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LOCAL CIRCUITS IN PRIMARY VISUAL CORTEX OF THE MACAQUE MONKEY

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ABSTRACT

The basic laminar organization of excitatory local circuitry in the primary visual cortex of the macaque monkey is similar to that described previously in the cat's visual cortex (Gilbert 1983). This circuitry is described here in the context of a two-level model that distinguishes between feedforward and feedback connections. Embedded within this basic framework is a more complex organization. Within the strictly feedforward pathway, these circuits distribute unique combinations of magno-, parvo-, and koniocellular input from the lateral geniculate nucleus (LGN) to neurons in layers 2–4B. Their input is dependent on the extrastriate cortical areas they target. The local feedback connections from deep layers (5 and 6) arise from a diverse population of pyramidal neurons. Each type forms local connections with a unique relationship to more superficial layers. In the case of layer 6 neurons, these connections are closely related to layer 4 subdivisions receiving input from different functional streams.

INTRODUCTION

The primary visual cortex (V1, striate cortex) of primates is perhaps the most specialized of all cortical areas. Over the past several decades, much progress has been made in unraveling the mysteries of this structure, particularly in the macaque monkey. An increasingly detailed understanding of its functional organization and the interconnections of its neurons has been obtained. This review focuses on recent advances in this area.

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Understanding V1 local circuits provides insight into numerous issues. Most obvious is the fact that these neural circuits underlie crucial stages in early visual processing. The visual response properties of individual neurons within V1 arise as a consequence of the organization and function of their local connections and relationships to inputs from subcortical and other cortical areas. And the functions of each of the dozens of other (extrastriate) visual cortical areas that receive input either directly or indirectly from V1 (Felleman & Van Essen 1991) hinge on the patterns of neural activity generated here. Also, circuitry in primary visual cortex has been more extensively studied than in other cortical areas. Knowledge of this structure might therefore provide important insight into more general rules of cortical organization.

To a first approximation, the flow of information through V1 to extrastriate cortical areas is straightforward. Information arriving indirectly from the retina through the lateral geniculate nucleus (LGN) of the thalamus enters layer 4C of V1. The layer 4C recipient neurons connect directly to extrastriate cortical projection neurons in more superficial layers. So, as the crow flies, only two synapses separate extrastriate visual areas from the geniculate input to V1. Although the precise organization of connections within this pathway certainly has a profound influence on the visual responses of extrastriate projection neurons, there is an impressive amount of neural tissue devoted to other local connections. These connections must also be crucial to V1's function. But understanding their functional roles and their precise patterns of connectivity is more elusive.

To facilitate description of the relationships between V1's local circuits, the visual responses of its neurons, and its sources of input and extrinsic targets, this review is organized into several sections. First, I briefly review the functional architecture of primate V1. What are the columnar and laminar distributions of neurons preferring various visual stimuli? Next I review the organization of input to V1 from the LGN. And finally, in the bulk of the review I consider the organization of the local circuits within V1 and their relationships to neurons projecting to subcortical and extrastriate cortical areas.

FUNCTIONAL ORGANIZATION

A fundamental feature of cortical organization is the spatial grouping of neurons with similar function (see Frostig 1994). In V1, this grouping, or functional organization, occurs both vertically into layers and horizontally into columns. Such groupings are likely to arise as a consequence of developmental mechanisms (Katz & Callaway 1992, Livingstone 1996) and may not be necessary for proper cortical function (Livingstone et al 1995, Livingstone 1996; but see Horton & Hocking 1996). This organization is indispensable, however, for the

experimental unveiling of cortical circuits. If neighboring neurons receive inputs from similar sources and provide output to similar targets, it is unnecessary to resolve circuits at the level of individual neurons: Coarser but more fruitful methods can often be used.

Functional organization also provides reference points for incorporating results from different experiments. For example, anatomical studies revealing the relationships between cortical architecture and neural circuits can be interpreted in view of functional studies that reveal the visual response properties of neurons in various compartments. The combined information allows insight into the functional significance of cortical circuitry.

The laminar organization of macaque V1 is one of its most striking features. Unlike the typical cortex in which layers 1, 2/3, 4, 5, and 6 are prominent, layers 2/3 and 4 are further subdivided. Using the numbering system of Brodmann (1909), layer 4C of the macaque monkey is analogous to layer 4 in other cortical areas, and layers 2–4B are analogous to layer 2/3 (Hassler 1967; see Casagrande & Kaas 1994). Layers 2–4B are subdivided into layers 2/3A, 3B, 4A, and 4B, while layer 4C is divided into layers 4Cα (upper layer 4C) and 4Cβ (lower layer 4C). These subdivisions are closely related to direct and indirect inputs from functionally different geniculate afferent pathways (see details below).

Functional columnar organization of macaque V1 was first described by Hubel & Wiesel (1968, 1974). They found that as in the cat's V1 (Hubel & Wiesel 1962) neurons were best activated by a visual stimulus having a particular orientation. Cells also varied from one another in the relative activation provided by stimulation of the ipsilateral versus the contralateral eye—ocular dominance. In vertical penetrations through the cortical layers (within a cortical column) neurons were found to have similar ocular dominance and orientation preferences. Unlike the cat, however, neurons in layer 4Cβ of the monkey lack orientation selectivity (Blasdel & Fitzpatrick 1984, Livingstone & Hubel 1984a). Neurons in layer 4C are also monocular, driven by visual stimulation of one eye or the other, but not both (but see Gur & Snodderly 1995, Snodderly & Gur 1995). With electrode penetrations more parallel to the cortical layers, Hubel & Wiesel (1968, 1974) found that orientation preference and ocular dominance shifted gradually. Neighboring neurons have similar functional properties.

More recent experiments using in vivo optical imaging have yielded a more detailed view of orientation and ocular dominance columns in monkeys (see Frostig 1994 for review), as well as columnar groupings according to other stimulus parameters such as direction selectivity (Weliky et al 1996) and spatial frequency tuning (Shoham et al 1997) in ferrets and cats. (Grouping according to the latter parameters are probably also present in macaque. See below.)

Orientation columns are arranged radially, into pinwheel-like structures, with orientation preference shifting gradually along contours circling the pinwheel center. At any given location, direction is mapped orthogonally to orientation, but since orientation pinwheels only represent 180 degrees per cycle, only half of the possible directions are mapped onto each pinwheel (Weliky et al 1996). Ocular dominance shifts abrubtly within the monocular layer 4C where there are alternating stripes (Wiesel et al 1974, LeVay et al 1985), but in more superficial layers the transition is more gradual, so intermediate regions are binocular (Malach et al 1993, see also Le Vay 1988).

The columnar organization of V1 is not restricted to orientation and ocular dominance columns. Staining for the mitochondrial enzyme cytochrome oxidase (CO) reveals periodic darker staining "blobs" in layer 2/3 (Carroll & Wong-Riley 1984, Horton 1984; for review see Wong-Riley 1994). The positions of these blobs are closely related to functional organization, particularly ocular dominance, contrast sensitivity, and spatial frequency selectivity. Blobs are centered above ocular dominance columns (Horton 1984) and contain neurons with greater contrast sensitivity and selectivity for lower spatial frequencies than the surrounding interblob regions (Tootell et al 1988a–c, Edwards et al 1995; see also Shoham et al 1997).

