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Long-Range Intrinsic Connections in Cat Primary Visual Cortex

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INTRODUCTION

One of the main tasks of our visual system is to extract features of a scene that belong to the same object and to segregate them from background. It is generally accepted that the activity of neurons in the primary visual cortex (area 17 or V1) is not only dependent on a stimulus appearing in their classical receptive field, but can be dramatically modulated by more global characteristics of a visual scene such as the contours and surfaces within which a stimulus is embedded. While the visual system is composed of a multitude of areas (like other sensory systems), all representing particular but different aspects of a visual stimulus, there is growing evidence that part of the process of spatial integration occurs in primary visual cortex. Long-range tangential connections within area 17 are hypothesized to be the anatomical substrate of these integrative capabilities. As the name indicates, long-range connections span large distances (up to 8 mm) within a cortical area. They are a characteristic feature not only of the primary visual cortex but also of other neocortical areas such as auditory, somatosensory, motor, and even prefrontal cortex. Neuronal computations within an area may be modulated by both feedforward (incoming sensory input) and "top-down" feedback projections, but they are also critically dependent on the layout of the intrinsic microcircuitry. This chapter

focuses on the detailed layout of long-range horizontal connections in the primary visual cortex of cats, their topographic relation to functional cortical maps, learning- and activity-induced modifiability, and possible functions.

HISTORICAL OVERVIEW

Long-range horizontal connections in the visual cortex were probably observed indirectly more than 200 years ago by the Italian medical student Francesco Gennari (1782) and by Vicq d'Azyr (1786). Both described a prominent stripe in the human occipital cortex, the stria of Gennari, which is visible macroscopically because of its strong myelination (Fig. 10-1). The stria corresponds to a fiber plexus in upper layer IV of the six-layered neocortex and was later called the external band of Baillarger. As inferred from lesions in human brain tissue, the stria is mainly of intracortical origin, as it does not show signs of degeneration after destruction of the underlying white matter (Braitenberg, 1962; see also Szentágothai, 1973).

METHODOLOGICAL DEVELOPMENTS

Long-range intrinsic connections are currently recognized as an important and characteristic feature of neocortical circuitry, but they did not become the subject of scientific investigation until 1970 for both methodological and conceptual reasons. The Golgi stain (Golgi, 1873), which has been used in neuroanatomical

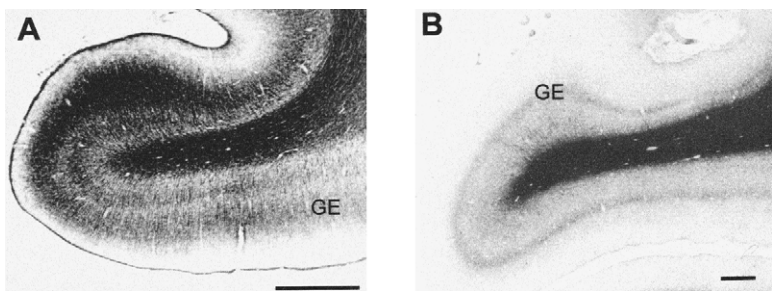

FIGURE 10-1. Myelin stained coronal sections of the cat's **(A)** and the human's **(B)** primary visual cortex (area 17, also termed striate cortex) demonstrating the stria of Gennari (GE). **(A)** Gulyas staining of the cat's primary visual cortex. The upper (also called external band of Baillarger) of the two dark stripes is situated in lower layer III and upper layer IV. Its lower part probably corresponds to the classic stria of Gennari. The lower stripe corresponds mainly to upper layer V. It is also called the internal band of Baillarger. After cortical lesions, horizontal degeneration was predominantly observed within these two stripes. **(B)** The prominent streak (GE) corresponds to upper layer IV and contains many fibers indicated by dark colour in the myelin stain. (Tissue prepared by W. Schlote). (Creutzfeld et al., 1975). Scale bars: 1 mm. (Also see Figs. 1-7 and 1-26, this volume.)

studies for more than a century, labels both dendritic and axonal fibers. This technique was used to detail and classify a variety of neuron types mainly on the basis of their dendritic morphology, and not their axon arbors, because axons are usually much thinner than dendrites and only stain in their proximal unmyelinated part immediately after leaving the soma (Ramón y Cajal, 1922; Lorente de Nó, 1922; O'Leary, 1941; Lund, 1973). Even so, Golgi studies revealed axon fragments that ran parallel to the cortical lamination, but they did not draw the anatomists' attention, because it seemed almost impossible to follow axons for long distances in the tangential plane, parallel to cortical layers. When the initial parts of axons were encountered, they were described as leaving the soma vertical to the cortical lamination and descending. From Golgi and myelin stains it was suggested that both the external and the less striking internal band of Baillarger (which is situated in layer Vb) contain oblique and horizontally running axon collaterals derived mainly from pyramidal cells of cortical layers III and Va (Clark and Sunderland, 1939; Braitenberg, 1962; for review see Braak, 1984). However, as soon as sensitive degeneration techniques became available, the extent of lateral axonal connections was immediately realized from the widespread extent of the degeneration induced by small electrical or mechanical lesions of cortex (Nauta and Gygax, 1953). In area 17 of the cat, the combination of Golgi stains, degeneration techniques, and electron microscopy finally revealed that the stria contained both terminals and preterminal passing fibers of specific afferents and terminals of intracortical origin, such as basket cell axons and collaterals of pyramidal neurons (Szentágothai, 1973). In macaque monkeys, and later also in cat visual cortex, horizontal axonal degeneration was observed up to a radius of 3.5 mm from the lesion site (Fisken et al., 1975; Creutzfeldt et al., 1977). However, degeneration studies could not differentiate between extrinsic and intrinsic cortical connections.

At the end of the 1970s, intracellular filling of single neurons allowed investigators to reconstruct all dendritic and axonal processes of a cell, revealing for the first time the detailed morphology of long axon collaterals (Gilbert and Wiesel, 1979; 1981; Lin et al., 1979). Finally, modern tracing techniques like intracellular and extracellular injections of horseradish peroxidase (HRP), injections of fluorescent latex microspheres, biocytin, and dextran amines visualized extensive horizontal connections travelling distances of up to 8 mm within specific layers, without entry into the white matter. These connections were termed long-range intrinsic, horizontal, tangential or intralaminar connections. They are especially prominent in supragranular layers II/III and in layer V.

CONCEPTUAL DEVELOPMENTS

The other reason long-range horizontal connections came late as a prime subject of neuroscientific investigations is the long-standing dominance of the columnar concept of the neocortical organization, which emphasizes vertical connections. The classical view was mainly derived from Golgi studies. For example,

in the somatosensory cortex, Mountcastle (1957) observed that neurons were grouped into columns extending vertically through all layers within bundles of separated vertical connections. Just a few years later, Hubel and Wiesel (1962) demonstrated that neurons in the primary visual cortex were also grouped into vertical domains according to their receptive field properties. In vertical electrode penetrations, neuronal response properties such as receptive field position, ocular dominance, orientation, and direction selectivity did not change significantly, so that neurons responding to similar visual stimuli are arranged in columns extending from layer I to layer VI. In contrast, tangential penetrations traveling for long distances parallel to the cortical lamination revealed more or less continuous changes in response properties (see Chapter 1). In a plane parallel to the cortical surface, neuronal selectivities vary systematically, and it is now known that columns or domains of similar functional properties form highly organized and periodic patterns (see Chapters 2 and 3).

