

The Functional Organization of Local Circuits in Visual Cortex: Insights from the Study of Tree Shrew Striate Cortex

We have used a combination of anatomical and physiological techniques to explore the functional organization of vertical and horizontal connections in tree shrew striate cortex. Our studies of vertical connections reveal a remarkable specificity in the laminar arrangement of the projections from layer IV to layer III that establishes three parallel intracortical pathways. The pathways that emerge from layer IV are not simple continuations of parallel thalamocortical pathways. Layer IV and its connections with layer II/III restructure the inputs from the LGN, combining the activity from ON and OFF channels and from the left and right eye and transmit the products of this synthesis to separate strata within the overlying layers. In addition, studies of two other prominent vertical connection pathways, the projections from layer VI to layer IV and from layer II/III to layer V suggest that the parallel nature of these systems is perpetuated throughout the cortical depth.

Our studies of horizontal connections have revealed a systematic relationship between a neuron's orientation preference and the distribution of its axon arbor across the cortical map of visual space. Horizontal connections in layer II/III extend for greater distances and give rise to a greater number of terminals along an axis of the visual field map that corresponds to the neuron's preferred orientation. These findings suggest that the contribution of horizontal inputs to the response properties of layer II/III neurons is likely to be greater in regions of visual space that lie along the axis of preferred orientation (endzones) than along the orthogonal axis (side zones). Topographically aligned horizontal connections may contribute to the orientation preference of layer II/III neurons and could account for the axial specificity of some receptive field surround effects.

Together, these results emphasize that specificity in the spatial arrangement of local circuit axon arbors plays an important role in shaping the response properties of neurons in visual cortex.

Neurons in visual cortex participate in a rich network of local connections that refines the patterns of activity supplied by the lateral geniculate nucleus and elaborates new response properties such as selectivity for the orientation of an edge or its direction of motion in visual space (Hubel and Wiesel, 1962, 1968, 1977). Despite an increasingly detailed picture of the anatomical organization of these intracortical circuits, we are still far from understanding the rules that relate the response properties of individual neurons to their patterns of intracortical connectivity. This review focuses on one element of this complex network—intracortical axon arbors—and considers how specificity in the arrangement of these processes contributes to the functions of intracortical circuits.

Based on their distribution relative to the cortical surface, two basic types of intracortical pathways can be identified. The most prominent type, and the first to be identified with anatomical techniques, includes axons that travel perpendicular to the pial surface, have terminal fields that arborize with relatively little lateral spread (roughly 0.5 mm), and provide much of the communication between cortical layers (Ramon y Cajal, 1911; Valverde, 1971; Lund, 1973; Lund and Boothe, 1975). Vertical connections play an essential role in transmitting activity from the main geniculorecipient layer, layer IV, to

the superficial cortical layers, and they also provide a major link between neurons in the superficial and deep cortical layers. The recognition of a second type of connectivity had to await the development of more sensitive anatomical tracing techniques, which revealed a system of horizontally oriented axon arbors extending long distances (2–3 mm) parallel to the pial surface (Rockland and Lund, 1982, 1983; Gilbert and Wiesel, 1983, 1989). Horizontal connections are most prominent in the superficial cortical layers (layers II–III), somewhat less so in the deeper layers (V and VI) and largely absent from cortical layer IV.

Critical for any attempt to relate the arrangement of vertical and horizontal axonal connections to the response properties of cortical neurons is the availability of morphological landmarks for functionally distinct populations of neurons. Lamination provides the functional framework for addressing specificity in the arrangement of vertical axonal connections, and a convenient starting point is the orderly termination of lateral geniculate axons in cortical layer IV. In species with well-developed visual systems, the projections from the lateral geniculate nucleus are composed of parallel pathways that differ in their response properties and terminate on neurons that lie at different depths within cortical layer IV (Hubel and Wiesel, 1972, 1977; Harting et al., 1973; Hendrickson et al., 1978; Fitzpatrick et al., 1983; Livingstone and Hubel, 1984). As a result, the vertical projections of layer IV neurons determine whether the information from parallel lateral geniculate pathways merges or remains separate, and specify the type(s) of information delivered to neurons that project to other cortical and subcortical visual areas.

For exploring specificity in the arrangement of horizontal connections, the relevant functional groups are the columns of cells with similar response properties that repeat at regular intervals across the cortical surface (Hubel and Wiesel, 1977; Livingstone and Hubel, 1984; Blasdel, 1992; Bonhoeffer and Grinvald, 1993). The fact that horizontal connections terminate in patches similar in size to these functional domains led to the identification of one simple rule: horizontal connections selectively link columns of neurons that have similar receptive field properties (Livingstone and Hubel, 1984; Ts'o et al., 1986; Gilbert and Wiesel, 1989; Blasdel et al., 1992; Malach et al., 1993; Fitzpatrick et al., 1994). But, another equally important feature of horizontal connections is their arrangement with respect to the map of visual space. This issue is of interest because the axon arbors of individual neurons are often elongated across the cortical surface, extending farther and giving rise to more terminals along one axis of the map than others (Gilbert and Wiesel, 1983; McGuire et al., 1991; Kisvárdy and Eysel, 1992). Thus, specificity in both the topographic and modular arrangement of intracortical axon arbors could make significant contributions to the functions mediated by horizontal connections.

The bulk of the work described in this review comes from experiments in which anatomical and physiological techniques were used to explore the organization of local circuits

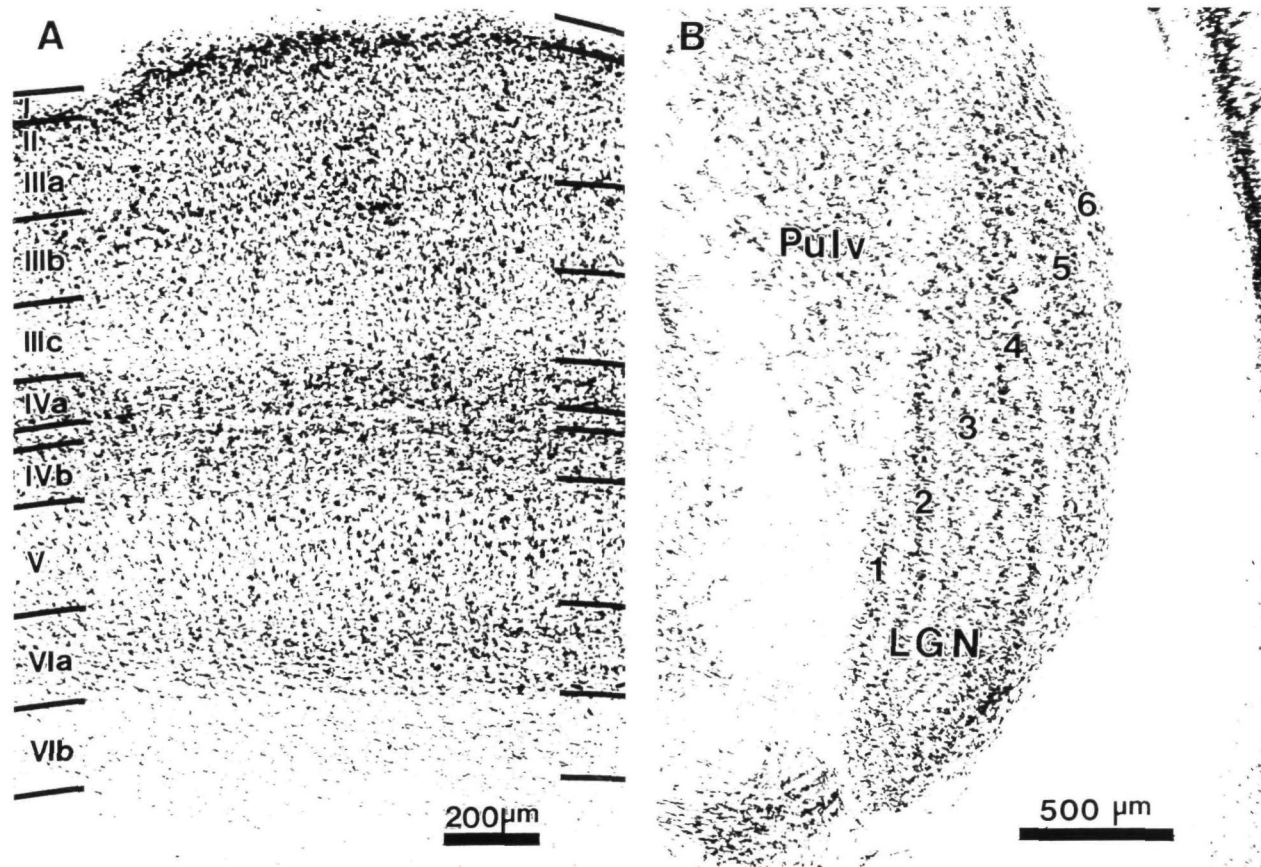


Figure 1. Cytoarchitecture of tree shrew striate cortex and lateral geniculate nucleus. *A*, Coronal section through striate cortex demonstrating the cell-rich layer IV, which is divided into ON- and OFF subdivisions IVa and IVb, respectively. *B*, Coronal section through the lateral geniculate nucleus. Layers 1, 2, 4, and 5 are the source of projections to cortical layer IV. Layers 1 and 2 receive input from ON-center retinal ganglion cells, layers 4 and 5 from OFF-center ganglion cells. Layers 1 and 5 are targets of the ipsilateral eye; layers 2 and 4 are targets of the contralateral eye. Layers 3 and 6 receive ON- and OFF-center information from the contralateral eye and relay this information to the supragranular layers of the cortex.

