Synaptic Physiology and Receptive Field Structure in the Early Visual Pathway of the Cat

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How does the cortical circuitry analyze the visual scene? Here we explore the earliest levels of striate cortical processing: the first stage, where orientation sensitivity emerges, and the second stage, where stimulus selectivity is further refined. The approach is whole-cell recording from cat *in vivo*. Neurons in the lateral geniculate nucleus of the thalamus have circular receptive fields whose subregions, center and surround are concentrically arranged and have the reverse sign, *on* or *off*. These neurons supply cortical simple cells, whose receptive fields have *on* and *off* subregions that are elongated and lie side by side. Feedforward models hold that orientation sensitivity depends on this thalamocortical change in receptive field structure and an arrangement within subregions such that stimuli of the reverse contrast evoke synaptic responses of the opposite polarity—*push–pull*. Our work provides support for feedforward models and emphasizes that *push–pull* is key in the geniculostriate pathway, preserved from retina by thalamic relay cells and reiterated, point by point, by cortical simple cells. Also, we help define the cortical *push–pull* circuit by identifying inhibitory simple cells. Lastly, separate experiments that compare the first and second levels of cortical processing suggest that differences in the synaptic physiology of connections at the two (thalamocortical versus intracortical) stages underlie differential selectivity for properties such as motion.

Introduction

Our interest is understanding the means by which each stage of striate cortical processing extracts new information about the visual scene. We use the technique of whole-cell recording *in vivo* to ask how receptive field structure and response properties are formed by the cortical microcircuit and the synaptic physiology of its component connections. Here the focus is on the two earliest stages of integration, the thalamocortical stage, where orientation selectivity emerges and the next, intracortical, level, where further types of sensitivity develop. At the outset, we wish to state that this review is not comprehensive; it is meant to give our general view of synaptic integration and functional organization at early stages of processing in the cat's geniculocortical pathway; previously published work deals with other perspectives and/or other species (Sillito, 1985; Volgushev *et al*., 1993; Ben-Yishai *et al*., 1995; Douglas *et al*., 1995; Somers *et al*., 1995; Fitzpatrick, 1996; Frégnac, 1996; Ringach *et al*., 1997; Sompolinsky and Shapley, 1997; Callaway, 1998; Debanne *et al*., 1998; Adorjan *et al*., 1999; McLaughlin *et al*., 2000; Wielaard *et al*., 2001).

Synaptic Structure of Receptive Fields of Thalamic Relay Cells and Cortical Simple Cells

While the functional differences between retina and thalamus are subtle (Kuffler, 1953; Hubel and Wiesel, 1961, 1962; Bullier and Norton, 1979), the transformation in visual response between thalamus and cortex is famously dramatic – cortical neurons are able to resolve stimulus orientation though their presynaptic partners in thalamus cannot (Kuffler, 1953; Hubel and Wiesel, 1961, 1962; Bullier and Norton, 1979). One popular model of orientation selectivity, push–pull, suggests that this property depends on the arrangement of thalamic inputs onto their cortical targets (Hubel and Wiesel, 1962; Palmer and Davis, 1981; Jones and Palmer, 1987; Ferster, 1988; Hirsch *et al*., 1998; Troyer *et al*., 1998; Ferster and Miller, 2000) rather than near complete reliance on the intracortical circuitry itself (Sillito, 1985; Ben-Yishai *et al*., 1995; Douglas *et al*., 1995; Somers *et al*., 1995; Frégnac, 1996; Sompolinsky and Shapley, 1997; Adorjan *et al*., 1999; McLaughlin *et al*., 2000; Wielaard *et al*., 2001). Here, beginning with the thalamus and moving to the cortex, we sketch evidence for elements of the push–pull circuit (see Fig. 4) from the synaptic perspective that whole-cell recording affords.

Structure of the Thalamic Receptive Field

Numerous extracellular studies of the thalamic receptive field have shown that it is built of a circular center and an annular surround, similar to that of the retinal ganglion cell. Further, within each of these subregions stimuli of the opposite contrast evoke responses of the opposite sign – push–pull (Kuffler, 1953; Hubel and Wiesel, 1961; Bullier and Norton, 1979; Wolfe and Palmer, 1998; Usrey *et al*., 1999, 2000, Herman and Guillery, 2001). For example, on center cells are excited (push) by bright stimuli and suppressed (pull) by dark stimuli shown centrally, while dark stimuli excite and bright suppress in the surround. Off center cells have the opposite preference.

