Ann. Rev. Neurosci. 1988. 11 : 253–88

ANATOMICAL ORGANIZATION OF MACAQUE MONKEY STRIATE VISUAL CORTEX

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Introduction

The internal neural anatomy of the primate primary visual cortex—variously known as striate cortex, area 17, or V1—is the subject of this review. In primates, unlike many other mammalian groups, nearly all visual information enters the other cortical processing areas via area V1. Visual information is relayed from the retina via the dorsal lateral geniculate nucleus (LGN) of the thalamus to V1. The geniculo-cortical pathway is composed of multiple channels, each of which is believed to have different functional characteristics. In addition to area V1, about 20 separate regions of visually related cerebral cortex have now been recognized, each of which is ultimately dependent either directly or indirectly on information processed in V1. The relays out of V1 to various cortical and subcortical destinations arise from different laminae and different cell groups within V1. Each of these efferent relays carries its own particular type of visual information derived within the neuropil of V1 from one or more of the inputs from the LGN. The evolution of multiple new abstractions of the visual information within V1 places a tremendous demand on the neuronal circuitry of this cortical area.

Early physiological exploration of V1 supported the view that neurons are arranged in a mosaic of small functionally distinct regions. Because neurons exhibit some of the same functional properties at any one cortical point through several layers in cortical depth, this mosaic was thought of as a set of columns, each with a particular function. We now know, however, that each lamina in cortical depth has its own unique properties

0147–006X/88/0301–0253$02.00

and functional mosaic, its own pattern of dependency on different inputs from the LGN, and its own efferent relay pattern. In this review I consider current knowledge of the anatomical substrates for this laminar organization of area V1 circuitry. An anatomical approach to this complex neuropil may be useful to investigations of other regions of cerebral cortex. The primates used for the majority of the studies described were macaque monkeys. While the description is often applicable to other primates, there appear to be subtle anatomical differences between the visual area of macaques and that of New world monkeys, apes, and man. However, the significance of these differences is not understood. In this review I cover those specific points that seem to be of current interest, rather than providing an exhaustive treatment of all that is known of this area. The extensive literature on the functional organization of the V1 region is not discussed in any detail. Figure 1, A–D, provides a set of landmarks that in part define the laminar architecture of V1.

Thalamic Afferents

A natural starting point for exploring the functional architecture of the striate cortex has been the definition of zones that receive input from the lateral geniculate nucleus (LGN) (Hubel & Wiesel 1972, Lund 1973, Hendrickson et al 1978, Livingstone & Hubel 1982, Blasdel & Lund 1983, Fitzpatrick et al 1983a). In the macaque these regions stand out clearly because they contain an especially rich content of the mitochondrial enzyme cytochrome oxidase (Wong-Riley 1979, Horton 1984), which provides valuable reference points and boundaries against which other anatomical features and functional patterns of the cortex can be compared (Figures 1*C* and 3). The use of tritiated amino acids or horseradish peroxidase (HRP) conjugated wheat-germ agglutinin (WGA) as well as earlier degeneration techniques has shown a parcellation of different thalamic fiber groups to different laminae in cortical depth; careful study of retrogradely transported HRP has indicated in which layers of the LGN (magnocellular, parvocellular or intercalated) these various afferent fiber groups originate. The diagram of Figure 2 summarizes the information currently available, and shows at least seven separate channels of LGN input that are known to exist. The most abundant inputs are to laminae 4Cα and 4Cβ, but only laminae 4B and 5 fail to receive at least some direct inputs from the LGN.

Intra-axonal filling with HRP by micropipette after recording from individual afferent fibers and filling by bulk injection of HRP has shown that in the adult the various thalamic fiber groups differ markedly from one another in the extent of lateral spread of each in their zones of termination (Blasdel & Lund 1983). It is believed, at least for laminae 4C

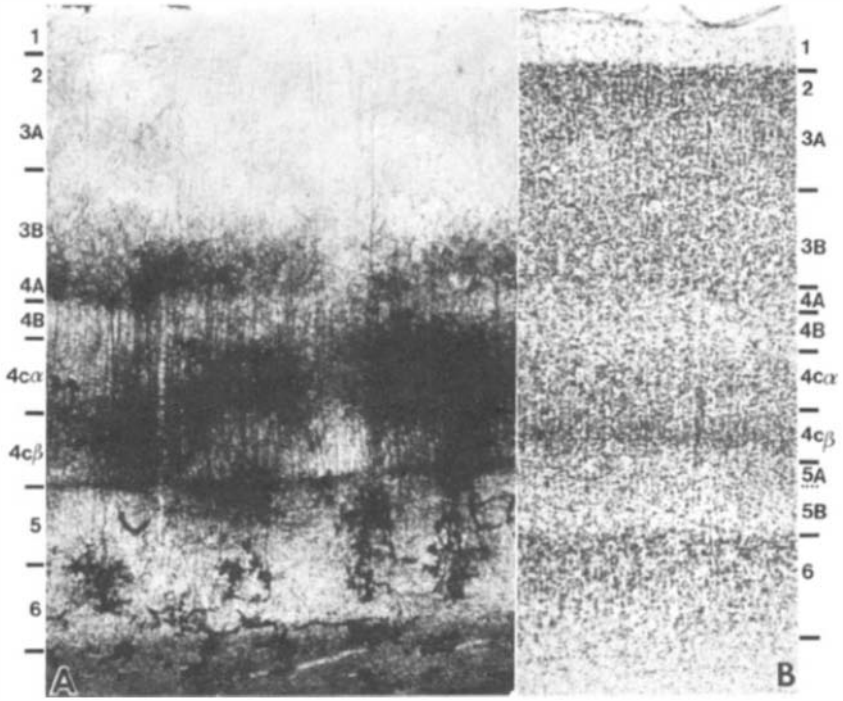


Figure 1(A–B) A Golgi-Rapid impregnation of cortical area V1 from a *Macaca nemestrina* monkey is shown in *A*. This impregnation reveals a tufted axon plexus in lamina 4A and 3B and a narrow horizontal fiber plexus at the junction of laminae 4Cβ and 5. Both these plexuses arise from the axon projections of spiny stellate neurons lying in 4Cβ. The junctional region, where laminae 4Cβ and 5 meet, is labelled lamina 5A in the Nissl stained section of V1 shown in *B*. Lamina 5A is an important recipient of axon relays from local circuit neurons lying in thalamic recipient layers 4A, 4Cα, 4Cβ, and 6; its projections can be seen in Figure 7. (From Lund 1987.)

and 4A, that the degree of lateral spread of single fiber arbors relates to the size of the receptive field to which each fiber responds. This in turn establishes the overall representation of the retinal surface within the particular cortical layer.

The degree of spatial overlap of terminal arbors for these geniculate inputs is an important issue, because it may determine the field size and properties of the postsynaptic neurons. Attempts to estimate this spatial overlap face the problem that there seem to be several different kinds of afferent fiber emerging from even a single parvocellular or magnocellular layer. If different populations terminate within a single cortical lamina, we must first disentangle the particular numerical balance of fiber per area of cortex for each *single*, functionally distinct population before a meaningful

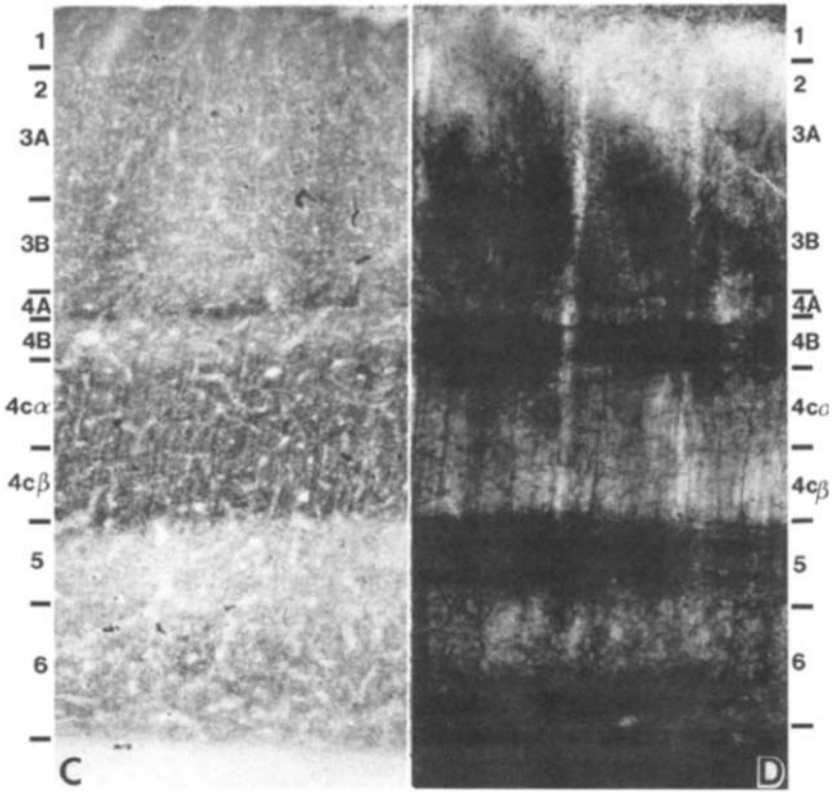


Figure 1(C–D) A section of V1 reacted for cytochrome oxidase is shown in *C*. The boundaries of thalamic recipient regions 4C and 4A are clearly seen with two cytochrome rich "blob" regions evident in layer 3. In *D*, a Golgi Rapid preparation of V1, laminae 4B and 5 show heavily impregnated fiber plexuses. Lamina 4A appears as a slightly translucent cleft immediately above the upper boundary of the fiber plexus of 4B. (From Lund 1987.)

statement of internal overlap can be obtained. This presumes of course that each fiber type provides coverage of the entire visual field for a particular quality of visual input [which, for instance, blue cone input does not (deMonasterio et al 1981, Williams et al 1981)] and distributes evenly over the lamina concerned (which, for instance, the input to the cytochrome-rich patches of lamina 2-3 does not).