in the striate cortex of the tree shrew, a small, highly visual mammal indigenous to Southeast Asia. Comparative anatomists were the first to draw attention to these curious animals because their gross anatomical features and their highly organized central visual structures suggested that they were closely related to primates, perhaps the modern day descendent of the mammals that gave rise to the primate line (LeGros Clark, 1924, 1971; Simpson, 1945). Although the evolutionary relationships between tree shrews and primates remain unresolved (Cronin and Sarich, 1980; Luckett, 1980; MacPhee, 1993), they are, for us, only a secondary concern. The highly developed visual cortex of the tree shrew, which includes a strikingly laminated layer IV, a sharply defined area 17-area 18 border, and a well-defined system of orientation columns, provides a unique system for teasing apart structure-function relationships in cortical circuitry (Harting et al., 1973; Humphrey et al., 1980a,b; Conley et al., 1984; Raczkowski and Fitzpatrick, 1990; Muly and Fitzpatrick, 1992; Usrey et al., 1992; Usrey and Fitzpatrick, 1996). In the following sections we summarize our analysis of vertical and horizontal connections in tree shrew visual cortex and we consider the implications of these findings for understanding the functional organization of intracortical circuits.

The Organization of Vertical Connections in Tree Shrew Striate Cortex

Parallel Pathways from Layer IV to Layer II/III

The two subdivisions of layer IV in tree shrew striate cortex that receive inputs from parallel LGN pathways are separated

by a prominent cell-sparse cleft (Fig. 1A). Unlike primates where differences in conduction velocity, receptive field size, and color responses distinguish the inputs to sublayers of layer IV, layer IV-projecting neurons in the tree shrew LGN are largely homogeneous in their response properties, with one striking exception: the sign of their response to luminance change. The LGN projections to layer IVa arise from neurons in layers 1 and 2 that receive their retinal input from ON-center ganglion cells (Figs. 1B, 2A). The LGN projections to layer IVb arise from neurons in layers 4 and 5 that receive their retinal input from OFF-center ganglion cells (Fig. 2B) (Harting et al., 1973; Conway and Schiller, 1983; Conley et al., 1984; Raczkowski and Fitzpatrick, 1990). Because the dendritic processes of layer IV neurons are horizontally stratified and sample selectively from either IVa or IVb, the segregation of the ON and OFF channels is maintained in the responses of layer IV neurons (Geisert and Guillery, 1979; Kretz et al., 1986). Thus, in the tree shrew, the vertical connections of neurons in layers IVa and IVb are responsible for transferring the information from ON and OFF channels to other cortical layers.

The primary targets of layer IV axons are the superficial cortical layers (layers I–IIIc). As a first step in tracing the intracortical course of the ON and OFF pathways, small injections of retrograde tracers were placed into the superficial layers and the distribution of labeled cells in layer IV directly below the injection site was evaluated (Muly and Fitzpatrick, 1992). In each case, labeled cells were found in both layers

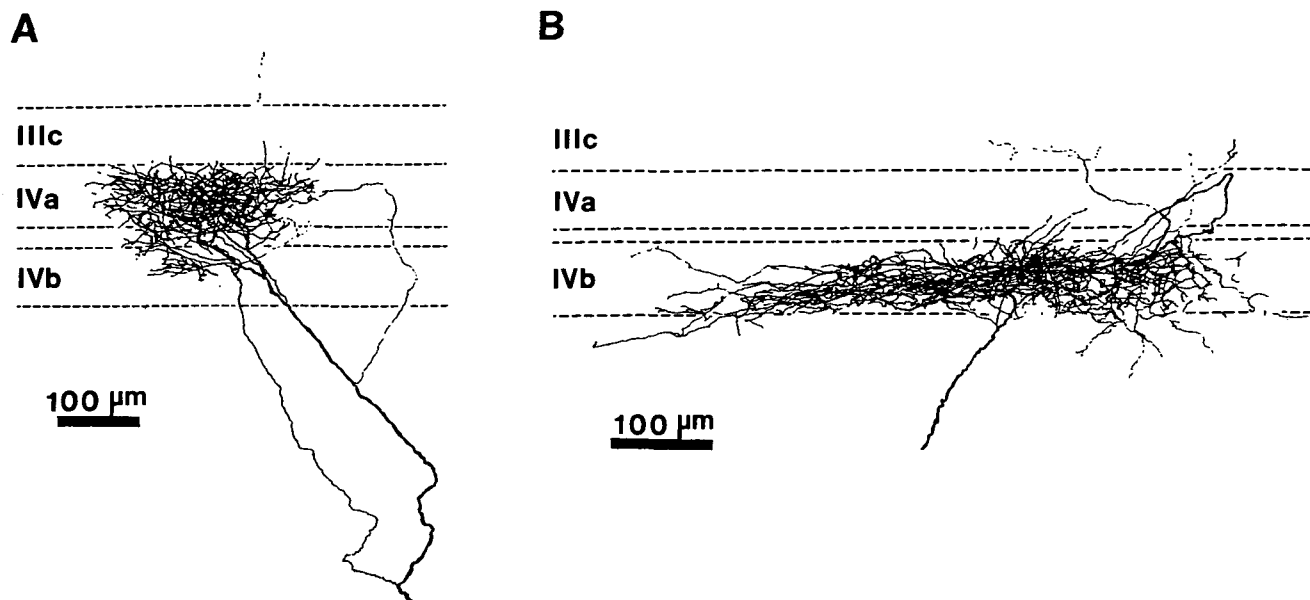


Figure 2. Examples of single geniculocortical arbors filled by intracellular injections of horseradish peroxidase. *A*, ON-center geniculocortical arbor driven by the contralateral eye. *B*, OFF-center geniculocortical arbor driven by the ipsilateral eye. From Raczkowski and Fitzpatrick (1990).

IVa and IVb, suggesting that the ON and OFF channels simply converge within the superficial cortical layers. Physiological recordings from neurons in layers II and III of tree shrew visual cortex confirm this result: unlike neurons in layer IV, most neurons in layers II and III respond well to both the onset and the offset of light stimulation (Muly, 1992). Thus, despite the specialized arrangement of LGN axons within layer IV, the ultimate fate of the ON and OFF pathways in tree shrews seems no different than that in other species: in monkey, cat, and ferret visual cortex, most neurons respond to both light increments and light decrements (Hubel and Wiesel, 1962; Schiller, 1982; Sherk and Horton, 1984; Zahs and Stryker, 1988).

But, a more careful examination of the pattern of labeled cells following injections in layers I-III revealed an additional sublaminal organization within layer IV, beyond that defined by ON- and OFF-center LGN axon terminals. Following injections of tracers that were restricted to more superficial parts of layers II/III, the labeled neurons were focused around the cleft in the middle of layer IV; in contrast, injections into deeper parts of layer III labeled cells near the edges of layer IV (the upper part of layer IVa and the lower part of layer IVb) (Fig. 3*A*). To further explore the organization of layer IV projections, we used extracellular injections of biocytin to label small populations of neurons at different depths in layer IV and reconstruct their axonal projections to layer III (Fig. 3*B-D*). What emerged from these experiments was a highly specific sublaminal arrangement of projections from layer IV to layer III, in which cells at mirror symmetric locations in layer IV project to the same depths within layer III. Neurons in the middle of layer IV (lower IVa and upper IVb) project most superficially; their axons terminate throughout layers I-IIIb. Neurons at the edges of layer IV terminate in the deepest parts of layer III (lower layer IIIc). Finally, neurons in the middle of IVa and the middle of IVb terminate in an intermediate stratum, in the upper part of layer IIIc (see Fig. 8*B*).

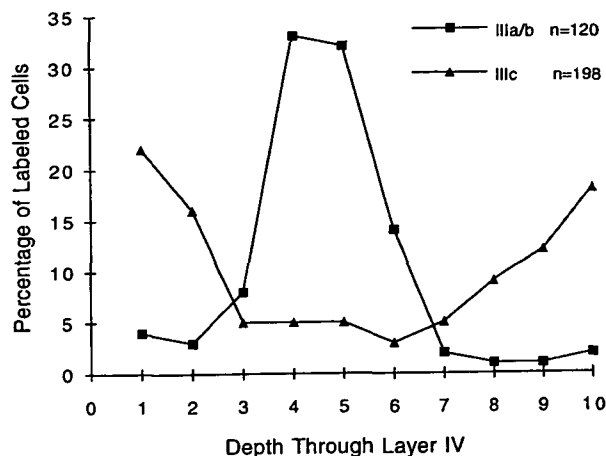
These results led us to conclude that the ON and OFF channels that are so faithfully segregated in the LGN and in the postsynaptic neurons of layer IV are blended by the projections from layer IV to layer III. But this blending is accomplished in a remarkably selective way. In effect, three distinct

parallel channels, each of which has ON and OFF components, emanate from layer IV and terminate at different depths within layer III.