Additionally, a strong vertical connection loop indicated multiple streams for parallel signal processing within the columnar structures. Vertical connections extend predominantly from layer IV, which receives the main thalamocortical input to supragranular (I–III) and infragranular (V, VI) layers (Lund et al., 1979) (see Figs 1-9 and 1-33) "backward" to subcortical structures and "forward" to extrastriate cortical areas (for review see Salin and Bullier, 1995). Studies that have investigated these connections in detail indicate that most of them (except for connections between area 17 and a few subcortical structures) (Salin et al., 1989) exhibit a point-to-point (vertical) topology by interconnecting locations within and between the different cortical areas representing retinotopically matching parts of the visual field. This is compatible with the view of a strong vertical processing stream within the cortical hierarchy. However, when intrinsic horizontal connections were first described, it appeared that they covered more than a "hypercolumn" of cortical distance (Rockland and Lund, 1982; Gilbert and Wiesel, 1989) and it was not readily appreciated how they contributed to cortical operations. However, it was recognized that they could allow intrinsic connections to combine signals of neurons with nonoverlapping receptive fields within primary visual cortex. In addition, there is now evidence of considerable convergence and divergence within the corticocortical connections in the visual system (Salin and Bullier, 1995). However, the issue of whether the distances in visual field angle spanned by the long-range intrinsic connections match or exceed those of extrinsic feedback connections is still an open question.

LAYOUT OF LONG-RANGE HORIZONTAL CONNECTIONS

Even though long-range horizontal connections had been described some 25 years ago, interest in their analysis was boosted only after the discovery of their patchy layout. In 1982 Rockland and Lund demonstrated for the first time that

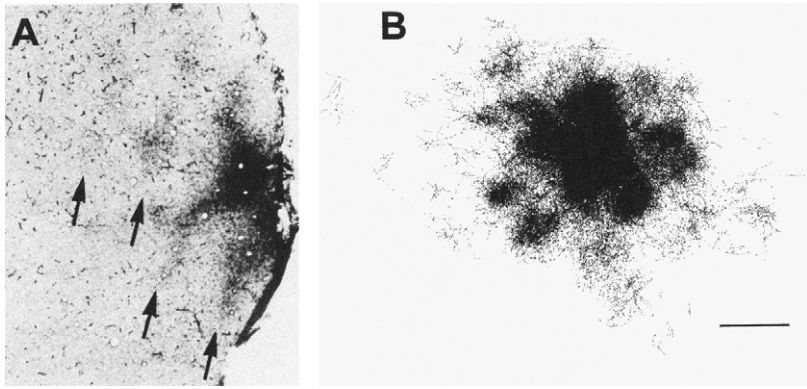

FIGURE 10-2. Long-range intrinsic connections in the primary visual cortex of the tree shrew **(A)** and the cat **(B). (A)** The discovery of the patchiness of intrinsic connections. Horizontal section through tree shrew visual cortex illustrating patches (arrows) of anterogradely labeled terminals and retrogradely labeled cell bodies resulting from an extracellular injection of horseradish peroxidase (HRP). Magnification ×35. (Modified from Anatomical banding of intrinsic connections in striate cortex of tree shrews *(Tupaia glis),* Rockland, Lund and Humphrey, *Journal of Comparative Neurology,* copyright © 1982 A. R. Liss inc., reproduced by permission of Wiley-Liss, Inc.) **(B)** Reconstruction of lateral connections in cat area 17. Distribution of synaptic boutons labeled anterogradely from a biocytin injection site (dark region in the center). Each dot represents one single bouton; excitatory and inhibitory boutons are plotted together. *Note that at least 20 distinct patches can be discriminated but interpatch regions are also heavily innervated.* Scale bar: 1000 μm. (Reproduced from Kisvárday, Toth, Rausch and Eysel, [1997], *Cerebral Cortex,* 7, by permission of Oxford University Press.)

extracellular injections of the tracer HRP into tree shrew visual cortex revealed a stripelike pattern of label in a plane tangential to the cortical surface (Rockland and Lund, 1982; Rockland et al., 1982) (Fig. 10-2). Dense patches of HRP were visible extending 2 to 3 mm around the injection sites, and these patches were most prominent in layers II and III A. The patches consisted of both anterogradely labeled terminals and retrogradely labeled neurons, mainly pyramidal cells. In coronal sections, the patches measured about 230 μm in diameter and were interleaved by label-free spaces at a center-to-center distance of 450 to 500 μm. Long horizontally and sometimes obliquely traveling axons were observed between the patches, probably giving rise to clustered axon terminals. In contemporaneous studies, intracellular injections of the same tracer permitted visualization and reconstruction of single axons emanating from pyramidal and spiny stellate cells. These studies were in the cat visual cortex (Gilbert and Wiesel, 1983; Martin and Whitteridge, 1984; Kisvárday and Eysel, 1992). The axons ran parallel to the cortical layers and were seen to give rise to terminal bundles at regularly spaced intervals (Fig. 10-3).

Early experiments using HRP injections in the tree shrew and the ferret indicated that the patches look more like periodically beaded stripes than round patches. This was true for both coronally cut sections and for horizontal sections

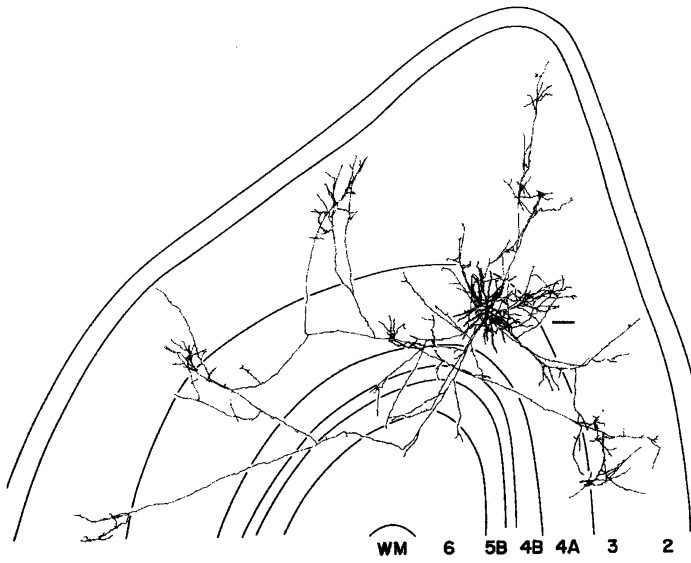

FIGURE 10-3. Camera lucida reconstruction of a HRP-filled spiny stellate cell of cortical layer IV displaying an extensive and patchy axonal distribution. The cell body of this neuron is located in layer 4A, whereas most of the collateral branches are restricted to cortical layers 2 and 3. Frontal section through the primary visual cortex of a cat. Scale bar: 100 μm. (Modified from Martin and Whitteridge [1984], *Journal of Physiology,* reproduced by permission of The Physiological Society.)

of some regions of primary visual cortex (Rockland et al., 1982; see also Ruthazer and Stryker, 1996). Reconstructions from serial sections revealed more or less regular rows of patches, sometimes with blind endings or twistings. Finally, both shapes seem to occur depending on the area, the species, and the technique used. In primate V1 and V2, large HRP injections revealed lattice-like or reticular patterns (Rockland and Lund, 1983, Rockland, 1985), whereas small injections labeled patches surrounded by unlabeled cortex (Livingstone and Hubel, 1984b). In the cat, the intrinsic connections are arranged in both irregular beaded bands and curved rows of isolated patches, both circular and oval-shaped (Luhmann et al., 1986, 1991; Gilbert and Wiesel, 1989; Callaway and Katz, 1990; Löwel and Singer, 1992; Schmidt et al., 1997a; Kisvárday et al., 1997; Yousef et al., 1999).

