CHAPTER 4

The generation of receptive-field structure in cat primary visual cortex

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Abstract: Cells in primary visual cortex show a remarkable variety of receptive-field structures. In spite of the extensive experimental and theoretical effort over the past 50 years, it has been difficult to establish how this diversity of functional-response properties emerges in the cortex. One of the reasons is that while functional studies in the early visual pathway have been usually carried out in vivo with extracellular recording techniques, investigations about the precise structure of the cortical network have mainly been conducted in vitro. Thus, the link between structure and function has rarely been explicitly established, remaining a well-known controversial issue. In this chapter, I review recent data that simultaneously combines anatomy with physiology at the intracellular level; trying to understand how the primary visual cortex transforms the information it receives from the thalamus to generate receptive-field structure, contrast-invariant orientation tuning and other functional-response properties.

Keywords: primary visual cortex; receptive field; orientation selectivity; simple cell; complex cell; cortical microcircuit.

Introduction

Receptive field is, nowadays, an elusive concept that cannot be easily defined (Bair, 2005; Hirsch and Martinez, 2006). It was introduced almost 70 years ago in the visual system when Hartline (1938) gave this name to the region of the retina where a change in light brightness modifies the firing rate of a retinal ganglion cell. Thus, in its original description, the term receptive field basically represented a spatial location in sensory, in this case retinal, coordinates. Kuffler (1953), Barlow (1953) and Hubel and Wiesel (1961) later demonstrated the receptive fields of retinal ganglion cells, and their targets in the lateral geniculate nucleus of the thalamus (LGN), are roughly circular in shape and comprise two concentric subregions known as the center and the surround (Fig. 1a). These subregions have opposite preferences for stimulus contrasts such that On cells are excited by bright spots shone in the center or by dark annuli in the surround; Off cells respond in a reciprocal manner (Kuffler, 1953; Hubel and Wiesel, 1961). As well, the center and surround have a mutually antagonistic relationship because stimuli of the reverse contrast evoke push–pull responses within each of the two subregions — where bright light excites and dark stimuli inhibit (Kuffler, 1953; Hubel and Wiesel, 1961). Remarkably, just the geometry of center and surround and suppressive interactions between them explain why retinal and thalamic cells remain largely indifferent to uniform patterns of illumination, while they are...
very responsive to local changes in stimulus contrast (Kuffler, 1953; Hubel and Wiesel, 1961; Barlow and Levick, 1976). However, to fully describe the functional properties of a visual neuron, the temporal aspects of the response should also be taken into account (Saul and Humphrey, 1990; DeAngelis et al., 1995). For example, retinal and thalamic cells can be further classified as transient or sustained, depending on whether the cell produces only brief responses after a long-lasting stimulus is switched on or kept firing for most of the duration of the stimulus presentation (Cleland et al., 1971). Furthermore, most thalamic receptive fields exhibit some degree of space–time inseparability (Cai et al., 1997). As a result, there is a progressive reduction in size of the receptive-field center as the surround response, delayed from that of the center, builds up over time. Finally, in recent years a new level of complexity has been introduced to the definition of the receptive field. Many observations have demonstrated that spike responses which evoked from the receptive field of

Fig. 1. Examples of the main types of receptive fields recorded in the visual thalamus and cortex. The receptive fields are shown as arrays of trace pairs in which each position in the stimulus grid is represented by averages of the corresponding responses to dark (black traces) and bright (gray traces) squares. Gray dashed lines code for On and black dashed lines code for Off subregions. For the relay cell in the thalamus (a) and the simple cell in layer 4, (b) stimuli of the reverse contrast evoked responses of the opposite sign (push–pull) in each subregion. For the complex cell in layer 4 (c), both bright and dark stimuli evoked excitation (push–push) in overlapping regions of visual space. Dark but not bright squares (push-null) excited the complex cell in layer 6 (d). The stimulus was flashed for 31 or 47 ms (vertical lines indicates stimulus onset); square size was 0.85° or 1.7° and grid spacing was 0.85°. Adapted from Martinez et al. (2005) and Hirsch and Martinez (2006).
visual neurons can be further modulated by stimulation of a surrounding region that has been called the non-classical, or extra-classical, receptive field (Hubel and Wiesel, 1968; Allman et al., 1985; Fitzpatrick, 2000; Angelucci et al., 2002; Cavanaugh et al., 2002; Bair, 2005).