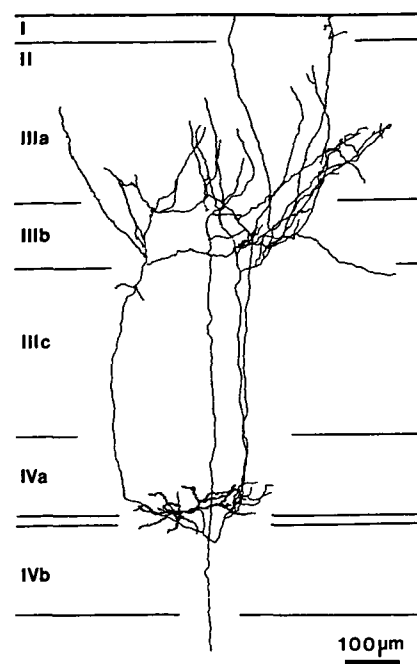
In an effort to understand the functional significance of these parallel layer IV-III pathways, our attention turned to response properties, other than ON and OFF, that might be distributed in a sublaminal fashion within layers IVa and IVb. An analysis of the terminal fields of LGN axons driven by the ipsilateral and contralateral eyes suggested one possibility. Unlike other species in which LGN axons terminate in eye-specific columns, in the tree shrew, LGN axons driven by the ipsilateral and contralateral eyes terminate in a stratified fashion across the depth of IVa and IVb. ON- and OFF-center geniculate afferents driven by the ipsilateral eye terminate in the outer edges of layer IVa and IVb, eschewing the region surrounding the cleft, while LGN afferents driven by the contralateral eye terminate throughout the depth of IVa and IVb, overlapping with ipsilaterally driven afferents at the edges of layer IV (Casagrande and Harting, 1975; Hubel, 1975; Conley et al., 1984; Raczkowski and Fitzpatrick, 1990) (see Fig. 8*A*). Given the horizontally oriented dendritic fields of layer IV neurons, and this stratified pattern of inputs one is led to the prediction that neurons located near the cleft are strongly dominated by input from the contralateral eye, with little input from the ipsilateral eye, while neurons near the outer edges of layer IV receive a more balanced input from the two eyes. Extracellular recordings of multiunit responses in layer IV by Kretz et al. (1986) are consistent with this interpretation.

The stratified pattern of connections from layer IV to layer II/III suggests that there should be a corresponding gradient in ocular preference across the depth of the supragranular layers: inputs from the contralateral eye should dominate superficially, while inputs from the two eyes should be more balanced in the deeper parts of these layers. Multiunit recordings of eye dominance at different depths within layer II/III confirm this hypothesis (Fig. 4). Neurons in the more superficial parts of layer II/III are the least responsive to inputs from the ipsilateral eye; at many of the recording sites at this depth we have been unable to drive the cells from the ipsilateral eye. In contrast, neurons in the deeper parts of layer

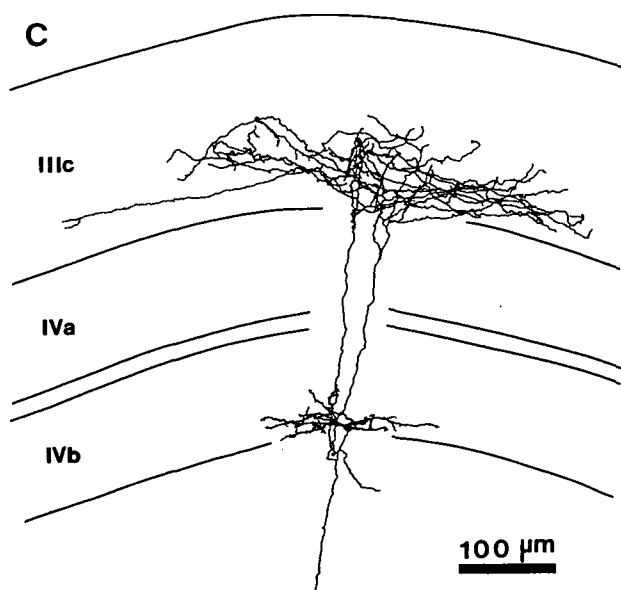
A



B



C



D

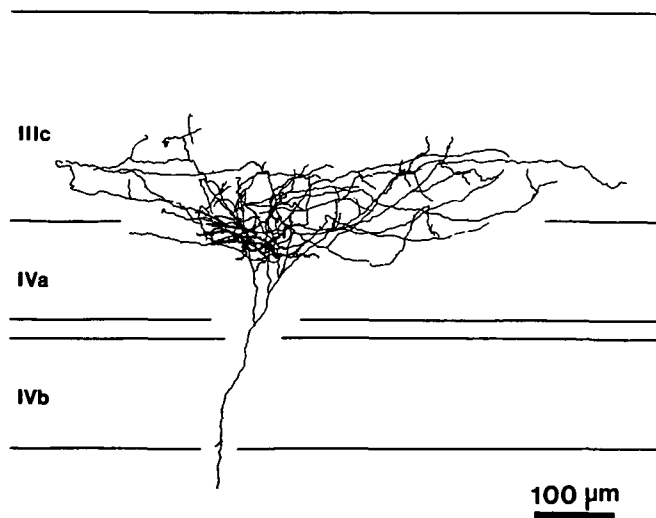


Figure 3. Sublaminar organization of projections from layer IV to layer III. From Muly and Fitzpatrick (1992). **A**, Distribution of labeled neurons across the depth of layer IV following injections at different depths in layer III. Layer IV was divided into 10 equal divisions and the number of cells in each division was computed for injections in IIIa/b and IIIc. Following injections into IIIa/b, the peak of the distribution is in the center of layer IV. Following injections into layer IIIc, most of the labeled cells are found at the edges of layer IV, with few in the middle. **B**, Single biocytin-labeled neuron located in layer IVa near the cleft. The axon of this cell branches to form three collaterals that rise to layer IIIb before forming their terminal branches. **C**, Single biocytin-labeled neuron located in layer IVb, near the border with layer V. This neuron terminates in layer IVb, but also arborizes in the lower part of layer IIIc. **D**, Single biocytin-labeled neuron located in the upper part of layer IVa. The axon from this cell also arborizes in the lower part of layer IIIc.

II/III respond robustly to stimulation of the ipsilateral and contralateral eyes (Muly, 1992).

While ocular dominance varies across the depth of layer II/III, this is unlikely to be the only difference between the targets of the parallel layer IV pathways. In our studies of ocular dominance, we noted that neurons in the superficial parts of layer II/III were sharply tuned for stimulus orienta-

tion; in contrast, those in the deeper parts of layer II/III were often broadly tuned, and, for many, the most effective stimulus was a small moving or flashing spot (Muly, 1992). 2-Deoxyglucose studies of orientation domains in tree shrew striate cortex are consistent with this observation: iso-orientation domains are striking in layers II-IIIb, but barely noticeable in layer IIIc (Humphrey et al., 1980). We suspect that a more