Our whole-cell recordings have permitted direct visualization of the patterns of excitatory and inhibitory synaptic input that define the push and the pull (McIlwain and Creutzfeldt, 1967). Figure 1 depicts records from an off center relay cell in layer A of the lateral geniculate nucleus; the stimulus was a series of bright and dark squares briefly flashed, one at a time, in pseudorandom order 16 times on 16 × 16 grid (Jones and Palmer, 1987; Hirsch, 1995). Figure 1*B* shows intracellular responses to dark and 1*C* to bright stimuli that fell in the peak of the receptive field center (top), here mapped as a contour plot with stimulus sign and position indicated within. Beneath each map are two individual trials of the stimulus, with the average of all trials shown in bold. Every dark spot that fell in the center evoked a depolarization capped by action potentials. This initial excitation, or push, was followed by a hyperpolarization, or pull, that, after a delay imposed by the circuitry (Cai *et al*., 1997), corresponded to the withdrawal of the stimulus. The introduction and removal of bright stimuli flashed in the same place produced the opposite response, an initial hyperpolarization followed by a depolarizing rebound.

Receptive fields with center–surround arrangements have long been understood to permit resolution of stimulus contrast, position and breadth (Kuffler, 1953; Shapley and Lennie, 1985). The synaptic basis of these abilities is easily appreciated by