Although most studies have considered blobs and interblobs to be two distinct compartments, recent evidence suggests that at least some functional properties shift gradually with distance from the blob center. This is reported for contrast sensitivity and spatial frequency selectivity (Edwards et al 1995; but see Shoham et al 1997), but adequate analyses have not been done to assess whether the relationships between selectivity for other stimulus parameters and blobs are binary (blob versus interblob) or shift gradually with distance from blob centers. Regardless, the strong relationship between blobs and functional architecture makes them a useful marker for relating findings from anatomical studies to functional organization.

GENICULATE INPUT TO V1

The pathway from the retina through the LGN and into primary visual cortex is the most direct conduit for visual information to reach the cerebral cortex. And unlike many other highly visual species, the geniculocortical projection in primates is focused nearly exclusively on V1 (Benevento & Standage 1982, Bullier & Kennedy 1983). Thus, understanding the laminar specificity with which functionally distinct geniculate afferents target V1 is an important first step toward understanding the role of V1 in processing visual information.

There are three major types of LGN neurons projecting to macaque V1: magnocellular (M), parvocellular (P), and koniocellular (K). Each receives input

from different types of retinal ganglion cells (RGCs) and projects axons to distinct zones in V1. Thus, from the retina to V1 there are three parallel pathways, each characterized largely by the functional properties of the RGCs from which they originate (see Casagrande 1994 for review).

The M pathway is characterized by large neurons. It arises from RGCs with large-diameter axons that project to the two most ventral, M layers of the LGN (Leventhal et al 1981, Conley & Fitzpatrick 1989). The LGN, M afferents project predominantly to layer 4Cα of V1 and have a weaker projection to layer 6 (Hubel & Wiesel 1972, Hendrickson et al 1978, Blasdel & Lund 1983).

Functionally, neurons in the M pathway have relatively large receptive fields, are wavelength insensitive, respond transiently to visual stimuli, prefer low spatial frequencies, and are relatively sensitive to luminance contrast (for review, see Shapley & Lennie 1985, Casagrande and Norton 1991). This makes them poorly suited for the analysis of fine shape or color but excellent for detecting subtle luminance changes or rapidly moving stimuli.

The P pathway originates from smaller RGCs, whose geniculate projections terminate in the four most dorsal, P layers of the LGN (Leventhal et al 1981, Conley & Fitzpatrick 1989). Neurons in these layers send their axons primarily to layer 4Cβ of V1, along with weaker projections to layers 6 and 4A (Hubel & Wiesel 1972, Hendrickson et al 1978, Blasdel & Lund 1983).

Neurons in the P pathway are more numerous in the central retina and have smaller receptive fields than those in the M pathway, allowing them to convey more detailed fine spatial information. They also have color opponent receptive fields, allowing them to detect color contrast, an important feature for the later processing of color information. But P cells have more sustained visual responses than M cells, and their finer caliber axons have slower conduction velocities, making them less useful for the detection of rapid movement (for review, see Shapley & Lennie 1985, Casagrande & Norton 1991).

The K pathway originates from RGCs with the smallest diameter axons (Conley & Fitzpatrick 1989). This pathway is present in all primate species studied but has been difficult to study in the macaque monkey (Casagrande 1994). This is largely because macaques (unlike galago monkeys, for example) do not have distinct K layers in the LGN. The finest caliber retinal axons, presumably originating from RGCs that are morphologically distinct from those projecting to M or P layers (Leventhal et al 1981), innervate the thin "intercalated" layers, between the M and P layers of the macaque LGN (Conley & Fitzpatrick 1989). The intercalated geniculate neurons in turn project to layer 1 and CO blobs in layer 2/3 of V1 (Livingstone & Hubel 1982, Hendry & Yoshioka 1994).

Studies in the galago monkey, where the K pathway is more amenable to experimental analysis, provide important insight into its function (see Casagrande

1994). These studies suggest that LGN K cells directly influence the receptive field properties of V1 blob cells in layer 2/3 and may also play important roles in the modulation of activity arriving at V1 through the M and P pathways. They may also play an important role in saccadic suppression (Casagrande 1994; see below)

In summary, the only regions in macaque V1 that do not receive direct geniculate input are layers 4B and 5, and the CO interblobs in layer 2/3. Layers 4Cα and 4Cβ receive M and P input, respectively. Layer 6 receives both M and P input. Layer 4A receives just P input, and layer 2/3 blobs and layer 1 receive just K input.

V1 LOCAL CIRCUITS—INTERLAMINAR CONNECTIONS

The most conspicuous feature of cortical circuits is their laminar organization. Neurons within a layer send axonal projections to only a subset of the other layers, and inputs to a particular layer arise from only a subset of the layers. Despite this organization, local circuits in macaque primary visual cortex are not simple. For example, understanding the precise connectivity between neurons is complicated by the multiple neuronal types that are found within a cortical layer and by the multiple sources of input to each layer. The methods that have been used in most studies do not allow detection of precisely which sources of input actually make synapses onto each type of neuron. Moreover, the dendritic arbor of an individual neuron is often not confined to a single layer, further increasing the number of sources from which it is potentially influenced.

Another complexity is that not all the inputs impinging on a neuron's dendritic arbor are functionally equivalent. There are both excitatory (glutamatergic) and inhibitory (typically GABAergic) synapses and multiple types of GABA and glutamate receptors, each potentially eliciting a different response to presynaptic transmitter release (for example, see Hollmann & Heinemann 1994). And there are a multitude of possible interactions between the different types of synapses. Thus, understanding the precise functional influence of an anatomically defined connection is generally quite difficult.

In view of this complexity, how can one hope to understand the organization and function of local circuits? With some straightforward reasoning, likely relationships between the most dominant neural pathways can be inferred. However, the role of many components of local cortical circuits are poorly understood, and one can only guess at more complex interactions or dynamic changes in these circuits in behaving animals.

Thus, I begin by considering local circuits in simpler terms. I take advantage of several simplifications to build a framework that describes the circuits

believed to be the most dominant. Other details can later be added to describe our present knowledge and to incorporate future findings. First, I focus on the contributions of excitatory synapses—inhibitory synapses can modify the effects of excitatory input, but can not act alone to generate responses to visual stimuli. [For descriptions of inhibitory local circuits, see Lund (1987), Lund et al (1988), and Lund & Yoshioka (1991).]

The next simplification is that each cortical layer provides its primary output to only one layer (i.e. 2/3, 4, 5, or 6); weaker, secondary outputs and connections within the home layer are less influential. This assumption substantially simplifies the local circuit and more importantly yields a good first approximation. However, the assumptions that less extensive axonal arborization or smaller numbers of synapses represent a weaker output can be inaccurate. For example, geniculate synapses onto spiny stellate neurons in layer 4 of cat primary visual cortex are substantially outnumbered by local inputs (Anderson et al 1994), but greater strength and reliability could compensate for their lower numbers (Stratford et al 1996). These observations might be explained by differences in the functional influence of feedforward (from the LGN) versus feedback (local input from layer 6) connections in layer 4 (see below).