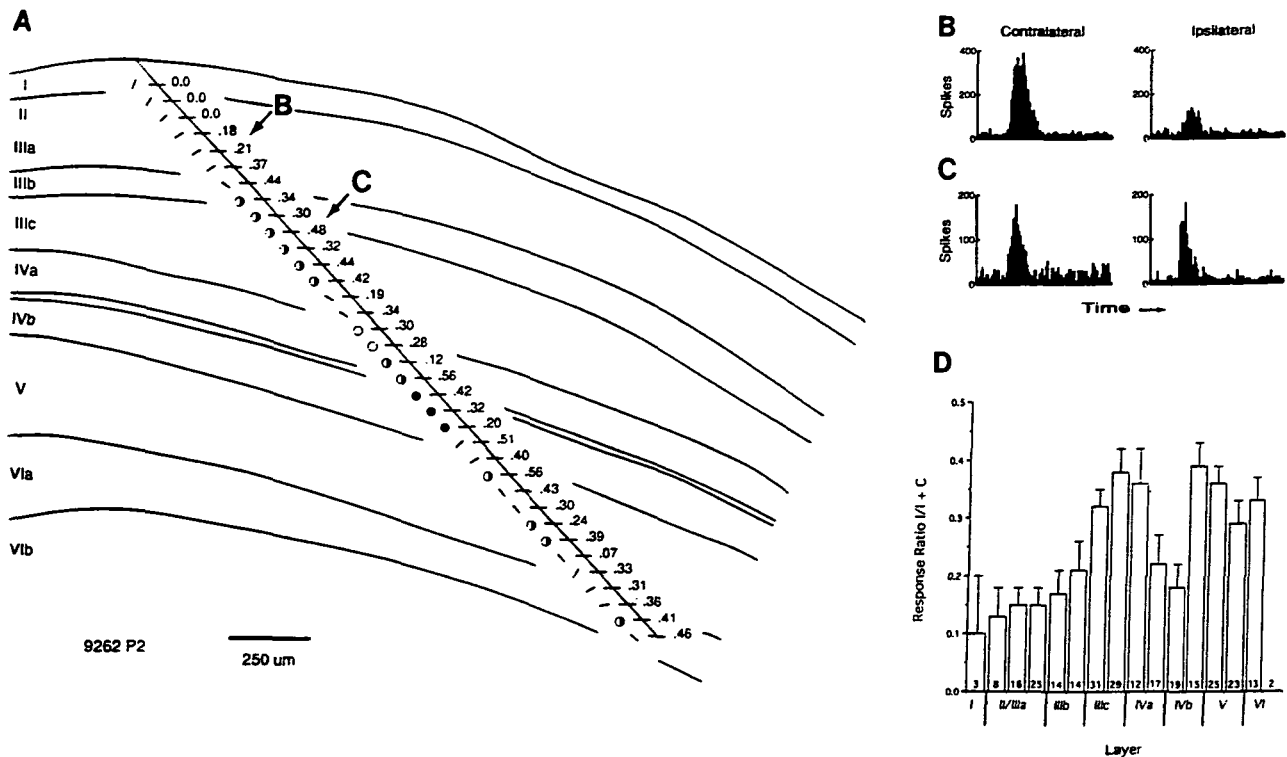


Figure 4. Laminar distribution of ocular dominance values in tree shrew striate cortex. *A*, Example of an oblique electrode penetration showing the ocular dominance values of multiunit activity recorded at different depths. Numbers to the right of the hash marks indicate the proportion of the total number of spikes recorded from the site that were contributed by stimulation of the ipsilateral eye [number of spikes from the ipsilateral eye/(number of spikes from the ipsilateral eye + contralateral eye)]. On this scale, zero represents activation by the contralateral eye only, 0.5 represents equal activation by both eyes. *B* and *C*, Peristimulus time histograms documenting the strength of response to stimulation of the ipsilateral and contralateral eye at the recording sites indicated in *A*. Bin width, 50 msec.; period of data acquisition, 4 sec. *D*, Average response ratios for 266 recording sites at different depths in tree shrew striate cortex. The number of recording sites for each depth are indicated at the bottom of each bar. Lines at the top of each bar indicate the standard error of the mean. Recording sites in the most superficial part of the supragranular layers are strongly dominated by the contralateral eye. The influence of the ipsilateral eye is greatest in the deepest parts of layer III. Note also the decline in response to the ipsilateral eye in the center of layer IV.

detailed analysis of the response properties of neurons that lie at different depths within layer II/III will reveal additional functional correlates for this anatomical stratification.

In sum, these results demonstrate that specificity in the laminar arrangement of LGN axon arbors and the axon arbors of layer IV neurons plays an important role in restructuring the information supplied by the LGN and generating three distinct parallel channels that terminate at different depths within layer II/III. In addition, they emphasize that the parallel pathways that emerge via the vertical connections of layer IV neurons are not simply continuations of parallel thalamocortical pathways. Layer IV and its connections with layer II/III achieve a new synthesis of the inputs from the LGN, combining the activity from ON and OFF channels and from the left and right eyes, and transmitting the products of this synthesis—with variation in ocular dominance and perhaps in other features as well—to separate strata within the overlying layers.

Although the specific details of the vertical connections we have described may be unique to the tree shrew, we suspect that the general organization of these connections—merging of parallel thalamic streams to generate parallel intracortical circuits—is characteristic of other species as well. For example, in primates, the axons from the magno- and parvocellular layers of the LGN terminate in separate tiers of layer IV (IVCa and b, respectively) (Hubel and Wiesel, 1972, 1977; Hendrickson et al., 1978; Fitzpatrick et al., 1983); the projections of layer IVC neurons to the supragranular layers are arranged in a complex sublaminar pattern that at least partially mixes the inputs from the magno- and parvocellular

streams (Fitzpatrick et al., 1985; Lund, 1987; Lachica et al., 1992; Yoshioka et al., 1994). Layer IVCb consists of upper and lower strata that differ in the sublaminar organization of their projections to the overlying layers (Fitzpatrick et al., 1985; Yoshioka et al., 1994). In fact, it has been suggested that the upper part of IVCb and the lower part of IVCa should be considered a separate functional zone with overlapping inputs from the magno- and parvocellular layers of the LGN and projections to selected regions within layer II/III (Yoshioka et al., 1994). Also, neurons in the most superficial part of IVCa differ in their response properties and connections from those deeper in IVCa (Blasdel and Fitzpatrick, 1984; Blasdel et al., 1985; Fitzpatrick et al., 1985; Anderson et al., 1993). Thus, based on their pattern of projections, there are at least three and perhaps four distinct strata within IVC that supply different populations of neurons in the overlying cortical layers.

Parallel Nature of Layer IV to II/III Pathways Is Reflected in Other Features of Tree Shrew Cortical Circuitry

In addition to the layer IV to III connections, there are two other prominent vertical pathways in striate cortex: one originates from neurons in layer VI and terminates in layer IV; the other originates in layers II/III and terminates in layer V (Lund, 1973; Lund and Booth, 1975). Our studies of these pathways in the tree shrew suggest that the parallel structure of intracortical circuits extends beyond the layer IV to II/III pathway to encompass the full array of vertical connections.

For example, biocytin injections reveal that individual layer

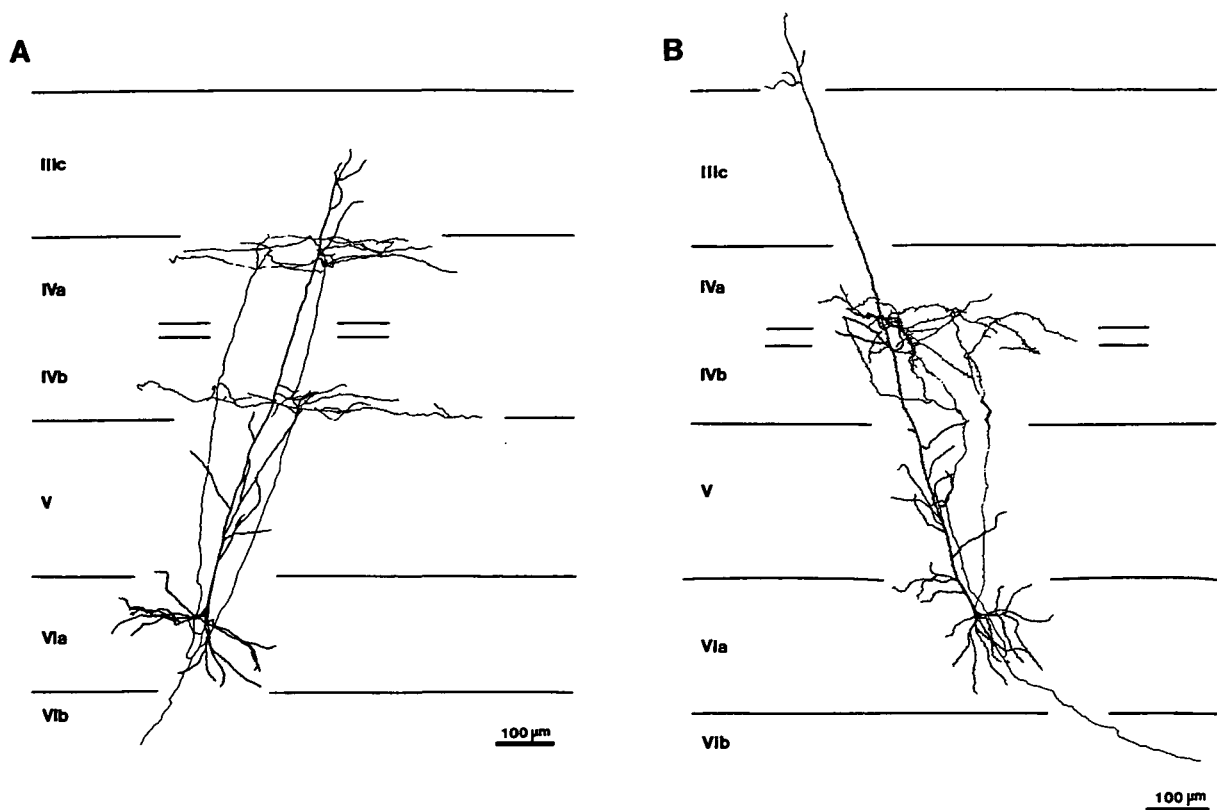


Figure 5. Examples of individual biocytin-labeled pyramidal neurons in layer VI of tree shrew striate cortex. *A*, Layer VI neuron that gives rise to two distinct terminal fields, one in the upper part of IVa and another in the bottom of IVb. *B*, Layer VI neuron that gives rise to a single terminal field in the center of layer IV.