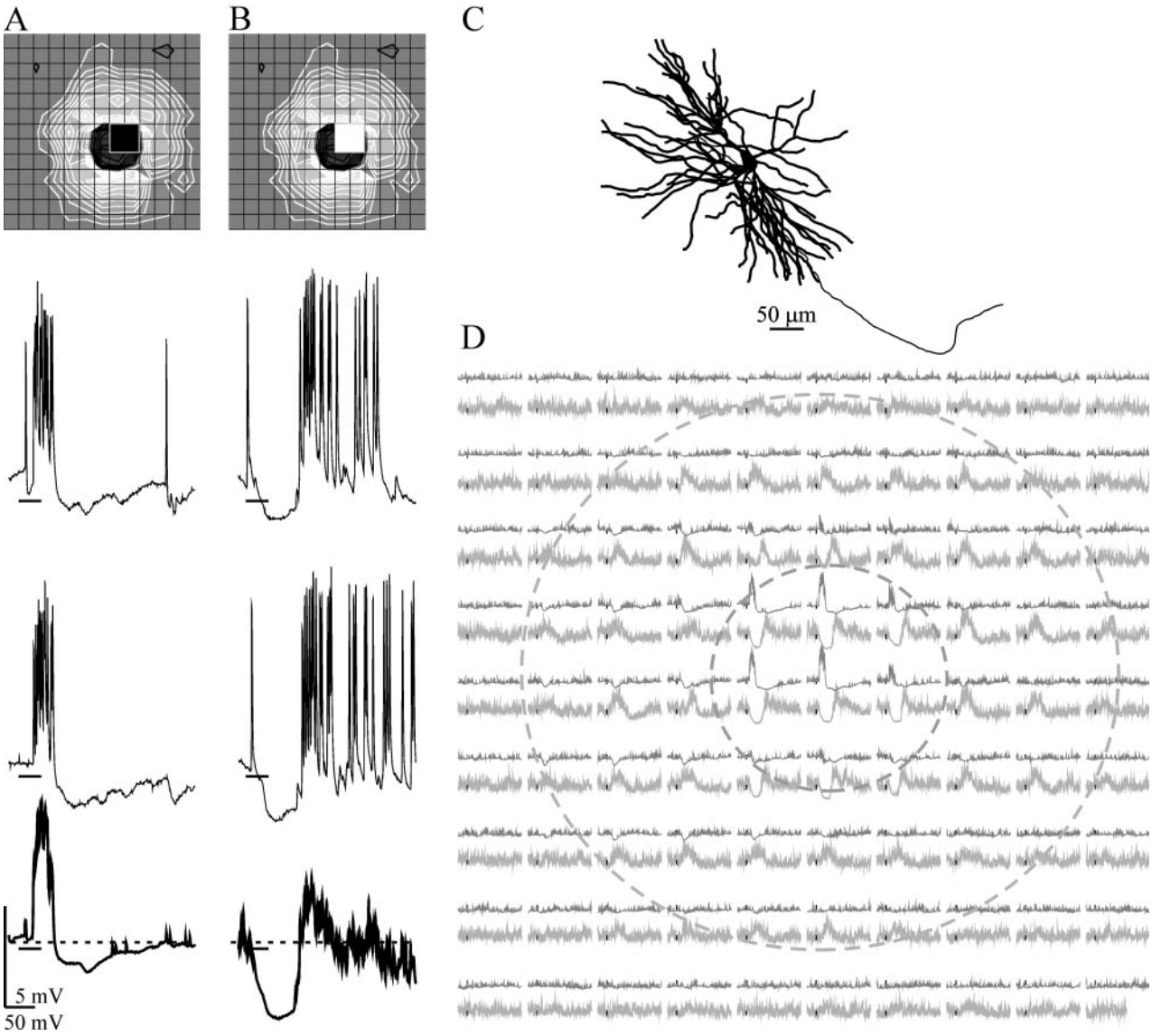

Figure 1. 'Push' and 'pull' in the receptive field of an off center relay cell in the lateral geniculate nucleus. (*A*,*B*) Responses to dark and bright stimuli flashed in the center of the field. At the top of each panel is a contour plot of the receptive field with the stimulus sign and position shown within (the off center is shaded in darker grays and the on surround in lighter grays; each contour represents a 10% decrement from the peak response; the map was made by subtracting responses to dark stimuli from those to bright ones; grid spacing was 0.8° and stimulus size was 1.6°). The traces below each map show two individual intracellular responses to the stimulus, with the average of all 16 emboldened at bottom; the thick bar under each trace marks stimulus duration and the dashed line indicates rest. (*C*) Anatomical reconstruction of the cell. (*D*) The receptive field shown as an array of trace pairs. Each pair shows the averaged response to a bright stimulus in light gray and the averaged response to a dark stimulus flashed in the same spot in dark gray. The dashed pale circle approximates the on surround and the dashed dark circle indicates the off center.

mapping the thalamic receptive field as an array of trace pairs, for which intracellular responses evoked from each spatial coordinate are shown as averages for all trials of the dark (darker gray) and bright (lighter gray) squares; the dotted circles approximate the borders of the center and surround. Throughout the center of the field, as indicated in Figure 1*B*,*C*, dark stimuli evoked strong excitation where bright stimuli elicited strong inhibition. This central push–pull allows stimuli of one contrast to have maximal effect, while ensuring that those of the reverse contrast not only fail to evoke firing but reduce spontaneous activity. Although responses evoked from the surround were weaker and more varied than those elicited from the center, a push–pull pattern emerged there as well. This is especially evident in the regions left and bordering the center (because the stimulus was large, 1.6°, it sometimes cross-cut the border between subregions so that some responses include contributions from both the center and surround). This rim of surrounding suppression improves spatial resolution by reducing activity to stimuli that spill outside the center.

Structure of the Simple Receptive Field: Excitatory and Inhibitory Cells

The main targets of thalamic afferents (LeVay and Gilbert, 1976; Martin and Whitteridge, 1984; Humphrey *et al.*, 1985) are the simple cells of cortical layer 4 (Hubel and Wiesel, 1962; Gilbert, 1977; Bullier and Henry, 1979; Ferster and Lindstrom, 1983; Martinez *et al.*, 1998). Like relay cells, simple cells have receptive fields built of on and off subregions in which stimuli of the reverse contrast evoke a push–pull response. Rather than the concentric arrangement seen in the thalamus, however, the