While the macaque has perhaps the clearest laminar separation of different thalamic fiber groups of any mammalian visual cortex so far described, very probably different fiber groups overlap at least partially in cortical depth. For instance, Blasdel & Lund (1983) showed an example of a magnocellular axon—one of the largest filled with HRP—that had

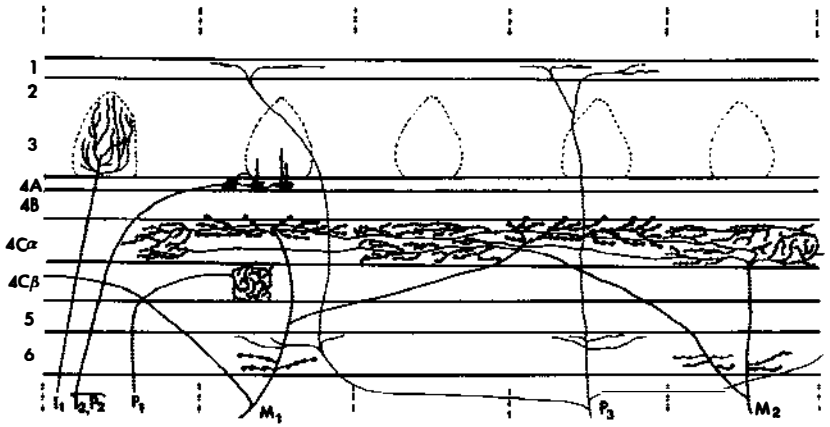


Figure 2 Diagram summarizing information currently available concerning the distribution of thalamic inputs from the LGN to V1. M_1, M_2 = inputs from magnocellular LGN layers; P_1, P_2, P_3 = inputs from parvocellular layers; I_1, I_2 = inputs from intercalated layers. The ocular dominance band dimensions are indicated by dashed lines, 450 μm apart (Hubel & Wiesel 1972, Hendrickson et al 1978, Blasdel & Lund 1983, Fitzpatrick et al 1983a). (Adapted from Fitzpatrick et al 1985.)

its terminal field limited to the upper half of lamina 4Cα, whereas the other magnocellular axons had fields that spanned the entire depth of this lamina. Another example of such an HRP-filled axon is currently under study by K. A. C. Martin and P. Somogyi (personal communication). This suggests that two populations of magnocellular axons with partial overlap in upper lamina 4Cα may exist in the macaque. We shall see later that intrinsic anatomical features distinguish upper lamina 4Cα from its lower part.

There is also some evidence that the input to lamina 4A comes from both the parvocellular layers and the intercalated layers (Fitzpatrick et al 1983a). Blasdel & Lund (1983) also showed that axons to 4A can contribute rising collaterals to the more superficial laminae (see Figure 2). These rising collaterals may converge upon the punctate, cytochrome-rich zones, which receive input from the intercalated layers of the LGN (Livingstone & Hubel 1982, Fitzpatrick et al 1983a). We shall also see that lamina 4Cβ—a primary input zone for parvocellular LGN input—is distinctly subdivided into upper and lower halves, yet the fields of HRP-filled axons from the LGN seem to span the entire depth of the lamina (Figure 2). It may well be that some, as yet unidentified, thalamic axon group may terminate uniquely in the lower of these β subdivisions and thus resemble the partial overlap of input to the α subdivision described above.

Thalamic axons also project to lamina 6 (Hubel & Wiesel 1972,

Hendrickson et al 1978). The magnocellular axons filled with HRP (with major terminal field in lamina 4Cα) have been found to contribute relatively sparse collaterals within lamina 6 where their distribution favors the deeper half of the layer (Blasdel & Lund 1983). Hendrickson et al (1978) show clear label in upper lamina 6 after injections of tritiated amino acids into the macaque LGN parvocellular layers. However, no collaterals have thus far been seen entering layer 6 from the parvocellular axons entering lamina 4Cβ or from those entering 4A (Blasdel & Lund 1983). One HRP-filled axon with color-coded properties (and therefore presumed to emanate from the parvocellular layers) was, however, filled by Blasdel & Lund, it was a widespreading, exceedingly fine-caliber axon that contributed terminals to upper lamina 6 and to lamina 1.

It is important to ascertain whether or not the thalamic inputs to layer 6 are relatively insignificant, in terms of relaying visual information, since their terminal fields in layer 6 are sparse relative to input to layers that are more superficial. However, a strategically placed, but sparse input might be as effective functionally as a numerically larger but less efficiently positioned input, in terms of the region of the postsynaptic cell contacted. Or it might be more likely that these thalamic inputs to lamina 6 target a very specific and, perhaps for the layer, numerically small population of neurons, which may explain the apparently sparse input. We shall see later that layer 6 contains a very diverse population of neurons and that all inputs to the layer appear sparse and are equally diverse in their origins.

The uncertainties concerning the distribution of subpopulations of thalamic axons are compounded by lack of specific information concerning the functional characteristics of these different thalamic inputs. We certainly do not yet know the difference between parvocellular inputs to laminae 6, 4Cβ, 4A, and 1, nor do we have any information as to why there are two types of magnocellular fibers ending in lamina 4Cα (though perhaps they correspond to the X and Y classes described by Blakemore & Vital-Durand 1986). The role of different fiber populations in relation to color-coded information is also obscure. Color response properties are clearly present in the LGN parvocellular layers (Wiesel & Hubel 1966, Schiller & Malpeli 1978, Creutzfeldt et al 1979, Schiller & Colby 1983). Clearly, there is color-coded input to 4Cβ, but it may not be a significant stimulus for all the cells of 4Cβ that lie postsynaptic to the LGN parvocellular inputs (e.g. Dow & Gouras 1973, Gouras 1974, Michael 1978, Livingstone & Hubel 1984a). The distribution of color-coded cells in the superficial layers may be discontinuous (Livingstone & Hubel 1984a), which raises the question as to whether the representation of color-coding in lamina 4Cβ is also patchy. The correlation suggested for color responses and cytochrome patches is somewhat enigmatic since in primates, in

general, the small cell, intercalated layers of the LGN, which provide input to the patches, are not noticeably color coded; perhaps the relay from lamina 4Cβ to the patches is responsible for the color coding of these regions, as suggested by Michael (1986); this indeed is an area in need of further study.

The physiological information available shows that the parvocellular inputs to lamina 4Cβ provide small receptive fields and, in terms of the postsynaptic responses, produce an exceedingly precise point-by-point representation of the visual field in lateral progression across the cortex within lamina 4Cβ (Hubel et al 1974, Blasdel & Fitzpatrick 1984, Parker & Hawken 1984). The magnocellular inputs to lamina 4Cα clearly provide larger receptive fields; but an equally precise progression of these fields can be recorded in the postsynaptic cell responses in lamina 4Cα, in register with the progression in 4Cβ (Blasdel & Fitzpatrick 1984). These inputs to laminae 4Cβ and α differ physiologically in a number of important characteristics other than field size and are served in part by different ganglion cell populations (Leventhal et al 1981, Shapley & Perry 1986). The magnocellular system projecting to laminae 4Cα has for some time been known to respond vigorously to motion (eg. see Dow 1974, Movshon et al 1985). Recently this system has been suggested to be an important element in establishing a foundation for depth perception (M. S. Livingstone and D. Hubel, personal communication). The sustained responses, color selectivity, and fine scale of representation in the inputs to laminae 4Cβ have suggested their role is a more detailed qualitative analysis of the visual world (see recent reviews by Schiller 1986, Shapley & Perry 1986).

The laminar distribution of different thalamic fiber types is only one dimension of the distribution pattern of these axons. Another important anatomical feature is the laterally distributed patterning of the thalamic axon terminations within their lamina of choice. The study of patterned distribution of inputs to striate cortex began with the demonstration by Hubel & Wiesel (1969, 1972) that right eye and left eye inputs are segregated—the ocular dominance stripe distribution of thalamic fibers to laminae 4Cα and 4Cβ. We now know (Hendrickson et al 1978, Livingstone & Hubel 1982, Weber et al 1983, Fitzpatrick et al 1983a) that in squirrel monkey and macaque the neurons of the intercalated LGN layers provide input to patches or blobs in lamina 2-3, aligned in rows above the centers of ocular dominance stripes in layer 4, and that physiologically these patches seem also to be monocular (Figure 3). An even more detailed patterning is seen in the honeycomb distribution pattern of the terminals of thalamic fibers, which also show ocular dominance banding, to lamina 4A (Hendrickson et al 1978, Blasdel & Lund 1983) (see Figure 3).

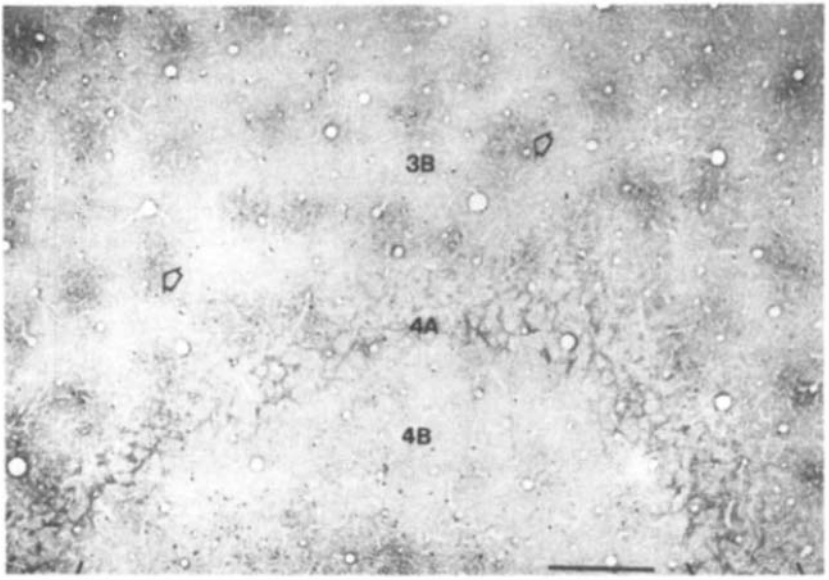


Figure 3 A tangential section through layers 4B, 4A, and 3B of V1 reacted for cytochrome oxidase. The thalamic input regions are seen as a dark reticular network in laminar 4A and as dark patches in lamina 3B. Scale bar = 500 μm. (From Fitzpatrick et al 1985.)

