinct selectivities are positioned near one another (Ohki et al. 2005, 2006; Ohki & Reid 2007; Ko et al. 2011). Mice also do not have the pattern of functional segregation by layer that carnivores and primates exhibit in which neurons in input layer 4 tend to be simple cells and those in the superficial layers tend to be complex cells (Hubel & Wiesel 1962, 1977; Martinez et al. 2005). In mice, simple and complex cells are distributed evenly across cortical layers (Niell & Stryker 2008). These differences in the functional architecture of orientation selectivity have emerged along with indications that the functional specificity of the afferent input from the LGN is distinct in mice relative to carnivores. In particular, it is now clear that many thalamic relay cells in mice exhibit orientation and direction selectivity (Marshel et al. 2012, Piscopo et al. 2013, Scholl et al. 2013a, Zhao et al. 2013). These selective inputs appear primarily to innervate both the superficial layers of the visual cortex (Cruz-Martin et al. 2014, Kondo & Ohki 2016) and layer 4 of the visual cortex (Sun et al. 2016). The precise role that orientation-selective thalamic inputs play in the generation of cortical orientation selectivity is still not clear: Orientation selectivity in the cortex could be reconstructed de novo, or these biases could form the basis for cortical orientation selectivity (**Figure 1*c***).

There remains a controversy about the impact of thalamic orientation selectivity on cortical orientation selectivity (Piscopo et al. 2013, Scholl et al. 2013a, Zhao et al. 2013, Vidyasagar & Eysel 2015, Kondo & Ohki 2016, Sun et al. 2016), but there is general consensus in the field supporting the original feedforward model by Hubel and Wiesel that the basic organization of V1 simple cell receptive fields, including their orientation preference, is derived from the LGN relay cell input received by these V1 neurons. The success of the feedforward model in describing this cortical computation has led to the view that new receptive field profiles emerge at each processing station by combining excitatory inputs with differing receptive field profiles, thus generating a novel and more complex receptive field. Less certain, however, is whether the feedforward model is sufficient to explain the menagerie of other V1 simple cell response properties beyond orientation selectivity or whether additional circuit elements and mechanisms are required. Indeed, a number of these other V1 receptive field properties are inconsistent with a purely linear feedforward model and suggest an important role for cortical inhibition in sculpting selectivity. Two such receptive field profiles have been the focus of intense study precisely because their appearance may be at odds with the simple framework of Hubel and Wiesel: contrast-invariant orientation tuning width and cross-orientation suppression. I begin by presenting the perspective on how these response properties emerge from a feedforward model before discussing the potential role of inhibitory interactions.

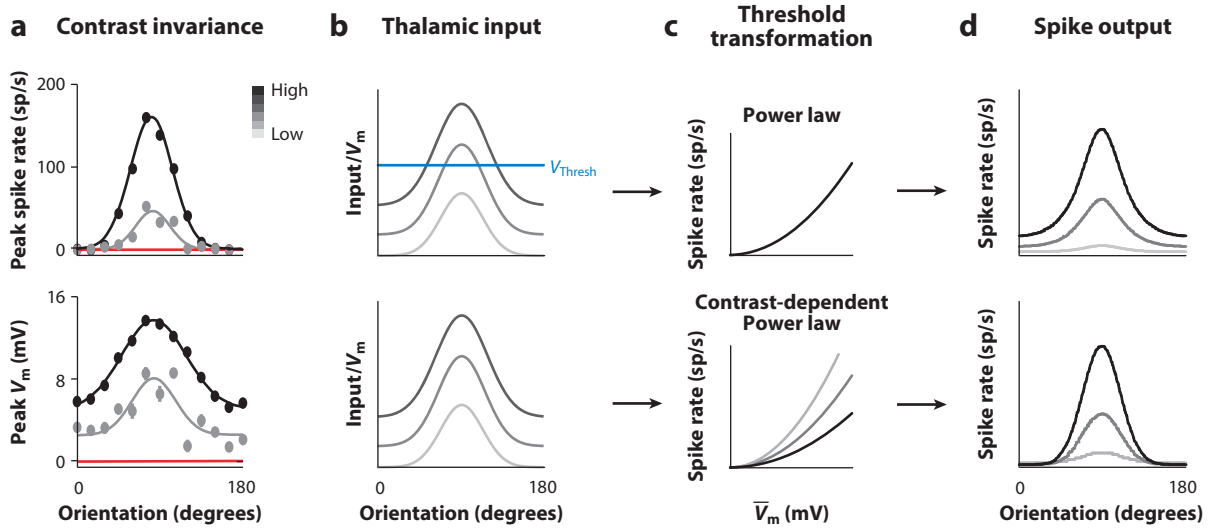

Figure 2

Emergence of contrast-invariant orientation tuning in the primary visual cortex (V1). (*a*) Example of contrast-invariant orientation tuning in cat V1. The spike-rate orientation tuning width is invariant to contrast, whereas membrane potential orientation tuning rises with increases in contrast. (*b*) Model of peak thalamic input to a cortical neuron. (*Top*) If a threshold is applied to the input tuning curves (*blue line*; V_{Thresh}), the tuning width will increase with increasing contrast. (*c*) Model transformation between membrane potential and spike rate. (*Top*) A power law describes the transformation between the mean membrane potential and spike rate for many cortical neurons. The power law depends on the variability of the membrane potential. The relationship is steeper for low-contrast stimuli with high membrane potential variance (*light gray*) than it is for high-contrast stimuli with low membrane potential variance. (*d*, *top*) A simple thalamic input model passed through a single power-law transformation predicts spike-rate responses that are not contrast invariant, whereas (*bottom*) a power-law transformation that depends on contrast predicts contrast-invariant tuning. Figure adapted from Finn et al. (2007). Abbreviation: sp, spikes; V_m, membrane potential.