To date, patchy patterns of intrinsic connections have been observed in the primary visual cortices of several species including tree shrew (Rockland and Lund, 1982; Rockland et al., 1982; Fitzpatrick, 1996; Bosking et al., 1997), cat (Gilbert and Wiesel, 1983; 1989; Martin and Whitteridge, 1984; Luhmann et al., 1986, 1991; Kisvárday et al., 1986; 1994; 1997; Kisvárday and Eysel, 1992, 1993; Callaway and Katz, 1990; Albus et al., 1991; Katz and Callaway, 1992; Löwel and Singer, 1992; Lübke and Albus, 1992; Galuske and Singer, 1996; Schmidt et al., 1997a, 1997b; Buzás et al., 1998; Yousef et al., 1999), ferret (Rockland, 1985;

Durack and Katz, 1996; Ruthazer and Stryker, 1996) and squirrel monkey and macaque monkey (Rockland and Lund, 1983; Livingstone and Hubel, 1984a; Amir et al., 1993; Malach et al., 1993, Lund et al., 1993; Yoshioka et al., 1996). Patchiness has also been observed in extrastriate visual areas (Price, 1986; Matsubara et al., 1985, 1987; Yoshioka et al., 1992; Amir et al., 1993; Levitt et al., 1994; Malach et al., 1994; Kisvárday et al., 1997; Malach et al., 1997) and for corticocortical connections between different visual cortical areas (Gilbert and Kelly, 1975; Wong-Riley, 1979; Montero, 1980; Tigges et al., 1981; Rockland and Lund, 1982; Gilbert and Wiesel, 1983, 1989; Bullier et al., 1984; Ferrer et al., 1988, 1992; Price et al., 1994) and between the two hemispheres of the brain (Houzel et al., 1994; Boyd and Matsubara, 1994; Schmidt et al., 1997a; for earlier citations see review of Innocenti, 1986). Finally, clustered intrinsic and corticocortical connections are also a common feature of cat and monkey somatosensory and motor cortex (Jones et al., 1978; Matsubara and Phillips, 1988; Keller, 1993), auditory cortex (Imig and Brugge, 1978; Imig and Reale, 1981; DeFelipe et al., 1986), monkey prefrontal (Pucak et al., 1996) and frontal cortex (Goldmann and Nauta, 1977), and human visual (Burkhalter and Bernardo, 1989) and temporal cortex (Galuske et al., 2000), and thus a general feature of cortical organization.

TYPES OF NEURONS FORMING LONG-RANGE HORIZONTAL CONNECTIONS

Most long-range horizontal connections arise from pyramidal or spiny stellate cells, the two types of cortical excitatory neurons (Gilbert, 1983; Gilbert and Wiesel, 1983; Martin and Whitteridge, 1984). Pyramidal cells constitute the main cell type in the neocortex, and their somata are distributed in all cortical layers, except layer I. They are characterized by a triangular cell body, several basal dendrites, and a large apical dendrite, which is directed radially toward the pial surface. Pyramidal cell dendrites are covered with spines in high density, dendritic protrusions that receive at least one excitatory synapse (Peters and Kaiserman-Abramof, 1969). Spiny stellate cells lack a dominant apical dendrite but also have spines (see Chapter 1). They are present almost exclusively in layer IV of primary sensory areas (Lund, 1973; Valverde, 1986) and are the major recipients of thalamocortical afferents terminating in layer IV (Gilbert, 1983 (see Chapter 8)). It has been estimated that at least half of the pyramidal and spiny stellate neurons in the cortex contribute to long-range clustered connections. A few supragranular pyramidal neurons even seem to participate only in intrinsic circuits and do not extend their axon into the white matter (Gilbert and Wiesel, 1983).

About 20% of all cortical neurons are immunopositive for γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the cerebral cortex (Gabbott and Somogyi, 1986). Compared with the excitatory network, the inhibitory connections have a much more restricted lateral extent. Nevertheless, the degeneration study of Fisken et al. (1975) showed that more than 10% of all degenerating

symmetrical terminals were located as far as 2 to 3 mm from the center of a cortical lesion. Among the GABA-immunopositive neurons, only large basket cells, large multipolar cells, and dendrite-targeting cells provide long-range axon collaterals extending up to 2 mm (Somogyi et al., 1983; Kisvárday et al., 1994, 1997; see Chapter 1). Their axons are relatively straight and surround the somata of both pyramidal and nonpyramidal neurons (Kisvárday and Eysel, 1993; see also Somogyi et al., 1983). The other inhibitory cell types have predominantly local axon collaterals (LeVay, 1988; Matsubara, 1988). The percentage of GABA-positive inhibitory neurons in areas 17 and 18 that give rise to long lateral connections is in the range of 3–10% depending on which tracers and immunohistochemical protocols are combined. Since HRP might travel transsynaptically, studies using this tracer might have overestimated the number of inhibitory neurons participating in long-range connections (Matsubara and Boyd, 1992). On the other hand, studies using a fluorescent tracer and peroxidase-based immunohistochemical detection of GABA (LeVay, 1988; Albus and Wahle, 1994) might underestimate the number of double-labeled neurons, because the peroxidase reaction might quench the fluorescence. The actual percentage of long-range projecting neurons which are GABA immunoreactive is probably about 5%. A study of Albus et al. (1991) indicated that approximately 70% of all GABAergic neurons send out projections shorter than 1 mm; the remaining 30% occasionally give rise to connections with a lateral spread of 1–2.5 mm. GABAergic neurons with projections longer than 1 mm seem to be more numerous in infragranular layers (Matsubara and Boyd, 1992; see also Fisken et al., 1975).

Inhibitory neurons labeled by retrograde tracers seem to be more or less homogenously distributed in the primary visual cortex. Only about 60% of GABA immunopositive neurons reside within the dense clusters produced by retrograde fluorescent tracing (Albus et al., 1991; Albus and Wahle, 1994). Taking into account that they constitute only about 20% of all cortical neurons, inhibitory cells do not contribute critically to the clustering of intrinsic connections.

SYNAPTIC TARGETS OF LONG-RANGE INTRINSIC CONNECTIONS

Most of the long-range axon collaterals in primary visual cortex contact other pyramids. The majority of axons make asymmetrical type 1 synapses that are not GABA-immunoreactive and therefore thought to be excitatory (Kisvárday et al., 1986; area 18: LeVay, 1988; McGuire et al., 1991). The most frequent postsynaptic targets are dendritic spines (84–87%) probably of pyramidal cells, because the main projecting layers of intrinsic axons, namely cortical layers II, III and V, are basically free of spiny stellate neurons (Lund, 1973). The remaining synapses are with dendritic shafts of both pyramidal and GABA-immunoreactive nonpyramidal neurons (Kisvárday et al., 1986; McGuire et al., 1991). In summary, only about 5% of the postsynaptic structures of long-range intrinsic connections in cat

primary visual cortex are GABAergic dendritic shafts and, rarely, somata (Kisvárday et al. 1986; area 18: LeVay, 1988). In the macaque monkey, Fisken et al. (1975) had reported that about 9% of all degenerating synapses in a column of 3 mm radius surrounding a focal cortical lesion were symmetrical and, therefore, presumably inhibitory. Later studies demonstrated that long-range connections in the monkey contacted the dendrites of spiny and nonspiny cells in the proportion to which these cell types occur in the cortex (spiny:nonspiny = 80%:20%) (Hendry et al., 1987; McGuire et al., 1991), so that there was no evidence for preferential connectivity between excitatory neurons. Nevertheless, given that about 80% of all cortical neurons are excitatory, the primary role of the long-range intrinsic connections is the activation of other excitatory cells.