The origin of the patterns of ocular dominant stripes in lamina 4C with aligned lamina 4A inputs and patches in the supragranular layers seems to occur prenatally. Horton (1984) has observed the cytochrome-rich "blob" pattern in layer 2-3 at E144 and points out the correspondence in time with the start of ocular segregation of fibers, which was shown, using densitometry, by Rakic (1976). Whether the framework for this patterning is built into the cortical matrix, and the incoming axons fit into this framework in early growth, or whether competitive interaction between axons in early growth determines the pattern, is one of the central questions in cortical development. Although Wiesel and Hubel (Hubel et al 1977, LeVay et al 1980) showed that the relative width of ocular dominance stripes could be changed by postnatal monocular occlusion, the framework spacing remains intact throughout all manipulations. For the "blobs" this framework changes subtly, over the surface of the visual cortex of the normal monkey, depending on the existence of monocular or binocular inputs and on eccentricity (Horton 1984). In apes and man the honeycomb lattice of input to 4A, as seen in macaques, seems to be lacking (Horton 1984, Tigges & Tigges 1986) and the cytochrome-rich patches extend down through 4B. In prosimians the cytochrome blobs are not present in all species (McGuiness et al 1986). The distribution of efferent neurons in the

superficial layers of macaque is clearly part of an intricate pattern that includes the cytochrome patch (blob) regions, and patterns of intrinsic connectivity and physiological patterning also occur in regular repeating sequences that are seemingly related to this same intrinsic framework. Understanding the origins and constraints of these anatomical and physiological patterns and whether or not they are derived from the thalamic inputs will be extremely important to our overall grasp of visual cortex function.

Postsynaptic Targets of Thalamic Inputs

The evidence for channelling of different types of input to different laminae in the depth of the cortex, though as yet far from complete, provides the rationale for a close examination of the cellular constituents of these thalamic recipient regions and for an attempt to trace the further projections of the neurons in these layers. The information about LGN fiber termination presented above suggests the following questions:

1. Do the neurons lying in these laminae restrict their dendritic surface to a particular thalamic fiber termination zone or do the dendrites reach into other laminae?
2. Do the thalamic afferents end on all available dendritic and somal surfaces in the layer or do they selectively establish contacts on particular cell types?
3. What are the distribution patterns of the axons arising from different types of neurons in the layer, both within and outside the lamina?
4. What inputs to the layer exist, other than the thalamic inputs that we have used to define the limits of the layer?
5. Do we believe that we have defined a single functional zone by using the thalamic input distribution to define the boundaries of each of the layers? These questions are discussed below.

The thalamic input zones of laminae 4Cα, 4Cβ, and 4A, are characterized by the presence of spiny stellate neurons (Lund 1973, 1984) and an almost complete lack of pyramidal neurons in 4C (Mates & Lund 1983). Intermingled with them are aspinous or sparsely spined stellate neurons, which comprise at least 15–19% of the total cell population on the basis of counts of neurons positive for GAD and GABA immunoreactivity—which most of these neurons show (Ribak 1978, Somogyi et al 1983a, Fitzpatrick et al 1983b, 1987). In addition, these laminae are transversed by the apical dendrites of pyramidal neurons with somata and basal dendrites in laminae 5 and 6. The apical dendrites of particular populations of layer 6 pyramidal neurons arborize within 4Cα, and this is accompanied by recurrent axonal arbors from these same layer 6 pyramidal cells within α. Another layer 6

pyramidal population provides dendritic arbors off the main apical dendrite at the border of laminae 5 and 4Cβ (lamina 5A), and a terminal tuft of dendrites on the 4A region (Lund & Boothe 1975); it is curious that while these lamina 6 pyramidal neuron dendritic arbors appear reluctant to enter lamina 4Cβ, these same neurons send vigorous axonal arbors into the β division with collateral extensions terminating in 4A. The lamina 5 pyramidal neuron apical dendrites pass through these layers without arborization but with variable spine populations (Lund & Boothe 1975). It is noticeable that spine number on the apical dendrite shafts and on intruding dendritic arbors falls off sharply in layer 4Cβ (Lund 1973).

These various dendritic arbor patterns suggest that the deeper pyramidal neurons, particularly those of layer 6, may receive thalamic input within 4C, particularly 4Cα, and within 4A; the basal dendrites of these same pyramidal neurons may also receive direct thalamic input in layer 6. The work of Katz et al (1984) suggests but does not prove that in primates these pyramidal neurons with dendritic and axonal relationship to the thalamic input zones of layer 4 comprise the neuron populations projecting back to the LGN known to exist in 6 (Lund et al 1975). Now that the cytochrome oxidase method has allowed a clearer definition of the depth and borders of lamina 4B (which is cytochrome poor but sandwiched between the clearly defined margins of cytochrome-rich laminae 4A and 4α), it seems probable, from examination of Golgi impregnations, that upper lamina 4Cα may interrelate to a different set of lamina 6 pyramidal neurons than does lower lamina 4Cα (Lund, unpublished observations). Lamina 4B itself may not have a significant relationship to layer 6 pyramidal neurons because, injection of HRP into lamina 6 produces very little label in lamina 4B (Blasdel et al 1985).

The recurrent axon collaterals of lamina 6 pyramidal neurons that give terminal arbors to divisions of lamina 4 differ in terminal morphology from the thalamic axons entering the same layers. The recurrent pyramidal neuron axons terminals are made from complex side-spine arrays (Fitzpatrick et al 1985) whereas the thalamic axons have en-passant, large diameter, beaded axon terminals; electron microscopy has shown that both are of type 1 morphology and therefore are believed to be excitatory. The physiological implications of this difference in axon morphology may be important, and in cat it seems to be coupled with a difference in the numerical balance of the postsynaptic site. The thalamic terminals end predominantly but not exclusively on spines (Garey & Powell 1971, Winfield & Powell 1983, McGuire et al 1984, LeVay 1986), whereas the layer 6 pyramidal neuron axons end predominantly but not exclusively on dendritic shafts of smooth dendritic neurons within layer 4 (McGuire et al 1984).

The projection of layer 6 upon layer 4 seems to rival the thalamic input in density, but the relative strength of these two important sources of afferents on single postsynaptic neurons—if the thalamic and layer 6 inputs do in fact share common postsynaptic targets—is unknown. It should also be remembered that some of the aspinous neurons of lamina 6 send direct axon projections to at least 4Cα, and so the influence of layer 6 upon layer 4 may be both excitatory and inhibitory (Lund 1987). Only by laborious EM reconstruction of the relationship between neurons (whose morphology is first identified by Golgi or HRP methods) and labelled afferent axons will the pattern of distribution of specific populations of terminals be solved. This approach is already underway in other species (Somogyi 1978, Peters et al 1979, Hornung & Garey 1981, Freund et al 1985), and is beginning in the primate (Kisvarday et al 1987), but its accuracy depends upon a clear identification of different classes of thalamic axon (or other afferents) as well as of the postsynaptic neurons. It is suspected that in single laminae there are different classes of spiny stellate neurons; certainly there are many kinds of smooth dendritic cells (Lund 1987). We have no idea of the degree or kind of patterns of synaptic specificities, and the danger is that small samples may be misleading. However, the importance of obtaining this information is undeniable and the rewards great, since the data obtained may illustrate general features of cortical organization.

Single axon terminal fields of the parvocellular LGN afferents to 4Cβ, identified so far by HRP filling, bridge the depth of the lower half of 4C (Blasdel & Lund 1983); the upper and lower limits of this 4Cβ zone were defined earlier by injecting tritiated amino acids into or making lesions in the parvocellular LGN layers (Hubel & Wiesel 1972, Lund 1973, Hendrickson et al 1978, Fitzpatrick et al 1983a). The dendrites of the neurons whose somata lie in 4Cβ may overlap into lamina 5A and into lamina 4Cα when they lie near the limits of the zone defined by the parvocellular inputs. Heavy cytochrome oxidase staining comes to an abrupt end at the lower border of lamina 4Cβ, but it is not entirely certain that this rich cytochrome zone excludes lamina 5A, which is an important but very narrow (approximately 50 μm in depth) lamina. Therefore, while the thalamic axons to 4Cβ seem to have a reasonably sharply defined upper and lower boundary to their distribution, the dendrites of potential postsynaptic neurons do not seem as sharply constrained to obey these boundaries. The same phenomenon is seen in lamina 4Cα, where the thalamic axons either bridge the depth of 4Cα or run along its upper half, but where the neurons lying at the borders of 4Cα have dendrites that stray into laminae 4Cβ and 4B respectively. There are, moreover, a group of spiny stellate neurons whose dendrites bridge the depth of the 4C division (Mates & Lund 1983).

Although they seem to be infrequent, these neurons may play an important role. These observations rise the question whether we can expect a clear physiological difference between neurons in the α and β halves of lamina 4C or whether a gradual transition of neuronal properties through the depth of 4C is more likely. This question is partially addressed in the papers of Blasdel & Fitzpatrick (1984), Parker & Hawken (1984), and Livingstone & Hubel (1984a), but a clear-cut answer may be difficult to obtain.

Axonal projections from different varieties of aspinous neurons, whose dendrites are restricted to either the α or β division, cross between the α and β thalamic input zones to provide arbors to both divisions and to 4A (see Figure 4). In addition, at least one class of lamina 4A aspinous neuron sends a prolific axon arbor back to 4C (Lund 1986). These axon relays—perhaps GABAergic—should be taken into account when considering the functional role of each channel of input. Equally important, but not yet clearly explored, is the question of whether the spiny stellate neurons of lamina 4Cα and β project between the α and β subdivisions. Although they may provide quite dense axon collaterals to the level at which their dendrite field lies within α or β (L. Katz, K. Martin, personal communications) it is not clear to what extent, if at all, axon collaterals of single, spiny stellate cells establish synaptic contacts in both α and β divisions.