CONTRAST-INVARIANT ORIENTATION TUNING IN V1

V1 simple cells maintain the shape and width of their tuning curves for orientation despite large changes that may occur in stimulus contrast (Sclar & Freeman 1982, Skottun et al. 1987, Alitto & Usrey 2004, Finn et al. 2007) (**Figure 2*a***). Whereas the amplitude of simple cell spiking responses changes systematically with stimulus contrast, the range of orientations that is able to elicit responses remains the same and does not depend on stimulus contrast.

This contrast-invariant feature of V1 neuron orientation selectivity presents a fundamental challenge to the simple feedforward models proposed by Hubel and Wiesel, largely as a consequence of what is termed the iceberg effect: At any stimulus orientation, increasing stimulus contrast increases the activity of LGN relay cells, thereby increasing the synaptic input to the target V1 simple cell across stimulus orientations. As the synaptic (LGN) input increases with contrast at all orientations, increasingly more orientations should evoke cortical responses that rise above threshold; therefore, the tuning width of the cortical spike output should broaden (**Figure 2*b***), thereby breaking contrast invariance.

Cross-orientation inhibition has long been invoked as a possible solution to this problem (see discussion of corresponding models below). Briefly, cortical inhibition tuned to the nonpreferred orientation, or to a broader set of orientations, could suppress any depolarization and spiking evoked by such nonpreferred stimuli. Threshold could then be lowered so that low-contrast stimuli of the preferred orientation evoke spikes, as is observed in V1 simple cells (**Figure 2*a***).

The feedforward model and the cross-orientation inhibition model make very distinct predictions about changes in membrane potential in simple cells evoked by stimuli presented in the null orientation. The feedforward model predicts that because LGN relay cells are not selective for orientation, the mean excitation evoked by null-oriented stimuli should be just as large as that evoked by preferred stimuli (although the peak depolarization at the preferred orientation is much larger). With cross-orientation inhibition, the net change in membrane potential evoked by null-oriented stimuli should be zero or negative. For a population of 120 V1 simple cells, however, null-oriented stimuli were observed to evoke a significant depolarization, on average 43% as large as that evoked by the preferred orientation stimulus (Finn et al. 2007). Further, the amount of null-evoked depolarization was equal to the proportion of excitatory input V1 simple cells received directly from the LGN (Finn et al. 2007). The more excitatory input a simple cell received from other cortical neurons, the less the null stimulus evoked depolarization, presumably because cortical neurons are strongly orientation selective and respond weakly at the null orientation. These results appear inconsistent with either untuned inhibition or cross-orientation inhibition serving primary roles in the generation of contrast-invariant orientation tuning.

An alternative proposal to a role for inhibition relies on changes in response variability that occur with stimulus contrast. Membrane potential responses vary dramatically on a trial-to-trial basis, and this variability affects the relationship between mean membrane potential and firing rate. Both trial-to-trial variability and moment-to-moment synaptic noise tend to smooth the relationship between average membrane potential and average spike rate so that there is no longer a sharp inflection. Instead, spike rate rises gradually with membrane potential, starting right from the resting membrane potential (**Figure 2*c***). This transformation from smoothed membrane potential to spiking narrows orientation tuning curves at all contrasts by approximately the same amount (Anderson et al. 2000b, Hansel & van Vreeswijk 2002, Miller & Troyer 2002).

Even after taking into account the smoothing of the relationship between membrane potential and spike rate, however, contrast invariance will still break down in the feedforward model at low spike rates; the predicted response to a high-contrast stimulus of the null orientation, though small, is still larger than the response predicted for a low-contrast stimulus at the preferred orientation (**Figure 2*d***). The solution to this problem comes from the observation that trial-to-trial variability of the membrane potential is contrast dependent (Finn et al. 2007). Variability increases with decreasing contrast, and because trial-to-trial variability is partly responsible for carrying the membrane potential above threshold, an increase in variability generates an increase in spikes, even when mean membrane potential is unchanged (**Figure 2*c***). As a result, even though a low-contrast stimulus of the preferred orientation evokes a smaller depolarization than does a high-contrast stimulus of the null orientation, it evokes more spikes. The null stimulus almost never evokes spikes, either because the underlying mean depolarization is too low (low contrast) or because the trial-to-trial variability is too low (high contrast). Contrast invariance therefore appears in the spike output of V1 simple cells, without any requirement for lateral cortical inhibition, even when the visually evoked synaptic inputs are not invariant (**Figure 2*d***) (Finn et al. 2007). Although this explanation for contrast-invariant orientation tuning does not explicitly include a role for inhibition, inhibition may nonetheless be a critical factor in shaping the degree of trial-to-trial variability. One potential source is trial-to-trial changes in cortical excitability. This could result from intracortically generated shunting inhibition, for example, which could modulate variability in a contrast-dependent manner (Monier et al. 2003), perhaps in association with the occurrence of cortical up and down states (Stern et al. 1997, Haider & McCormick 2009). Measures of membrane potential variability when the cortical circuit is inactivated, however, indicate that intracortical circuitry does not alter response variability in a contrast-dependent manner (Sadagopan & Ferster 2012).

An alternative source of contrast-dependent changes in cortical response variability is the feedforward thalamic input. In this hypothesis, correlated fluctuations in the retina and the LGN are suppressed during visual stimulation. To test this possibility, Sadagopan & Ferster (2012) made simultaneous extracellular recordings from groups of nearby LGN cells and constructed a simple model to test whether thalamic input would exhibit the changes in variability required to account for contrast-invariant orientation tuning. Their predicted input to V1 neurons matches the changes in response variability found in real simple cells in both the relative amplitude of the mean responses and the contrast-dependent—and relatively orientation-independent—change in trial-to-trial variability. This explanation for the emergence of contrast-invariant orientation tuning is constrained by the measured biophysics of the feedforward input and suggests that inhibition is not a required element.