DIVERGENCE AND CONVERGENCE OF LONG-RANGE HORIZONTAL CONNECTIONS AT THE ULTRASTRUCTURAL LEVEL

Long-range intrinsic connections are formed by myelinated collaterals that leave the main (vertically) descending axon trunk before it enters the white matter. Collaterals can arise from the same axon in more than one layer (Gilbert and Wiesel, 1983; Kisvárday et al., 1986). They do not always run strictly parallel to the lamination but may also ascend and/or descend (Gilbert and Wiesel, 1983). In any case, patches of terminal branches are in register in supragranular and infragranular layers (Gilbert and Wiesel, 1983; Kisvárday et al., 1986), with the most prominent projections extending within layers II/III and V. In the literature, the term *cluster* or *patch* is commonly used to describe a group of labeled terminals or neurons that are separated from each other by more than 500 μm. These patches are variable in size but usually cover an average area of about 300 to 400 μm in diameter when labeled with HRP (Kisvárday et al., 1986) and 500 to 600 μm when labeled with biocytin (Kisvárday et al., 1997). Only about 5% (Albus and Wahle, 1994) of all neurons in the cortical volume covered by a patch participate in projecting to another distinct columnar volume. Average interpatch distances are in the range of 800 to 1100 μm in cat area 17 (Gilbert and Wiesel, 1983, using HRP: 800 μm; Martin and Whitteridge, 1984, using HRP, 1000 μm; Kisvárday and Eysel, 1992, using HRP, 1100 μm; Galuske and Singer, 1996, using DiI: 900 μm; Kisvárday et al., 1997, using biocytin: 900μm) and slightly larger in cat area 18 (Kisvárday et al., 1997, using biocytin: 1200 μm). Up to 10% of the retrogradely labeled excitatory neurons in a distance of more than 1000 μm from the injection site center are located between clusters (Albus and Wahle, 1994).

Estimates based on reconstructed biocytin-labeled axons indicate that about 80 of 300 to 1200 synapses of individual pyramidal neurons are localized within a single patch. This suggests that each pyramidal cell contributes afferents to four to eight different patches. Because only up to 4 of about 4800 (about 0.1%) excitatory inputs to a pyramidal neuron are from the same axon, a single pyramidal

cell axon might contact from 20 to as many as 80 different pyramidal cells in a distant patch. Another estimate was made for the overall influence of a patchy axon on the total cell population of a single patch (400 μm diameter). The results showed that, on average, only about 1–3% of the cells in a given patch are contacted by the same axon originating from a remote site (Kisvárday and Eysel, 1992). On the other hand, inhibitory neurons seem to have much more target cells: one basket cell makes about 2000–3000 synaptic contacts with 300 to 600 neurons (Kisvárday et al., 1993; Eysel et al., 1999a).

The density of anterogradely labeled boutons (within the patches) decreases with increasing distance from the pyramidal cell soma. Proximal patches lying within the dendritic field of the parent soma have more than twice as many boutons as do remote ones outside the dendritic field of the parent soma (Kisvárday and Eysel, 1992) (Fig. 10-2B). This suggests, on a semiquantitative level, that the impact of shorter-range connections on neocortical circuitry is much higher than that of long-range connections.

Another interesting feature of the network of long-range intrinsic connections is reciprocity. Injections of HRP had revealed a patchy distribution of both retrogradely labeled cell somata and anterogradely labeled axon terminals (Rockland and Lund, 1982). The assumption that a reciprocal network of clustered connections is responsible for these observations was confirmed by Kisvárday and Eysel (1992). Using biocytin as both an anterograde and a retrograde tracer, they visualized a patchy network of 10 interconnected pyramidal neurons in supragranular layers of cat area 17 (Fig. 10-4). Indeed, several remote pyramidal cells participated in the very same patchy network, with their terminal patches overlapping. The connections between the patches were predominantly reciprocal and made by contacts with distal segments of basal and apical dendrites. The largest distance observed between reciprocally interconnected patches in cat primary visual cortex was 2.7 mm (Kisvárday and Eysel, 1992).

TOPOGRAPHIC RELATIONS BETWEEN LONG-RANGE INTRINSIC CONNECTIONS AND FUNCTIONAL CORTICAL MAPS

MODULAR SELECTIVITY

When the clustering or patchiness of long-range connections was first observed, it was debated whether the pattern reflected that only a certain subpopulation of neurons gave rise to and received long-range connections (“fixed lattice hypothesis”) or that different subsets of neurons (with different morphology and/or function) were specifically interconnected. The characteristic spacing of the observed clusters suggested a relationship to the functional architecture of the primary visual cortex, namely to orientation and/or ocular dominance columns, consisting of neurons with similar functional properties (Hubel and Wiesel, 1962)

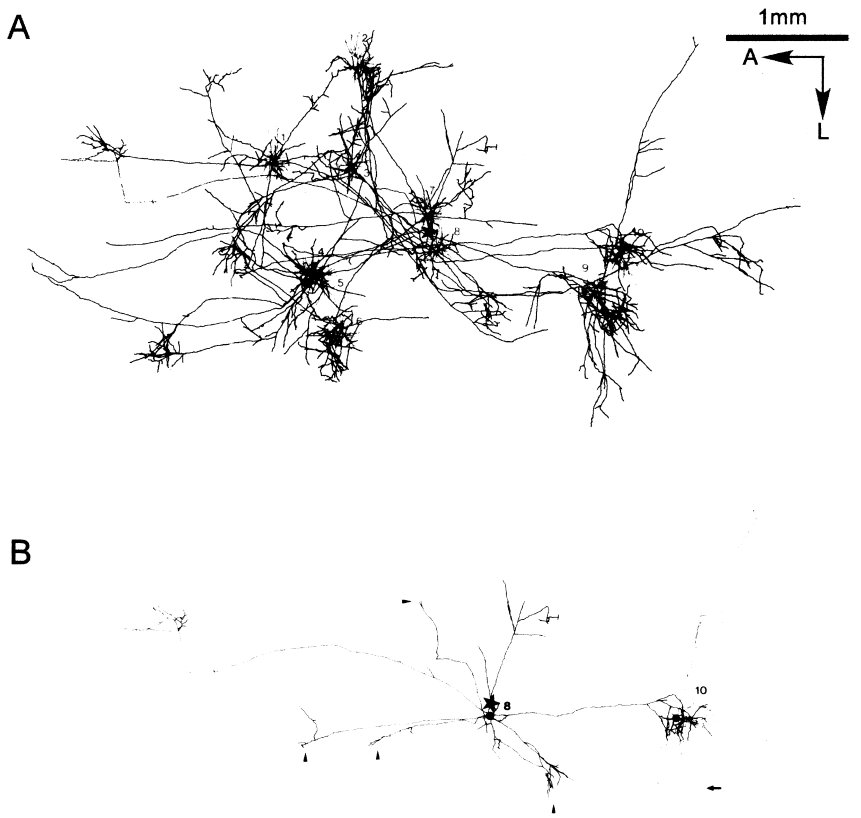

FIGURE 10-4. Reciprocity of the long-range lateral network. **(A)** Reconstruction of the complete axonal (black) and dendritic (gray) arborizations of 10 pyramidal neurons labeled from the same biocytin injection (black star) in cat area 17. Many of the patches receive overlapping axons from up to five pyramidal cells at different sites (e.g., the patch at the site of cell No. 3). **(B)** Some of the cells (e.g., cells No. 8 and 10) provide clustered axonal terminals to each other's dendritic field indicating the reciprocity of intrinsic connections. (Modified from *Neuroscience,* 46(2), Kisvárday and Eysel, Cellular organization of reciprocal patchy networks in layer III of cat visual cortex [area 17], p275–286, copyright 1992, with permission from Elsevier Science.)