Intrinsic Relays of Thalamic-Recipient Neuron Populations

Because of the clear boundaries established for lamina 4Cβ by the parvocellular afferents, it was surprising to find evidence of a sharp subdivision in the layer that split it into an upper and a lower half (Fitzpatrick et al 1985). This subdivision is demonstrated by the retrograde labelling of cell bodies in 4Cβ after injecting HRP into the principal projection region of the 4Cβ spiny stellate neurons, lamina 3B and adjacent 4A (see Figure 5). Following such an injection, the upper half of lamina 4Cβ and the lower part of 4Cα contain a population of well-labelled neurons; these labelled neurons extend laterally at least as far as the margins of the overlying injection site. However, in lower β, only a very narrow column of cells is retrogradely labelled, lying directly under the center of the injection site. The boundary between the upper and lower zones of retrograde labelled cells in 4Cβ is very sharp. Although nothing in the dendritic field organization of the neurons in 4C has so far alerted us to this division (the labeled neurons would be expected to have dendrites passing freely across this boundary between upper and lower β), differences in the way the axons of these cells of upper and lower β target the 4A-3B region sharply define a neuronal population that resides in upper 4Cβ and lower 4Cα but which is absent from the lower half of 4Cβ. Fitzpatrick et al (1985) suggest

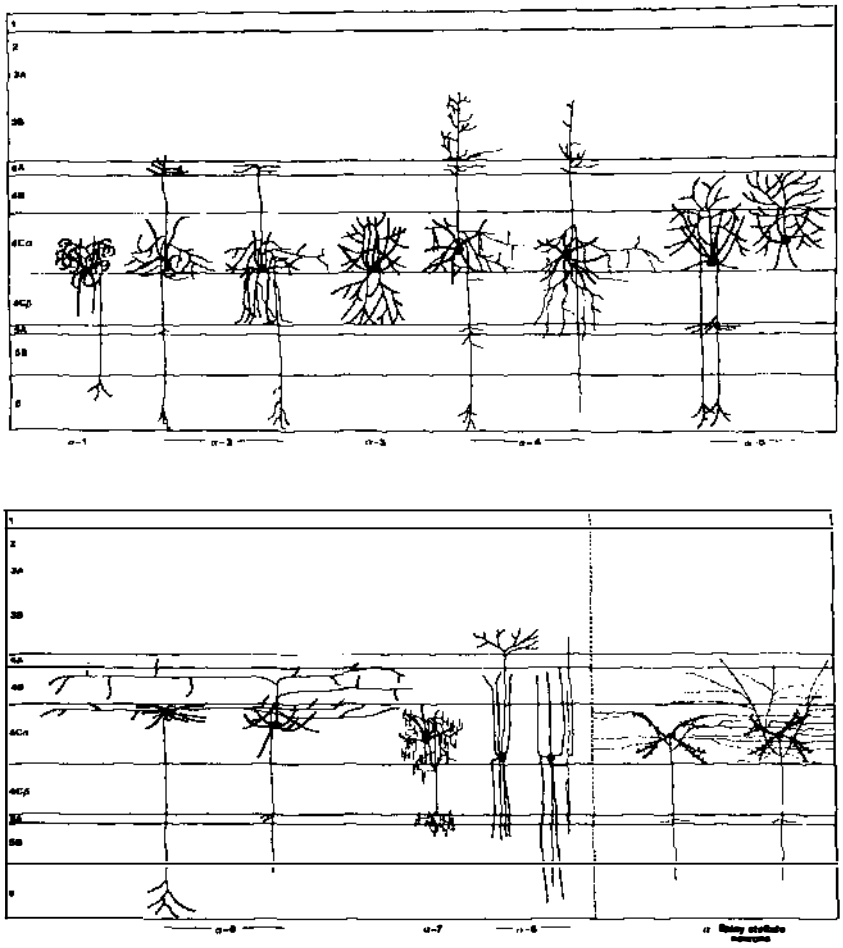


Figure 4 Diagrams summarizing the varieties of local circuit neurons (usually GABAergic) found in lamina 4Cα. Note the patterns of interlaminar axon projections differ for each variety. The axon projection patterns of two varieties of spiny stellate neurons of lamina 4Cα are shown for comparison. (From Lund 1987.)

a difference in the lateral spread of the terminal fields of the 4Cβ neurons in laminae 4A and 3B. One might suppose that the deeper β cells have a more local axon field and that the upper neurons a wider terminal distribution, but this hypothesis needs careful confirmation. So far, a physiological correlate of this split has not been discovered, though the current

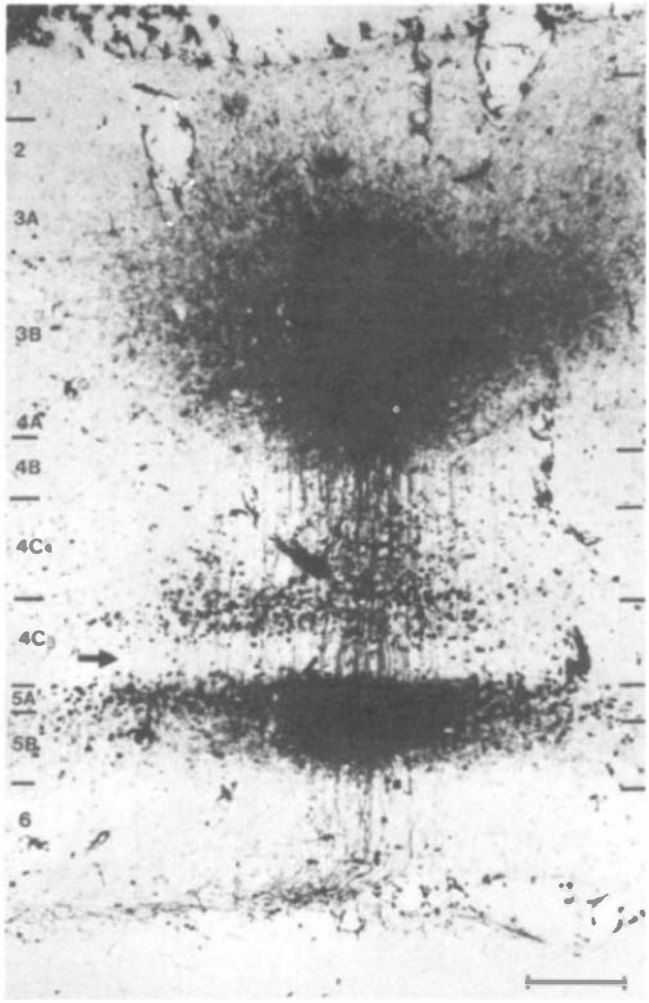


Figure 5 Photomicrograph showing the distribution of labelled neurons following a large injection of HRP into laminae 3B and 4A. Note the presence of a distinct cleft (*arrow*) of unlabelled neurons in lower lamina 4Cβ. Scale bar = 200 μm. (From Fitzpatrick et al 1985.)

source density analysis of Mitzdorf & Singer (1979) may show such a boundary.

Some years ago, using Golgi impregnations, Lund (1973) found that spiny stellate neurons of lamina 4Cα differed in their axonal projection from those of 4Cβ. Because magnocellular LGN projects to 4Cα and the parvocellular to 4Cβ, this observation suggests a continued separation of

magno- and parvocellularly derived information within the cortex. While the principal projection of the 4Cβ spiny stellate neurons is to laminae 3B and 4A, the projection of the majority of 4Cα spiny stellate neurons is to lamina 4B (Lund 1973, Fitzpatrick et al 1985) or solely within 4Cα itself (K. Martin, personal communication). It now seems probable that there is a gradual diminution, rather than a sharp cutoff, of neurons projecting to the 3B lamina region, as one moves up from lamina 4Cβ into lower lamina 4Cα, and a gradually increasing number contribute instead to projections to lamina 4B and within lamina 4Cα itself (Fitzpatrick et al 1985). The lateral spread of the 4Cα axon projections can be considerable, and periodic clusters of termination are visible in the upper half of the 4Cα layer after HRP injections within 4Cα (Fitzpatrick et al 1985). Both spiny and aspinous neurons contribute laterally spreading axons, so both may add terminals to these clusters (K. Martin, personal communication, Lund 1987). Although some projections into lamina 4B from the 4Cα neurons are wide spreading, the bulk of the lamina 4Cα to lamina 4B projection forms a more narrowly focused vertical cylinder (Fitzpatrick et al 1985). The lateral spread of axons within lamina 4Cα or passing from lamina 4Cα to 4B is probably 1.0–2.0 mm on each side of a single point. Laterally spreading connectivity is further emphasized by neurons lying within lamina 4B whose axons spread over 4.5 mm to either side of a small injection of HRP tracer—again, with periodic terminal zones occurring every 400–500 μm. Both pyramidal and spiny stellate neurons contribute to these connections (Rockland & Lund 1983).

Within the neuropil of upper 4Cα itself and, with clearest definition, in 4B, the physiological properties of orientation specificity, binocular fusion, and recognition of direction of motion are all generated from the magnocellular thalamic input, an input that at entry is comprised of circularly symmetric receptive fields (Blasdel & Fitzpatrick 1984, Parker & Hawken 1984, Livingstone & Hubel 1984a). In 4B lie neurons with efferent projections to at least areas V2, V3, PO, and MT (Lund et al 1975, Rockland & Pandya 1979, Lund et al 1981, Colby et al 1983 and personal communication, Van Essen 1984), although it is not yet known if the same neurons project to all regions or if separate groups project to individual cortical destinations. The efferent neurons are clearly of different sizes, even when projecting to a single area, and the largest neurons of the layer, the spiny stellate neurons, are included in the efferent neuron pool projecting to MT as well as pyramidal neurons. The periodicity of organization in the layer may also be reflected in clustering of efferent neurons projecting to these different destinations.

The diversity of smooth dendritic neurons within lamina 4Cα is considerable (Figure 4), and this probably reflects the multiple tasks

accomplished functionally within the layer (Lund 1987). These neurons have not only local axon projections within the layer but also axon projections to many intralaminar destinations outside the confines of 4Cα. With the exception of one variety of aspinous neuron that contributes laterally widespreading axon arbors within 4Cα and 4B (Figure 6), the axons of these neurons have a columnar trajectory to their interlaminar projections, which target one or more of the following laminae: 6, 5A, 4Cβ, 4B, 4A, and 3B (Lund 1987). The projection of these neurons to 3B must contribute to the rather fine orthograde label in 3B after injections of HRP into 4Cα (Fitzpatrick et al 1985). The organization of the smooth dendritic neurons in 4Cα also suggests a division between upper and lower halves of the layer, with different cell types associated with the two regions (Lund 1987).