CROSS-ORIENTATION SUPPRESSION IN V1

The most compelling evidence that the simple feedforward model cannot account for the response selectivity of V1 simple cells has come from the strong functional interactions between stimuli of different orientations, called cross-orientation suppression. In psychophysical experiments, detectability of an oriented stimulus (test) is lowered by superimposing another stimulus of orthogonal orientation (mask) (Campbell & Kulikowski 1966). At the single-cell level, spike responses of a V1 neuron to a stimulus of the preferred orientation are reduced by superimposing an orthogonal stimulus (Bishop et al. 1973) (**Figure 3*a*,*b***). Spiking responses to high-contrast preferred-orientation stimuli can be suppressed by as much as 50%; spiking responses to low-contrast preferred-orientation stimuli can be suppressed almost entirely. It has long been thought that this suppression arises from inhibition between cells with orthogonal preferred orientations. In support of this interpretation, antagonists of $GABA_A$-mediated inhibition reduce cross-orientation suppression in visual evoked potentials (Morrone et al. 1982, 1987).

Cross-orientation may be a cortical phenomenon because it seems sensitive to the orientation of the mask, but there are aspects of cross-orientation suppression that also seem at odds with cortical inhibition as its source. First, cross-orientation suppression is largely monocular (Ferster 1981, Walker et al. 1998); a null-oriented mask stimulus presented to one eye has little effect on a preferred orientation test stimulus presented to the other eye, whereas the majority of cortical neurons, presumably including inhibitory interneurons, are binocular. Second, strong suppression can be evoked by mask stimuli of high temporal frequency, beyond the frequencies to which most cortical neurons can respond (Freeman et al. 2002). Third, suppression is insensitive to contrast adaptation, whereas the responses of most cortical cells—presumably including inhibitory interneurons—are strongly suppressed by adaptation (Freeman et al. 2002). Fourth, the onset of suppression is coincident with the onset of neuronal responses, leaving no time for the activation of inhibitory circuits (Smith et al. 2006). Finally, evidence from intracellular recording for strong inhibition evoked by stimuli of orthogonal orientation is equivocal, and both inhibition and excitation appear to decrease when test and mask stimuli are presented (Priebe & Ferster 2006).

All these properties of cross-orientation suppression are more reminiscent of LGN relay cells than of V1 inhibitory interneurons: Relay cells are monocular, respond at high temporal frequency, adapt little to contrast, and respond simultaneously with excitatory input to the cortex. Thus, cross-orientation suppression may arise from nonlinear interactions within the LGN relay cell pathway (Ferster 1986, Carandini et al. 2002). One such nonlinearity is synaptic depression: The mask stimulus could increase the level of depression at the synapses between relay cells and cortical cells, thereby reducing the excitatory drive evoked by the test stimulus. Because thalamocortical depression may not be strong enough to account fully for strong cross-orientation suppression