The receptive-field concept has thus evolved over the years to represent the shape of a spatiotemporal filter that ultimately determines how visual input is analyzed by each element of the visual pathway (Barlow, 1953; Kuffler, 1953; Hubel and Wiesel, 1959; Wiesel, 1959; Hubel and Wiesel, 1961; Hubel and Wiesel, 1962; Hubel and Wiesel, 1968; Levick et al., 1972; Enroth-Cugell and Lennie, 1975; Barlow and Levick, 1976; Gilbert, 1977; Henry, 1977; Movshon et al., 1978a, b, c; Bullier and Henry, 1979a, b; Victor and Shapley, 1979; Toyama et al., 1981; Dean and Tolhurst, 1983; Wiesel and Gilbert, 1983; Enroth-Cugell and Robson, 1984; Martin and Whitteridge, 1984; Cleland and Lee, 1985; Baker and Cynader, 1986; Hegelund, 1986; Jones and Palmer, 1987; Ferster, 1988; Chapman et al., 1991; Emerson et al., 1992; DeAngelis et al., 1993a, b; Volgushev et al., 1993; McLean and Palmer, 1994; Pei et al., 1994; DeAngelis et al., 1995; Reid and Alonso, 1995; Fitzpatrick, 1996; Bosking et al., 1997; Cai et al., 1997; Ohzawa and Freeman, 1997; Borg-Graham et al., 1998; Debanne et al., 1998; Hirsch et al., 1998a, b; Troyer et al., 1998; Murthy and Humphrey, 1999; Usrey et al., 1999; Ferster and Miller, 2000; Hirsch et al., 2000; Lampl et al., 2001; Martinez and Alonso, 2001; Wielandt et al., 2001; Abbott and Chance, 2002; Hirsch et al., 2002; Kagan et al., 2002; Martinez et al., 2002; Mechler and Ringach, 2002; Troyer et al., 2002; Chisum et al., 2003; Hirsch, 2003; Hirsch et al., 2003; Lauritzen and Miller, 2003; Martinez and Alonso, 2003; Monier et al., 2003; Usrey et al., 2003; Van Hooser et al., 2003; Douglas and Martin, 2004; Moos et al., 2004; Pribe et al., 2004; Ringach, 2004; Bair, 2005; Martinez et al., 2005; Mata and Ringach, 2005; Hirsch and Martinez, 2006). The view of the receptive field as a filter conveys two ideas that are central to our understanding of sensory systems in general. First, not all available sensory information is processed by the brain; in fact, most of it is actually discarded. Second, each stage along a sensory pathway is in charge of analyzing a distinct aspect of its sensory input; for example, changes in local contrast by retinal ganglion cells. As a result, redundant information is discarded early on while the relevant structure of the visual image is preserved and transmitted to more advanced stations of processing.

In this chapter, we summarize current research in receptive fields in primary visual cortex (V1). First, we concentrate on the circuits that are responsible for the generation of the various classes of cortical cells: simple and complex. Second, we review recent data suggesting that a purely feed-forward circuit can achieve contrast invariant orientation tuning at the first stage of cortical processing. Third, we discuss how successive stages of the cortical microcircuit modify the synaptic structure of complex receptive fields and orientation tuning. Understanding how such cortical circuits are built may ultimately help explain orientation selectivity in other species, like primates, where it develops fully at intracortical stages of processing rather than at the thalamocortical level (Hubel and Wiesel, 1968; Bosking et al., 1997; Ringach et al., 1997, 2002, 2003; Chisum et al., 2003; Mooser et al., 2004).

**Receptive fields in primary visual cortex**

When Hubel and Wiesel first recorded from the primary visual cortex they used the same simple stimuli that had been so successful in mapping the spatial structure of retinal and thalamic receptive fields (Hubel and Wiesel, 1959, 1962). The cortex, however, turn out to have a larger variety of receptive-fields structures. Attending to their functional response properties, Hubel and Wiesel classified cortical cells into two main categories: simple cells and complex cells. The simple cell category included the population of neurons that reminded them of presynaptic cells in the thalamus, for their receptive fields were divided into On and Off subregions that had an antagonistic effect on one another (Hubel and Wiesel, 1962; Hirsch and Martinez, 2006) (Fig. 1b). Unlike the subcortical concentric arrangement, however, the On and Off subregions of simple cells are elongated and lay side by side. What made this observation so
interesting was that the new geometric configuration correlated with the emergence of neural sensitivity to stimulus orientation. In the retina and thalamus, a bar of any orientation drove cells vigorously. Cortical cells, on the other hand, responded briskly to an oriented stimulus aligned with the long axis of sign matched subregions, but fired less vigorously, if at all, to stimuli rotated away from the preferred angle. Complex cells were also orientation selective. Unlike simple cells, however, they formed a much more diverse population and were defined by exclusion. The main classification criteria for a complex receptive field was that they lacked spatially discrete subregions (Figs. 1c, d) and their preferred orientation and responses to variously shaped stimuli could not be predicted from a spatial map of their receptive fields.

The hierarchical model of receptive-field construction

Inspired by the comparison of functional response properties in the thalamus and primary visual cortex, Hubel and Wiesel (1962) introduced the idea of a hierarchical organization of receptive-field structures. According to their model, the elongated subregions of simple cells are constructed from the convergent input of On and Off thalamic relay cells with receptive fields aligned in visual space. In turn, complex receptive fields originate from the convergence of simple cell inputs with similar orientation preferences but different spatial phases (Fig. 2). Thus, simple receptive fields emerge as the most direct approach to build orientation detectors from geniculate cells with circularly symmetric receptive fields. Complex cells, on the other, originate from the need to build orientation detectors that are independent of the contrast polarity and position of the stimulus within the receptive field. The initial success of this hierarchical (or feed forward) model was that it provided a mechanistic account of the generation of cortical receptive fields while it served to explain the functional roles of the main cellular components of the cortical circuit (Martinez and Alonso, 2003).

Over the years, the feed-forward model has received substantial experimental support and refinement. Concerning the first part of the model, some studies have reported that the majority of cells in layer 4 have simple receptive fields (Hubel and Wiesel, 1962; Gilbert, 1977; Gilbert and Wiesel, 1979; Hirsch et al., 1998a, b; Martinez et al., 2002, 2005; see also, Orban, 1984; Jacob et al., 2003; Ringach, 2004). Cross-correlation analysis demonstrated that monosynaptic connections between relay cells in the LGN and cortical cells are largely restricted to cases for which relay cells share the same sign and spatial position with the cortical targets (Tanaka, 1983; Reid and Alonso, 1995; Alonso et al., 2001). In addition, other studies have also provided compelling evidence that the generation of orientation selectivity in cat V1 relays primarily on thalamocortical mechanisms (see Ferster and Miller, 2000; Hirsch and Martinez, 2006, for review). For example, recordings from the axonal arbors of LGN cells in the cortex showed that thalamic receptive fields line up along the axis of orientation of local

![Fig. 2. Hierarchical model of receptive-field construction in primary visual cortex. Simple and complex cells represent two successive stages of cortical processing. Simple receptive fields are generated in layer 4 from the convergent input of geniculate neurons with receptive fields properly aligned in visual space. Complex receptive fields, in turn, pool the input from layer 4 simple cells with similar orientation preferences but different spatial phases. Black and gray code Off and On subfields respectively.](image-url)
cortical cells (Chapman et al., 1991). Intracellular recordings from V1 neurons made when cortical firing was greatly suppressed by cooling (Ferster et al., 1996) or inhibition (Chung and Ferster, 1998), showed that the remaining excitatory (presumably thalamic) input is tuned for orientation.