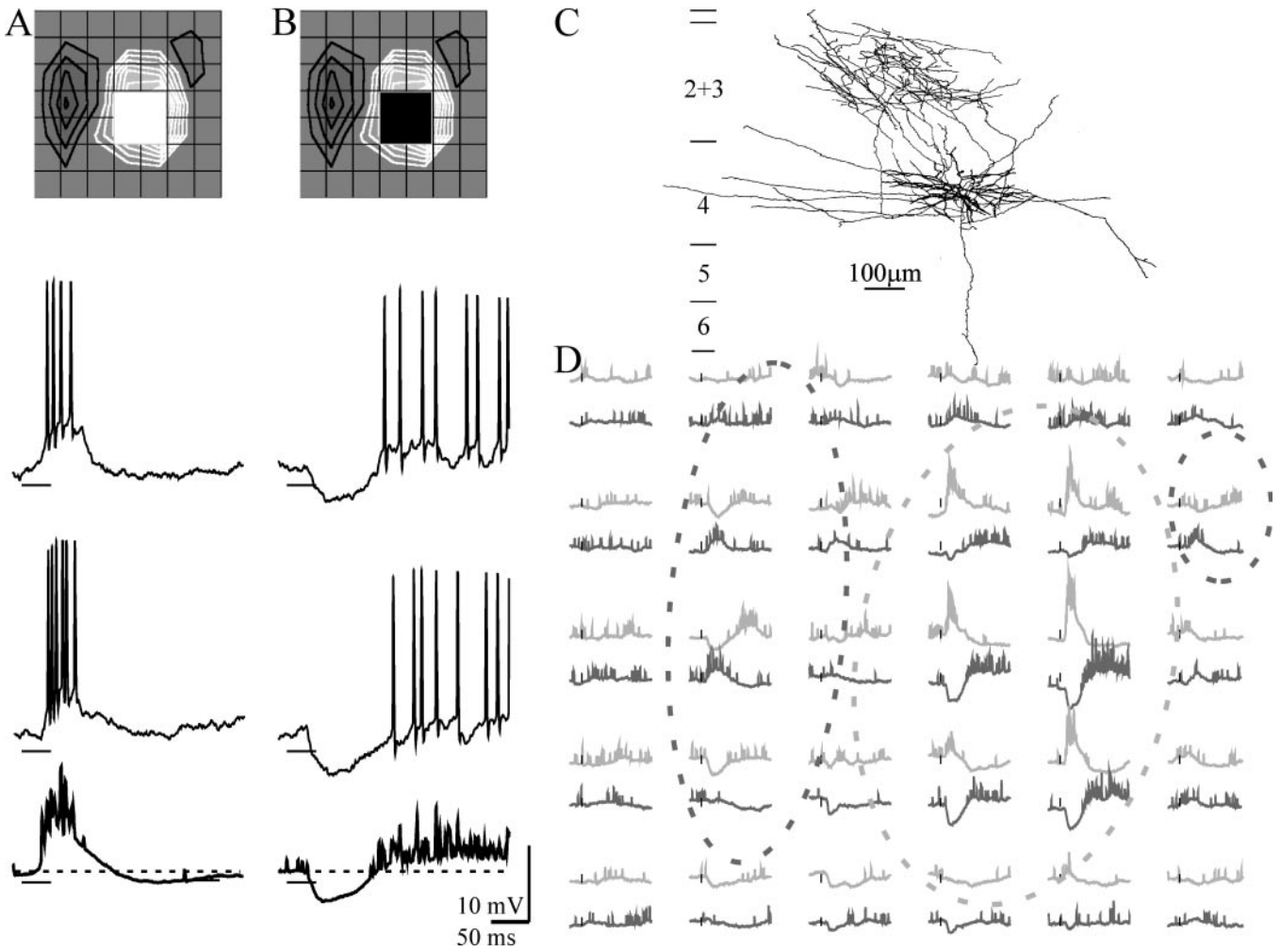

Figure 2. 'Push' and 'pull' in the receptive field of a spiny stellate cell with a simple receptive field in cortical layer 4. The conventions in this figure are as for Figure 1*A*,*B*. Panels show intracellular responses to bright and dark stimuli flashed in the peak of the on subregion, with stimulus sign and position indicated in the overlying contour plots of the receptive field. These responses are very similar in structure to those recorded from the thalamus. (*C*) Anatomical reconstruction of the cell, which was located in mid-layer 4 and projected densely to the superficial layers. (*D*) Receptive field as an array of trace pairs, with the on subregion approximated with the pale ellipse and the off subregions with the dark ellipses.

on and off subregions in the simple receptive field lie side by side (Hubel and Wiesel, 1962; Movshon *et al*., 1978a; Palmer and Davis, 1981; Ferster, 1986, 1988; Heggelund, 1986; Jones and Palmer, 1987; De Angelis *et al*., 1993a,b; Ferster *et al*., 1996; Hirsch *et al*., 1998; Ferster and Miller, 2000). This transformation in the geometric arrangement of the receptive field is central to the push–pull model (Hubel and Wiesel, 1962).

Figure 2 illustrates properties of a spiny stellate cell in cortical layer 4 (Fig. 2*C*); the design of the figure is as for Figure 1. Individual cortical responses to bright and dark stimuli flashed at the peak of the on subregion strongly resemble thalamic responses to the same stimuli (Fig. 2*A*,*B*). The layout of the entire simple field is shown in Figure 2*D* as an array of trace pairs with the subregions indicated by dotted lines. At a glance, it is clear that the motif of push–pull dominates the receptive field (as for the relay cell, stimuli that spanned adjacent subregions evoked composite responses).