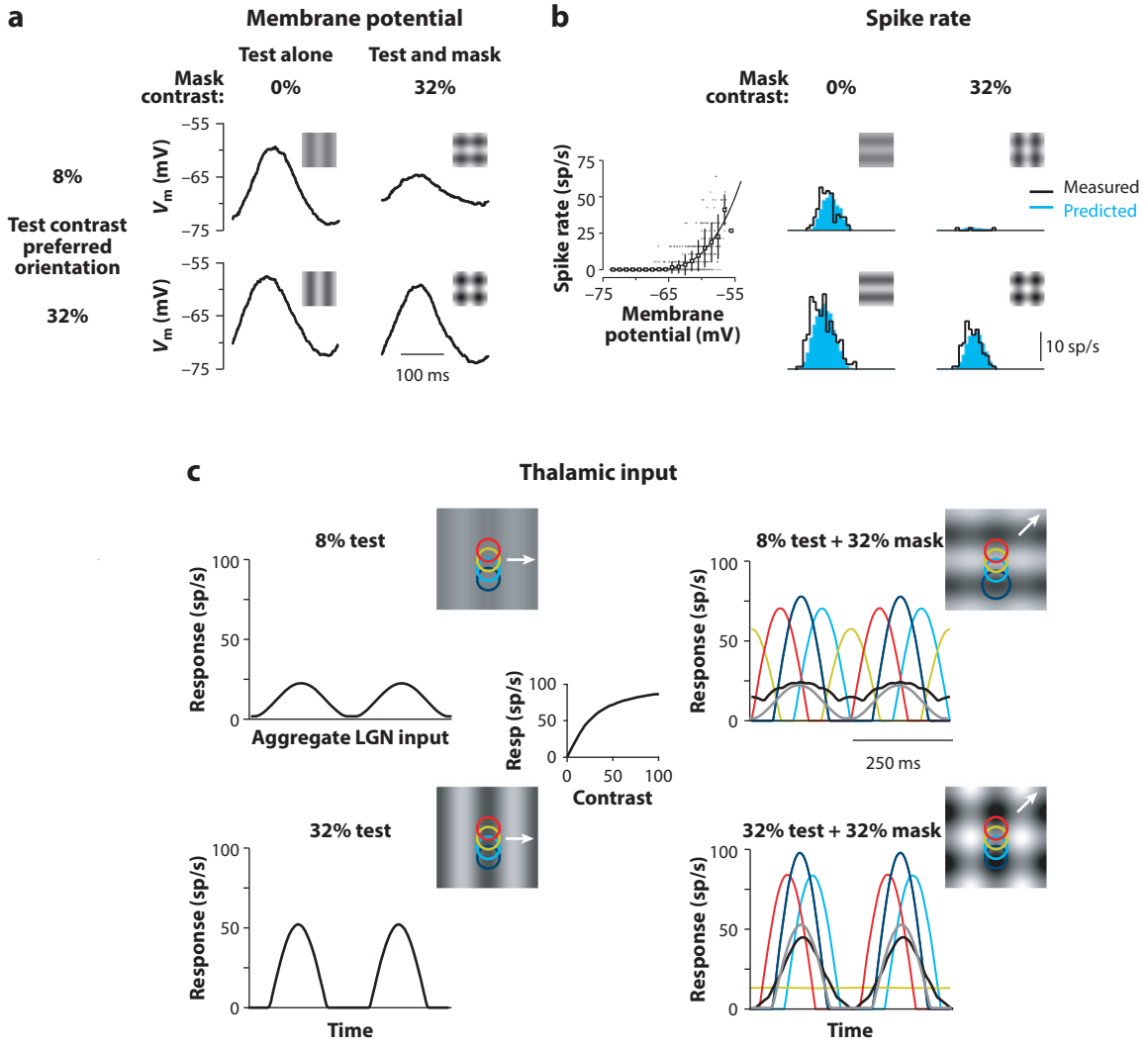

Figure 3

Cross-orientation suppression in models and responses of simple cells. (*a*) Membrane potential responses are shown for four different grating and plaid stimuli. Simple cells in the primary visual cortex demonstrate strong cross-orientation suppression when a 32% mask is presented with an 8% test stimulus, but they show more mild suppression when both test and mask have matched contrasts. (*b*) Spike-rate responses to the same stimulus conditions show a dramatic increase in cross-orientation suppression: (*Inset*) the mean relationship between membrane potential and spike rate; (*cyan histograms*) predictions of spike rate based on the mean membrane potential and power-law transformation. (*c*) Spiking responses of model lateral geniculate nucleus (LGN) relay cells are shown in the colors of their receptive field centers, and the aggregate response is shown in black. For the two conditions with no mask stimulus (*left panels*), aggregate and individual relay cell responses are equivalent. For conditions in which a mask is also presented, there are systematic changes in the amplitude and timing of relay cell responses. Gray indicates the response to the test stimulus alone, and white arrows indicate the direction of perceive motion. Abbreviations: sp, spikes; V_m, membrane potential.

(Boudreau & Ferster 2005, Li et al. 2006, Reig et al. 2006), cross-orientation suppression may also arise from two nonlinearities in the responses of LGN relay cells: contrast saturation and firing-rate rectification (Ferster 1986, Li et al. 2006, Priebe & Ferster 2006).

To understand how nonlinearities in the feedforward pathway generate cross-orientation suppression, it is useful to consider how LGN relay cells respond to drifting gratings. LGN relay cells modulate their response to drifting gratings, but their responses are not purely sinusoidal. Because LGN relay cells have a low spontaneous firing rate, high-contrast drifting gratings induce response rectification, clipping the neuronal response at zero spikes per second (**Figure 3*c***). Further, LGN relay cell responses do not increase linearly with contrast, instead saturating for contrasts above 32% (see in the inset in **Figure 3*c***). These two nonlinearities have strong effects on the total input that a target V1 neuron receives when a stimulus composed of preferred (test) and orthogonal (mask) gratings is presented.

The presentation of the superimposed test and mask gratings (i.e., a plaid stimulus) causes systematic changes in the contrast of the stimulus for each LGN relay cell. When test and mask contrasts are matched in the plaid stimulus, some LGN relay cells will encounter locations in the plaid stimulus where the dark bars from the two gratings superimpose, alternating with the locations where the bright bars superimpose (the blue cell in the bottom right of **Figure 3*c***). The result is a luminance modulation exactly twice as large as that generated by either grating stimulus alone. For other LGN relay cells, their receptive fields lie at a location within the plaid stimulus where the bright bars from one grating superimpose on the dark bars from the other grating. As a result, there is no modulation of luminance in the relay cell's receptive field, and its response falls to zero (the gold cell in the bottom right of **Figure 3*c***). Including the mask stimulus therefore causes systematic shifts in the contrast of the stimulus that falls over each LGN relay cell's receptive field.

For a purely linear system, these changes in contrast would not affect the total input to V1, but contrast saturation and response rectification exhibited by LGN relay cells significantly change cortical input. The response of relay cells that receive no contrast modulation still falls to zero because its stimulus has zero contrast. But, the response of relay cells that receive twice the contrast modulation does not double. Although the mask stimulus doubles the local contrast relative to the test stimulus alone, as the test stimulus was already nearly saturating, the relay cell's response increases only slightly. For low-contrast test gratings, mask gratings cause a dramatic reduction (almost 50%) in the amplitude of the modulation input (**Figure 3*c***).

Suppression of excitatory relay cell input to V1 simple cells as predicted by the nonlinear LGN model (15% for high-contrast test gratings and 50% for low-contrast test gratings) matches closely the observed suppression in the membrane potential responses of V1 simple cells (Priebe & Ferster 2006) (**Figure 3*a*,*c***). To account fully for the larger effects observed in V1 neuron spiking responses, it is necessary to take into consideration the nonlinearity of spike threshold. Threshold amplifies the effects of the mask gratings in the same way it sharpens orientation tuning. Together with the nonlinearity of relay cell responses, it accounts quantitatively for the cross-orientation effects in V1 simple cells (Priebe & Ferster 2006).