In relation to the second part of the model, earlier studies combining anatomical reconstruction and functional characterization had shown that cells in layer 4 with simple receptive fields send a strong axonal projection to the superficial layers (Gilbert and Wiesel, 1979; Martin and Whitteridge, 1984; Hirsch et al., 1998a; Martinez et al., 2002, 2005), where most cells are complex (Hubel and Wiesel, 1962; Gilbert, 1977; Gilbert and Wiesel, 1979; Hirsch et al., 2002; Martinez et al., 2002, 2005; cf. Orban, 1984; Jacob et al., 2003; Ringach 2004). Recent evidence based on cross-correlation analysis and pharmacological blockades suggests that complex receptive fields in the superficial layers are constructed by a mechanism that requires monosynaptic inputs from simple cells in layer 4 (Alonso and Martinez, 1998; Martinez and Alonso, 2001). In addition, Tony Movshon and colleagues demonstrated that complex cell’s responses depend on nonlinear interactions between at least two positions in space and time within their receptive fields (Movshon et al., 1978b). Thus, when complex cells are tested with sets of two bars with different spatiotemporal configurations, their responses along the direction perpendicular to the cells’ preferred orientation display On and Off linear subunits resembling simple-cells’ subregions (Movshon et al., 1978b; Heggelund, 1981; Baker and Cynader, 1986; Szulborski and Palmer, 1990; Gaska et al., 1994; Touryan et al., 2005). Movshon et al.’s (1978b) results were extended by others to show that the functional properties of the underlying subunits could explain the emergence of direction-selective complex cells (Emerson et al., 1992) and binocular complex cells (Ohzawa et al., 1990, 1997; Ohzawa and Freeman, 1986; Anzai et al., 1999).

Alternatives to the hierarchical model

Alternative lines of evidence suggest that a simple feed-forward circuit may not explain the emergence of cortical receptive fields and their related functional response properties, like orientation selectivity. For example, earlier versions of the feed-forward model cannot account for various aspects of cortical responses such as the maintenance of orientation selectivity over a range of stimulus contrasts (Sclar and Freeman, 1982; Ohzawa et al., 1985; Geisler and Albrecht, 1992; Troyer et al., 1998; Lauritzen and Miller, 2003); or the sharpening of orientation and spatial frequency tuning due to the presence of delayed suppression extending the classical receptive field (Ringach et al., 1997, 2002, 2003; cf. Gillespie et al., 2001). However, perhaps the most widely used argument against hierarchical models is the nature of the cortical circuit itself. Since the number of excitatory synapses provided by feed-forward connections is only a small fraction (less than 10%) of the total excitatory synapses made onto cortical cells (LeVay and Gilbert, 1976; Kisvarday et al., 1986; Peters and Payne, 1993; Ahmed et al., 1994; Braaten and Schuz, 1998; Binzegger et al., 2004), it is usually assumed that the influence of the feed-forward input on cortical response properties is weak. Therefore, some authors have proposed that cortical responses, even those in thalamorecipient layers, should be determined mostly by cortical inputs and not by thalamic inputs (for review see references, Martin, 2002; Nelson, 2002; Douglas and Martin, 2004). Although it is true that cortical cells (simple or complex) receive most of their input from other cortical neurons both inhibitory and excitatory (Ahmed et al., 1994; Fitzpatrick, 1996; Braaten and Schuz, 1998; Callaway, 1998; Thomson et al., 2002; Thomson and Bannister, 2003), it is usually chancey to estimate the strength of a given pathway based solely on the number of synaptic contacts. If this type of assumption was correct, the thalamic receptive fields should resemble more cortical receptive fields than retinal receptive fields, since the number of corticothalamic synapses onto LGN cells (~40%), largely outnumber retinal inputs (about 4%; Van Horn et al., 2000). Moreover, thalamocortical synapses have many features that make it possible for thalamocortical excitatory postsynaptic potentials (EPSPs) to be larger than corticocortical EPSPs (Stratford et al., 1996; Gil et al., 1999); they are located more proximally in
the dendrites, are bigger (Ahmed et al., 1994) and have more release sites (Gil et al., 1999).

Another important critique to the hierarchical model originated in the discovery that some complex cells, like simple cells, receive direct thalamic input (Hoffmann and Stone, 1971). Since then, an agreement on whether or not there is a laminar segregation of simple cells and complex cells has been difficult to attain (see for example, Jacob et al., 2003 and Martinez et al., 2005, in the cat; and Kagan et al., 2002 and Ringach et al., 2002, in the monkey; for review see Martinez and Alonso, 2003; Ringach, 2004; Hirsch and Martinez, 2006). Moreover, results from other studies blurred the distinction between simple and complex receptive fields. For example, Debanne et al. (1998) showed that, in few cases, the relative strength of cortical On and Off responses, and hence their spatial distribution, could be subtly modified by pairing visual stimuli with current injections. More pronounced changes could be generated when the precise balance between cortical excitation and inhibition was manipulated (Sillito, 1975; Nelson et al., 1994; Rivadulla et al., 2001; see also Martinez and Alonso, 2003, for an alternative explanation).