A second example of the simple receptive field is shown in Figure 3, in this case for a smooth, or inhibitory cell (Fig. 3*B*). Again, push–pull is evident within subregions (Fig. 3*C*). These cases are typical of over 25 recordings we have made from simple cells when the membrane potential was held above the reversal potential for inhibition and the membrane time constant was ≥10 ms. Lastly, all the simple cells we have identified, as with those illustrated here, have been located in thalamorecipient zones or had dendrites that reached those regions (Hirsch *et al*., 1998, 2000, 2002; Martinez *et al*., 1998, 1999, 2002).

The Push–Pull Rationale

From the maps above, the appeal of the push–pull model is clear. A stimulus that fills but is confined to a given subregion would recruit push from along the length of that subregion, thus generating a robust response. By contrast, a stimulus that cross-cuts the field, or straddles the border between subregions, would recruit both push and pull, so reducing response strength (Hubel and Wiesel, 1962; Movshon *et al*., 1978a; Tolhurst and Dean, 1987; Skottun *et al*., 1991; De Angelis *et al*., 1993b).

The model is also attractive for its conservation of a single mechanism, push–pull, from retina to thalamus to cortex and for the simplicity of its basic circuit (Hubel and Wiesel, 1962; Palmer and Davis, 1981; Jones and Palmer, 1987; Ferster, 1988; Hirsch *et al*., 1998; Troyer *et al*., 1998; Ferster and Miller, 2000). Figure 4 presents a wiring diagram for push–pull. A simple subregion is made from aligned rows of thalamic centers by means of relay cells that converge on a single cortical target to generate