Distinguishing between likely feedforward and feedback connections is also useful. Feedback connections arise from neurons that are not likely to be activated unless the neurons they connect to are activated first. Conversely, feedforward connections arise from neurons that are usually activated before those that are receiving the connection. Studies of cortico-cortical circuits have shown that feedforward connections (i.e. from V1 to extrastriate areas) (cf Felleman & Van Essen 1991) are focused, while feedback connections (i.e. from extrastriate cortex to V1) are more widespread (e.g. Zeki & Shipp 1985; Shipp & Zeki 1989a,b; Salin & Bullier 1995). Despite the widespread nature of feedback connections, classical receptive fields in V1 are relatively small. The feedback connections appear to play a modulatory role, influencing neuronal responses primarily when visual stimuli are placed outside the classical receptive field (e.g. Knierim & Van Essen 1992, Bullier et al 1996). Similar distinctions are used to aid in defining local feedforward and feedback circuits within V1.

A Basic Framework for V1 Laminar Connections

A two-level model of information processing by V1 local circuits can be extracted by making the simplifications described above. The laminar connectivity in macaque V1 is similar in many respects to that described for cat primary visual cortex (for review, see Gilbert 1983, Martin 1984). In the cat, the primary target of geniculate input is layer 4. Layer 4 neurons in turn project axons primarily to layer 2/3, layer 2/3 projects to layer 5, layer 5 projects to layer 6, and layers 5 and 6 provide projections to layers 2/3 and 4, respectively.

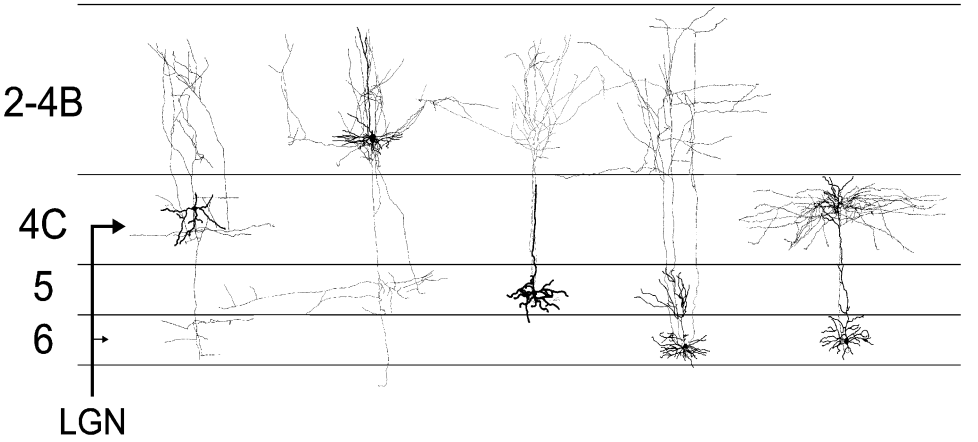

Figure 1 Contributions of individual neurons to local excitatory connections between cortical layers. From *left to right*, typical spiny neurons in layers 4C, 2–4B, 5, and 6 are shown. Dendritic arbors are illustrated with *thick lines* and axonal arbors with *finer lines*. Each cell projects axons specifically to only a subset of the layers. This simplified diagram focuses on connections between layers 2–4B, 4C, 5, and 6 and does not incorporate details of circuitry specific for subdivisions of these layers. A model of the interactions between these neurons is shown in Figure 2. The neurons shown have been modified for illustrative purposes from actual reconstructions of intracellularly labeled cells (see Callaway & Wiser 1996, Wiser & Callaway 1996). [Modeled after Gilbert (1983).]

A similar circuit exists within macaque V1 (Anderson et al 1993, Callaway & Wiser 1996) if we consider layer 4C to be analogous to the cat's layer 4 and layers 2–4B analogous to layer 2/3 (Casagrande & Kaas 1994; see also above). Layer 4C is the primary recipient of geniculate input, and the spiny stellate neurons in the layer project mostly to layers 2–4B, with a weaker projection to deeper layers (Figure 1, *far left*). Layer 2–4B spiny stellate and pyramidal neurons in turn project to layer 5 (Figure 1, *middle-left*). However, unlike cat V1, there may not be a dense projection from layer 5 to layer 6 (Callaway & Wiser 1996; see below for details). Instead, most layer 5 pyramids provide extremely dense feedback projections to layers 2–4B (Figure 1, *middle*). Layer 6 pyramidal neurons with dense dendritic arbors in layer 5 are also likely to receive input from layers 2–4B (Figure 1, *middle-right*), as well as from horizontal axons of layer 5 pyramids (not shown in Figure 1) (Callaway & Wiser 1996). Like layer 5 pyramids, these layer 6 cells provide a strong feedback projection to layers 2–4B (Figure 1, *middle-right*) (Wiser & Callaway 1996). A second class of layer 6 pyramid has few dendritic branches in layer 5 and makes a strong feedback projection to layer 4C (Figure 1, *far right*) (Wiser & Callaway 1996).

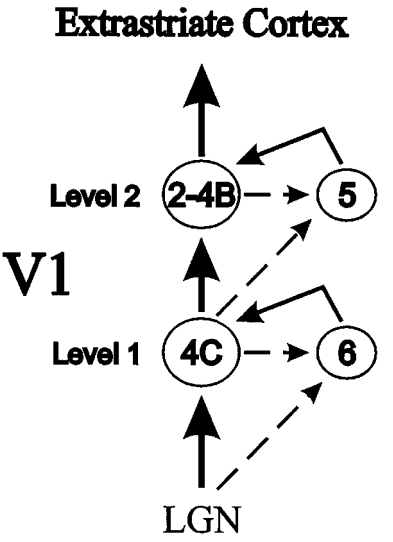

Figure 2 A two-level model of local cortical circuitry. Each level has a feedforward module (*larger circles to the left*) and a feedback module (*smaller circles to the right*). Feedforward modules receive strong excitatory input from the next lower level and make a similar strong connection to the next higher level (*thick arrows*). Feedback modules receive weaker input from the next lower level and from the feedforward module at the same level (*dashed arrows*). Finally, the feedback modules provide heavy feedback connections to the feedforward module at the same level (*thin arrows*). Thus, feedforward modules relay information directly to the next level, while feedback modules combine information about the input to and output from the level and send it back to modulate the activity of the output neurons.

By considering the relative strengths of these connections and making inferences about which are feedforward versus feedback, it is possible to construct the two-level local circuit model illustrated schematically in Figure 2. In this model there are two levels of local information processing, with each level composed of one feedforward and one feedback module (*large and small circles*, respectively, in Figure 2). At the first level, the feedforward module is layer 4C and the feedback module is layer 6. At the second level, the feedforward module is composed of layers 2–4B, while feedback comes from layer 5. At each level, the feedforward module receives strong forward input from the feedforward module of the next lower level and makes a strong forward connection to the feedforward module at the next higher level (Figure 2, *thick arrows*). Thus, the most direct path for information flow from the LGN to extrastriate cortex is through the feedforward modules, from LGN to layer 4C, to layers 2–4B, to layer 4 of extrastriate cortex.

Unlike the feedforward modules, which receive dominant forward input from just one source, feedback modules receive weak to moderate input from two sources (Figure 2, *dashed arrows*). These inputs arise from axon collaterals of the same cells that provide the strong forward input to and from the feedforward module at the same level. For example, layer 6 receives weak input from collaterals of the same LGN axons that provide strong input to layer 4C (Figure 1) (Blasdel & Lund 1983); and it also receives weak input from the same layer 4C spiny stellate cells that connect strongly to layers 2–4B (Figure 1) (Katz et al 1989, Anderson et al 1993, Usrey & Fitzpatrick 1994, Callaway & Wiser 1996). Similarly, layer 5 receives weak input from the same layer 4C cells that provide strong input to layers 2–4B, as well as input from layer 2–4B cells that provide strong feedforward input to extrastriate cortex (Figure 1) (Katz et al 1989, Anderson et al 1993, Usrey & Fitzpatrick 1994, Callaway & Wiser 1996). Thus, at each level, the feedback module samples two types of input: the input to and the output from the feedforward module at the same level. Finally, the feedback module provides strong feedback connections to the feedforward module at the same level (Figure 2, *thin arrows*): from layer 6 to 4C, or from layer 5 to layers 2–4B. At each level, the feedback module can therefore sample activity representative of both the input to and output from the feedforward neurons and modulate their output via its feedback connections.