These diverse views about how simple and complex receptive fields are made in the cortex have been likely developed for two main reasons (Hirsch and Martinez, 2006). First, experiments with different species are often pooled in discussion, even though the organization of primary visual cortex changes with phylogeny (Lund et al., 1979; Gilbert, 1983; Martin and Whitteridge, 1984; Coogan and Burkhalter, 1990; Fitzpatrick, 1996; Callaway, 1998; Dantzker and Callaway, 2000; Binzegger et al., 2004; Douglas and Martin, 2004; Martinez et al., 2005). Second, Hubel and Wiesel’s (1962) description did not provide a quantitative test to clearly distinguish between the two populations of cortical receptive fields. In fact, complex receptive fields were originally defined by exclusion and therefore, they comprise a heterogeneous population. The lack of such a quantitative test led to the proposal of many different classification criteria (Palmer and Rosenquist, 1974; Schiller et al., 1976; Henry, 1977; Toyama et al., 1981; see also Orban, 1984; Mechler and Ringach, 2002; Martinez and Alonso, 2003, for review). Simple cells and complex cells have been classified based on the presence and degree of overlap of On and Off subregions, spontaneous activity level, response amplitude, length summation, responses to patterns of random dots, responses to moving light and dark bars, responses to moving edges, responses to drifting or contrast-reversal gratings, responses to flashed light bars and reverse correlation maps (Skottun et al., 1991; Mechler and Ringach, 2002; Martinez and Alonso, 2003). A quantitative test to classify simple and complex cells was introduced by De Valois et al. (1982) and further refined by other authors (Skottun et al., 1991). The new method was inspired by linear system analysis and spatial and temporal frequency methods that had been very successful in explaining the functional response properties of retinal and thalamic neurons (Shapley and Hochstein, 1975; Enroth-Cugell and Robson, 1984; Shapley and Lennie, 1985). This new classification criterion is based on the different response modulation of simple and complex cells to drifting sinusoidal gratings. While simple cells tend to modulate their firing rate in phase with the stimulus, complex cells elevate their firing rate with little or no modulation. Thus, the ratio between the amplitude of the first response harmonic (F1) and the mean spike rate (F0) can be used as a quantitative index of ‘response linearity’ or ‘receptive field complexity’. Interestingly, the F1/F0 method rendered two clearly discrete cell populations that allegedly corresponded to the Hubel-and-Wiesel simple/complex cells (Skottun et al., 1991).

However it is highly controversial how response modulation correlates with the degree of overlap of receptive field subregions (Kagan et al., 2002; Priebe et al., 2004; Mata and Ringach, 2005), indicating that the spatial organization of receptive fields cannot reliably be predicted from response modulation values. Therefore, classifying simple and complex cells by the F1/F0 method rather than receptive field structure could not be equivalent, making it even more difficult to compare results from different studies to evaluate the classical model of cortical receptive fields.

The controversy about the generation of cortical receptive fields also reached the field of computational neuroscience (for a more comprehensive
review see Martinez and Alonso, 2003; Ringach, 2004). Influenced by Hubel and Wiesel (1962) hierarchical model and Movshon et al.’s (1978b) results, many authors have modeled complex receptive fields as the result of a square sum of the output of four simple cells with similar orientation and spatial frequencies but with phases that differ in steps of 90 degrees (a quadrature pair of subunits and their mirror image; Pollen et al., 1989; Ohzawa et al., 1990, 1997; Emerson et al., 1992; Fleet et al., 1996; Qian and Zhu, 1997; Sakai and Tanaka, 2000 Okajima and Imaoka, 2001). Mathematically, this can be described as a square sum of two linear operators, each characterized by a Gabor function of the same frequency but with phases 90° apart from each other. These models are collectively known as energy models (Adelson and Bergen, 1985) and recently, Okajima and Imaoka (2001) demonstrated that they render complex cells that are optimally designed from an information theory point of view. Other authors have looked for developmental and coding strategies that would generate a hierarchy of simple and complex cells (Olshausen and Field, 1996; Hyvarinen and Hoyer, 2001; Einhauser et al., 2002).

Alternative approaches moved the field’s focus from feed-forward connections to networks of cortical neurons that are reciprocally connected. Most of these new models consider that thalamic inputs confer cortical cells with only a small bias in orientation and spatial-phase (or subfield segregation) preferences. Therefore, cortical receptive-field structures and functional response properties must emerge from the computations performed by local connections that are isotropic and nonspecific. This new framework has been widely used to generate theoretical models of the simple receptive field (Somers et al., 1995, 1998; Wielandt et al., 2001) and orientation and direction selectivity (Ben-Yishai et al., 1995; Douglas et al., 1995; Carandini and Ringach, 1997; Sompolinsky and Shapley, 1997). In recent years, it has been extended to obtain both simple and complex receptive fields following different strategies (Debanne et al., 1998; Chance et al., 1999; Tao et al., 2004). For example, Debanne et al. (1998) used recurrent cortical circuits to generate simple and complex cells. In their model, both cell types receive input from LGN cells with overlapping On and Off receptive-field centers (and from other cortical cells). Simple-cell responses are generated when cortical inhibition is strong enough to impose a bias toward either On or Off responses. Complex-cell responses are obtained when inhibition is reduced to unmask On–Off responses. Chance et al.’s (1999) model, in contrast, uses local, recurrent excitatory connections to generate the spatial-phase invariance of complex-cell responses. In their model, a first layer of simple cells (equivalent to layer 4) feeds into a second layer of cells with similar orientation preferences (equivalent to layers 2 + 3). The model assumes that connections from layer 4 to layers 2 + 3 are weaker than connections within layers 2 + 3 and that vertical connections link cells with similar spatial phase while recurrent connections link cells with a broader range of spatial phases. Under these conditions, neurons in the second layer exhibit simple-cell responses when recurrent connections are weak and complex-cell responses when they are strong. Tao et al. (2004) presented a related model in which the balance between lateral connections and thalamic drive determines whether individual neurons in the recurrent cortical circuit behave like simple or complex cells.