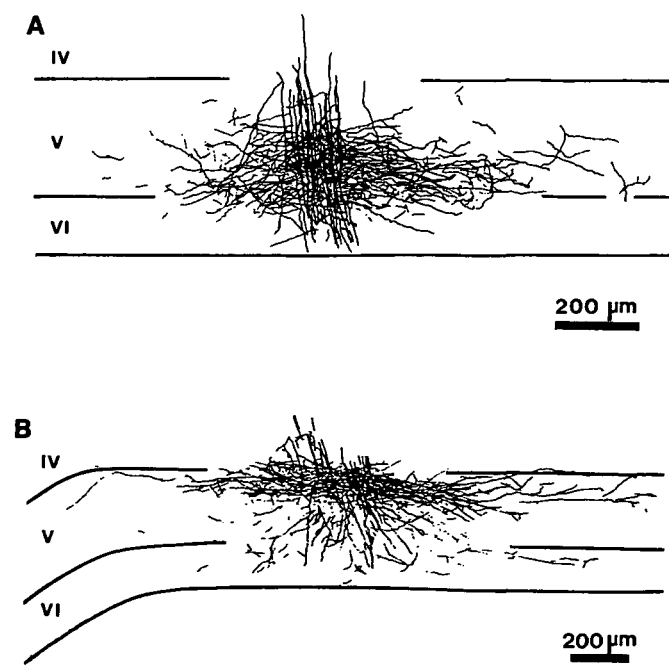


Figure 6. Sublaminar distribution of axon arbors in layer V following injections of biocytin into different subdivisions of layer III. *A*, Distribution of labeled terminals following an injection into layer IIIa. Terminal branches and boutons are largely restricted to the bottom half of layer V. *B*, Distribution of labeled terminals following an injection into layer IIIc. Terminal branches and boutons are largely restricted to the upper part of layer V.

VI neurons project to both the ON and OFF subdivisions of layer IV and terminate selectively on neurons that are the source of projections to particular subdivisions of layer III (Usrey and Fitzpatrick, 1996). One class of layer VI neurons gives rise to a terminal field that is confined to the middle of layer IV, terminating in the region surrounding the cleft. A second class of neurons has axon arbors that give rise to two distinct terminal fields, one in the upper part of IVa and the other in the lower part of IVb (Fig. 5). Whether there is a third class of layer VI neurons that projects to the middle of IVa and the middle of IVb and is specific for the neurons that project to upper IIIc is not so clear; but support for this idea comes from the observation that some layer VI terminal fields are confined to narrow strips along the edges of layer IV while others extend deeper into each tier without entering the region surrounding the cleft.

Continuation of the parallel IV to II/III pathways is also suggested by the sublaminar organization of the projections from layers II/III to layer V. Neurons in the superficial parts of layer III (II-IIIb) give rise to axon arbors that terminate in the deepest part of layer V; in contrast, neurons in layer IIIc give rise to axon arbors that terminate in the upper part of layer V (Muly, 1992; Stawinski et al., 1993) (Fig. 6).

Finally, neurons that lie in the superficial and deep parts of layer II/III not only receive parallel inputs from layer IV, they also receive parallel projections directly from the LGN. In the tree shrew, two distinct LGN layers serve as the source of projections to cortical layer III: layer 6, which lies adjacent to the optic tract, and layer 3, which is sandwiched between the ON and OFF pairs of layers (Fig. 1) (Carey et al., 1979). The projections from LGN layer 6 terminate in the lower part of layer IIIc, overlapping with the terminal fields of the neurons that lie at the edges of layer IV. In contrast, the projec-

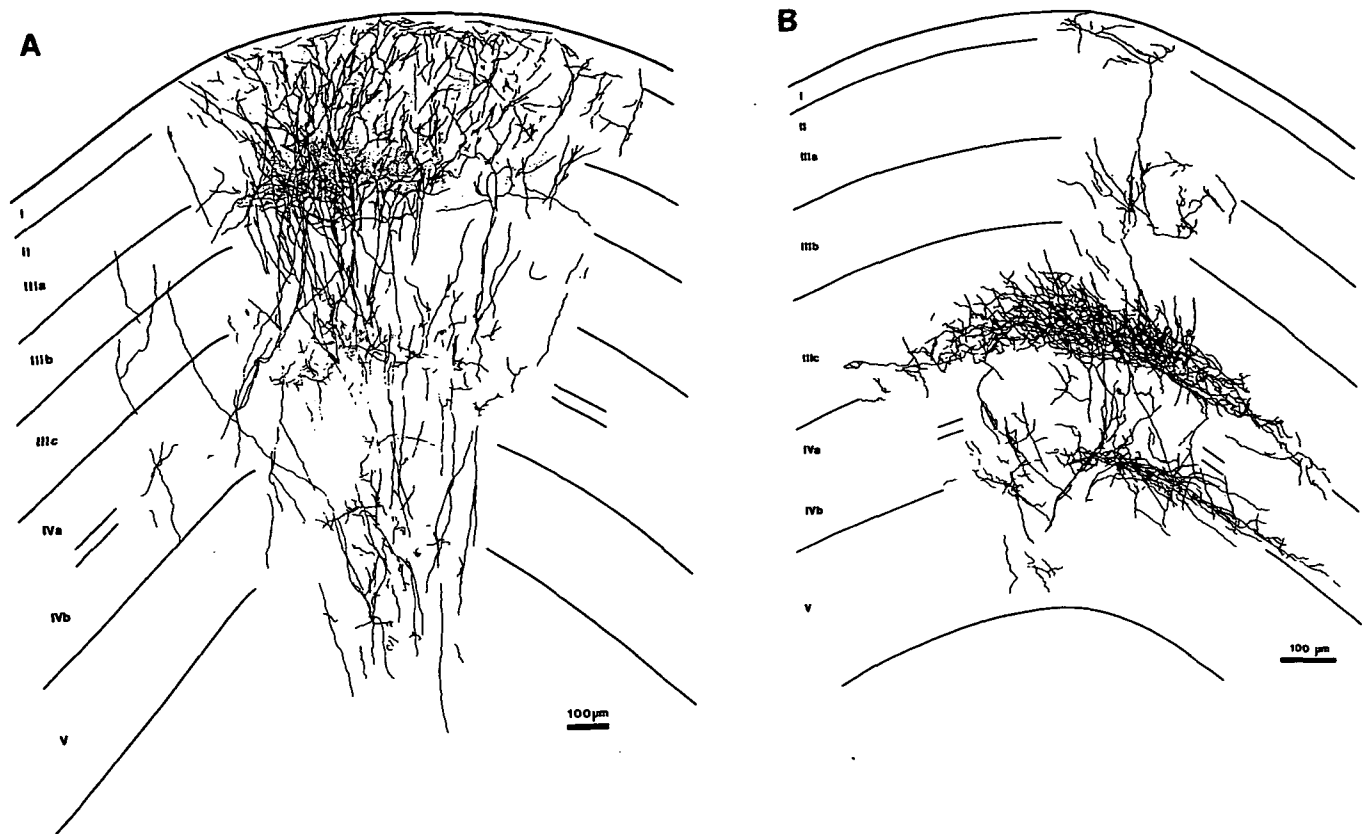


Figure 7. Distribution of labeled axons and terminals in striate cortex following injections of biocytin into the small-cell layers of the LGN. From Usrey et al., 1992. *A*, Injection of biocytin into LGN layer 3. Labeled terminals are most dense in layers I–IIIb. In addition, a smaller number of labeled terminals are found in the middle of layer IV and in layer V. *B*, Injection of biocytin into LGN layer 6. Labeled terminals are most dense in the bottom part of layer IIIc. An additional terminal field is found in the bottom part of layer IVb.

tions from LGN layer 3 terminate in layers I–IIIb, overlapping with the projections of the neurons that lie near the cleft of layer IV (Conley et al., 1984; Usrey et al., 1992) (Fig. 7). In addition, both of these layer III-projecting systems give rise to collaterals in layer IV. The terminal fields of these collaterals are also specific for one of the parallel cortical circuits: neurons that terminate in layers I–IIIb send collaterals to the region surrounding the cleft; those that terminate in the lower part of layer IIIc, send collaterals to the lower part of layer IVb.

Parallel Intracortical Circuits

Figure 8 summarizes the intricate sublaminar arrangement of axonal connections in tree shrew striate cortex. We suggest that specificity in the arrangement of vertical connections defines parallel circuits that are composed of distinct sets of interconnected neurons in layers IV, II/III, V, and VI. The evidence points to at least two distinct circuits: one involves the edges of layer IV, the layer VI neurons that terminate in this region, the lower part of layer IIIc, and the upper part of layer V; the other involves the middle of layer IV, the layer VI neurons that terminate in this region, layers II–IIIb, and the deep part of layer V. Studies of layer IV have identified a third pathway that terminates in the upper part of layer IIIc, but we have been unable to determine whether this pathway has its own parallel system in the other layers.