(see also Chapter 2 and 3). Theoretical considerations from Mitchison and Crick (1982) predicted that neurons sharing similar functional properties such as orientation preference are selectively interconnected, which argued for a continuous system rather than a fixed lattice of patchy connections. The first trial to solve these issues by comparing the layout of both clustered long-range connections and orientation columns in the tree shrew visual cortex, however, showed only that the basic features of the two patterns are similar, but it did not reveal a systematic topographical relationship (Rockland et al., 1982).

Intrinsic Connections and Blobs

Historically, a systematic relationship between clustered long-range connections and a cortical functional system was first shown in the primary visual cortex of macaque and squirrel monkeys. Regions of high cytochrome oxidase activity (so-called cytochrome oxidase blobs) corresponded to neuronal domains with nonoriented, monocular, color- and low spatial fequency specific responses (Horton and Hubel, 1981; Livingstone and Hubel, 1984a; Tootell et al., 1988a, 1988b; Shoham et al., 1997) and received distinct thalamocortical input in both monkeys (Livingstone and Hubel, 1982; Fitzpatrick et al., 1983; Hendry and Yoshioka, 1994; for review see Casagrande, 1994) and cats (Boyd and Matsubara, 1996 (see Chapter 5)). Although cytochrome oxidase blob and interblob regions were initially described to be independent but reciprocally interconnected subcompartments (Livingstone and Hubel, 1984b), it is still a matter of debate whether blobs really represent a functionally separate compartment.

Biocytin tracing studies in both V1 and V2 of macaque and squirrel monkeys confirmed Livingstone and Hubel's original observations (Malach et al., 1993, 1994; Levitt et al., 1994; Yoshioka et al., 1996). Quantitative analysis showed that 68% of the intrinsic connections extended between cytochrome oxidase-rich blob regions, which occupied only about 20% of the cortical surface. When injections were made into nonblob regions (80% of cortical surface), patches of labeled neurons and terminals were located in nonblob compartments only with a probability of 73%, which seems to be random. A distinct border area between blob and nonblob territories (discriminable on the basis of its intrinsic connectivity) could not be specified (Yoshioka et al., 1996). In the cat, a colocalization of cytochrome oxidase blobs and patchy connections has so far been demonstrated for both callosal (Boyd and Matsubara, 1994) and feedforward connections from areas 17/18 to lateral susprasylvian cortex (Boyd and Matsubara, 1999) but *not* for long-range intrinsic connections (see Chapter 5).

Excitatory Long-Range Intrinsic Connections and Orientation Domains

First experimental evidence for the original hypothesis of Mitchison and Crick (1982) was obtained by cross-correlation studies (Michalski et al., 1983; Nelson and Frost, 1985; Ts'o et al., 1986). It was shown that the probablilty of synchronized spiking between neurons was higher when they had similar orientation preference, even if the neurons were separated by up to 2 mm (Ts'o et al., 1986; Ts'o and Gilbert, 1988). Because the ability to synchronize spikes on a short time scale is taken as evidence for a direct synaptic connection, it was concluded that neurons with similar orientation preference are selectively connected by long intracortical fibers (Ts'o et al., 1986).

The first direct alignments of anatomical connectivity patterns and functional domains in cat area 18 painted a different picture. Combining the patterns of HRP-labeled neurons with electrophysiologically recorded functional maps, Matsubara and colleagues observed connections predominantly between sites of dif-

ferent, frequently even orthogonal orientations (Matsubara et al., 1985, 1987). As discussed earlier, however, results from experiments using large extracellular injections of HRP are difficult to interpret because of distinct methodological difficulties (i.e., transneuronal transport of HRP). Two years later, Gilbert and Wiesel (1989) demonstrated that long-range intrinsic connections preferentially connected domains activated by the same orientation; they used a combination of 2-deoxyglucose (2-DG) labeling and fluorescent tracing. At that time, a new retrograde tracer, latex microspheres coupled with either rhodamine or fluorescein as the chromophore, the so-called beads, had become available (Katz et al., 1984; Katz and Iarovici, 1990). One of the big advantages of beads, compared with other retrograde tracers, is that they do not diffuse and thus allow small and localized injection sites. Gilbert and Wiesel (1989) injected beads into electrophysiologically characterized orientation preference domains. Subsequently, the pattern of iso-orientation domains was visualized by labeling with 2-DG while the animals were stimulated with moving gratings of the "injected" orientation. Post mortem, the retrogradely labeled neurons and the 2-DG domains were superimposed in the same sections of flat-mounted visual cortices. There was a strong tendency of the neurons to be located in the 2-DG-labeled domains and thus in regions preferring the same stimulus orientation as the injection site. However, no quantification of the data was delivered. Using the same experimental design in a different context (the analysis of connections in strabismic animals) our own analyses allowed a crude estimate of the actual percentage of retrogradely labeled neurons in the 2-DG-labeled orientation domains. In area 17 of a normally raised cat, about 56% (60% in strabismic cats) of all retrogradely labeled neurons were localized in domains of the same orientation preference (± 27°) as at the injection site, but only about 21% of the cells were localized in cross-oriented domains (± 27°) (Schmidt et al., 1997a). Thus the density of retrogradely labeled neurons in iso-orientation compartments as assessed with 2-DG (the compartment was defined to cover 30% of the cortical surface) was significantly higher than outside as can also be seen in the data of Gilbert and Wiesel (1989) (Fig. 10-5).

Kisvárday et al. (1997) gave a detailed quantification of the specificity of long-range intrinsic connections by combining anterograde biocytin tracing with electrophysiological mapping of cat areas 17 and 18. The distribution of labeled synaptic boutons was superimposed on orientation preference maps interpolated from the electrophysiological data. In area 17, 53% of the excitatory boutons were located in iso-orientation domains (± 0–30° difference from the orientation preference at the injection site), 30% in oblique (± 30–60°) and 17% in cross-oriented (± 60–90°) domains. The bouton distributions in area 18 were very similar (iso, 59%; oblique, 30%; cross, 11%). The selectivity for iso-orientation domains was higher in the close vicinity (distances less than 500 μm) of the injection site than in more remote patches. The advantage of that study over previous ones is that the finest details of excitatory connections, the boutons making the synaptic contacts, are matched with the functional maps of an area. While retrograde tracing studies can provide numbers of neurons participating in a particular pro-

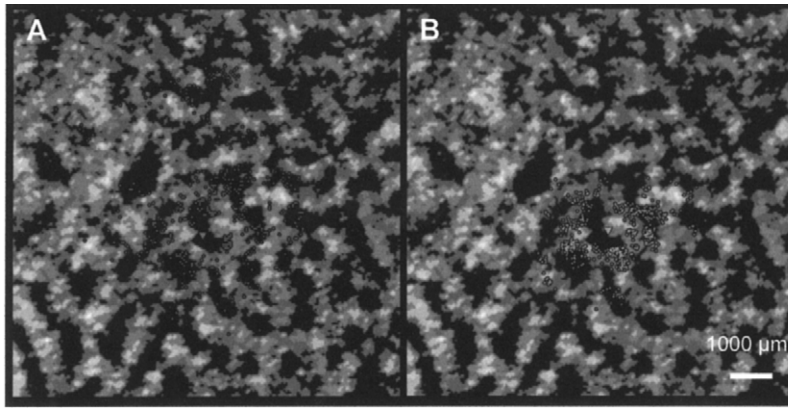

FIGURE 10-5. Superposition of retrogradely labeled neurons and 2-DG labeled horizontal orientation columns in cat primary visual cortex. **(A)** An injection of red microspheres was made into a column preferring horizontal contours. Of the labeled neurons, 54.6% (n = 414) are localized in iso-orientation domains. **(B)** Cell distribution after an injection of green microspheres in a column preferring vertical contours. Only 22% of the labeled neurons (n = 360) are localized in the 2-DG labeled horizontal orientation domains. (From Schmidt, Kim, Singer, Bonhoeffer and Löwel, 1997, *Journal of Neuroscience* 17, p5480–5492, copyright 1997 by the Society for Neuroscience.) See color insert for color reproduction of this figure.

jection, the quantification of axonal boutons additionally allows to estimate the functional strength of these connections, when it is assumed that individual synapses have the same functional impact.