The population of aspinous neurons in lamina 4Cβ, while complex, does not include such a large number of varieties as is seen in lamina 4Cα. Indeed, physiologically, the generation of new functional complexity in the 4Cβ layer seems less than that accomplished within 4Cα; the neurons largely retain characteristics of the circular field organization that is seen

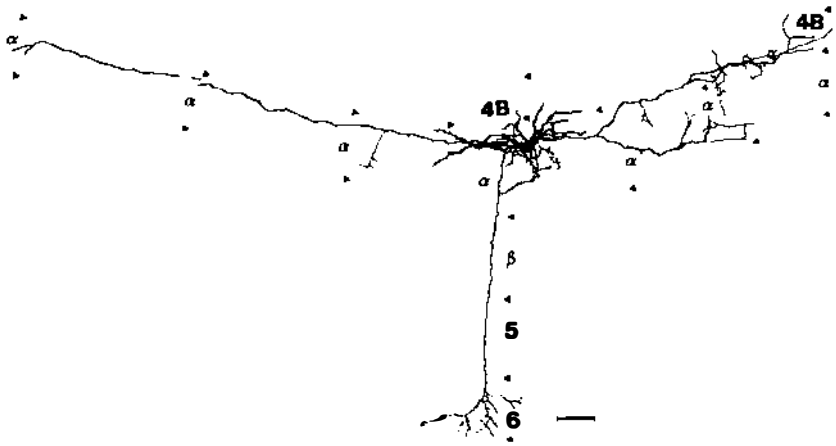


Figure 6 A drawing of a Golgi Rapid impregnation of a variety of interneuron, probably GABAergic, in lamina 4Cα of monkey V1 cortex. This variety is recognized for its large diameter axon trunks that spread away from the neuron for long distances in 4Cα and 4B. Short, beaded collaterals with predominantly vertical orientation branch off from these trunks, suggesting that the neuron is a "basket" neuron with axon contacts onto somata and initial dendritic segments of pyramidal neurons. A descending axon trunk passes to lamina 6, with a terminal arbor of limited lateral extent. Another tier of similar basket neurons is seen at the junction of laminae 5 and 6 (see Figure 11). These two tiers are the regions in monkey V1 where direction-selective neurons are located. Scale bar = 50 μm. (From Lund 1987.)

in the parvocellular afferents entering the layer (Bullier & Henry 1980, Blasdel & Fitzpatrick 1984, Parker & Hawken 1984, Linvingstone & Hubel 1984a). Orientation specificity and binocular fusion do not seem to be generated to any marked extent, at least within the lower β division. The aspinous neurons of lamina 4Cβ, like those of 4Cα, contribute axon projections to other laminae, in tight columnar trajectories, and the long distance lateral projections of smooth dendrite neurons seen in lamina 4Cα do not occur in the 4Cβ lamina. The axon projections of these local circuit neurons of 4Cβ target one or more of laminae 6, 4Cα, 4A, 3B and seem also to include 5A.

The smooth dendritic neurons of 4Cα and 4Cβ have interlaminar projections that share many of the same target regions, namely 6, 5A, 4A, and 3B, plus the other half of the 4C division—α or β; the α division differs from the β division because it has projections to 4B that the β division lacks. It is also evident that neither division projects to 5B or apparently above lamina 3B. The projections to laminae 5A and 6 are accompanied by fine caliber, weak axonal projections from the spiny stellate neurons of the 4Cα and 4Cβ divisions. Again: how does one assess the importance of quantitatively weak projections? The strong axonal projections of the α and β spiny neurons to 4B, and to 4A and 3B respectively suggest that the predominant "forward" flow of information from 4C passes to these two destinations rather than to infragranular layers. The different destinations of these prominent α and β spiny neuron projections [which are of type I synaptic morphology and therefore presumed to be excitatory (LeVay 1973)] also suggest a continued separation, in some fashion, of the two streams of visual information entering 4Cα and 4Cβ, at least in these first interlaminar relays, even though the streams are interrelated by aspinuous neuron axon relays.

To understand the anatomical substrates for function in laminae 4C, apart from the lamina 6 input, one must consider two other laminae—5A and 4A—that contain smooth dendritic neurons with clear axon projections into 4Cα and 4Cβ (Lund 1986, 1987). Laminae 5A and 4A are also axonally linked in reciprocal fashion to each other by aspinous neuron axon relays, and a weak spiny stellate neuron axon projection passes from lamina 4A to 5A. As we have already discussed, 4Cα and 4Cβ both project to 5A and 4A by a variety of both smooth and spiny neuron axon links. Lamina 5A therefore seems to occupy a special role in terms of the smooth dendrite populations contained within its narrow limits (Figure 7). These 5A neurons are extremely diverse in their morphologies but they include varieties that have clear projections to each of the thalamic input layers—4A, 4Cα, 4Cβ, and 6; additionally, in 5A, varieties of these neurons project to the superficial laminae 3, 2 and 1 (Lund 1987). Only this last projection

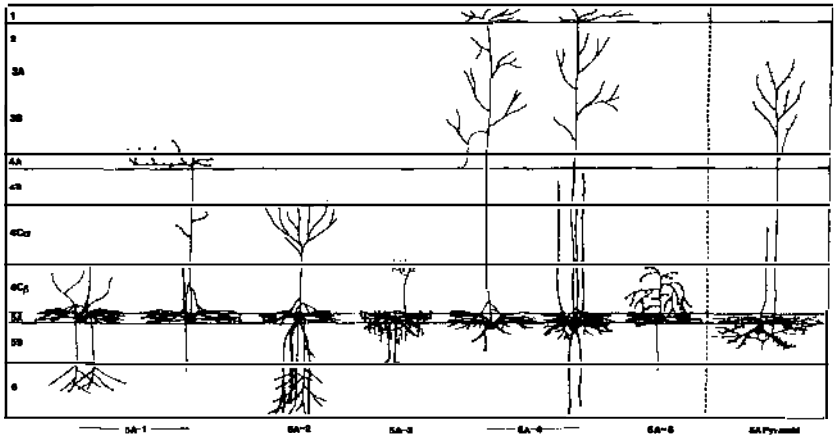


Figure 7 Diagram summarizing the varieties of local circuit neurons (usually GABAergic) found in lamina 5A of monkey cortical area V1. The axon projection of a typical pyramidal neuron of the same region is illustrated for comparison. Note the different patterns of axon projections to other laminae shown by the local circuit neuron populations. (From Lund 1987.)

pattern is shared by the spine-bearing neurons of 5A; these are small pyramids with vestigial, thread-like apical dendrites (Lund 1973).[1]

The axonal links of aspinous lamina 5A neurons (with perhaps GABAergic properties) to thalamic recipient laminae suggest an important role for the 5A layer. A gating function is possible through which the neurons of the lamina determine the relative weighting of outflow from each of the thalamic input zones and coordinate it with input from layer 6. The crucial question is what would drive the layer 5A neurons in order for them to achieve such decisive activity, and what function does the primary excitatory projection from the layer (presumably from the pyramidal neurons) perform in the superficial layers? Another important question concerning this 5A region is whether or not its neurons receive direct thalamic input.

[1] It was previously stated (see legend to Figure 15 of Blasdel et al 1985) that smooth dendritic neurons of lamina 5A also contributed axon arbors to lamina 4B. With continued careful examination of Golgi impregnation and reexamination of the cells in question, the author now believes that in fact these smooth dendritic projections from 5A target 4Cα, or upper 4Cα alone in some cases, and that so far, there is no clear evidence that their arbors enter 4B (see Lund 1984). In Golgi Rapid material the 4B borders are not always well defined and upper 4Cα may stain heavily, thus providing a misleading upper boundary, while 4B remains unstained. Perhaps we will find a 5A to 4B projection after all, or perhaps the injections intruded sufficiently on laminae 4A or 4Cα, both recipients of 5A projections, to retrogradely label the cells in lamina 5A.

Figure 1(*A–B*) shows the position and narrow depth of this lamina; interestingly, V1 in the infant monkey shows a narrow, cytochrome-rich band at approximately the same position and with a pale stain band that covers much of 4Cβ. A cytochrome oxidase pattern resembling that of the infant is seen in adult macaque monkeys treated systematically with monomeric acrylamide, which apparently induces degeneration of color opponent ganglion cells in the retina (Eskin & Merigan 1986) and sharply reduces both cytochrome oxidase staining of the parvocellular layers of the LGN and cytochrome oxidase staining in much of 4Cβ. Thus input to this lower narrow cytochrome-rich band may come from other than the parvocellular layers. For the moment, however, whether 5A in fact coincides with the narrow cytochrome-rich band currently placed within the lowermost limit of 4Cβ, or whether 5A lies below this cytochrome-rich band, must be decided by further experiments.

The limits of lamina 4A are, for convenience of description, here defined as the narrow zone of cytochrome-rich thalamic terminations that form a reticular or honeycomb network; this network exhibits circular lacunae, free of thalamic terminals, that vary in size, but generally measure about 100 μm across (see Figure 3). The problem with this definition is that although this region is rich in cell bodies, the dendrites and axons of these neurons are distributed above and below this narrow zone and arborize significantly in the neuropil of laminae 4B and 3B. There are a few exceptions where particular neuron varieties have dendrites that seem stratified within or against this zone [in particular, small, spiny stellate neurons and a very small class of aspinous neurons of the chandelier variety (Lund, unpublished observations)] but, here again, even the local axon distribution of these neurons does not restrict itself to the 4A lamina. It is clear from our earlier discussion that this lamina is also targeted by axonal relays from 4Cβ and α (including both aspinous and spiny neuron axon components). In addition, we have already mentioned layer 6 pyramidal neuron axonal collaterals and their apical dendrite terminal tufts, both of which enter 4A; input to lamina 4A also comes from aspinous neurons of 5A.

Physiologically, lamina 4A shows characteristics of the parvocellular LGN layers that innervate it (Blasdel & Fitzpatrick 1984); its field map resembles in its fine detail that of 4Cβ to which it is related, point by point, by rising 4Cβ axon relays. Lamina 4A is the most superficial layer in the cortex that contains a distinct population of spiny stellate neurons; although pyramidal cell bodies also lie in the layer, their dendrites largely spread above and below the layer (Lund 1973). The predominant axon projection of the small, spiny stellate neurons of the region is upward into layers 3 and 2, although a fine descending process to lamina 5A and on down to lamina 6 can be traced. Much work, both anatomical and

physiological, is needed before we can understand lamina 4A. For example, an as yet unanswered question is whether the absence of a rich cytochrome band at this point in the human and ape striate cortex (Horton 1984, Tigges & Tigges 1986) is indicative of the absence of both thalamic input and the elaborate neuropil evident in this region of the macaque monkey striate cortex.