Although this model accounts for the mask-induced reduction in the modulation component of membrane potential, it also predicts a rise in the mean LGN input to V1 neurons, corresponding to an increase by approximately 50% in mean membrane potential (**Figure 3*c***). However, a large rise in the mean is not observed experimentally. Short-term synaptic depression at the thalamocortical synapse (Carandini et al. 2002, Freeman et al. 2002) or the fact that many simple cells receive less than half of their excitatory input from the LGN (Ferster et al. 1996, Chung & Ferster 1998) may account for this discrepancy. The change in cortical response variability that is also seen when an orthogonal stimulus is presented could also contribute to the lack of a large

mean increase to cortical neurons. As shown for contrast-invariant orientation tuning, stimulus contrast reduces trial-to-trial response variability in cortical simple cells, regardless of whether the stimulus is at the preferred (test) or orthogonal (mask) orientation. Also similar to contrast-invariant orientation tuning, an account of cross-orientation suppression is consistent with the feedforward circuitry proposed by Hubel and Wiesel and does not require cortical inhibitory circuitry to sculpt orientation selectivity.

Although feedforward models may account for aspects of orientation selectivity in V1, there is also clear evidence that the functional architecture within V1 contributes to orientation selectivity. For example, orientation tuning width, at the level of spike rate, is related to the diversity in the selectivity of nearby neurons. V1 neurons within iso-orientation domains, where surrounding neurons prefer similar orientations, have more narrow orientation tuning than do neurons in domains with larger heterogeneity of orientation preference (e.g., pinwheels) (Nauhaus et al. 2008). In addition, the degree of cross-orientation suppression also depends on the local homogeneity of orientation preference: Greater cross-orientation suppression exists in iso-orientation domains than in heterogeneous-orientation domains (Koch et al. 2015). Therefore, although feedforward models for the emergence of orientation selectivity are able to account for many aspects of V1 orientation selectivity, interactions within the visual cortex, particularly between nearby neurons, also sculpt selectivity. As yet, it is unclear whether those influences are primarily between excitatory neurons, inhibitory neurons, or both.

THE ROLE OF INHIBITION IN ORIENTATION SELECTIVITY

Psychophysics has suggested a comprehensive solution to the origin of simple cell orientation selectivity: In the tilt-aftereffect illusion, the perceived orientation of a set of vertical lines is shifted away from vertical after prolonged viewing of a slightly oblique set of lines. This result was interpreted to mean that intracortical inhibition, specifically inhibition between cortical neurons of different preferred orientations, may sharpen orientation tuning or even create it de novo (Blakemore & Tobin 1972). This proposal was strengthened by pharmacological experiments: Cortical application of $GABA_A$ antagonists causes a broadening of orientation tuning (Sillito 1975), whereas agonists reveal cross-orientation inhibition (Eysel et al. 1990). Cross-orientation inhibition is a form of lateral inhibition (Hartline 1949) found in the orientation rather than the spatial domain. It is considered a natural extension of similar mechanisms either observed or proposed to operate throughout the brain. Because of the columnar organization of orientation preference in the cortex, the orientation domain translates into the spatial domain on the cortical surface. Cross-orientation inhibition can then emerge from simple, spatially defined rules of cortical connectivity.

Inhibition in the visual cortex may operate in several ways according to orientation dependence and amplitude of the inhibitory interconnections. In attractor models, feedback inhibition forms a set of multistable attractors (Ben-Yishai et al. 1995, Somers et al. 1995), where the width of orientation tuning of V1 cells is determined by the lateral extent of cortico-cortical connections (**Figure 4*a***). In recurrent models, recurrent excitatory connections amplify feedforward inputs in a way that is sculpted by lateral inhibitory connections (Douglas et al. 1995). Here again, the tuning width and other aspects of cortical responses are primarily set by intracortical rather than thalamocortical interconnections (**Figure 4*b***). In balanced models, strong recurrent excitation and inhibition are thought to balance each other tightly (van Vreeswijk & Sompolinsky 1996, 1998; Hansel & van Vreeswijk 2012) (**Figure 4*c***). This balance can explain the large variability of cortical spiking responses (Shadlen & Newsome 1998) as well as many other aspects of simple cell behavior. In push-pull models, cross-orientation inhibition is the result of feedforward inhibition from