The latter type of studies became possible with the development of optical imaging of intrinsic signals to visualize functional cortical maps (Bonhoeffer and Grinvald, 1996) (see Chapter 2). By making it possible to record all kinds of functional maps in a certain cortical area in vivo, intrinsic signal imaging overcomes the major limitation of the 2-DG technique, namely the visualization of one, maximally two (see Chapter 3), different activity patterns (e.g., orientation domains) in one brain region (e.g., visual cortex). Optically recorded functional maps can be used for both targeting of precise tracer injections into identified domains (Kisvárday et al., 1994; Schmidt et al., 1997a, 1997b; Yousef et al., 1999) and for superimposing of labeled neuron and bouton distributions with the functional architecture (e.g., Malach et al., 1993, 1994; Kisvárday et al., 1994; Yoshioka et al., 1996; Bosking et al., 1997). In monkey V1, superimposition of biocytin-labeled patches with orientation preference maps visualized by optical imaging, demonstrated that connections were as orientation specific as in the cat (Malach et al., 1993). Similarly, in the primary visual cortex of the tree shrew, 57% of biocytin-labeled boutons contacted sites in the optically imaged orientation preference map with the same orientation preference as the injection site (± 35°; Bosking et al., 1997) (Fig. 10-6).

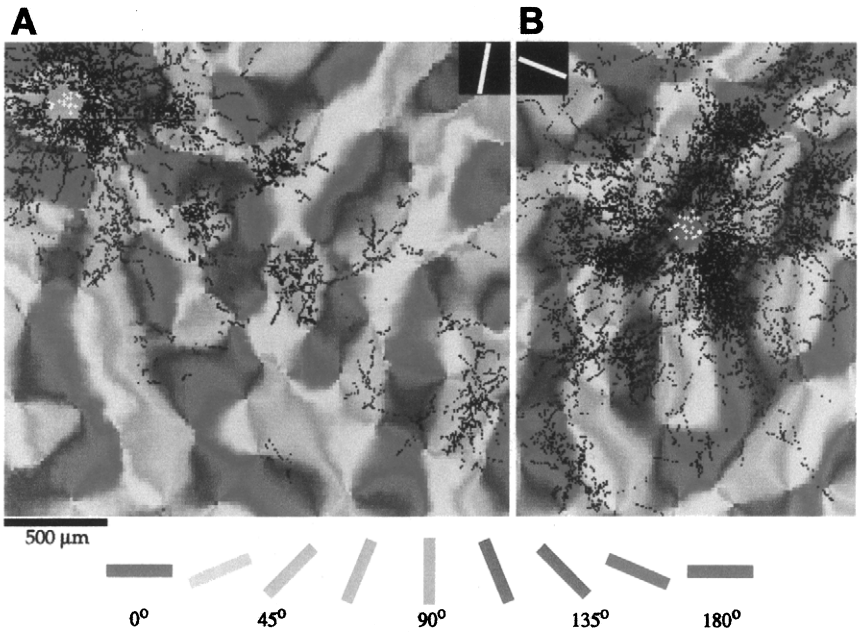

FIGURE 10-6. Topographic relationship between long-range intrinsic connections and iso-orientation domains in tree shrew primary visual cortex. The functional architecture of the cortex was visualized using optical imaging of intrinsic signals. In these maps, the preferred orientation for every region of the imaged cortex is color-coded according to the scheme below the figure (e.g., red codes for 0° and blue codes for 90° orientation preference). Biocytin was injected extracellulary into a domain preferring contours of 80° (light blue) **(A)** or 160° (red) **(B).** Both retrogradely labeled neurons (white symbols) and anterogradely labeled boutons (black dots) are superimposed with the optically recorded orientation preference map. Near the injection site, labeled boutons are found at sites with all orientation preferences, whereas at longer distances, boutons are located preferentially at sites preferring the same orientation as the injection site. (From Bosking, Zhang, Schofield and Fitzpatrick, 1997, *Journal of Neuroscience* 17, p2112–2127, copyright 1997 by the Society for Neuroscience.) See color insert for color reproduction of this figure.

More recently, Yousef et al. (1999) quantitatively analyzed the degree of orientation selectivity of long-range intrinsic connections with respect to the different cortical layers. Using a combination of optical imaging and injections of both latex microspheres and biocytin they analyzed connections in supragranular, granular, and infragranular layers of cat area 18. Layer IV lateral networks are in general much shorter (about 50%) than layer III networks and display a less clear patchy pattern. Moreover, long range (> 500 µm) connections in layer IV were distributed almost equally across orientations (iso, 35%; oblique, 34%; cross, 31%), suggesting that the long-range layer IV circuitry has a different functional role from that of the iso-orientation biased layer II/III circuitry.

To date, the most elaborate protocol for the detailed analysis of intrinsic circuitry is to reconstruct single intracellularly filled (with biocytin) neurons and to superim-

pose the reconstructions with optically imaged functional maps (Buzás et al., 1998). This technique makes it possible to analyze the relationship between the 3-dimensional anatomy of individual neurons, their receptive field properties (measured in vivo), and the functional map in which the neuron is embedded (Fig. 10-7).

So far, only injections into orientation domains (i.e. regions of low orientation gradient) have been considered. It is possible, however, that lateral connections in regions of high orientation gradient such as orientation (or pinwheel) centers are organized differently. Some evidence in this direction was recently obtained in cat area 18. Orientation center injections resulted in patchy labeling, although the patches were less remarkable than after injections into orientation domains (Kisvárday et al., 1996, 1998). Quantitative analyses of bouton distributions with optically recorded orientation preference maps revealed striking differences between the two experimental paradigms. Injections into orientation centers pro-