The rich composition of different 4A smooth dendritic neurons and their complex interdigitation with both lamina 4B and the superficial layers in the macaque suggest that lamina 4A may help coordinate the ongoing patterns of activity in 4B with that of the layers above, two regions that we have suggested are driven primarily by different streams of incoming visual information. The insertion of thalamic input from both parvocellular and intercalated layers into lamina 4A is interesting, and it will be valuable to learn more about the physiological properties of the LGN cells that give rise to these inputs in comparison to those that project to other laminae. If this region does coordinate the activity of lamina 4B with the more superficial cortex, then the properties of this thalamic input may be expected to reflect particular qualities that would aid in this coordination.

Organization of the Superficial Laminae

We now consider the superficial laminae 3B, 3A-2, and 1. The intrinsic neuronal organization reaches an extreme complexity within these superficial layers, with relays from all the other deeper cortical laminae also entering into its neuropil. Within these superficial laminae are found a more diverse population of smooth dendritic neurons than is seen in any of the other layers, and the topography of laterally spreading, intrinsic axonal projections from the pyramidal neurons of the region is extraordinarily elaborate. Moreover, the region contains a diverse population of efferent neurons, projecting to cortical areas V2, V3A, V4, and PO (Rockland & Pandya 1979, Lund et al 1981, Tigges et al 1981, Colby et al 1983, Yukie & Iwai 1985, Van Essen et al 1986) that often occur in regularly patterned arrays and at least some of which are apparently spatially segregated from each other according to both function and efferent destination (Livingstone & Hubel 1984a).

The principal intrinsic input to lamina 3B is from spiny stellate neurons of 4Cβ, but neurons of lowermost 4Cα and 4A also contribute. We have already seen the pattern of retrograde label if an HRP injection is placed in 3B; such an injection into the superficial laminae (3A, 2, and 1) gives no labelled cells within any of the regions of 4A or 4C that received LGN input. Instead, this more superficial injection labels a cluster of cells in lamina 4B immediately under the injection site, a laterally spread popu-

lation of retrogradely labelled cells in lamina 5, mainly in 5A, and a few labelled neurons in lamina 6.

The thalamic input from the intercalated layers of the LGN focusses its patchy projections chiefly on the 3B region (Livingstone & Hubel 1982, Fitzpatrick et al 1983a), and lamina 3B is also served by collaterals of the thalamic projection to 4A (Blasdel & Lund 1983). To understand more fully the organization of inputs from other layers to lamina 3B, the interested reader should examine the results of the small injection studies of Blasdel et al (1985) and Fitzpatrick et al (1985) and of the smooth dendritic neuron relays from 4C and 5A detailed by Lund (1987). The 3B region receives its predominant lamina 5 input from 5A rather than from 5B and receives only a narrowly focussed, weak input from lamina 6.

Properties such as binocular fusion, orientation, and end stopping seem to be generated in the neuropil of 3B (Hubel & Wiesel 1968, Hubel et al 1977, Livingstone & Hubel 1984a). I suggest, however, that these properties are generated in more than one lamina. I have already proposed that 4Cα and 4B neurons also achieve some of the same functional characteristics (and see Malpeli et al 1986, Schwark et al 1986, for evidence of such a pattern for cat), but perhaps these properties are kept in vertical alignment between laminae by interlaminar relays—an alignment that may be initiated developmentally from properties developing in a single layer, e.g. 4Cα.

This functional elaboration and the eventual parcellation of different functions to different efferent neuron groups must continue via the prominent and broadly spreading axon projections that rise from lamina 3B neurons into laminae 3A-2 and 1 (Blasdel et al 1985). Joining this projection to 3A-2 and 1 are axon relays from 4B that rise in strong columnar point-to-point fashion; in addition, lamina 5B neurons contribute rising axon projections that spread broadly in the lateral direction on reaching lamina 2-3A (Blasdel et al 1985). Lamina 6 provides a very light projection to this superficial cortex, where it distributes in a point-to-point vertical fashion. These projections from laminae 4B, 5, and 6 include the axons of neurons of both aspinous (Figure 10) and spiny neuron varieties.

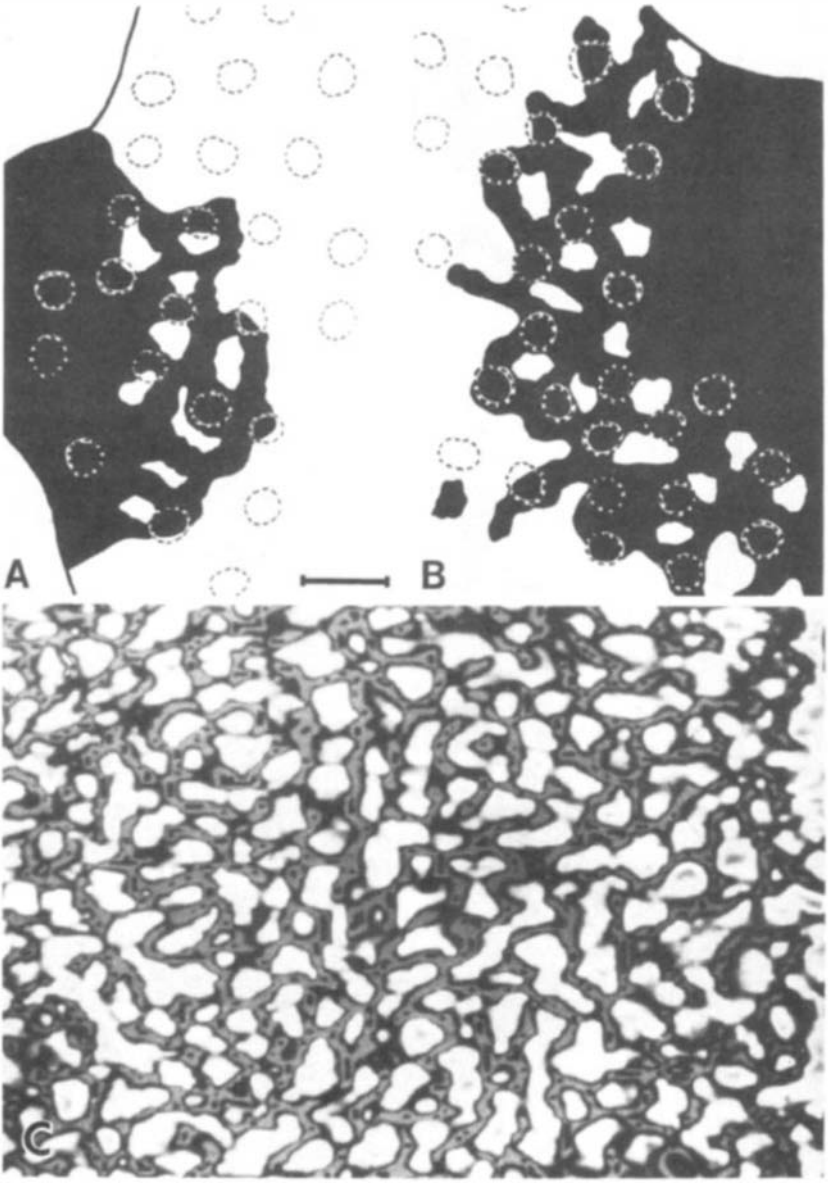
Evidence for the complex lateral patterning of intrinsic projections in the superficial layers was first seen in the studies of Rockland & Lund (1983). HRP injected into layers 2 and 3 is found to be transported laterally both retrogradely and orthogradely in elaborate lattice patterns. Close to the injection site in macaque and squirrel monkey striate cortex, the HRP fills processes and cell bodies that form walls around regularly spaced, sparsely labelled, lacunae (Figures 8 and 9). Further distant from the injection site, the HRP label, both retrograde and orthograde, forms regularly spaced clusters about 500 μm apart in layer 2-3 around the site

of the injection. While of roughly the same spacing, these labelled patches do not regularly coincide with the cytochrome-rich patches of thalamic input in the same layers (Figure 8*B*). Livingstone & Hubel (1984b) demonstrated, using small injections of HRP, that when this tracer is placed within a cytochrome-rich patch, or "blob", labelling occurs only in neighboring cytochrome-rich patches, and when the injection is in an intervening cytochrome-poor region, cytochrome-poor regions are labelled, but again of similar 500 μm spacing. Curiously, when using WGA-HRP in larger injections (Livingstone & Hubel 1984a), transport was most clearly shown to cytochrome-rich patches. Note, however, that these labelling patterns may reflect the affinity of uptake between specific neuron groups and the tracer substance used, and that activity levels may also play a role in amount of uptake. Nonetheless, these results indicate a lateral parcellation of neuron groups into discrete, interconnected patches in the superficial layers, each set of patches of similar spacing, but each group offset from one another spatially in a series of lattice-like arrays.

The functional role of these lattices has begun to be realized as the results of studies examining the relationship of V1 to V2 have become available. Livingstone & Hubel (1984a) have shown that efferent neurons in the cytochrome-rich patches of V1 project to bands in area V2 characterized by narrow width and rich cytochrome oxidase content. These same bands show a predominance of color-coded neurons and project, in turn, to V4 (DeYoe & Van Essen 1985, Shipp & Zeki 1985), a region thought to be of particular importance for color vision. Patches of efferent neurons in cytochrome-poor regions in V1 superficial layers project to cytochrome-poor bands of V2 that seem to be functionally more concerned with orientation than color properties. Since the superficial layers of V1 also send projections to cortical areas other than V2 [at least to V3A (Zeki 1980, Ungerleider & Mishkin 1982, Van Essen et al 1986), to V4 (Zeki 1978, Yukie & Iwai 1985), and to area PO (Colby et al 1983 and personal communication)], it is likely that the spatial organization of the efferent neurons in this region will be found to hold still further complexities in terms of both anatomy and physiology.