The designation of these intracortical circuits as parallel is based on specificity in the stratification of axonal connections; however, axon arbors are not the only means of communication between cortical layers. The apical dendrites of pyramidal cells freely cross laminar borders and could pro-

vide the substrate for interactions between the circuits defined by axonal arrays. While we cannot rule out this possibility, the available evidence suggests that specificity in the arrangement of dendritic processes contributes to the parallel nature of intracortical circuits. For example, the apical dendrites of layer VI cells whose axons terminate in the middle of layer IV, branch in the same region of layer IV and in layer IIIb. In contrast, the apical dendrites of layer VI cells whose axons terminate at the edges of layer IV, rarely extend above the layer IIIc and often branch in this layer (see Fig. 5). Likewise, the dendritic processes of neurons with cell bodies in layers IIIb and IIIc ensure that these neurons sample from largely nonoverlapping populations of layer IV axon arbors. Most of the neurons in layer IIIc are spiny stellate cells that lack an apical dendrite and thus are unable to sample from axon terminal fields that lie above this layer (Lund et al., 1985).

It seems reasonable to suggest that parallel microcircuits, like those identified in the tree shrew, are functionally distinct processing units that play unique roles in mediating the input-output functions of striate cortex. The fact that these circuits have a common organizational framework—they involve parallel sets of neurons in layers II–VI—raises the possibility that highly specialized areas of the neocortex have evolved, at least in part, by the duplication of a prototypical circuit design (see Martin, 1988; Douglas and Martin, 1991). If so, then we might expect to find certain basic similarities in the operations performed by these circuits as well as differences that reflect specializations related to their sources of inputs.

While this discussion has emphasized parallel intracortical circuits that are defined by specificity in the sublaminar or-

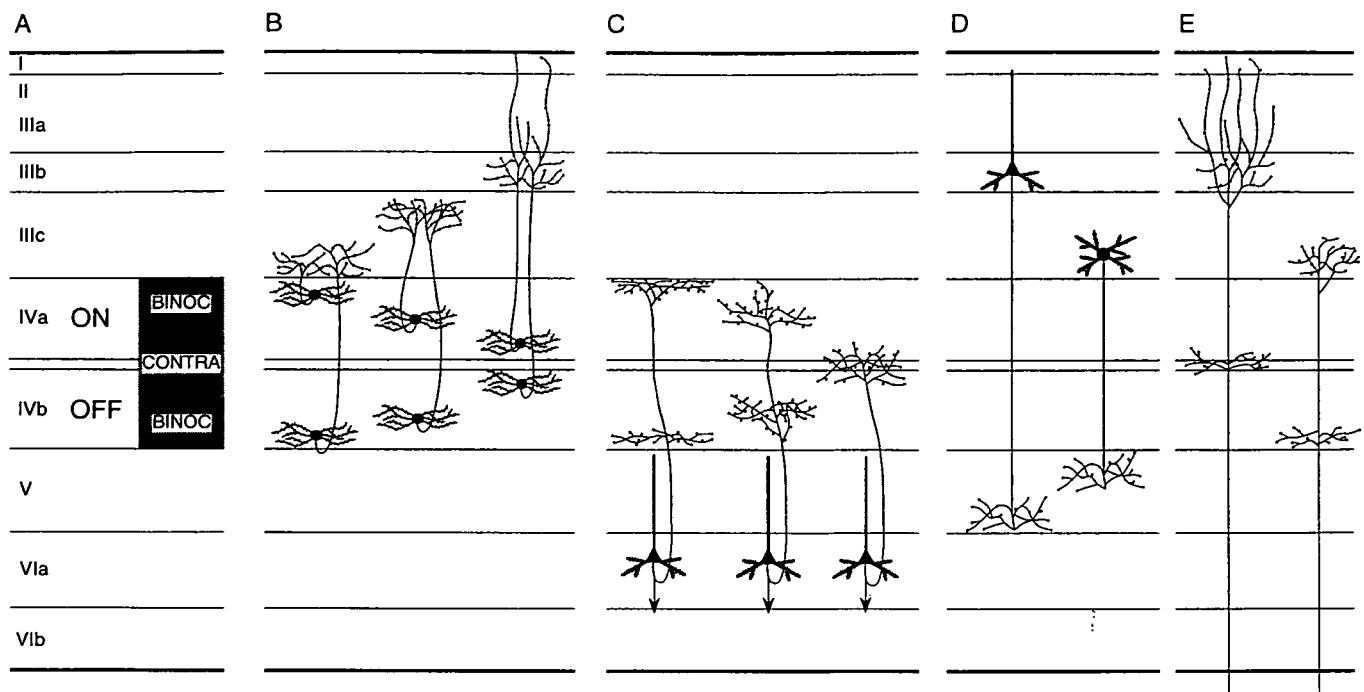


Figure 8. The organization of vertical connections in tree shrew striate cortex and their relation to lateral geniculate inputs. *A*, Organization of lateral geniculate inputs to layer IV. ON-center LGN axons terminate in layer IVa, OFF-center LGN axons terminate in layer IVb. Axons driven by the contralateral eye terminate throughout the depth of layer IVa and IVb. Axons driven by the ipsilateral eye terminate near the outer edges of IVa and IVb. *B*, Sublaminal organization of projections from layer IV to layer III. Neurons at the outer edges of layer IV terminate in the lower part of layer IIIc. Neurons in the middle of layer IV, in the region surrounding the cleft, project to layers I–IIIb. Neurons in the middle of layer IVa and the middle of layer IVb terminate in the upper part of layer IIIc. *C*, Sublaminal organization of layer VI inputs to layer IV. Layer VI neurons have highly stratified terminal fields in layer IV. One population terminates in the middle of layer IV, in the region surrounding the cleft. Another has two distinct terminal fields one in IVa and the other in IVb. Of these, some have terminal fields that are restricted to narrow strata near the outer edges of layer IV; others extend farther into IVa and IVb, but still eschew the region surrounding the cleft. *D*, Sublaminal organization of projections to layer V from neurons at different depths within layer II/III. Neurons in the upper parts of layer III (II–IIIb) project to the lower part of layer V. Neurons in the lower parts of layer IIIc project to the upper part of layer V. *E*, Distribution of direct geniculate inputs to layer III. Projections from LGN layer 3 terminate in layers I–IIIb, with a secondary projection to the middle of layer IV. Projections from LGN layer 6 terminate in the lower part of layer IIIc, with a secondary projection to the lower part of layer IVb.

organization of axon arbors, laminar stratification per se is not a prerequisite for parallel intracortical circuits. Laminar stratification facilitates the identification of these circuits, and undoubtedly serves a functional role as well; but it seems unlikely that parallel intracortical circuits are restricted to those species and those cortical areas that display an exaggerated sublaminal organization. Indeed, it seems likely that parallel intracortical circuits play an important role in generating diversity in the response properties of neurons in cat striate cortex where laminar stratification is far less apparent. There also are likely to be functional subsystems within the parallel circuits we have identified in the tree shrew. Unfortunately, without some guide such as laminar stratification, there is no easy way to tease out the patterns of vertical connections that link neurons in different cortical layers and whose identification is essential for testing this hypothesis.

Ultimately, an understanding of the functional significance of parallel intracortical circuits must consider how they are organized with respect to projections to other cortical areas and to subcortical targets. For layers II/III and V, the projections to distant targets are arranged in a partially stratified fashion, consistent with, but not identical to the arrangement of parallel intrinsic circuits. For example, the projections to the temporal dorsal area of extrastriate cortex (TD) originate from neurons in the most superficial parts of layer II/III, whereas those to area 18 originate from neurons throughout the depth of layer II/III (Sesma et al., 1984; Lund et al., 1985). Likewise, neurons in the upper and lower parts of layer V differ in their subcortical projection patterns. Projections to the ventral lateral geniculate nucleus and the pons originate

exclusively from neurons that lie in the upper part of layer V, while the projections to the superior colliculus and the pretectal nuclei arise from neurons that are distributed across the depth of layer V (Muly, 1992; Stawinski et al., 1992). Teasing apart the extrinsic projections of layer VI neurons is more difficult, since neurons with different patterns of projection to layer IV are intermingled at the same depth within layer VI. However, reconstructions of individual biocytin-labeled corticogeniculate axons within the LGN have revealed classes of axons that differ in the laminar distribution of their terminal arbors; perhaps these differences are correlated with differences in the arrangements of layer IV terminal fields (Usrey and Fitzpatrick, 1996).