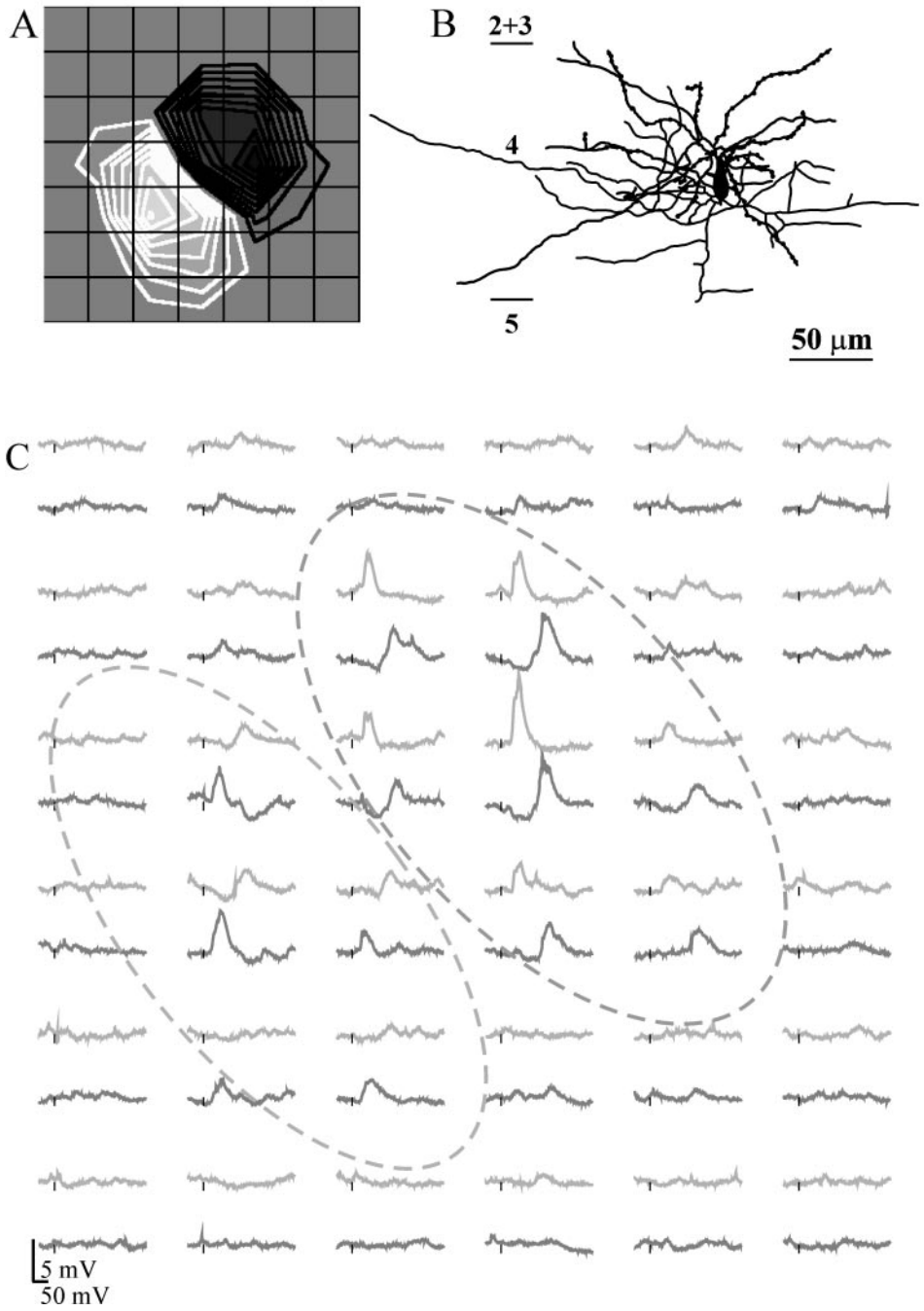

Figure 3. The receptive field structure of smooth (inhibitory) cells resembles that of spiny (excitatory) cells. Conventions are as for Figures 1 and 2. (*A*) Contour plot of the receptive field. (*B*) Anatomical reconstruction of the cell, which was located in layer 4; it had beaded dendrites and a dense, intralaminar axonal arbor. (*C*) Map of the receptive field as an array of trace pairs.

the push. The pull is made by thalamic input routed through cortical interneurons whose simple receptive fields have shapes similar to those of their postsynaptic partners but whose subregions have the reverse preference for stimulus contrast.

Although this circuit (Fig. 4) has yet to be demonstrated explicitly, it continues to receive experimental support. Certainly, our finding of the point-by-point iteration of push and pull throughout the simple field supports the model, as do earlier physiological studies (Palmer and Davis, 1981; Ferster, 1986, 1988; Heggelund, 1986; Jones and Palmer, 1987; Tolhurst and Dean, 1987; De Angelis *et al.*, 1995) and the placement of the simple field in thalamorecipient zones (Hubel and Wiesel, 1962; Gilbert, 1977; Bullier and Henry, 1979; Ferster and Lindstrom, 1983; Martinez *et al.*, 1998). More support comes from cross-correlation studies that have shown that thalamic relay cells and cortical simple cells, whose respective receptive field centers and subregions have the same sign and spatial position, are likely to be monosynaptically connected (Tanaka, 1983; Reid and Alonso, 1995; Alonso *et al.*, 2001). As well, time-courses of thalamic and cortical responses are similar (Cai *et al.*, 1997; Hirsch *et al.*, 1998, 2002; Alonso *et al.*, 2001). Further, recordings from thalamic afferents in silenced cortex suggest that these are organized in appropriately oriented rows (Chapman *et al.*, 1991) and intracellular recordings from silenced cortex suggest

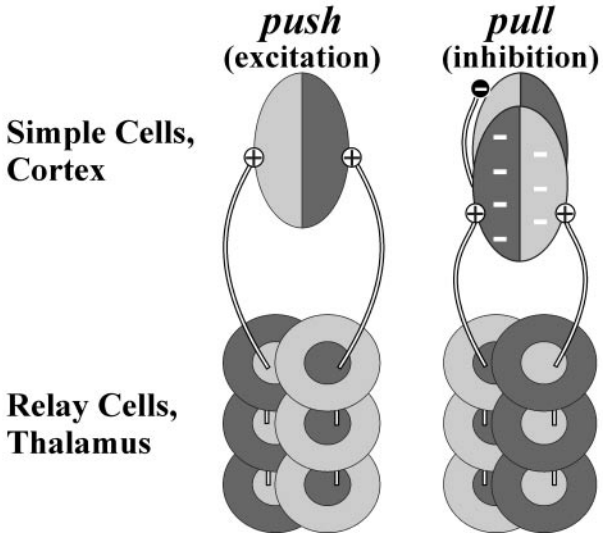

Figure 4. Push–pull circuits for the simple receptive field. Cells are drawn as their receptive fields; off subregions are shaded dark gray, on subregions are shaded light gray. Dashes scattered through the receptive field indicate an inhibitory rather than excitatory cell; the sign of a given synaptic connection is indicated as either excitatory (white with plus sign) or inhibitory (black with minus sign). The circuit is drawn with the fewest possible elements for clarity. See text for further description.

that the thalamus provides a substantial fraction of the tuned cortical response (Ferster *et al.*, 1996; Chung and Ferster, 1998). Lastly, a missing piece of evidence for the model had been the demonstration of cells that could provide the pull, which is thought to result from intracortical inhibition (Ferster, 1986; Borg-Graham *et al.*, 1998; Hirsch *et al.*, 1998; Anderson *et al.*, 2001). We, however, have now shown that such inhibitory simple cells exist — see Figures 3 and 4 (Hirsch *et al.*, 2000).