Thus, this new breed of recurrent models suggests that simple and complex receptive fields might actually represent two functional states of a unique cortical circuit. Similarly, Mechler and Ringach (2002) have recently suggested that simple and complex cells, rather than two discrete categories, might represent the ends of a continuum distribution of receptive-field structures (see also reference 1). Their new proposal originated in the demonstration that the bimodality seen in the F1/F0 distribution (Skottun et al., 1991) could be the consequence of the output non-linearity imposed by the spike threshold acting upon what appears to be a continuous distribution in the spatial organization of synaptic inputs (Mechler and Ringach, 2002; Priebe et al., 2004).

A fresh look into receptive-field structure

Investigating the organization of receptive-field structure in primary visual cortex is therefore
not a minor issue. Whether simple and complex cells are discrete classes or ends of a continuum has strong implications on our understanding of the precise nature of thalamocortical and cortico-cortical circuits, on how they interact to generate cortical response properties and, finally, on the specific contribution of each cell class to visual processing.

Since most previous quantitative studies of receptive-field structure have been made with extracellular recordings, we wanted to use a technique, whole-cell recordings in vivo, that would allow us to explore directly the patterns of synaptic inputs that build receptive fields in the cat (Hirsch and Martinez, 2006). The method also provided a means to label cells intracellularly so that we could determine their laminar location and morphological class. Our main result is that simple cells are restricted to regions where thalamic afferents terminate, layers 4 and upper 6 (Hirsch et al., 1998a; Martinez et al., 2002, 2005). By contrast, complex receptive fields are found throughout the cortical depth, though the precise synaptic structure of the complex receptive field changes with laminar location (Hirsch et al., 2002, 2003; Martinez et al., 2002, 2005). Further, we found two populations of inhibitory interneurons in layer 4 with receptive-field structures that resembled those of excitatory simple cells and complex cells, respectively. The orientation selectivity of these two classes of inhibitory cells helps us understand how orientation sensitivity is built and preserved over a wide range of contrasts (Hirsch et al., 2003). All told, our most recent results are consistent with feed-forward, thalamocortical models (Hubel and Wiesel, 1962; Troyer et al., 1998; Ferster and Miller, 2000; Lauritzen and Miller, 2003; Hirsch and Martinez, 2005) for cortical receptive fields and with the general idea that each layer of the cortex is adapted to serve unique functional demands.

Receptive-field structure in the thalamus and cortex

To explore how the synaptic structure of cortical receptive fields is transformed at successive stages in the early visual pathway, we mapped the spatial distribution of excitation and inhibition in the receptive fields of neurons at identified anatomical sites. An overview of the receptive fields we recorded is provided in Fig. 1 and includes recordings from the thalamus, the main thalamorecipient zone in the cortex, layer 4, and its main postsynaptic target, layers 2+3. The stimulus was a sparse-noise protocol (Jones and Palmer, 1987), light and dark squares singly flashed on pseudorandom order. The detailed maps in Fig. 1 are arrays of trace pairs in which each spatial coordinate is represented by the averaged responses to bright and dark stimuli flashed there.

The receptive field of an Off center relay cell is representative of recordings made in the LGN, Figure 1a. In both the center (dashed gray circle) and the surround (dashed black circle), stimuli of the reverse contrast evoked responses of the opposite sign, or push–pull. That is, dark squares at the center coordinates evoked an initial depolarization (push) followed by a hyperpolarization that corresponded to termination of the stimulus. Bright squares flashed at the same positions evoked the opposite response, a hyperpolarization (pull) followed by a depolarization. The responses from the surround, though weak (flashed spots are suboptimal stimuli for the surround), revealed a push–pull pattern as well.

The large majority of cells in thalamorecipient zones of the cortex, layer 4 and upper layer 6, were also built of On and Off subregions with push–pull (Martinez et al., 2005; Hirsch and Martinez, 2006). Unlike thalamic subfields, however, cortical subregions are elongated and parallel to each other, as first noted in the extracellular studies of Hubel and Wiesel (1962) and subsequent quantitative studies (Movshon et al., 1978a; Palmer and Davis, 1981; Dean and Tolhurst, 1983; Jones and Palmer, 1987; DeAngelis et al., 1993b). Fig. 1b shows an example of a simple field with an upper On subregion and a lower Off subregion. At every position along the length of the Off subregion, dark squares evoked excitation where bright squares evoked inhibition. A complementary pattern was obtained in the On subregion. Most remaining cells in layer 4 had complex receptive fields built of superimposed On and Off subregions (Hirsch et al., 2002, 2003; Martinez et al., 2005). Because bright and dark
excitation overlapped, these fields had a push–push rather than a push–pull infrastructure (Fig. 1c). Many cells at later stages of processing, layers 2+3, 5 and lower 6, failed to respond to sparse static stimuli, although they were strongly driven by richer stimuli such as those including motion (Hirsch et al., 2002; Martinez et al., 2002). Of the responsive group, there was often a strong, or virtually absolute preference, for stimuli of one polarity (Hirsch et al., 2002; Martinez et al., 2005); the map shown in Fig. 1d is from a cell that responded to dark but not bright squares.