Organization of Horizontal Connections in Tree Shrew Striate Cortex

Specificity in the Topography of Horizontal Connections

Our interest in the topography of horizontal connections emerged from the observation that the distribution of labeled terminals around a biocytin injection site in the upper part of layer II/III was often elongated across the cortical surface. Anisotropy in the arrangement of horizontal connections also has been described in the visual cortex of other species, but generally it has been related to a corresponding anisotropy in cortical magnification factor (Gilbert and Wiesel, 1983; Matsubara et al., 1987; Malach et al., 1993; Yoshioka et al., 1995). For example in primates, the extent of horizontal connections is related to the arrangement of ocular dominance columns: the long axis of horizontal connections tends to be oriented

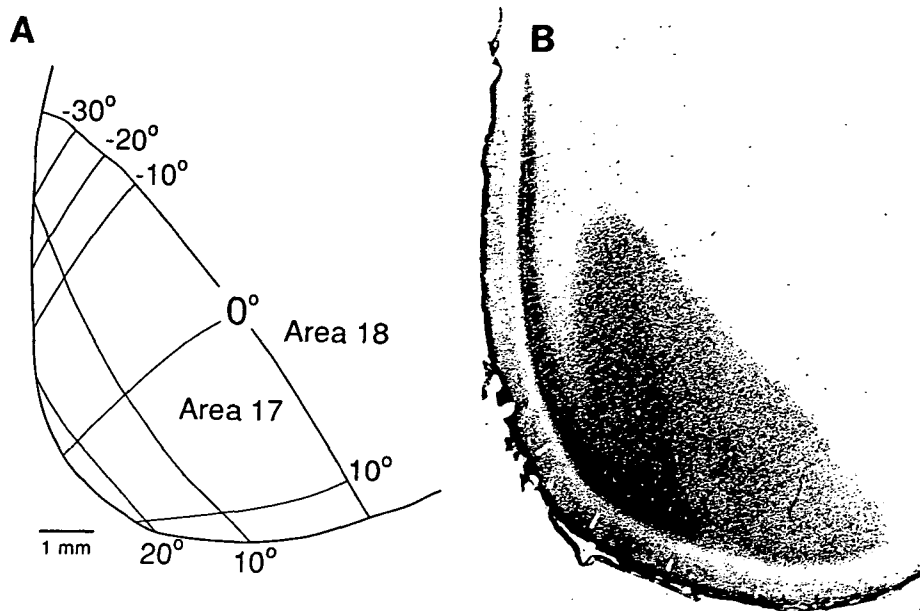


Figure 9. *A*, Map of the visual field in striate cortex of the tree shrew. The area 17–18 border represents the vertical meridian of visual space. Horizontal meridians are oriented perpendicular to the border. *B*, Nissl-stained tangential section through the caudal end of the cerebral cortex in the tree shrew. The midline is towards the left, rostral is towards the top. Note the prominent area 17/area 18 border.

perpendicular to the borders of ocular dominance columns, presumably reflecting the fact that the map of visual space is duplicated across ocular dominance bands, but not along them. However, the anisotropy in the organization of horizontal connections in the tree shrew cannot be explained in this way. First, there are no ocular dominance columns in the tree shrew and anisotropy in cortical magnification factor is relatively small (see Fig. 9) (Kaas et al., 1972; Kaas, 1980). Furthermore, when tracer injections are used to label the axon arbors of small populations of neurons in roughly the same visuotopic locus, they often give rise to terminal distributions that are elongated along different axes of the visual field map. If anisotropy in cortical magnification was responsible for the elongated distribution of horizontal connections, we would expect a consistent axis of elongation from experiment to experiment. These observations led us to consider what other factors might explain the anisotropic arrangement of horizontal connections in the tree shrew.

Single-unit studies (Nelson and Frost, 1985; Bolz and Gilbert, 1989; Schwartz and Bolz, 1991) and attempts to explain the patchy distribution of horizontal connections following large tracer injections (Mitchison and Crick, 1982; Lund et al., 1985) have led some to propose that the topography of a neuron's horizontal connections, might be systematically related to a neuron's orientation preference. The sharp tuning of layer II/III neurons for oriented edges and the well-defined area 17/18 border have made the tree shrew visual cortex an ideal system for examining this possibility. Micropipettes containing biocytin were used to determine the orientation preference of recording sites within the superficial parts of layer II/III, where cells are highly selective for orientation. Small extracellular injections of biocytin were then made at these sites and the resulting distributions of labeled terminals were reconstructed from tangential sections (Fitzpatrick et al., 1993) The area 17–18 border in the tree shrew was used as a referent for the vertical axis in visual space: terminal fields that are oriented parallel to the 17–18 border are oriented along the vertical axis of visual space; those that are oriented perpendicular to the 17–18 border are oriented along the horizontal axis of visual space (Fig. 9).

Examples of two injections of biocytin into regions of known orientation preference are shown in Figure 10. In both cases the distribution of labeled terminals around the injection

site has a patchy appearance and appears elongated. However, the long axes of these terminal distributions are strikingly different. In the experiment illustrated in Figure 10*a*, the long axis of the terminal distribution is oriented roughly perpendicular to the area 17–18 border, while in the experiment illustrated in Figure 10*b* the long axis is shifted clockwise so that it lies almost parallel to the 17–18 border. The stippled lines on each distribution show how the preferred stimulus orientation of the neurons at the injection site appears when plotted onto the cortical map. (The midpoint of the response peak was chosen as a measure of preferred orientation.) In each case, the long axis of the terminal field distribution corresponds to the cortical representation of the preferred orientation. Polar plots that summarize the results from four different experiments confirm this result: the horizontal connections of neurons in superficial layer II/III of tree shrew striate cortex extend for greater distances and give rise to a greater number of terminals along an axis of the visual field map that corresponds to the neuron's preferred orientation (Fig. 11). Taken together with the earlier studies (Gilbert and Wiesel, 1989), these results suggest that both the modular and topographic features of a neuron's horizontal connections are correlated with its orientation preference (Fig. 12).

Functional Significance of the Collinear Arrangement of Horizontal Connections

In theory, the collinear arrangement of horizontal connections in tree shrew striate cortex could play a role in sharpening the orientation tuning of layer II/III neurons. Because horizontal connections are reciprocal, (Kisvárdy and Eysel, 1992) neurons in layers II/III will receive inputs from a population of neurons whose receptive fields are distributed along an axis in visual space—an axis that corresponds to the neuron's preferred orientation. Thus, rather than viewing horizontal connections as links between columns whose properties are determined solely by local vertical circuitry, these results suggest that the network of horizontal connections could play a significant role in shaping the response properties that define cortical columns. To be sure, horizontal connections are not essential for orientation tuning: layer IV neurons in the tree shrew and in cats exhibit orientation tuning, and yet, these layers lack long distance horizontal connec-

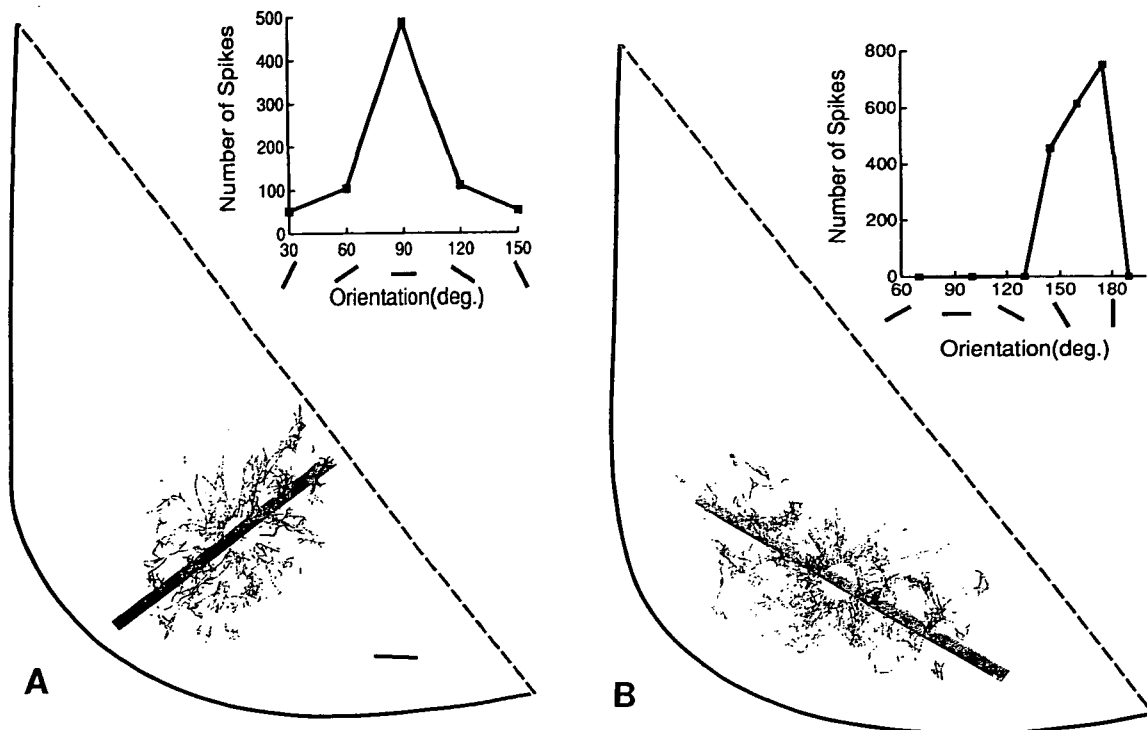
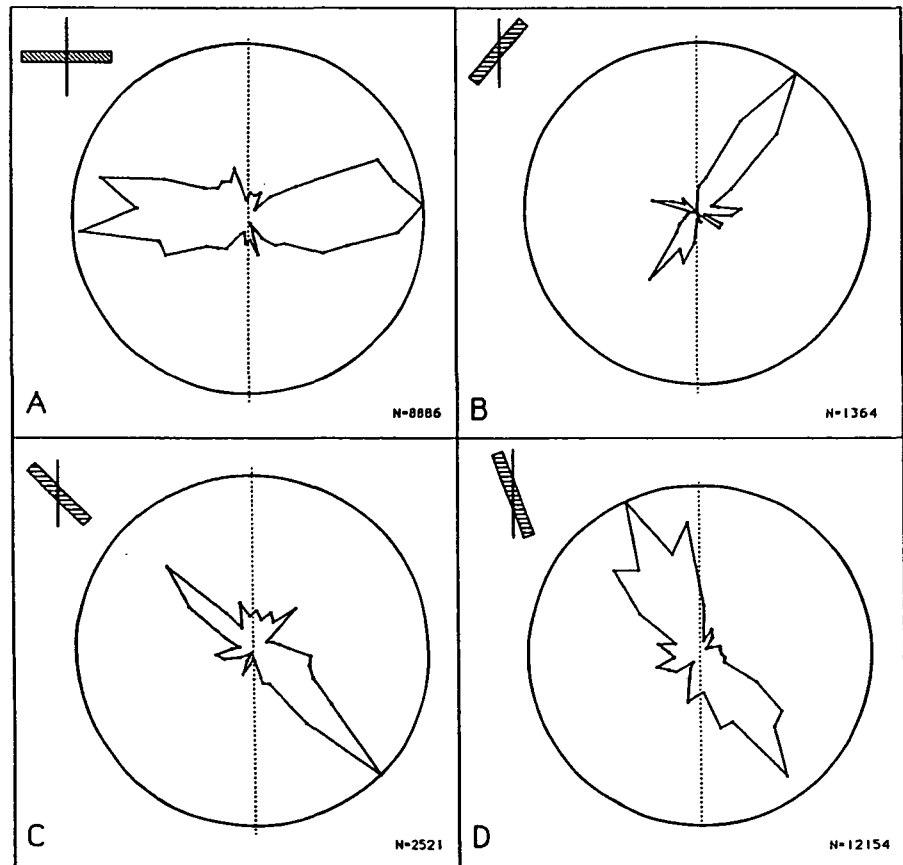