Another line of support for the role of push–pull comes from comparisons of the shape of the receptive field with the degree of orientation tuning. The model predicts that as simple subregions become more elongated, thereby increasing the ratio between the amounts of excitation recruited by the preferred versus orthogonal stimulus, orientation selectivity sharpens. This expectation, to a first approximation, has been corroborated both by extracellular recordings (Jones and Palmer, 1987; Gardner *et al.*, 1999) and intracellular recordings (Martinez *et al.*, 1998, 2002; Lampl *et al.*, 2001). All told, the push–pull circuit appears to lay the foundation for orientation tuning that auxiliary mechanisms help refine.

Laminar Differences in Synaptic Physiology

All the cortical records we have shown so far are from cells that were easily driven by simple static patterns of light. Yet many cells in primary visual cortex, particularly those that depend on intracortical rather than thalamic input, do not respond well to such sparse stimuli. Rather, richer stimuli, such as those including or simulating motion (Hubel and Wiesel, 1962; Gilbert, 1977; Movshon *et al.*, 1978b; Szulborski and Palmer, 1990), are usually required to activate cells at later stages of processing. In an earlier study (Hirsch *et al.*, 2002) we asked whether laminar differences in synaptic physiology might help explain the basis for such new forms of stimulus selectivity.

Our approach was to compare response of cells in layer 4 to layer 2 + 3, which receives dense input from layer 4 but virtually none from the lateral geniculate. Although, most cells in layer 4 are simple, a small number of them are complex. Complex receptive fields lack segregated on and off subregions; they may

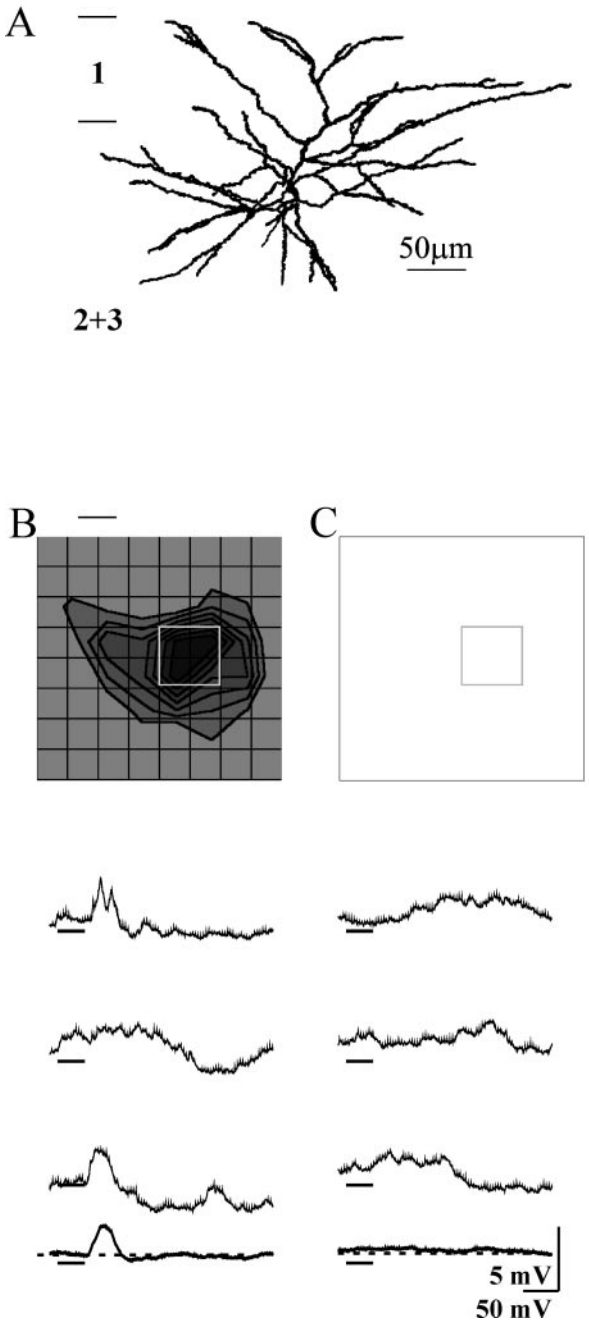

Figure 5. In the superficial layers, responses to the sparse stimuli are brief and intermittent. (*A*) Reconstruction of the cell, a pyramid whose dendrites spanned the upper half of layer 2 + 3; axon not shown. (*B*) Conventions as for Figures 1 and 2, except that the contour plot was made from responses to dark stimuli alone. Three individual traces and the average (bold) showing the brevity and intermittence of response to a dark stimulus flashed in the peak of the receptive field. (*C*) Bright stimuli were ineffective, even where dark stimuli were most effective; thus the traces here show only ongoing fluctuations of the membrane.