Quantification of receptive-field structure

Our results show that simple and complex receptive fields have different synaptic signatures (Martinez et al., 2005). To clearly establish whether they represent two different functional classes that correlate with specific locations of the cortical microcircuit, it is necessary to quantify the visually evoked responses of the recorded cells. Thus, we chose two measures that capture the most salient spatial features of cortical receptive fields. First, we used an overlap index (Schiller et al., 1976) to measure the spatial configuration of On and Off subregions within the receptive fields. Values equal or smaller than 0 indicate segregated subregions and those approaching 1 denote symmetrically overlapped subfields. A graphical explanation of the index is given in Fig. 3a beneath the distribution of values we measured. The distribution divides into two statistically significant modes; the columns containing cells whose receptive fields had a simple arrangement of On and Off subregions are shaded gray in this and the following histograms. The distribution was equally bimodal when measures were based on spiking responses rather than on membrane potential responses (see Fig. 3d in Martinez et al., 2005). Second, we used a push–pull index (Martinez et al., 2005) to determine the balance of antagonistic responses to stimuli of the opposite contrast within individual subregions; the absolute values of the index range from 0 for push–pull to 2 for push–push or pull–pull. As for the overlap index, the resulting distribution of push–pull index values was not unimodal, as seen in histogram above the graphical explanation of the index (Fig. 3b).

In addition, cells that had segregated subregions also had push–pull, as did two cells with only one subregion recorded in layer 4. By contrast, cells with overlapping On and Off subregions had high values of the push–pull index. When values for the overlap index were plotted against those for the push–pull index, the points divided into two statistically independent clusters; one composed of simple cells and the other of complex cells (note that only cells that responded to bright and dark stimuli are plotted here) (Fig. 3c). Similar distributions were found for plots of the correlation coefficient against push–pull or against overlap index, not shown. Thus simple receptive fields are easily defined by two features, segregated On and Off subregions and the presence of push–pull, that are the quantitative counterpart of the qualitative classification criteria originally used by Hubel and Wiesel in 1962.

Other authors (Priebe et al., 2004), using Pearson’s correlation coefficient as an alternative to Schiller’s overlap index, have found that cortical cells form two distinct populations when measures were based on spiking responses, whereas they formed a single, continuous distribution when measures were based on membrane potential responses (as proposed by Mechler and Ringach, 2002, see discussion above). Using the same method, however, we have obtained a bimodal distribution also when measuring membrane potential responses (Fig. 3d, bimodality was determined with Hartigan’s dip test; the probability of rejection for a unimodal distribution was 0.99). Part of the controversy may arise because any measure of subfield overlap is susceptible to certain artifacts (Martinez et al., 2005). For example, stimuli that cross the borders between subregions can conflate boundaries by evoking various balances of push and pull simultaneously. As well, it is important to record from cells whose resting levels are well above the threshold for inhibition. Had we made recordings near the reversal potential for inhibition, then our values for the push–pull or the cross-correlation indices could have also formed unimodal distributions.
Receptive-field structure and laminar location

But even if simple and complex cells had represented the ends of a continuum rather than two distinct populations, that would not necessarily argue against a feed-forward model of receptive-field construction in primary visual cortex. The model would still essentially be correct if both cell types tended to appear at different laminar locations: simple cells in layer 4 and complex cells outside the reach of the thalamic afferents. Thus, we examined the relationship between receptive-field structure and laminar location.

Fig. 3. Quantification of receptive-field structure in the visual cortex. (a) Histogram showing the distribution of values for the overlap index. Dashed line separates simple cells with segregated On and Off subregions (filled columns) from complex cells with overlapped subfields. The difference between the two populations is statistically significant. The overlap index is depicted graphically below the histogram and is defined as

$$\text{Overlap index} = \frac{0.5W_p + 0.5W_n - d}{0.5W_p + 0.5W_n + d}$$

where $W_p$ and $W_n$ are the widths of the On and Off subregions and $d$ the distance between the peak positions of each subregion. The parameters $W_p$, $W_n$ and $d$ were determined by separately fitting each On and Off excitatory response region with an elliptical Gaussian (Schiller et al., 1976). (b) The distribution of the values for the push–pull index was also bimodal; cells that had simple scores on the overlap index are shown in filled columns; NR indicates that there was no response to the flashed stimulus. The push–pull index is depicted graphically below the histogram and is defined as

$$\text{push–pull} = |P + N|$$

where $P$ and $N$ represent synaptic responses to bright and dark stimuli, respectively. (c) A scatter plot of values for subregion overlap vs. push–pull forms two clusters; the leftmost defining simple cells. The intersection of the crosses in each cluster corresponds to the mean, and the length of each line to the 95% confidence intervals. (d) The distribution of values for Pearson’s correlation coefficient also suggests that simple cells and complex cells form two distinct populations in cat primary visual cortex. Bimodality was determined with Hartigan’s dip test; the probability of rejection for a unimodal distribution was 0.99 for all distributions. Adapted from Martinez et al. (2005) and Hirsch and Martinez (2006).
and location in the cortical microcircuit. We found that all cells with simple receptive fields had dendrites in regions where thalamic afferents terminate, layer 4, its borders or upper layer 6 (Martinez et al., 2005). Figure 4a presents a view of simple receptive fields plotted as a function of laminar depth of the soma, with the deepest cells in each layer at the left and the most superficial at the right. The plot reveals a trend for cells with more compact subregions to lie in lower aspects of layer 4 and those with elongated subregions to occupy the superficial half of the layer. This intralaminar distribution recalls the primate cortex, in which lower layer 4 is supplied by the parvocellular layers of the thalamus and the upper tiers by the magnocellular layers (Callaway, 1998).