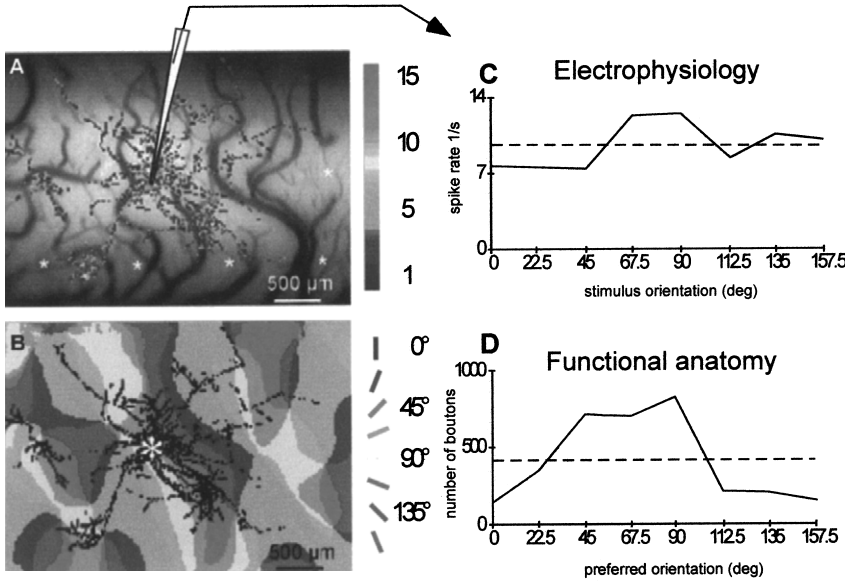

FIGURE 10-7. Relationship between a neuron's axonal projections, its receptive field properties, and the functional map in which the neuron is embedded. **(A)** Superposition of a density map of all axon terminals (colored dots) of a biocytin-filled pyramidal neuron with the vascular image containing five reference penetrations (white stars). Color scheme indicates the number of terminals per image-pixel. **(B)** Superposition of the bouton distribution (shown in black) with the optically visualized orientation map. The preferred orientation for every region of the imaged cortex is color-coded according to the scheme on the right side of the figure. Panels **(C)** and **(D)** provide a quantitative comparison between the electrophysiologically measured orientation tuning of the neuron **(C)** and the orientation distribution of all labeled boutons **(D).** (Modified from *Brain Research Protocols,* 3, Buzás, Eysel, and Kisvárday, Functional topography of single cortical cells: an intracellular approach combined with optical imaging, p199–208, copyright 1998, with permission from Elsevier Science.) See color insert for color reproduction of this figure.

duced boutonal patches whose "orientation" distribution varied from each other and from the injection site, whereas injections into orientation domains produced patches of axonal boutons with "orientation" preferences rather similar to the injection site. The combination of all patch distributions into a single one yielded a distribution similar to the one of the injections site. This kind of relationship was found applicable also for other cases regardless of the exact location of the injection site (Kisvárday et al., 1996). However, further experiments in area 17 are needed to establish the generality of this observation.

Methodologically, it is important to keep in mind that studies counting boutons and relating them to functional maps might underestimate the specificity of long-range connections, because synaptic contacts are also made on dendrites that can be located up to several hundred microns away from the parent soma (and thus in a different orientation domain). On the other hand, "simply" outlining patches after mass tracer injections might overestimate the specificity of the long-range circuitry because neurons connecting interpatch regions are usually omitted.

Inhibitory Connections and Orientation Domains

Most of the studies analyzing the topographic relationship between functional maps and intrinsic connections did not explicitly discriminate between excitatory and inhibitory connections. Because HRP, latex microspheres, and biocytin label both excitatory and inhibitory neurons and terminals, inhibitory connections must be identified by either GABA-immunohistochemistry or single cell reconstructions (Albus and Wahle, 1994; Kisvárday et al., 1994, 1997; Yousef et al., 1999). Although, their number is relatively small, Kisvárday et al. (1994, 1997) managed to reconstruct biocytin-labeled large basket cells, the main substrate of long-range inhibitory connections in cat visual cortex. Basket cell axons are characterized by segments with clusters of boutons aligned in rows separated by larger bouton-free segments (see Chapter 1). The inhibitory network is about one third to one half the extent of the excitatory network (Kisvárday et al., 1997; Crook et al., 1998) and involves more neurons. Inhibitory and excitatory terminals labeled from the same injection site do not overlap extensively. In cat areas 17 and 18, the density of inhibitory boutons is highest in the surround of excitatory terminal clusters outside the injection site core. In all, 48% of inhibitory boutons were located in iso-orientation domains (± 30°), 28% in oblique, and 24% in cross-oriented domains (Kisvárday et al., 1997). These data indicate that there seem to be slightly fewer inhibitory connections between iso-orientation domains than excitatory ones.

Relationship of Intrinsic Connections to Ocular Dominance

In the primary visual cortex of cats, long-range intrinsic connections extend between domains of left and right eye dominance with equal probability (Löwel and Singer, 1992; Schmidt et al., 1997a, see also Matsubara et al., 1987), so that there is no specific relationship between the two systems.

The situation is different in macaque monkey V1, in which intrinsic connections seem to have a preference for same-eye targets. First evidence was provided

by cross-correlation studies showing interactions between cells with matched orientation and eye preference, at varying horizontal separations (Ts'o and Gilbert, 1988). More recently, two studies using anterograde biocytin labeling and optical imaging showed that the percentage of connections between same eye territories is on average 60–65% (Malach et al., 1993) thus, despite strong inter-individual variability, significantly greater than that of connections between opposite eye territories (Yoshioka et al., 1996). This difference in ocular dominance "selectivity" of the long-range intrinsic connections may be due to the different ocular dominance distribution in supragranular layers of the monkey compared with the cat primary visual cortex. In macaque monkeys, ocular dominance columns in the supragranular layers I–III are relatively obvious, and they are in precise register with the termination zones of thalamocortical afferents in layer IVc (Hubel and Wiesel, 1969; Hendrickson and Wilson, 1979; Horton and Hubel, 1981) in which monocular neurons predominate (Hubel and Wiesel, 1968). In contrast, the majority of supragranular neurons in normally raised cats are binocular, and they display only slight preferences for one eye or the other. However, when cats are reared with artificial strabismus, the ocular dominance distribution in area 17 changes dramatically and comes to resemble that in monkey V1. In strabismic cats, the segregation of thalamocortical afferents in layer IV is enhanced compared with normally raised animals (Shatz et al., 1977; Löwel, 1994) and two almost exclusively monocular subpopulations of neurons develop in supragranular and infragranular layers, in addition to the monocular population in layer 4 (Hubel and Wiesel, 1965). This experience-dependent change has a dramatic influence on the selectivity of the long-range intrinsic connections. Monocular injections of fluorescent beads combined with 2-DG autoradiography in area 17 of strabismic cats revealed that up to 85% of the retrogradely labeled neurons were located in the domains of the same eye preference than at the injection site (Löwel and Singer, 1992; for review see Löwel and Singer, 2000).

Other Columnar Systems

A relationship between long-range intrinsic connections and other functional systems such as direction selectivity or spatial frequency domains has so far not been reported in the cat. However, there is evidence from the ferret primary visual cortex that local, and to a lesser extent distant (up to ≈ 2 mm), excitatory synaptic inputs are iso-direction tuned, indicating the existence of a network of direction-specific, long-range horizontal connections (Roerig and Kao, 1999).

AXIAL SELECTIVITY

As originally postulated by Mitchison and Crick (1982), the pattern of long-range intrinsic connections is not only related to the system of orientation domains but also to the topography of visual space. The reconstruction of single axons in cat primary visual cortex revealed that the axonal fields are not circular but elliptically elongated, extending for a greater distance along one cortical axis

compared with the orthogonal one (Gilbert and Wiesel, 1983; Kisvárday and Eysel, 1992). The observed anisotropy could not fully be explained by a different cortical magnification factor. Gilbert and Wiesel (1983) had already speculated that the axis of a cell's axonal field elongation is related to its receptive field orientation translated into cortical coordinates, but experimental evidence was missing. Studies in the visual cortex of both tree shrews (Fitzpatrick, 1996; Bosking et al., 1997) and cats (Schmidt et al., 1997b) later confirmed this suggestion, showing that in addition to the modular selectivity, long-range horizontal fibers exhibit axial specificity (i.e., there is a systematic relationship between a neuron's orientation preference and the distribution of its axon arbors across the cortical map of visual space). In tree shrews, biocytin-labeled horizontal axons extended for longer distances and gave rise to a larger number of terminal boutons along an axis of the visual field map that corresponded to the neuron's preferred orientation. In area 17 of cats use of latex microspheres to label interconnected neurons revealed a tendency for cell distributions to be elongated along the cortical axis corresponding to the orientation preference of the injection site (Schmidt et al., 1997b). Tracer injections into domains preferring horizontal contours resulted in distributions of retrogradely labeled cells elongated along an axis parallel to the cortical representation of the horizontal meridian; injections into domains preferring vertical contours resulted in cell distributions elongated parallel to the cortical representation of the vertical meridian at the 17/18 border (Fig. 10.8). Thus, long-range horizontal connections preferentially link neurons with co-oriented and co-axially aligned (colinear) receptive fields.