Rockland & Lund (1983) suggested that the connections between these lattice patches are made by the axons of pyramidal neurons, since the retrograde label clearly filled pyramidal neuron somata and proximal dendrites. Indeed, pyramidal neurons in the superficial layers of striate cortex establish patchy terminal fields from laterally spreading axon trunks (Gilbert & Wiesel 1983, Martin & Whitteridge 1984, McGuire et al 1985). The terminal sites of these patchy projections in the monkey seem to be predominantly dendritic spines (McGuire et al 1985, Rockland 1985,

Figure 8(*A–B*) (*A*) Reconstruction of HRP-labelled loci (*black*) around an injection site in macaque monkey striate cortex, layers 2 and 3, in tangential section. (*B*) The same reconstruction of HRP-labelled loci as seen in *A* but with the position of cytochrome-rich thalamic input patches indicated by hatched profiles. (The alternately stained section series were matched by blood vessel patterns.) The two labels clearly do not coincide, but both may surround common lacunae (see Figure 9). (From Rockland & Lund 1983.)



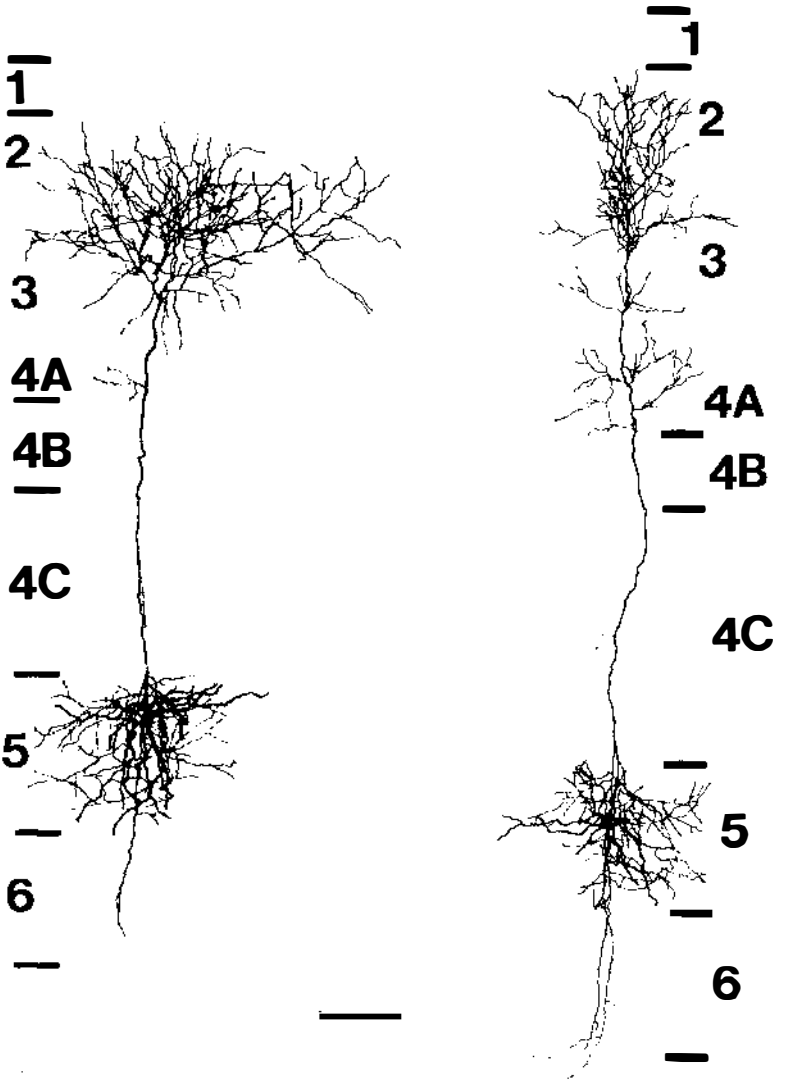
Kisvarday et al 1986), but, so far, the actual weight of these inputs on single postsynaptic pyramidal neurons or smooth dendritic neurons is unknown. The degree to which the axons of GABAergic neurons participate in the long distance connections of these lattice arrays is also unknown.

We have already discussed the fact that patchy lateral connections made by cells within the superficial layers are found also in upper lamina 4Cα and lamina 4B and, evidence for laterally patchy connections by cells intrinsic to the lamina is also found in lamina 6 (Blasdel et al 1985). With injections of HRP that bridge the depth of the cortex, patches of label are found to be in columnar register around the injection site in laminae 2 and 3, 4B, upper 4Cα, 5, and 6 (Rockland & Lund 1983). Patches continue the furthest distance lateral to the injection site in lamina 4B. If the injection is kept to the superficial layers, above lamina 4B, patches of label occur only in laminae 4B, 5, and 6 immediately under patches produced in the superficial layers without further lateral spread.

These patterns of label are difficult to explain. If one thinks of the system of lattices in the superficial layers as creating a continuum of interconnected points across the surface of the cortex, why is it that large or small injections in the superficial layers produce patches around them of the same spacing distance? Since we know that both cytochrome-rich and cytochrome-poor points are each interconnected by axon lattices as separate systems in the superficial layers, this should potentially at least double the number of labelled points if the injection site includes both systems. When injections include all layers, one might suppose that the intrinsic lattices in different layers would be labelled somewhat haphazardly—so why are the labelled patches in alignment through the layers and why do they maintain the roughly 500 μm spacing? One could suggest

Figure 9(A–C) (*A* and *B*) Two maps from tangential sections through HRP injections in squirrel monkey striate cortex, layers 2 and 3. The HRP label adjacent to the injection sites forms solid walls (*indicated in black*) that surround unlabelled lacunae. The dotted circles indicate the position of cytochrome-rich patches of thalamic input in the same layers in sections adjacent to those stained for HRP. The cytochrome-rich patches fit into the HRP-labelled walls but avoid the unlabelled lacunae. (*C*) Computer-derived image from study of orientation preference maps using voltage-sensitive dye monitoring in live macaque monkey V1 cortex. The dark lines mark the position of rapid or abrupt change in orientation sequence, and the white areas mark where orientation change occurs in a continuous and even manner. The cytochrome-rich patches in this same region of cortex lie in the dark regions of rapid change or of break in orientation sequence. It is suggested that the HRP pattern seen above in *A* and *B* may be following the same regions as indicated by dark lines in *C*. (Blasdel & Salama 1986.) (*A* and *B* from Rockland & Lund 1983. *C*, modified from Blasdel & Salama 1986.) Scale bar = 500 μm.

that connections between the laminae only serve one of the lattice systems in the superficial layers, but this reasoning still leaves much unexplained since Livingstone & Hubel (1984b) found that small HRP injections in either cytochrome-rich blobs or in non-blob regions give label in the deeper layers.



The kinds of theoretical arguments put forward by Mitchison & Crick (1982) in regard to data on patchy connections in tree shrews and by Mitchison (1985) when discussing the primate patchy connections are of considerable interest because of the possibility of obtaining discontinuous patterns of label, when using neuronal tracers such as HRP, in sheet-like systems of neural connections made with continuous but highly ordered patterns of connectivity. Testing models with a continuous lateral connectivity by computer produces discontinuous patterns of simulated label. The discontinuous label patterns that are produced derive from the properties of the connectional rules in the continuum and show the anatomist that discontinuity of label need not necessarily indicate an absence of long-distance connections in lightly labelled regions.

In discussing the form of interlaminar projections, either vertical columnar point-to-point form or spreading and fan-like in macaque cortex, Blasdel et al (1985) suggest that these patterns of projection may reflect the match, or mismatch, of the functional map in the interconnected laminae. For instance, in terms of its neurons' responses, lamina 4Cβ has a detailed point-by-point representation of the retinal surface, made up of small, circularly symmetric receptive fields. The lamina 4Cβ projection to lamina 4A is made in a vertical point-to-point fashion, and indeed 4A also shares a similarly accurate map of the retina (Blasdel & Fitzpatrick 1984). However, the 4Cβ projection to lamina 3B has spreading axon fans, and some collateral processes even take sideways steps on entering 3B (Fitzpatrick et al 1985).

The visual "map" in 3B, as physiologically characterized, has a locally disjointed topographic order in terms of retinal surface and has instead substituted a spatially highly ordered map of directionally selective units (Hubel & Wiesel 1978). The spreading fans and lateral "steps" of the 4Cβ axon arbors therefore may represent the redistribution of the retinal map in order to build a sequence of oriented units where retinal locus is repeated several times, each time for a different orientation. The vertical point-to-point projection of lamina 4B upon 3A-2 in turn may reflect a similarity

Figure 10 Two examples of local circuit neurons (perhaps GABAergic) with somata and dendritic fields in lamina 5 of macaque monkey V1. Both neurons have a local axon arbor in lamina 5 and a strong projection to the superficial layers, especially to lamina 2-3A. Descending axon trunks are present, and from at least one of these cells enters the white matter. Pyramidal neurons of layer 5 also project to the superficial layers and out of V1. Lamina 5 receives its principal input from neurons of lamina 2-3A, so the reciprocal projection can be presumed to contain both excitatory and inhibitory components. The neurons were drawn from Golgi Rapid preparations of infant monkey. Scale bar = 100 μm. (Lund, work in progress.)

of map in the two regions, since both contain ordered arrays of orientation-specific neurons that seem to be in strict alignment (Hubel & Wiesel 1968, 1978), whereas in both lamina 4B and the 3A-2 region the retinal map is locally disordered. It is of some interest that the layer 5 projection upon lamina 2-3A is fan-like and spreading, even though there is apparently alignment of periodicity in the relationship between lamina 2-3A and 5B. It may be that the individual axons from lamina 5B cell groups search out more than one period in the lamina 2-3A lattices.

The relationship of the supragranular lattice arrays to the circuits responsible for encoding the orientation of linear visual stimuli is poorly understood. The lattice relays probably do not literally reflect the pathways by which orientation signals are generated but rather represent some topographic relationship between the layout of neurons, with different orientation specificities, and the lattice connections. The voltage-sensitive dye study of Blasdel & Salama (1986) shows the overall topography of orientation domains relative to cytochrome-rich patches and to ocular dominance domains in the supragranular layers. The cytochrome-rich patches, which clearly form part of a lattice array (Livingstone & Hubel 1984b), lie in regions where a break in orientation sequence occurred. But the cytochrome-rich patches, known from the work of Livingstone & Hubel (1984a) to lack orientation specific responses, make up only part of the walls around roughly circular regions of smoothly changing sequences of orientation-specific neurons; these walls mark the regions where rapid shifts in orientation (Figure 9*C*) preference occur. The form of this pattern of gradual versus abrupt change in orientation resembles that of the overall pattern of HRP filling of walls around lacunae (Figure 9*A*, *B*), as seen in the Rockland & Lund (1983) study where the cytochrome-rich patches were found to always lie in the HRP-labelled walls of the lattice. This suggests that the break-points or fractures in orientation sequences may form the regions that interconnect heavily in lattice form and that the regions of slow orderly change are less widely connected.