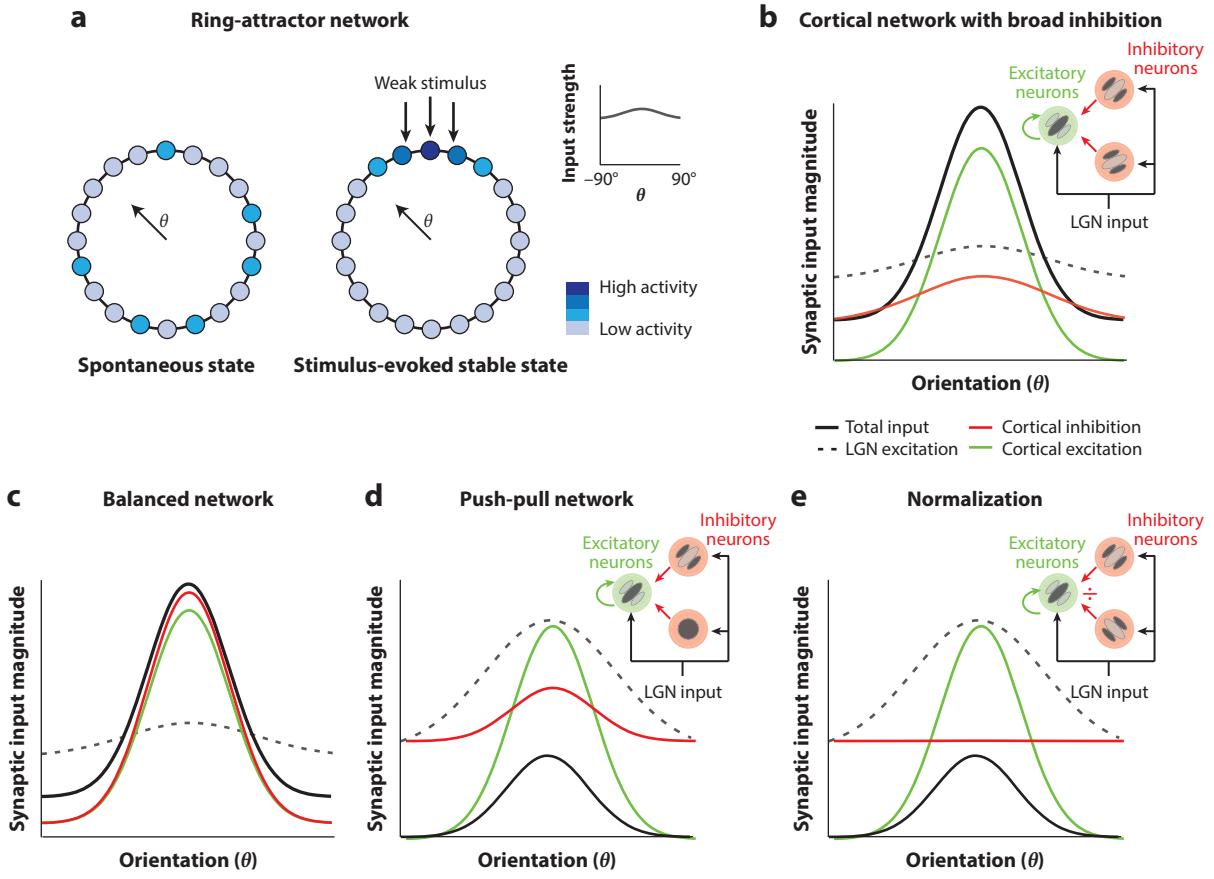

Figure 4

Cortical mechanisms of orientation tuning. (*a*) Ring attractor networks produce cortical orientation tuning independent of stimulus parameters. An attractor network representing all orientations (θ) explores distinct modes of activity without external input. Small external input, such as weak orientation selectivity from the lateral geniculate nucleus (LGN) (*inset*), pushes the ring into a stable configuration with neural activity centered around the orientation bias of the input. (*b*) Orientation tuning curves of different inputs onto a single cortical neuron in the model of Somers et al. (1995). Weakly tuned LGN excitation is combined with sharply tuned cortical excitation and more broadly tuned inhibition to generate orientation selective input. (*c*) Orientation tuning curves for a balanced network model or an inhibitory-stabilized network (Rubin et al. 2015). (*d*) Schematic of the layer 4 cortical circuit for push-pull inhibition and resulting orientation tuning curves. LGN relay cells innervate both cortical excitatory and inhibitory neurons. Inhibitory neurons provide suppressive input onto excitatory neurons. There are two inhibitory components: an orientation-selective with opposite receptive field phase component generating a push-pull network and an unselective contrast-sensitive component providing DC suppression. These components may arise from separate neuron populations (Hirsch et al. 2003). (*e*) Orientation tuning curves for a normalization model in which cortical excitatory neurons receive divisive inhibitory inputs from neuron with similar and distinct preferences for orientation.

simple cell-like inhibitory interneurons (Troyer et al. 1998, 2002), which receive no inhibition and thus fire at null orientation, helping to establish contrast-invariant orientation tuning (**Figure 4*d***). In normalization models, a large pool of cortical interneurons of varying preferred orientations generates shunting inhibition proportional in strength to the stimulus contrast at all orientations (DeAngelis et al. 1992, Heeger 1992, Carandini & Ringach 1997). Thus, excitatory thalamic inputs are normalized (divided) by a signal proportional to contrast (**Figure 4*e***). Normalization

models have been highly successful in explaining many contrast-dependent nonlinear properties of simple cells such as cross-orientation suppression.

Feedforward explanations for orientation selectivity described in the previous section are able to generate orientation tuning without cortical inhibition only if specific assumptions are made. For example, to account for contrast-invariant orientation tuning, the change in variability could be subcortical, and yet cortical inhibition could also play a role in controlling response variability. The change in effective threshold could be caused by changes in membrane potential variance, but it could also result from a change in the balance of excitation and inhibition (Holt & Koch 1997, Chance et al. 2002). V1 neurons that receive monosynaptic LGN input also receive considerable cortical input (Finn et al. 2007). Because a given depolarization could arise from a continuum of possible excitatory-to-inhibitory ratios, the mix of excitation and inhibition that comprises the cortical contribution is not well constrained.

To account for contrast-invariant orientation tuning, Troyer et al. (1998) began with a purely feedforward model and extended it to include cortical excitation and inhibition (Troyer et al. 1998). V1 neurons receive excitatory LGN input that has two components: one modulated component that varies with spatial phase and is orientation tuned and another temporally unmodulated component that is phase insensitive and entirely untuned for orientation. Troyer et al. (1998) demonstrated that the untuned component of the LGN input could disrupt contrast invariance and suggested that cortical inhibitory neurons that are tuned for orientation but respond to all orientations could counteract this untuned component.

To explain how inhibitory neurons suppress the untuned component from the LGN, Troyer et al. (1998) initially proposed a model with inhibitory neurons that are contrast variant, as opposed to their excitatory counterparts. Alternatively, it is also possible to construct a model in which the excitatory and most inhibitory simple cells are contrast invariant, but where an additional set of inhibitory neurons, characterized as nonorientation-tuned complex cells, act to cancel the untuned component of the net thalamic input (Lauritzen & Miller 2003). Both forms of the model by Troyer et al. (1998) predict the existence of cortical inhibitory neurons whose spike response properties differ substantially from those of cortical excitatory neurons. Evidence has demonstrated distinct receptive field properties for excitatory and inhibitory cortical neurons, but the relative frequency with which excitatory and inhibitory neurons exhibit receptive field differences is still not known (Martin et al. 1983, Ahmed et al. 1997, Azouz et al. 1997, Hirsch et al. 2003, Cardin et al. 2007, Nowak et al. 2008).