Receptive-field structure does not appear to vary with general morphological class (Gilbert and Wiesel, 1979; Gilbert, 1983; Martin and Whitteridge, 1984; Hirsch et al., 2002; Martinez et al., 2002, 2005; Hirsch, 2003). Simple cells take various shapes including spiny stellate, pyramidal and interneuronal profiles (Fig. 4b). We have, however, found a correlation between receptive field and anatomical structure for patterns of interlaminar connectivity. Specifically, simple cells in layer 6 have robust dendritic and axonal arborizations in layer 4, where simple cells dominate, while complex cells in layer 6 target the superficial layers and hence prefer other complex cells (Hirsch et al., 1998b). Katz (1987) found that cells in layer 6 with dense arbors in layer 4 projected to the thalamus. Thus, it is possible that only simple cells provide geniculocortical feedback. To date, we find that all excitatory cells in layer 4 project heavily to the superficial layers, but do not have sufficient information to assay for intralaminar preferences nor for differences in projections to the deep layers or extrastriate regions.

Complex cells, on the other hand, populate all cortical layers and, like simple cells, they formed an anatomically diverse population (Fig. 4c). However, response patterns of complex cells change with laminar location (Hirsch et al., 2002; Martinez et al., 2002, 2005; Hirsch, 2003). Complex receptive fields in layer 4 had co-spatial On and Off subfields (large values of the push–pull and overlap indices; Hirsch et al., 2002, 2003; Martinez et al., 2005). Like simple cells, complex cells in thalamorecipient layers responded robust and reliably to the flashed spots and the time course of their responses followed the temporal envelop of thalamic activity (Hirsch et al., 2002). Thus all cells in layer 4, whether simple or complex, seem to capture and relay ascending patterns of thalamic drive. Conversely, complex cells in positions further removed from the thalamus, layers 2 + 3, 5 and lower 6, responded poorly if at all to the static stimuli, even though they are easily driven by richer stimuli like moving bars (Movshon et al., 1978b; Hirsch et al., 2002; Martinez et al., 2002, 2005). Moreover, when they did respond to the flashed spots, they usually showed preference for just one stimulus polarity, either bright or dark (Hirsch et al., 2002; Martinez et al., 2005).

Remarkably, not only the structure of the complex receptive field changes with laminar location. Our results show that the relative orientation tuning of excitatory and inhibitory inputs in complex cells also varies with position in the cortical microcircuit (Martinez et al., 2002; Hirsch et al., 2003). In layer 4, complex cells, at least the inhibitory ones, are insensitive to stimulus angle (Bullier and Henry, 1979a, b; Hirsch et al., 2003; Usrey et al., 2003). In layers 2 + 3 and 5 both excitatory and inhibitory complex cells are orientation tuned (Hirsch et al., 2000; Martinez et al., 2002). However, while in the superficial layers tuning curves for excitation and inhibition have similar peaks and bandwidths (Fig. 5b), in layer 5 their preferred orientation diverges such that the peaks of the tuning curves for excitation and inhibition can be as far as 90° apart (Martinez et al., 2002) (Fig. 5c).

All told, at the thalamocortical stage, a lot of energy must be expended to translate temporal patterns of thalamic input into either excitation or inhibition to generate new functional response properties, like orientation selectivity. By contrast, the transmission of information is strongly filtered and reconfigured at later stages of processing. As a result, only stimuli that meet certain standards, including particular motion patterns, evoke activity (Hirsch et al., 2002; Martinez et al., 2002).
Fig. 4. Laminar distribution of receptive fields and morphology in cat primary visual cortex. (a) Cells with simple receptive fields were found exclusively in layer 4, its borders or in upper layer 6. The receptive fields are ordered from left to right according to the depth of the soma. Back and white code Off and On subregions, respectively. The asterisk marks the receptive field of a pyramidal cell recorded in layer 3 whose basal dendrites branched extensively into layer 4. (b,c) A sample of our three-dimensional reconstructions taken from the simple cell (a) and the complex cell (b) populations. The figure shows coronal views (from left to right, top) of a pyramid in upper layer 6, a pyramid at the 4–5 border, a spiny stellate cell in layer 4, a smooth cell in layer 4 and a pyramid at the 3–4 border; and (from left to right, bottom) of a pyramid in mid layer 6, a pyramid in layer 5, two pyramids in the superficial layers, a basket cell in layer 4 and a spiny stellate cell in the same layer. Cell bodies and dendrites are gray and axons are black. Adapted from Martinez et al. (2005) and Hirsch and Martinez (2006).
The extended feed-forward (push–pull) model of the simple receptive field

Hubel and Wiesel (1962) proposed that simple cell subregions were constructed from excitatory inputs provided by thalamic afferents properly aligned in visual space, a hypothesis that has received substantial experimental support (Tanaka, 1983, 1985; Chapman et al., 1991; Reid and Alonso, 1995; Ferster et al., 1996; Chung and Ferster, 1998; Hirsch et al., 1998a; Martinez et al., 2005). Since Hubel and Wiesel (1962) used extracellular recordings, the way in which inhibitory inputs contribute to the simple receptive field was left open in their model, and remains an issue of strong debate (Sillito, 1975; Pei et al., 1994; Allison et al., 1996; Borg-Graham et al., 1998; Crook et al., 1998; Hirsch et al., 1998a; Murthy and
Humphrey, 1999; Anderson et al., 2000; Martinez et al., 2002, 2005; Monier et al., 2003; Marino et al., 2005). We have recently recorded from a population of smooth cells in layer 4 whose receptive fields were indistinguishable from those of their neighboring, spiny neurons (Hirsch et al., 2003). Receptive fields of excitatory and inhibitory simple cells are similar in terms of geometry and number of component subregions and the layout of push–pull (Hirsch et al., 2003), which strongly suggests that they are built by a common mechanism (Fig. 6). In addition, a combination of excitatory and inhibitory simple receptive fields reciprocally connected explains why layer 4 simple cells have orientation tuning curves for excitation and inhibition with similar peaks and bandwidths (Anderson et al., 2000; Martinez et al., 2002). Such a feed-forward model of the simple receptive field is also consistent with the observation that the sharpness of orientation selectivity depends primarily on the degree of elongation of the On and Off subregions (Lampl et al., 2001; Martinez et al., 2002).