Figure 10. Distribution of labeled terminals following injections of biocytin into sites of known orientation preference. *A*, Injection of biocytin into a region of layer II/III that responded best to a horizontally oriented edge. Tuning curve is shown in the *upper right*. The distribution of labeled terminals was reconstructed from tangential sections and is displayed on an outline of area 17. Medial is to the left and the *dotted line* represents the area 17/area 18 border. Labeled terminals within 200 μm of the injection site have not been included. *B*, Injection of biocytin into a region of layer II/III that responded best to near vertical stimuli (the midpoint of the tuning curve was 20 degrees off vertical).

Figure 11. Polar plots from four different experiments showing the distribution of labeled terminals in 10 degree increments around the biocytin injection sites. The distance of each point from the center indicates the number of labeled terminals at that angle and the plots have been scaled to fit the largest value for each injection site. The *dotted line* through each plot approximates an isoazimuth line: a line drawn through the center of the injection site, parallel to the area 17/area 18 border. The *thick bar* in the upper left of each panel represents the preferred stimulus orientation of the cells at the injection site. *N* refers to the total number of terminals labeled at each injection site.



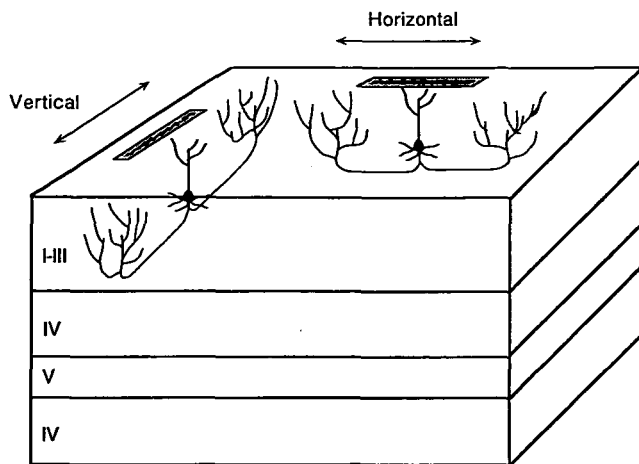


Figure 12. Summary diagram showing the relationship between preferred stimulus orientation and the topography of horizontal connections in layers II and III of tree shrew striate cortex. Horizontal connections are anisotropic: they extend farther and give rise to more terminals along an axis of the cortical map that corresponds to the neuron's preferred stimulus orientation. Vertical and horizontal refer to isoazimuth and iso-elevation lines in the cortical map of visual space. The rectangles indicate the neuron's preferred stimulus orientation.

tions (Hubel and Wiesel, 1962; Humphrey et al., 1980; Ferster, 1986). In tree shrews, the orientation selectivity of neurons in superficial layer II/III is much greater than that in layer IV, consistent with a role for topographically aligned horizontal connections in refining orientation selectivity.

Regardless of their contribution to orientation tuning, any discussion of horizontal connections must take into account the fact that they extend for long distances across the cortical map. In the tree shrew, these connections extend for more than 2 mm from the injection site, a distance that corresponds to roughly fifteen degrees of visual space. Since this value is much greater than the dimensions of the classically defined receptive field (less than 5 degrees at this eccentricity), horizontal connections link neurons with nonoverlapping classical receptive fields. For this reason, it has been suggested that horizontal connections are one of the substrates for receptive field surround effects—changes in the excitability of cortical neurons that can be elicited by stimulating regions that lie beyond their classical receptive field (Nelson and Frost, 1985; Gilbert and Wiesel, 1990, 1992; Pettet and Gilbert, 1992; Fiorani et al., 1992). If horizontal connections contribute to receptive field surround effects, then for neurons in layer II/III of tree shrew striate cortex one would expect to see some sign that these effects are more robust in regions of visual space that lie along the cell's axis of preferred orientation (i.e., in the "end zones") than in the regions that lie to the side ("side bands"). Consistent with this hypothesis, many of the neurons in layer II/III of tree shrew striate cortex exhibit the property of length summation: they respond with increasing vigor to appropriately oriented bars that extend beyond the length of their classical receptive field (Bosking and Fitzpatrick, 1995). Our preliminary results also indicate that some of these neurons can be driven by appropriate stimulation in the surround (full field grating with classical receptive field occluded), and that the effect is more robust for oriented gratings that are presented to the end zones, than to the sidebands.

Evidence for Topographic Alignment of Horizontal Connections in Other Species

While the topographic alignment of horizontal connections described in the tree shrew has not been described in other

species, there are some hints from physiological experiments and from perceptual studies that support the idea of an orientation specific anisotropy in the functional organization of horizontal interactions. For example, it has been suggested that the elongated receptive fields of neurons in layer VI of cat striate are constructed by the convergence of inputs from layer V cells whose oriented receptive field are aligned along an axis in visual space (Bolz and Gilbert, 1989; Schwartz and Bolz, 1991). Likewise, facilitatory surround effects that are selective for receptive field endzones have been demonstrated in cat and monkey striate cortex (Nelson and Frost, 1985; Kapadia et al., 1995), and neurons in the optic disk representation of monkey striate cortex can often be driven by the contralateral eye when the stimulus is a grating that activates collinear regions on either side of the optic disk (Fiorani et al., 1992).

Perhaps the most interesting evidence for anisotropy in horizontal interactions comes from perceptual studies that examine the features that underlie the perception of continuity in visual patterns. The perception of continuity in a pattern of oriented line segments depends critically on the orientation of adjacent line segments and on their alignment. Small variations in the alignment of the line segments or aligning the elements orthogonally (side to side rather than end to end) significantly reduces the detectability of continuity. Similarly, the threshold of detection for an oriented line segment is reduced by flanking the stimulus with other collinear line segments (Kapadia et al., 1995). The specificity in the orientation and alignment relationships that underlie the perception of continuity bear a striking resemblance to the modular and topographic arrangement of horizontal connections in layer II/III of tree shrew striate cortex (Field et al., 1993).

Summary and Conclusion

Specificity in the Arrangement of Vertical and Horizontal Axon Arbors

Our goal has been to exploit some of the unique features of tree shrew striate cortex to gain insights into the general principles that underlie the organization of vertical and horizontal intracortical connections. The striking specificity in the laminar arrangement of vertical connections has made it possible to observe the merger of parallel thalamocortical pathways and the emergence of parallel intracortical pathways that extend through the supra- and infragranular layers. The well-defined area 17-18 border, sharp orientation tuning, and relatively isotropic map of visual space have made it possible to demonstrate a relation between the orientation preference of cortical neurons and the topographic arrangement of their horizontal connections. No doubt, the details of intracortical circuitry and the functional attributes with which they correlate vary significantly across species. Nevertheless, we believe that rules identified in the tree shrew visual cortex are likely to apply to the visual cortices of other species and perhaps to other cortical areas as well.

Notes

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