Troyer et al. (1998) also suggested a particular architecture for inhibitory and excitatory neurons in terms of spatial preference. They suggested that inhibitory neurons converge onto excitatory neurons in the push-pull architecture: If a bright bar at a particular location elicits an increase in excitation, a dark bar at the same location elicits an increase in inhibition. Indeed, when spots or bars of light are flashed at different positions in the receptive field, membrane potential records indicate a characteristic push-pull spatial receptive field structure: Where bright spots of light evoke excitation, dark spots evoke inhibition; where dark spots evoke excitation, light spots evoke inhibition (Hirsch et al. 1998). This push-pull architecture in spatial receptive fields is also revealed in responses to moving sinusoidal gratings where excitation and inhibition are temporally out of phase (Ferster 1988, Anderson et al. 2000a, Monier et al. 2003, Priebe & Ferster 2006). This push-pull relationship between excitation and inhibition thus places constraints on the circuitry underlying cortical receptive fields.

Further, the model by Troyer et al. (1998) predicts that moving sinusoidal gratings evoke inhibition that contains an untuned inhibitory component. This is consistent with the imperfect push-pull network suggested by Borg-Graham et al. (1998) and with the clear excitatory and inhibitory responses evoked by gratings oriented orthogonally to those that evoke maximal responses

(Borg-Graham et al. 1998, Monier et al. 2003, Priebe & Ferster 2006). Finally, as suggested by Troyer et al. (1998), excitatory and inhibitory inputs to most cortical neurons appear to have the same preferred orientation and similar tuning widths (Ferster 1988, Anderson et al. 2000a, Monier et al. 2003, Marino et al. 2005).

Even though measures of excitation and inhibition provide support for the proposal by Troyer et al. (1998), they do not yet distinguish between alternative models of cortical architecture. For example, compared with excitatory input, inhibitory input may be more broadly tuned (Ben-Yishai et al. 1995, Somers et al. 1995). Sharp orientation selectivity in these models is produced by recurrent horizontal connections between V1 neurons in the same cortical layer. When considering horizontal connections, researchers have also used the characteristic two-dimensional pinwheel pattern of orientation selectivity across the cortex to model the functional organization of V1 (McLaughlin et al. 2003). Subthreshold inputs to neurons close to pinwheel centers, as well as their spiking responses, are more broadly tuned and more variable than are those to neurons distal from pinwheels centers (Schummers et al. 2002, 2004; Marino et al. 2005; Nauhaus et al. 2008). The cortical functional map may therefore influence synaptic input; thus, the generation of the receptive field in V1 could also depend critically on local cortical architecture (Stimberg et al. 2009).

Finally, orientation selectivity appears to emerge in considerably diverse ways. Monier et al. (2003) demonstrated, for example, that excitation and inhibition are cotuned for some neurons but have distinct orientation preferences for others (Volgushev et al. 1993, Monier et al. 2003, Fregnac & Bathellier 2015). In stark contrast, according to the above models, excitatory and inhibitory circuit elements that generate orientation selectivity follow simple and stereotyped architectures. One of the methods that may be employed to create diversity in the cortical circuitry is to include the spatial distribution of preferred orientations on the cortical surface (Stimberg et al. 2009). Finally, diversity in the circuitry may be a result of differences in circuit elements across cortical layers (Martinez et al. 2002). In sum, the apparent diversity of mechanisms may reflect the presence of multiple methods to generate orientation selectivity, or it may be the consequence of our limited perspective on cortical circuitry.

THE ROLE OF BIOPHYSICAL PROPERTIES OF NEURONS IN SELECTIVITY

Among the biophysical mechanisms that contribute to cortical receptive fields, intrinsic neuronal nonlinearities exert a large influence. Cortical neuron membrane potential normally rests well below threshold, and there is very little spontaneous activity (Deweese & Zador 2004, Tan et al. 2014). The resulting iceberg effect narrows orientation tuning for spikes relative to membrane potential by as much as threefold or more, increases direction selectivity by at least fourfold (Carandini & Ferster 2000, Lampl et al. 2001, Finn et al. 2007, Nowak et al. 2010, Tan et al. 2014), increases spatial frequency selectivity (Lampl et al. 2001), enhances the distinction between simple and complex cells (Priebe et al. 2004), increases both direction and disparity selectivity (Scholl et al. 2013b), and increases ocular dominance (Priebe 2008, Scholl et al. 2013b). Because of the iceberg effect, cortical connections need not be nearly as specific as they appear to be in measurements derived from spike responses: Threshold conceals membrane potential responses at the periphery of the tuning curve. Threshold might also have important implications for cortical plasticity and development. The dramatic changes seen, for example, in ocular dominance plasticity are most often measured from spike responses. Changes in spike responses, however, are surely generated by smaller shifts in the ocular dominance of membrane potential responses and therefore by relatively smaller changes in connectivity (Priebe 2008, Scholl et al. 2015).