The rationale for proposing these particular relationships between the cortical layers is based not only on the laminar specificity and relative densities of axonal projections, but also on their apparent functional roles. For example, the connection from layer 6 to 4C is considered a feedback connection in part because layer 6's input from the LGN is weak, suggesting that geniculate input alone may not strongly activate layer 6 neurons. But it is also useful to note that activity in layer 6 does not appear to be independently capable of driving activity in layer 4C, despite its dense axonal projections to the layer. In particular, visual responses of layer 4C neurons are typically more similar to their geniculate afferents than the layer 6 neurons that connect to them. Most notably, projections from layer 6 to layer 4C are not specific for ocular dominance columns (Wiser & Callaway 1997). Nevertheless, layer 4C neurons are monocular (e.g. Blasdel & Fitzpatrick 1984; but see Gur & Snodderly 1995, Snodderly & Gur 1995). Thus, layer 6 neurons connect to layer 4C neurons that will fail to fire action potentials under monocular stimulation conditions that clearly activate layer 6 input. These observations strongly suggest that local projections from layer 6 to layer 4C are modulatory, a hallmark of feedback connections (see above).

Similar arguments can be made regarding the apparent functional influence of layer 5 neurons on layers 2–4B. These connections are extremely dense and widespread and have no apparent specificity for the blob/interblob system in

layer 2/3 (Callaway & Wiser 1996). Nevertheless, there are distinct relationships between the visual responses of layer 2/3 neurons and their positions relative to blobs (see above). These distinctions appear to arise from the specificity of feedforward connections from layer 4 (see below). Thus, the connections from layer 5 to layers 2–4B also appear to be modulatory.

Interestingly, in the two-level model, superficial layers provide feedforward connections, while deep layers provide feedback. This is similar to the situation for cortico-cortical connections where superficial and deep layers also provide feedforward and feedback connections, respectively (see Felleman & Van Essen 1991). However, most of the deep layer neurons providing local feedback in V1 do not make projections to subcortical targets. In particular, layer 5 pyramidal neurons with dense local projections to layers 2–4B, and layer 6 pyramids with dense dendrites in layer 5 and axonal arbors in layer 2–4B both lack axons that project to the white matter (Callaway & Wiser 1996, Wiser & Callaway 1996). Only a minority of layer 6 pyramids providing local feedback to layer 4C project to the white matter (presumably to the LGN) (Fitzpatrick et al 1994, Wiser & Callaway 1996; see below for further details).

This basic model of local circuitry may represent a more generic organization that is present to varying degrees in most cortical areas. Such an organization could arise due to developmental influences common to all cortical areas. For example, the growth of developing axonal arbors is specific for layers 2/3, 4, 5, and 6 from the outset and apparently dependent on cues intrinsic to the cortex (i.e. molecular markers) (Lund et al 1977, Yamamoto et al 1989, Blakemore & Molnar 1990, Katz 1991, Bolz et al 1992, Callaway & Katz 1992, Callaway & Lieber 1996). Such cues could be common to all cortical areas. However, axonal projections that are specific for subdivisions of these layers in macaque V1 (i.e. 3 versus 4B, 4Cα versus 4Cβ; see below) initially develop specificity for only the main layers (2–4B, 4C, 5, and 6). The sublaminar specificity arises by a later reorganization, including elimination of axonal projections to incorrect sublayers, possibly utilizing activity cues (Callaway et al 1996). Thus, the sublaminar specializations that are characteristic of primate V1 (see below) may arise uniquely due to the disparate patterns of activity supplied by the M, P, and K afferents.

In the next several sections I use this framework to organize a more detailed description of V1 local circuits. I first consider the feedforward projections from geniculate recipient layers to extrastriate projection neurons in superficial layers (2–4B), particularly the relationships between functional streams and extrastriate projections. I then describe the connections from layers 2–4 to neurons in deep layers (5 and 6), and the reciprocal feedback projections from deep to superficial layers. Descriptions of the deeper layer neurons focus on the diversity of cell types and its implications for their function.

From LGN to Extrastriate Cortex—Feedforward Local Circuits and Functional Streams in V1

The dominant pathway from the LGN to extrastriate cortex through V1 originates in the M, P, and K geniculate recipient zones: layer 4Cα, layer 4Cβ, and layer 2/3 blobs, respectively (Figure 3, see above). The extrastriate projection neurons are only one synapse (or less) away. But their spatial distributions and the organization of the circuits from layer 4C to more superficial layers distributes unique combinations of M, P, and K influence to different populations of projection neurons. Every projection neuron is likely to be influenced by each type of geniculate input (Merigan & Maunsell 1993, Nealy & Maunsell 1994), but the extent and functional influence of each pathway varies. Thus, understanding the details of these circuits is crucial to understanding the roles

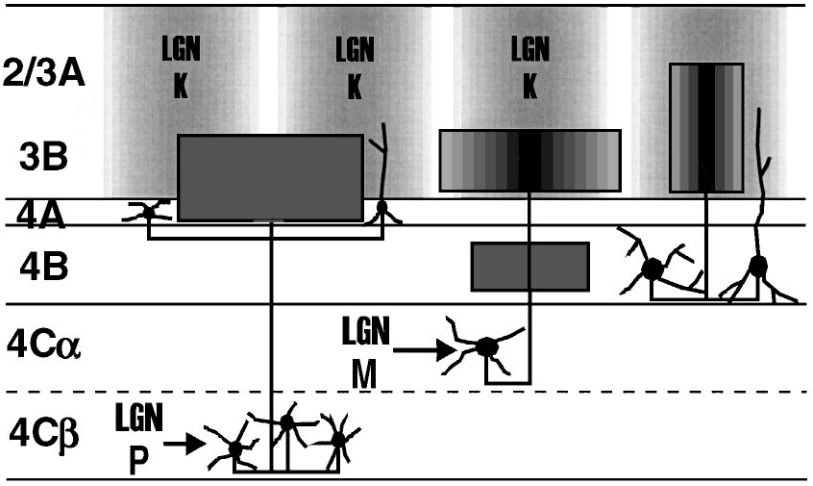

Figure 3 Schematic diagram of hypothesized relationships between cytochrome oxidase "blobs" in layer 2/3 (*shaded areas*) and local excitatory input from magno- and parvocellular-recipient subdivisions of layer 4. (*Left*) Spiny neurons in the parvocellular-recipient layers 4A and 4Cβ have connections to layer 3B that are distributed evenly with respect to blobs and interblobs (indicated by *lines connecting the schematized neurons to the evenly shaded box* in layers 4A and 3B). (*Middle*) Magnocellular-recipient spiny neurons in layer 4Cα connect evenly to layer 4B and with a bias toward blobs to layer 3B. The density of connections to layer 3B falls off gradually with distance from the blob center (indicated by *decreasing darkness of shading in the box*), but even the interblob regions furthest from blob centers receive some input. (*Right*) Layer 4B neurons that receive strong magnocellular input indirectly from layer 4Cα make connections that are heavily biased toward blobs in layers 2/3A and 3B. There is little or no input to interblob regions far from blob centers. See text for further details and discussion.

that M, P, and K pathways play in the neural computations that underlie visual perception.