In an attempt to test directly for patterns of connectivity relative to the voltage-sensitive dye patterns, Blasdel and Lund in preliminary studies have made small HRP injections into regions of single orientations or fracture points as visualized in the living cortex using voltage-sensitive dye techniques. The resultant transport of HRP to patches around the injections sites, even when the injection was in a center of slow orientation change, does not appear to match well to repeating regions of the same or even opposite orientation; instead the transported HRP patches appeared to always lie in the walls where the orientation sequences fracture, rather than in regions where smooth orientation change occurs. As in the Livingstone & Hubel (1984b) study, injections in cytochrome-rich patches were

found to project to neighboring cytochrome-rich patches. Additional studies of intrinsic connectivity in relation to function are required but undoubtedly the results will further illustrate an exquisite precision of intrinsic cortical connectivity in the superficial layers.

One particularly intriguing and, as yet, unsolved problem in striate cortex is the nature of the anatomical substrate for the generation of orientation specificity. I have suggested that responses to stimulus orientation may be generated in more than one lamina (in 4Cα and in 3B), and there is no reason that layer 6 should not also generate orientation-specific responses within its substance (see Mapeli et al 1986, Schwark et al 1986). It is possible, as suggested by theoretical models such as those proposed by Linsker (1986a,b,c), that we shall never be able to recognize the circuitry anatomically, since the network properties of the relevant connections may not be recognizable in conventional anatomical terms. Still unknown is how, or whether (Bauer et al 1980, 1983), the orientation sequences in each of the laminae showing them are aligned vertically. The multiple vertical interlaminar connections that exist might seem likely pathways for ensuring correlated firing patterns to help alignment (Hubel & Wiesel 1968, 1978) during development, and the work of Bauer et al (1983) shows that the orientation specificities of neurons of lamina 4B and lamina 2-3 seem to be in alignment, even if the deeper layers are not.

Laminae 5 and 6

The deeper layers of the striate cortex, laminae 5B and 6, are the source of subcortical afferent relays and, in the case of layer 6, are also a source of projections to extrastriate regions of visual cortex. Earlier I noted that lamina 5 should be subdivided into 5A and 5B. This subdivision is based on a number of criteria: 5A makes prominent connections to the principal thalamic input zones of the cortex (layers 4C and 4A), whereas 5B projections do not (Blasdel et al 1985); Lamina 5A does not seem to be a promiment source of efferents, whereas lamina 5B contains several efferent cell populations, with strong projections to the pulvinar and superior colliculus (Lund et al 1975) that include cells of a variety of sizes and of both spine bearing and aspinous morphologies and perhaps therefore of different functions.

We have seen that the principle sources of afferents to 5B are from the supragranular laminae, especially lamina 2-3A, and from lamina 4B. Lamina 5B receives only weak projections from layer 6 (Blasdel et al 1985). In contrast, layer 6 receives no strongly marked projections from more superficial layers, but each superficial lamina seems to contribute a vertically focused light projection to which aspinous neurons make considerable contribution (see the studies of Fitzpatrick et al 1985, Blasdel et

al 1985; Lund 1987). In these HRP injection studies, the most prominent and spreading input to layer 6 seems to come from lamina 5—but one should be aware that the injection of HRP in layer 5 may encroach upon a specialized border zone at the junction of layers 5 and 6 that contributes both axonal and dendritic elements to lamina 6 in a wide-spreading fashion. This border zone can be recognized in fiber stains as having a distinct and prominent horizontal fiber plexus.

In this same region lie the cell bodies of giant pyramidal neurons (sometimes called Meynert cells), whose basal dendrites sweep down to the base of lamina 6 and spread horizontally for considerable distances (see Lund 1973). These cell bodies usually occur in upper lamina 6, but occasionally also intrude over the border into lowermost lamina 5. In material stained for cell bodies they may be confused in lamina 5 with another population of large pyramidal neurons whose basal dendrites spread purely within lamina 5 and whose apical dendrite, in contrast to that of the cells with dendrites spreading in deep 6, is well developed and presents a vigorous spreading arbor of terminal branches to layers 3A-2 and 1. The giant pyramidal neurons with basal dendrite fields in layer 6 have been shown to project to both cortical area MT and to the superior colliculus (Spatz 1975, Lund et al 1975, Fries 1984, Fries et al 1985); they share these efferent destinations with some smaller neurons that are mostly clustered in upper lamina 6.

The laminae 5-6 border stratum also contains a group of horizontally oriented smooth dendritic neurons whose axons spread laterally over long distances at the junction of laminae 5 and 6 and emit, at intervals, vertically oriented, beaded collaterals into both laminae 5 and 6 (Figure 11) (Lund, work in progress). In their axon morphology and extensive lateral spread, these neurons resemble ones seen in 4Cα whose axons spread horizontally for long distances in upper α and 4B (see Figure 6). Cells with similar axon morphology in cat cortex have been termed "basket" neurons, and their axon terminals have been found to contact cell bodies and initial apical dendritic segments of pyramidal neurons (Somogyi et al 1983b).

This coincidence in form may be related to that fact that lamina 6 and upper lamina 4Cα plus lamina 4B are the two strata of monkey cortex where neurons with markedly direction-selective responses to movement are found (Dow 1974, Livingstone & Hubel 1984a, Movshon et al 1985). Both regions also have populations of cells projecting to the extrastriate cortical area MT (V5) where motion and specific direction of motion are primary driving stimuli. These long, lateral projections by neurons with smooth dendrites, possibly GABAergic and inhibitory in function, may play a role in the generation of direction-selective response properties. It might be that the property of direction selectivity is generated more

than once in V1, as was proposed for orientation selectivity, and the system in lamina 6 might therefore have an independent substrate for directionality from that in 4B. Neurons of layer 6, particularly in upper 6 and lowermost 5 (Kennedy & Bullier 1985) as well as those of 4B, project to area V2 where, in the case of the fibers from 4B, it is suggested that the projection terminates in a system of broad, cytochrome-rich, stripes (Van Essen et al 1986). Neurons in these broad stripes are direction selective, and the stripes include neurons efferent to area MT (DeYoe & Van Essen 1985, Shipp & Zeki 1985).

Additional Inputs to V1

A large number of subcortical structures project to the primary visual cortex, apart from the lateral geniculate nucleus. A recent review of these projections—in terms of retrograde cell labelling within subcortical regions following tracer injections within area V1—was carried out by Tigges & Tigges (1984). The strength of these projections and which laminae they target in V1 are in many cases unknown. The pulvinar contributes two, or even three, separate projections to V1 (see Perkel et al 1986 for a recent account), but how each of these inputs contributes to the reported laminar pattern of terminals in layers 1 and 2 is unclear (Ogren & Hendrickson 1976). Information about the laminar patterning of projections to V1 from extrastriate cortex is also incomplete, but a useful review is provided by Van Essen (1984); projections to V1 from V2, V3, and V4 terminate in layer 1, and, in the case of V2, the projection adds

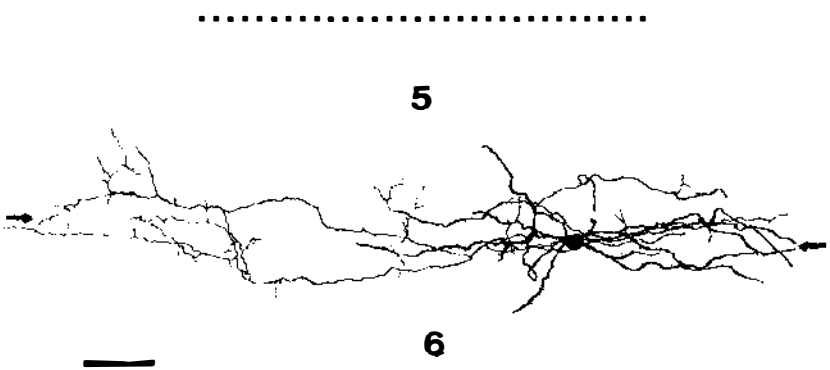


Figure 11 Golgi Rapid impregnation of a local circuit neuron at the border of laminae 5 and 6. This neuron is of the "basket" variety, similar to a population seen in laminae 4Cα (see Figure 6). These neurons influence the neuropil in laminae of V1 (upper 4Cα, 4B, and 6) where neurons with direction-specific responses are located. Scale bar = 50 μm. (Lund, work in progress.)

lighter input to layers 4B and 5B. The projection from V3 and MT to V1 terminates most heavily in lamina 4B and also contributes to layer 6. The function of these inputs is not known.

Summary

I hope that this review of the internal anatomy of the monkey primary visual cortex makes clear the high degree of specialization that exists in each of the cortical laminae and their constituent neurons. Each lamina is driven by different patterns of relays from the LGN and by different patterns of intrinsic interlaminar projections. The elaborate laminar and intralaminar segregation of efferent neuron arrays suggests that the extraordinary precision of inter- and intralaminar connectivity provides a unique functional role for each set of efferent neurons. The organization of aspinous (presumed inhibitory) local circuit neurons suggests that they are highly specialized, and within each lamina and via interlaminar relays each variety may only accomplish a single, particular task. The cortex neuropil does not give the immediate impression of "random" networks, and if such exist, they must surely be between very tightly determined subgroups of neurons. Clearly a very detailed physiological exploration of V1 is still needed, with new consideration of thalamic axon function, of efferent neuron characteristics, of laminar differences, and of spatial organization of properties within laminae, in order to match known anatomical detail with function. The concept of columnar organization in cortical organization of V1 may eventually be redefined in more complex terms that accurately describe the anatomical and functional parcellation evident in cortical depth and perhaps may link it to a means by which a correlation of different aspects of the visual image is achieved.

ACKNOWLEDGMENTS

I would like to thank Dr. Raymond Lund for his critical comments on the manuscript and Roberta Erickson and Thomas Harper for their help with its preparation. My work was supported by grant EY-05282 from the National Eye Institute.

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