Inhibitory contributions to contrast invariant orientation tuning

What early feed-forward models (Hubel and Wiesel, 1962; Troyer et al., 1998; Ferster and Miller, 2000; Troyer et al., 2002; Lauritzen and Miller, 2003; Hirsch and Martinez, 2006) of orientation selectivity fail to explain is how cortical neurons retain their orientation sensitivity over a wide range of stimulus contrasts (Sclar and Freeman, 1982; Ohzawa et al., 1985; Geisler and Albrecht, 1992; Priebe and Ferster, 2002). While cortical responses to stimuli at or near the preferred orientation grow stronger with increasing stimulus strength, responses to orthogonal stimuli remain small. Thus, stimulus contrast has little effect on the bandwidth of cortical orientation tuning curves (Sclar and Freeman, 1982; Ohzawa et al., 1985; Geisler and Albrecht, 1992). The situation is different for relay cells; as contrast grows stronger these neurons fire harder to stimuli of any orientation (Sclar and Freeman, 1982; Ohzawa et al., 1985; Geisler and Albrecht, 1992). Therefore, feed-forward models hold that a subset of the afferent input to each simple cell is ‘untuned’ as it is activated by stimuli of any orientation, including the orthogonal. Yet these models do not provide a means to counter the contrast-dependent increases in untuned thalamic firing that should elevate cortical tuning curves and increase bandwidth (Troyer et al., 1998, 2002). For at the orthogonal orientation, inhibitory simple cells are minimally active (Troyer et al., 1998, 2002).

The remaining inhibitory neurons we have recorded from in layer 4 had complex rather than simple receptive fields (Hirsch et al., 2003). These cells are insensitive to both stimulus polarity, they lack segregated subregions, and to stimulus angle, they respond equally well to stimuli of any orientation. In addition, their responses to static stimuli are as strong as those of simple cells, and they also follow temporal patterns of thalamic activity which indicates that they could be built by convergent input from On and Off relay cells with spatially overlapping receptive fields (Hirsch et al., 2002, 2003; Hirsch and Martinez, 2006). Untuned inhibitory cells are not an exclusive feature of the primary visual cortex, they are present in layer 4 of the somatosensory cortex as well (Simons, 1978; Swadlow and Gusev, 2002). In a recent report, Lauritzen and Miller (2003) demonstrated that a combination of simple and complex smooth cells in layer 4, tuned and untuned for orientation, respectively (Fig. 7), would supply the inhibition needed to explain simple-cell response properties. First, it would provide a component of feed-forward

Fig. 6. Push–pull circuitry in layer 4. Wiring diagram for inputs that built simple excitatory neurons (left) and inhibitory neurons (right) in layer 4. See the text for further explanation. Black and gray code Off and On subfields, respectively.
inhibition that is untuned for orientation (complex smooth cells) to generate contrast invariant orientation tuning and regulate general levels of excitability. Second, orientation tuned push–pull inhibition (from simple smooth cells) would contribute to sharpen spatial frequency tuning, lower responses to low temporal frequency stimuli and control the excitability of the cortical network.

**Summary**

Anatomical evidence emphasizes the importance of laminar specialization. Evidence discussed here suggests that connections in different layers are specialized for different tasks. In particular, receptive field-structure changes and new response properties arise at successive stages of visual cortical processing. In layer 4, the computations performed by a synaptic network consisting of feed-forward inputs from the thalamus and two different sources of intracortical inhibition (push–pull tuned and push–push untuned) contribute to the generation of the simple receptive field and contrast invariant orientation tuning (Hirsch and Martinez, 2006).

This extended version of the feed forward (push–pull) circuit of layer 4 simple cells could be common to other parts of the visual pathway as well. For example, in the visual thalamus we also find push–pull and two different types of inhibitory inputs. The first one is analogous to that provided by layer 4 inhibitory neurons with simple receptive fields; it is sensitive to stimulus polarity (On or Off) and shares receptive field structure (center–surround) with neighboring excitatory relay cells. This type of inhibition is provided by local interneurons in the LGN. The second one resembles the inhibition provided by layer 4 inhibitory complex cells; it is insensitive to stimulus polarity (On–Off) and it is provided by neurons in the adjacent perigeniculate nucleus. It is thus conceivable that other stations along the visual pathway might also have similar circuit designs including a source of unselective inhibition. Such inhibitory circuits could be responsible for normalizing functional response properties and could also be involved in regulating excitability or mediating contextual effects of complex visual stimuli at a local level.

Finally, circuits outside layer 4 change the synaptic structure of the complex receptive field and orientation tuning with each step of cortical integration. As a result, new functional response properties, like the sensitivity to stimulus motion, emerge. Systematic changes in response properties with laminar location are observed in other sensory modalities as well. Our hope is that a better understanding of the structure and function of the visual cortical microcircuit will expose fundamental principles of neocortical function.

**Acknowledgments**

I would like to specially thank J.A. Hirsch for contributing to all aspects of this research and for her
support, encouragement and inspiration over the years. I am also deeply grateful to Jose-Manuel Alonso for many helpful discussions and for his contribution to the early phases of these projects. I also thank T.N. Wiesel for support and guidance, R.C. Reid for participation in early experiments, F.T. Sommer and Q. Wang for contributions to analysis and C. Gallagher Marshall, K. Desai Naik, C. Pillai and J.M. Provost for skilful anatomical reconstructions. Funding the experiments reported here was provided by NIH EY09593 to J.A. Hirsch.

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