I consider three major populations of extrastriate projection neurons. These populations are not, however, defined by their extrastriate targets, but by their positions within V1: layer 4B, layer 2/3 blobs, and layer 2/3 interblobs. Because the sources of local input to neurons with identified extrastriate projections have not been directly determined, one must rely on less direct correlative evidence. The three regions are correlated with (but do not strictly define) the extrastriate area(s) that their neurons target. Layer 4B neurons project to CO thick stripes in area V2 and to areas in the dorsal stream involved in analyses of spatial relationships and object location. Layer 2/3 neurons project both directly and via V2 to areas in the ventral stream involved in object identification. Layer 2/3 blobs project to V2 thin CO stripes, and layer 2/3 interblobs project to pale stripes (see Desimone & Ungerlieder 1989, Van Essen & DeYoe 1994 for reviews).

LAYER 4B Spiny neurons in layer 4B have both spiny stellate and pyramidal dendritic morphologies (Figure 3, *far right*), and it appears that nearly all of these project to extrastriate cortical areas (Callaway & Wiser 1996). These cells' extrastriate targets include V2 (CO thick stripes), V3, MT, and MST (see Felleman & Van Essen 1991). In the macaque monkey, the V2 projection originates from pyramidal neurons, and the MT projection from spiny stellates (Shipp & Zeki 1989a). The neuronal types projecting to areas V3 and MST have not been clearly identified.

Both spiny stellate and pyramidal neurons in layer 4B receive strong input from layer 4Cα and are thus heavily influenced by the M pathway (Figure 3) (Lund & Boothe 1975, Lund et al 1977, Fitzpatrick et al 1985, Valverde 1985, Lund 1988, Lachica et al 1992, Anderson et al 1993, Usrey & Fitzpatrick 1994, Yoshioka et al 1994, Callaway & Wiser 1996). This influence is reflected in the visual response properties of these neurons. They are orientation and direction selective but not wavelength sensitive. They have excellent contrast sensitivity, low spatial frequency selectivity, and large receptive fields (see Merigan & Maunsell 1993 for review). The M pathway dominance of layer 4B neurons is not surprising in view of the lack of strong direct anatomical input to the layer from neurons in the P or K recipient zones. Spiny stellate neurons in layer 4Cβ send axon collaterals through layer 4B without branching (Figure 3) (Lund & Boothe 1975, Lund et al 1977, Fitzpatrick et al 1985, Valverde 1985, Lund 1988, Anderson et al 1993, Usrey & Fitzpatrick 1994, Callaway & Wiser 1996), and layer 2/3 pyramidal neurons (presumed K recipients in blobs) have only very sparse axons in layer 4B (Anderson et al 1993, Callaway & Wiser 1996).

Nevertheless, there is evidence for a sizable, albeit less dominant connection from layer 4Cβ to layer 4B pyramidal neurons. Stimulation of 4Cβ neurons in

brain slices elicits monosynaptic excitatory postsynaptic currents in layer 4B pyramidal and spiny stellate neurons (Sawatari & Callaway 1996). For most pyramidal neurons, these are as frequent as those recorded following stimulation of 4Cα. Since pyramidal neurons have apical dendrites that extend into layers 4A and 3B, which contain dense axonal arbors from layer 4Cβ spiny stellates, it is presumed that most of these connections are onto apical dendrites (Figure 3). If connections to basal dendrites have a more dominant influence, this can explain the apparent lack of influence of the P pathway on the receptive field properties of layer 4B neurons. These observations suggest that closer scrutiny would reveal direct or modulatory effects of visual stimuli that activate the P pathway. Finally, it is also likely that layer 4B pyramids beneath blobs receive direct K input onto their apical dendrites.

The presence of an apical dendrite apparently influences the sources of input to layer 4B spiny neurons. Unlike pyramidal neurons, spiny stellate neurons lack substantial dendritic branches in layers 4A and 3B and are thus likely to be affected little by the P or K pathways. Since spiny stellates, not pyramidal neurons, project to area MT (Shipp & Zeki 1989a), the direct pathway through V1 to area MT is influenced minimally (cf Maunsell et al 1990). However, area MT could receive less direct P influences via area V2 thick stripes, since they receive input from layer 4B pyramidal neurons and project to area MT (DeYoe & Van Essen 1985; Shipp & Zeki 1985, 1989a,b). In contrast, other cortical areas receiving direct input from layer 4B pyramids are likely to be influenced more by the P and K pathways.

LAYER 4A Since a neuron's dendritic arbor is often more extensive than the layer in which its soma is located, understanding the sources that provide its input is not simply a matter of determining what cells send axons to the home layer. This is particularly true of neurons in layer 4A. Layer 4A is relatively narrow and most of its neurons have dendrites that extend well beyond its borders (Lund 1988, Lund & Yoshioka 1991, Callaway & Wiser 1996). Thus, these cells sample inputs to layers 4B and/or 3B as well as 4A. Consistent with a similarlity to layer 3B and 4B neurons, layer 4A neurons can make projections to the same regions in area V2 as layer 3B and 4B cells (Van Essen et al 1986, Levitt et al 1994; see also below).

Nevertheless, layer 4A seems to have a unique organization. The thalamic input and CO staining in this layer are arranged in a honeycomb pattern that coincides with dendrite-rich regions separated by clusters of cell bodies (see Peters 1994). Further studies are required to understand the significance of this organization.

LAYER 2/3 The sources of local, feedforward input to layer 2/3 neurons depend on depth within the layer and position relative to CO blobs. The extrastriate

cortical area targeted also depends on the location relative to CO blobs, and perhaps laminar depth.

Spiny neurons in M and P geniculate recipient layers (4Cα, and 4Cβ and 4A, respectively, see above) restrict their layer 2/3 axonal projections to just its lower third (layer 3B) (Fitzpatrick et al 1985, Lachica et al 1992, Yoshioka et al 1994, Callaway & Wiser 1996). In contrast, indirect recipients of this input, layers 3B and 4B, project axons throughout the depth of layer 2/3. Thus, neurons in the upper two thirds of layer 2/3 (layer 2/3A) are one synapse further than layer 3B neurons from the M and P LGN input, and it has been suggested that this extra step is a necessary prelude to the transfer of information from layer 2/3 to extrastriate cortical areas (Lachica et al 1992). This suggestion arises from reports of preferential labeling of layer 2/3A but not of 3B neurons following injection of retrograde neuronal traces in extrastriate areas V2 or V4 (Rockland & Pandya 1979, Yukie & Iwai 1985). But results from V2 appear to be variable. Van Essen et al (1986) illustrated retrograde labeling in layers 3B, 4A, and 4B following one V2 injection and in layer 2/3A following another. And intracellularly labeled layer 3B neurons are just as likely to project to the white matter as layer 2/3A neurons, regardless of their position relative to blobs (roughly half of each population) (Callaway & Wiser 1996). These variations might reflect differences in the sublaminar distribution of layer 2/3 neurons projecting to different cortical areas or compartments within those areas (i.e. CO stripes in V2, see below). If this is the case, more detailed analyses of cortico-cortical connectivity will resolve which extrastriate targets receive geniculate influences via two- versus three-synapse pathways and whether these neurons differ in their receptive field properties.