SPONTANEOUS ACTIVITY AND CORTICAL DYNAMICS

The work detailed thus far has sought to understand a V1 neuron's receptive field via its neuronal responses to visual stimuli. Studies have also probed spontaneous cortical network activity to understand the circuitry underlying the receptive field. By demonstrating which aspects of the cortical circuit are synchronously active, ongoing spontaneous activity in the absence of a visual stimulus may reveal much information regarding the overall connectivity and functional structure of V1 (Arieli et al. 1995, 1996; Shoham et al. 1999; Tsodyks et al. 1999; Fitzpatrick 2000; Kenet et al. 2003; Nauhaus et al. 2009; Tan et al. 2014). Although ongoing spontaneous activity could represent a background cortical state to which the cortical network relaxes in the absence of a stimulus, experimental evidence suggests it may represent dynamic switching between a set of intrinsic cortical states that are also present during stimulus-driven activity. For example, spontaneous cortical activity is often highly correlated with activity elicited by a single orientation when imaged using voltage-sensitive dye (Tsodyks et al. 1999, Kenet et al. 2003). The spatial structure of these spontaneous activity patterns reveals an underlying cortical circuitry in which neurons with similar orientation selectivity are coupled across the cortex. Surprisingly, spontaneous maps resembled the evoked maps with a correlation coefficient almost as high as the relationship found between a single stimulus presentation and an averaged orientation map. Over the duration of the experiment, the relationship between instantaneous spontaneous activity and an averaged orientation map fluctuated between high and low correlations with a Gaussian distribution. However, when correlating spontaneous activity with an arbitrary orientation map not found during evoked activity, such as the inverse of a stimulus-evoked map, high correlations disappeared, resulting in a narrower distribution of correlation coefficients. Because high correlations were found across all stimulus-evoked orientations, Grinvald and colleagues suggested that ongoing activity in V1 reflected dynamic switching between a set of intrinsic states, many of which correspond closely to stimulus-evoked orientation maps (Kenet et al. 2003, Goldberg et al. 2004).

To make constraints on the cortical architecture and connectivity that could give rise to the dynamic network behavior observed by Grinvald and colleagues, investigators have proposed different models that could result in similar dynamics. One proposal that reproduced these dynamics is a cortical network with balanced amplification, a circuit characterized by strong recurrent excitation and stabilized by feedback inhibition (Murphy & Miller 2009, Rubin et al. 2015). The interplay between excitation and inhibition in this architecture could allow the cortical circuit to distinguish and amplify specific activity patterns from unstructured inputs. In this manner, noisy inputs result in spontaneous activity that switches among activity modes that are similar to those found in stimulus-evoked orientation maps, as observed by optical imaging.

Other studies have suggested that the similarity between spontaneous and evoked cortical maps could be equivalent to switching among attractor states in a dynamical system (Ben-Yishai et al. 1995, Goldberg et al. 2004). In this perspective, cortical dynamics are assumed to settle into attractor states that are manifested as activity patterns across the cortex and are determined by the underlying functional connectivity of the network. Goldberg et al. (2004) examined whether spontaneous maps in the visual cortex, as observed by Kenet et al. (2003), were a result of a single background state or multiple attractor states with noise-driven spontaneous switching between the two states. Comparison of a single-state model to a ring attractor, where each location on the ring corresponds to an orientation preference, revealed that a single-state model reproduced the observed Gaussian-distributed correlations more robustly than did a ring-attractor model (see **Figure 4*c***).

Although many open questions remain regarding the similarity between spontaneous and evoked activity in V1, ongoing cortical activity and its relationship and interaction with stimulus-evoked responses could provide insight into the circuit architecture and functional connectivity of

cortical networks and their role in sensory perception. The high variability present in spontaneous cortical activity could degrade response reliability. Such response unreliability—potentially the root source of creativity—is an essential component for reinforcement learning, which enables organisms to adapt to changing environments (Barto et al. 1983, Mazzoni et al. 1991). Although such a role for spontaneous activity is highly speculative, the requisite synaptic plasticity is present in V1 (Fregnac et al. 1988, Gilbert et al. 2001, Meliza & Dan 2006). Synaptic plasticity changes cortical circuit organization according to an animal's experience and could contribute to the generation of receptive field diversity (Volgushev et al. 1993, Monier et al. 2003, Rust et al. 2005). In the model by Hubel and Wiesel, orientation-tuned neurons can be interpreted as the edge detectors necessary for animals to make sense of almost all natural scenes (Hubel & Wiesel 1962, Shapley & Tolhurst 1973, Marr & Hildreth 1980, Daugman 1985). Yet, receptive field diversity beyond the paradigm of Hubel and Wiesel may subserve flexible object recognition and is therefore also interpretable in terms of scene analysis (Riesenhuber & Poggio 1999, Lampl et al. 2004, Ullman & Bart 2004). Balancing these perspectives suggests that the requirements of specific tasks promote fine-scale diversity, whereas statistical symmetries of natural scenes constrain the large-scale structure of the visual cortex (Kaschube et al. 2010).

SUMMARY POINTS

1. Orientation selectivity emerges in V1 of cats and primates.
2. Hubel & Wiesel (1962) originally proposed a simple feedforward model in which V1 orientation selectivity results from the convergence of afferent thalamic neurons with spatially offset receptive fields. This model for orientation selectivity relies only on excitatory inputs from the thalamus, with no required role for inhibition.
3. Disrupting inhibition within the neocortex, however, can change orientation selectivity, suggesting a role for inhibition in sculpting orientation selectivity.
4. V1 neurons exhibit contrast-invariant orientation tuning and cross-orientation suppression, two response properties that are not accounted for by the feedforward model. Combined with experiments that have altered inhibition, these properties suggest that the simple feedforward model is insufficient to account for orientation selectivity.
5. Invocation of the known biophysical properties of thalamic and neocortical neurons aids in accounting for contrast-invariant orientation tuning and cross-orientation suppression without inhibition.
6. Visual input alters spontaneous ongoing activity and can affect neuronal selectivity.

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