respond to bright and dark stimuli positioned the same place in the field — push–push — or stimuli of only one contrast — push–null (Hubel and Wiesel, 1962; Movshon *et al.*, 1978b; Palmer and Davis, 1981; De Angelis *et al.*, 1995). We found that all cells in layer 4, simple and complex alike, seemed to capture and relay thalamic input — that is, responses reliably reprised the time-course of each thalamic volley evoked by the flashed

stimulus and typically crossed the threshold for firing, for example Figure 2 (Hirsch *et al*., 1998; Hirsch *et al*., 2002).

At later stages of processing, such as layer 2 + 3, complex cells compose the dominant, if not the entire, population (Hubel and Wiesel, 1962; Gilbert, 1977; Movshon *et al*., 1978b; Ferster and Lindstrom, 1983). We found that the synaptic physiology of response in layer 2 + 3 was very different from that in layer 4, despite dense projections from that layer (Gilbert and Wiesel, 1979; Martin and Whitteridge, 1984; Hirsch *et al*., 2002); that is, the synaptic physiology of response seemed to depend on position in the cortical microcircuit rather than the spatial structure of the receptive field. In the superficial layers, postsynaptic responses to the sparse stimulus were brief, labile and did not reprise antecedent activity. Figure 5 illustrates the case of a pyramidal cell near the top of layer 2 + 3. Responses to the dark spots lasted less than half the duration typical of layer 4 (Fig. 5*B*, first and third trace); for a fuller and quantitative description of such behavior see previously published work (Hirsch *et al*., 2002). As well, the stimulus often failed to evoke a response (e.g. Fig. 5*B*, second trace). This impoverishment of response is best illustrated for the case of bright stimuli (Fig. 5*C*); these had no effect at all (traces illustrate ongoing changes in the membrane potential). Furthermore, almost half of the superficial cells (n = 11) we have tested failed to respond to the sparse stimulus at all, though all cells had healthy membranes and responded vigorously to rich stimuli such as moving bars (Hirsch *et al*., 2002).

At first, one might have assumed a simple explanation for why so many complex cells are poorly driven by sparse static stimuli. That is, postsynaptic responses at the soma might reflect patterns of antecedent activity, just as at the thalamocortical stage, but would be too weak to cross spike threshold (recall that the sparse stimulus drives cells in layer 4 very well). Instead, we find that flash-evoked responses in the superficial layers are intermittent and brief. Thus, a straightforward scheme such as thresholding does not appear to hold; rather, the physiological processes that govern intracortical responsiveness seem subtle and complicated.

In fact, work *in vitro* and *in vivo* has revealed diverse mechanisms operating at the level of the dendrite or the synapse proper that regulate communication from one cell to the next. These processes include changes in dendritic membrane properties induced by local inputs (Fatt and Katz, 1951; Bernander *et al*., 1991; Pare *et al*., 1998; Destexhe and Pare, 1999) and differential strength and security of transmission at various connections (Allen and Stevens, 1994; Stratford *et al*., 1996; Feldmeyer *et al*., 1999, 2002; Gil *et al*., 1999; Feldmeyer and Sakmann, 2000). It is likely that many such mechanisms play a part in gating the intracortical transfer of information (Hirsch *et al*., 2002).

Conclusion

At the first visual cortical stage, a large investment is made to incorporate ascending input. Save differences in the spatial structure of the receptive field, there is enormous similarity in the quality of the thalamic and cortical response patterns. After the geniculocortical stage, however, the nature of cortical processing changes markedly. Limited energy is devoted to a stimulus unless it meets novel standards; gating between intracortical connections seems to operate economically.

The extent to which the synaptic physiology of laminar processing in the visual cortex resembles that in other sensory systems is not yet clear, largely because studies of synaptic integration *in vivo* are few. The combined results of varied studies of the barrel cortex, however, suggest a measure of similarity between somatosensory and visual areas — specifically that processing within the thalamorecipient zone is more robust than at later stages (Moore and Nelson, 1998; Brumberg *et al*., 1999; Feldmeyer *et al*., 1999, 2002; Gil *et al*., 1999; Zhu and Connors, 1999; Feldmeyer and Sakmann, 2000; Swadlow and Gusev, 2000).

Notes

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