Relationships between extrastriate projections and position relative to CO blobs have been more clearly demonstrated. Neurons projecting to CO thin stripes in area V2 are found predominantly within blobs, while those projecting to pale stripes are found predominantly in interblobs (Livingstone & Hubel 1983, 1984a). However, in view of the observation that selectivity for some stimulus parameters varies gradually with distance from the center of blobs (Edwards et al 1995, see above), it would be helpful to have more detailed information about the precise distribution of labeled cells following small retrograde tracer injections at various positions relative to stripes in V2. The probability that a V1 neuron projects to a particular region of V2 may vary gradually with distance from the center of a blob.

Since neurons at different locations relative to blobs project to different regions in V2 and have different visual response properties, it is logical to expect that they will receive input from different sources. As described above, LGN K input is focused onto blobs. The observation that intercalated layers of the LGN are retrogradely labeled by tracer injections in blobs but not interblobs (Hendry & Yoshioka 1994) implies that interblobs are unlikely to receive substantial

K input. However, indirect evidence suggests that the amount of K input may fall off gradually with distance from the center of a blob (Figure 3). The density of CO staining is highly correlated with the density of geniculate input (Livingstone & Hubel 1982), and CO density shifts gradually with distance from blob centers (Edwards et al 1995).

Sources of local input to layer 2/3 neurons are also dependent on position relative to blobs. Most evidence indicates that neurons in blobs are more heavily influenced by the M pathway—indirectly via layers 4Cα and 4B—than by the P pathway—indirectly via layers 4Cβ and 4A (see Merigan & Maunsell 1993). To account for their physiological data, Edwards et al (1995) proposed a model in which indirect M inputs are focused on blobs but decrease gradually with distance from the blob center, while P inputs have a more uniform distribution. The model in Figure 3 is an adaptation of their model that also accounts for likely differences in blob specificity of input from layer 4Cα versus 4B. This model is consistent with most published details.

The relationships between local connections from layer 4 and CO blobs in layer 2/3 have been investigated in three published reports (Lachica et al 1992, Yoshioka et al 1994, Callaway & Wiser 1996). All three studies describe a high degree of selectivity of projections from layer 4B to blobs. Since layer 4B neurons are most heavily influenced by the M pathway (see above), this should result in greater M input to blobs. In the intracellular labeling study of Callaway & Wiser (1996), it can be seen that axons of layer 4B pyramidal and spiny stellate neurons are focused in a narrow window around blob centers; few axons were found more than 100–150 μm from blob centers, and they therefore seldom fell into interblob regions. But it is not known whether the distribution of synaptic boutons from these cells falls off gradually or abruptly. The model in Figure 3, however, shows a gradual reduction in the input from layer 4B. A gradual change in the influence on individual postsynaptic neurons in layer 2/3 is expected regardless of how abrubtly the input falls off, because the distributions of basal dendrites of layer 2/3 pyramids are not dependent on their position relative to blobs (Hubener & Bolz 1992, Malach 1992). Thus, the gradual shift in M input relative to blob centers proposed by Edwards et al (1995) could arise simply from the unequal distribution of layer 4B input without any bias of inputs from other sources.

Nevertheless, other observations suggest that the distribution of input from layer 4Cα is also unequal, with a bias toward blobs. Lachica et al (1992) made retrograde tracer injections in blobs or interblobs of layer 3B and detected labeling in layer 4Cα only after blob injections (interblob injections labeled layer 4Cβ but not 4Cα, see below). This report focused on tracer injections centered on blob or interblob regions; results from injections at intermediate locations that might help to distinguish between gradual versus abrupt shifts

in the density of projections from layer 4Cα were not described. However, Yoshioka et al (1994) reported retrograde label in layer 4Cα after interblob injections (but they report no label after blob injections, see below). And intracellularly labeled layer 4Cα spiny stellates do have substantial axonal arbors in both interblobs and blobs (Callaway & Wiser 1996). However, the number of 4Cα neurons in this sample is small, thereby precluding meaningful quantitative analyses of the distribution of synapses relative to blobs.

The distribution schematized in Figure 3 is one model that is consistent with these reports. It is proposed that layer 4Cα input is most dense at blob centers and falls off with distance. The fall-off is more gradual, however, than for layer 4B input, in keeping with the observed projections from layer 4Cα to interblobs that are not observed from layer 4B (Yoshioka et al 1994, Callaway & Wiser 1996). An absence of retrograde labeling in layer 4Cα following layer 3B interblob injections (Lachica et al 1992) can be attributed to a lack of adequate sensitivity for detection of weaker input to these regions. Although I favor this hypothesis, it remains plausible that the distribution of projections from 4Cα is more uniform or might vary from blob to blob (Callaway & Wiser 1996), perhaps even occasionally favoring interblobs (cf Yoshioka et al 1994).

The distribution of axonal arbors from layer 4A and from layer 4Cβ spiny stellates relative to blobs appears to be more uniform than that from 4Cα or 4B. Retrograde tracer injections can label layer 4A and 4Cβ neurons regardless of whether they are centered on blobs or interblobs in layer 3B (Lachica et al 1992), and intracellularly labeled layer 4A spiny neurons and 4Cβ spiny stellates project to both regions (Callaway & Wiser 1996). The schematic in Figure 3 therefore shows a moderately dense and even distribution of connections from these cells relative to blobs.

It should be noted that this model is at odds with the report by Yoshioka et al (1994), who did not observe retrograde labeling in either layer 4Cα or 4Cβ following biocytin injections in layer 3B blobs. But these same injections also failed to label neurons in layer 4B that clearly provided strong input to blobs (see above), suggesting that they did not pick up even relatively strong connections. Only the densest projections, from layer 5 neurons (Callaway & Wiser 1996), picked up the label.

The model in Figure 3 does not account for the likelihood that there are more subtle relationships between the depth of a neuron's soma within layer 4C and its pattern of axonal arborization. Like M versus P geniculate neurons, cells at the top of layer 4C have greater contrast sensitivity and larger receptive fields than those at the bottom. However, these transitions are gradual, suggesting that neurons in the middle of layer 4C receive input from both M and P afferents, while only those at the edges receive exclusive M or P input (Blasdel & Fitzpatrick 1984). The convergence of M and P pathways in mid-layer 4C could

occur despite the sharp segregation of M and P afferents due to extension of dendrites between layers (Mates & Lund 1983, Anderson et al 1993, Callaway & Wiser 1996). However, this convergence may be limited to just some mid-layer 4C cells, since many appear to have asymmetric dendritic arbors that avoid crossing between 4Cα and 4Cβ (Katz et al 1989, Callaway & Wiser 1996). These observations could be incorporated into the model in Figure 3, by assuming a gradual reduction in the blob specificity of axons from layer 4C neurons with increased dendritic arborization in layer 4Cβ. But better resolution of these issues awaits quantitative analyses of the distributions of synaptic boutons and dendrites from a large population of intracellularly labeled layer 4C spiny stellates.

Reciprocal Feedforward/Feedback Connections Between Superficial and Deep Layers

Pyramidal neurons in the infragranular layers, 5 and 6, receive forward input from layers 2–4 and make dense feedback projections to the same layers. As described briefly above, these relationships differ between layers and between cells within a layer. In this section I focus on the greater diversity in morphology of pyramidal neurons in the deep versus superficial layers, the diverse circuits formed by these cell types, and their functional implications.

LAYER 5 Layer 5 contains at least three types of pyramidal neuron, each with distinct patterns of dendritic and axonal arborization (Callaway & Wiser 1996). The most common layer 5 pyramids ("class A" of Callaway & Wiser) (see Figure 1, *middle*) probably account for about two thirds of the population. Their basal and apical dendritic branches are confined almost exclusively to layer 5, and they are therefore likely to receive the overwhelming majority of their input from neurons with axonal branches in this layer. Such inputs come mainly from layers 2–4B (there are also connections from layer 4C) (Blasdel et al 1985, Fitzpatrick et al 1985, Katz et al 1989, Anderson et al 1993, Callaway & Wiser 1996). This class of layer 5 pyramid does not project out of V1 but has extremely dense axonal arbors in the same layers that provide its input, layers 2–4B (Callaway & Wiser 1996). As described above (see Figure 2), the projections from superficial layers appear to be feedforward, while the reciprocal connections provide feedback. This reciprocal feedforward/feedback relationship is typical of most layer 5 and layer 6 pyramids.

But the involvement of other layer 5 pyramids does not fit as neatly into this model. Back-branching layer 5 pyramids (a subset of Callaway & Wiser's "class B"), like those described above, confine their dendritic branches (but not their apical dendrite) to layer 5. Thus, they are likely to receive inputs from similar sources, but instead of projecting axons to superficial layers, they have

long lateral axonal arbors primarily within layer 5 and occasional branches dipping into layer 6 (Callaway & Wiser 1996). They are further distinguished from class A cells in that they do project to the white matter. Since their cell bodies appear to be too small for superior colliculus-projecting neurons, they probably project to the pulvinar nucleus of the thalamus (Lund et al 1975).

The last population of layer 5 pyramids has been identified only in Golgi preparations, so their local axonal projections are unknown. These neurons have very large cell bodies and an apical dendrite that extends to and branches in layer 1 (Lund & Boothe 1975, Valverde 1985). Based on their large size, it appears likely that they project to the superior colliculus (Lund et al 1975). The apical dendritic branches in layer 1 suggest that they could receive input from LGN K afferents in addition to sources projecting to layer 5 (Casagrande 1994). Since the superior colliculus projects to LGN K layers (Harting et al 1991, Fieg & Harting 1994), Casagrande (1994) has proposed that a loop involving the superior colliculus, the K pathway, and layer 5 tall pyramids is involved in suppression of vision during saccadic eye movements. Such a loop may preferentially involve LGN K cells that project to layer 1 rather than layer 2/3 blobs (Hendry & Yoshioka, 1994), since colliculus-projecting neurons are located under interblobs, not blobs (Lia & Olavarria 1996).

LAYER 6 Layer 6 contains the most varied population of pyramidal neurons (Lund et al 1977, Callaway & Wiser 1996). Wiser & Callaway (1996) describe two classes and several types within each class for a total of at least seven types (Figure 4). Class I neurons have dense axonal projections to layer 4C, while class II neurons have few or no axonal branches in layer 4C. In addition, class II cells have many dendritic branches in layer 5, but class I cells have no layer 5 branches, just short branches at the 4C/5 border. Thus, each class is likely to receive input from different sources and provides output to different layers. Similar distinctions exist for each neuronal type within these classes.

Class II neurons make up about half of all layer 6 pyramids. They are divided into two types, IIA and IIB. Type IIB neurons are the most distinctive in this class. They do not project axons out of V1, but they have dense dendritic arbors in layer 5 and widespread, likely feedback, axonal arbors in layers 2–4B (Figure 4, IIB). Thus, they are similar to layer 5, class A pyramids in that they are reciprocally connected to layers 2–4B and lack projections outside V1. However, they differ in that they also have roughly half of their dendritic arbor in layer 6, where they can potentially sample direct geniculate input. These cells therefore do not fit neatly into the two-level model of Figure 2. But in this context they could belong in level 2, where they provide a unique feedback projection to layers 2–4B, integrating information from LGN afferents not available to layer 5 pyramids.

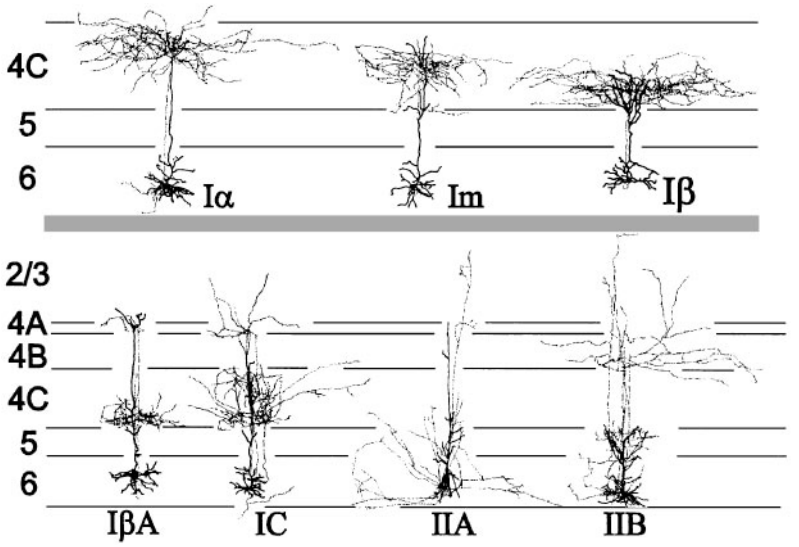

Figure 4 Seven types of pyramidal neuron identified in layer 6 of macaque V1. Class I neurons have dense axonal and apical dendritic arbors in layer 4C. Each type of class I neuron has a unique distribution of axons and dendrites within layer 4C and therefore a unique relationship to the M and P streams. Class II neurons have more extensive dendritic arbors in layer 5 and project axons primarily either to layers 2–4B (type IIB) or to deep layers (type IIA). See text for further details. [From Wiser & Callaway (1996).]

Like type IIB cells, type IIA neurons have many dendritic branches in layer 5. But instead of having strong axonal projections to superficial layers, most of these cells have axonal arbors predominantly in deep layers (5 and 6) (Wiser & Callaway 1996) (see Figure 4, IIA). Thus, these cells might be considered a geniculate-sampling counterpart to layer 5, back-branching pyramids. A further analogy to back-branching pyramids is suggested by the observation that type IIA cells situated in the middle of layer 6 can project to the white matter. The laminar distribution of type IIA projection neurons and their similarity to claustral-projecting cells in the cat (Katz 1987) suggests that they project to the claustrum (Wiser & Callaway 1996). Thus, both layer 5 class A and back-branching pyramids appear to have a class II counterpart in layer 6, with the additional capability of sampling LGN input.

Layer 6 class I pyramids provide the dense feedback to layer 4C illustrated in the two-level model (Figure 2). They lack strong input from layers 2–4B because they have few or no dendritic branches in layer 5 (Figure 4). Not illustrated in the model is the diversity of class I neurons (Figure 4). The neuronal processes

of each type of class I pyramid have a unique laminar distribution, with similar distributions of axonal and apical dendritic branches. These distributions are closely related to the laminar distributions of M versus P geniculate afferents within layer 4, suggesting that there are separate feedback circuits involved in computations related to M (type Iα), P (types Iβ and IβA), and combinations of M and P [M and P (type Im), M or P (type IC)] pathways.

Two types of class I neuron have axonal and dendritic distributions that closely mimic LGN P afferents. Type Iβ and IβA neurons both have apical dendritic branches and strong axonal projections in layer 4Cβ (Figure 4). In addition, type IβA neurons have dendritic branches in layer 4A and weak axonal projections to layers 4A and 3B. The weak feedforward inputs to these cells (Figure 2) are therefore likely to come preferentially from LGN P afferents and layer 4Cβ spiny stellates. This is suggested not only by the laminar distributions of apical dendritic branches, but also by the laminar distributions of these cell types within layer 6. Type IβA cells are found in only the upper half of layer 6 (Wiser & Callaway 1996), which might receive stronger input from P afferents and layer 4Cβ than the lower half of layer 6 (Blasdel & Lund 1983, Usrey & Fitzpatrick 1994). However, some type Iβ neurons could be influenced more by the M stream, since they are found throughout the depth of layer 6. These cells also make feedback connections that can specifically modulate activity in neurons receiving direct feedforward input from LGN P afferents. Type Iβ and IβA neurons could therefore implement feedback in a P-stream-specific subsystem within level 1 of the two-level model (Figure 2). This specificity might also extend to corticogeniculate feedback, since cells of these types that also project to the white matter are found at the same depths in layer 6 as those projecting to P layers of the LGN (Fitzpatrick et al 1994, Wiser & Callaway 1996).

Similarly, type Iα pyramidal neurons, with apical dendritic and axonal branches specifically in layer 4Cα (Figure 4), could execute M-stream-specific local feedback. But so far, no type Iα neurons that project to the white matter have been identified (Wiser & Callaway 1996). The remaining two types of class I neuron, types Im and IC (see Figure 4), might be utilized during combinations of M- and P-stream activity. Type Im neurons provide feedback to spiny stellate neurons in the middle of layer 4C that are likely to receive both M and P geniculate input (Mates & Lund 1983, Blasdel & Fitzpatrick 1984, see above). These layer 4C neurons could therefore require concurrent activity in both M and P pathways for their activation. If type Im cells receive weak input from both M and P afferents, and from mid-layer 4C spiny stellates, they could mediate feedback specifically to neurons that respond preferentially to concurrent M and P pathway activity. Type IC neurons, with no apparent specificity for divisions within layer 4C, might provide feedback throughout both M and P geniculate recipient layers (4Cα, 4Cβ, and 4A) whenever there is adequate activity in

either the M or P pathway. The type IC neurons might also provide feedback to both M and P layers of the LGN, since they and both M and P LGN-projecting neurons are found at the bottom of layer 6 (Fitzpatrick et al 1994, Wiser & Callaway 1996).

The precise relationships I have hypothesized are clearly speculative. Future studies using laser-scanning photostimulation to identify the sources of local input to each type of layer 6 pyramid, and in vivo studies to determine their receptive field properties, could make important contributions to a more detailed understanding of their actual functional roles.

INTRINSIC HORIZONTAL CONNECTIONS IN V1

The functional organization of visual cortex reflects the similarity between neurons within a cortical column. This organization is in keeping with the largely vertical organization of local cortical connections. But many local connections in visual cortex have a more widespread lateral distribution. These lateral spreading axons include not only the links between layers, as described above, but generally longer intralaminar connections spreading several millimeters.

The most studied long-distance intralaminar connections are those originating from and terminating in layer 2/3 of visual cortex (layers 2–4B of macaque V1). These connections arise from pyramidal and spiny stellate neurons whose long-distance axon collaterals form periodic clusters (Gilbert & Wiesel 1979, 1983; Rockland & Lund 1983; Martin & Whitteridge 1984; McGuire et al 1991; Anderson et al 1993; Callaway & Wiser 1996). These clusters tend to preferentially link columns of neurons with similar response properties. In cats, ferrets, and monkeys they have been shown to preferentially link columns with similar orientation preference (Ts'o et al 1986, Gilbert & Wiesel 1989, Malach et al 1993, Weliky & Katz 1994, Kisvardy et al 1996).

By combining optical imaging to reveal functional columnar organization, with extracellular biocytin injections to reveal horizontal projections in layer 2/3 of macaque V1, Malach et al (1993) also observed specificity according to ocular dominance. Injections in monocular regions resulted in preferential labeling in other monocular regions corresponding to the same eye. Injections in binocular regions preferentially labeled other binocular regions. Since CO blobs tend to be monocular and interblobs binocular, these observations are in concert with the earlier observation that blobs are preferentially linked to blobs and interblobs to interblobs (Livingstone & Hubel 1984b). They further suggest that blobs are connected selectively to other blobs having the same ocular dominance.

However, recent findings suggest that the picture is not so clear. Yoshioka et al (1996) analyzed a large sample of biocytin injections in layer 2/3 of V1

using similar methods. Although connections were blob-specific and ocular dominance–specific overall, there were many examples that provided clear exceptions to these rules. In some cases biocytin labeling was more prominent in ocular dominance columns corresponding to the opposite eye, and in other cases labeling was not blob specific. Some of the apparent lack of ocular dominance specificity can be attributed to differences between the analyses of Yoshioka et al (1996) and Malach et al (1993). Yoshioka et al (1996) considered biocytin injections and labeling to be located in either one or another ocular dominance column, even though most layer 2/3 neurons are binocular and ocular dominance shifts gradually. Similarly, blobs and interblobs were also considered to be distinct compartments, but specificity for some parameters appears to shift gradually with distance from the center of a blob (Edwards et al 1995, see above). Unpublished observations of the distributions of synaptic boutons from intracellularly labeled layer 2/3 neurons show a strong relationship between the distance of the cell body from a blob center and the distribution of the distances between boutons and the nearest blob center (NH Yabuta & EM Callaway, unpublished observations). Nevertheless, there is considerable variance in the bouton distribution. And even specificity for orientation columns is far from perfect; about one third of biocytin-labeled patches observed by Malach et al (1993) are in regions with neurons selective for an orientation that differs from the injection site by 45 degrees or more (see also Kisvardy et al 1996).

These observations appear to be at odds with the notion that clustered long-distance connections selectively link columns with similar functional specificity. But studies of the developmental mechanisms that shape the adult organization of these connections would seem to demand that neurons that are linked by horizontal connections have temporally correlated activity (Callaway & Katz 1990, Lowel & Singer 1992, Ruthazer & Stryker 1996). One resolution to these discrepancies is the possibility that horizontal connections can be formed and maintained during development as long as the neurons they interconnect have correlated activity at least some of the time, but not necessarily all the time. Activity is likely to be correlated under some visual conditions but not others. For example, under monocular viewing conditions a binocular neuron would tend to have activity that is correlated with monocularly driven neurons corresponding to either eye, and monocular neurons would have little correlation with monocular neurons driven by the opposite eye. Under most conditions, however, scenes are viewed binocularly, and all of these neurons could be synchronously activated, as long as they were similar in their specificity for other stimulus parameters (e.g. orientation or spatial frequency). In view of the many stimulus parameters for which neurons are selective, it is probably not possible for horizontal connections to be highly selective for all

the attributes that are systematically mapped in V1. Instead they are likely to be modestly selective for all of them.

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