The axial selectivity of intrinsic connections is hypothesized to be the anatomical substrate for the physiological finding that responses to optimally oriented stimuli in the classical receptive field of a neuron are enhanced when colinearly aligned contours are presented outside the classical receptive field (Nelson and Frost, 1985; Kapadia et al., 1995).

Tracer injections into cat area 18 or monkey V2 revealed distributions of retrogradely labeled neurons elongated predominantly along a cortical axis parallel to the 17/18 (V1/V2) border (macaque and squirrel monkey: Rockland, 1985; cat: Matsubara et al., 1987). In that area, the cortical magnification factor is twice as large for the vertical compared with the horizontal orientation (e.g., Cynader et al., 1987) (see Chapter 1). Elongation of intrinsic networks in a direction parallel to the 17/18 border, therefore, might at least partly compensate for the large asymmetry in cortical magnification. Thus a possible axial selectivity of the horizontal network in area 18 is difficult to detect, given the pronounced asymmetry in the visual field representation. The same reasoning applies in the case of large extracellular tracer injections into monkey V1, which generally result in elliptical anterograde labeling. Microinjections of biocytin into layer III result in an asymmetrical field (average anisotropy = ratio long axis/short axis = 1.8) of labeled axon terminal clusters in layers I-III, with the longer axis of the label oriented orthogonal to the rows of blobs and ocular dominance domains, parallel to the V1/V2 border (Yoshioka et al., 1996; see also Malach et al., 1993). In contrast to

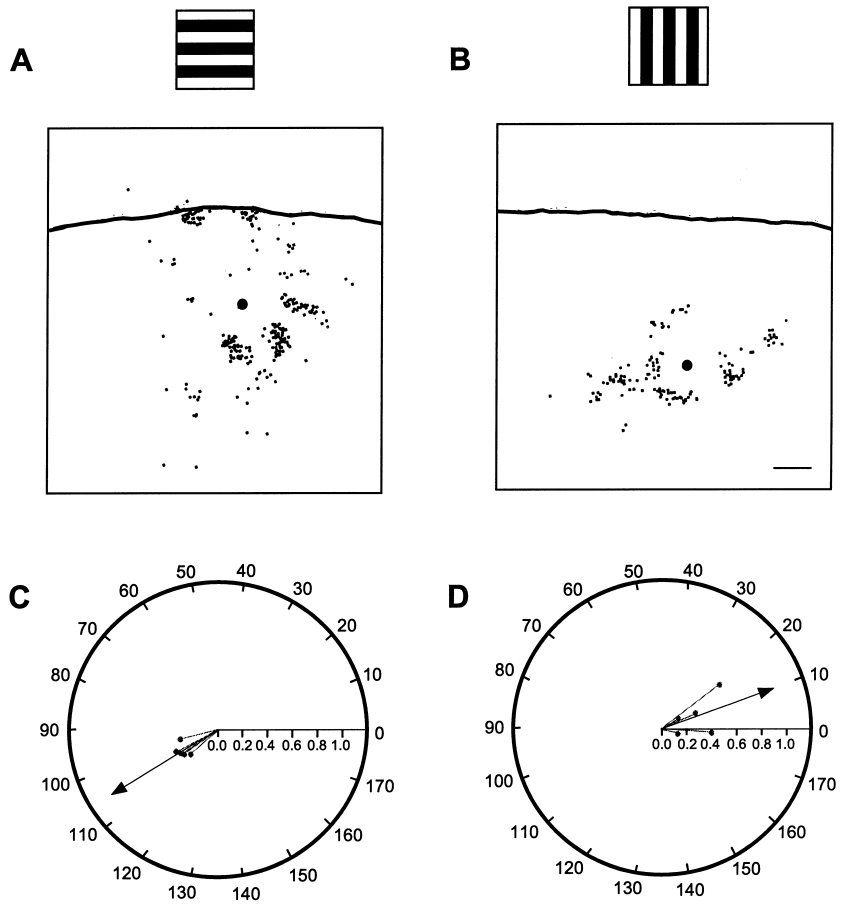

FIGURE 10-8. Axial selectivity of long-range intracortical connections in cat area 17. **(A, B)** Distribution of retrogradely labeled neurons resulting from extracellular injections of fluorescent latex microspheres in domains preferring horizontal **(A)** or vertical **(B)** contours. The continuous line in the upper parts of the pictures represent the 17/18 border (i.e., the representation of the vertical meridian). Labeled neurons are indicated by small dots and injection sites by large dots. *Note that cell distributions are elongated orthogonal to (A) or along (B) the vertical cortical axis.* **(C)** and **(D)** are vector plots of the distributions of labeled neurons in the different directions reduced to a range of 180°. Gray dots are the end points of section mean vectors reflecting the mean amount, distance, and direction of labeled neurons by the same injection site in five representative sections. The black arrows are the resulting vectors of all sections for an injection in a domain preferring horizontal **(C)** or vertical contours **(D).** *Note, that the vectors are separated by 95° and orthogonal to each other.* (Modified from Schmidt et al. [1997b]. The perceptual grouping criterion of colinearity is reflected by anisotropies of connections in the primary visual cortex, *European Journal of Neuroscience,* with permission from Blackwell Science Ltd.)

the cat, monkey V1 has an anisotropic cortical magnification factor (Van Essen et al., 1984; Dow et al., 1985), whereby the cortical representation of the horizontal meridian measures only half the representation of the vertical meridian (Malach et al., 1993; Grinvald et al., 1994). Nevertheless, there is some evidence for axial selectivity of long-range intrinsic connections also in the monkey (squirrel monkey: Sincich and Blasdel, 1995).

SUMMARY: FUNCTIONAL TOPOGRAPHY OF LONG-RANGE INTRINSIC CONNECTIONS

There is general agreement that excitatory long-range horizontal connections preferentially link neurons with similar orientation preference and colinearly aligned receptive fields. In contrast, inhibitory long-range connections are both shorter than excitatory ones and less orientation selective. Furthermore, the functional preference of long-range intrinsic connections may depend both on the layer (supragranular and infragranular layers I-III/V-VI versus layer IV) and on the exact position of the injections site within a functional map (linear region versus pinwheel-center). Published data further indicate that there is massive cross-talk between domains of different orientation preference both in excitatory and inhibitory networks.

Rockland and Lund (1982, 1983) originally suggested a lattice-like, but fixed, pattern of connections that link neurons only at certain cortical locations. This hypothesis has not been supported by experimental evidence, as almost every tracer injection into visual cortex resulted in a patchy pattern of labeling. Furthermore, double tracer injections into immediately adjacent cortical territories revealed both interdigitating and overlapping patch systems, depending on the relation between the functional properties of the cells at the two injection sites (Matsubara et al., 1987; Schmidt et al., 1997a). These observations indicate a rather continuous system of patchy connections between subsets of orientation-selective neurons.

POSSIBLE FUNCTIONS

Long-range horizontal connections in the primary visual cortex span a cortical region much larger (up to 8 mm) than that corresponding to the classical receptive field of a neuron (the part of visual space that must be stimulated to evoke a rate modulation of a neuron's spiking activity). This fact, along with what is known about their specific functional topography, suggests that horizontal connections may be important for the integration of information from widely distant points in the visual field and for context-dependent modifications of neuronal responsivity. Contrary to long-standing belief, recent physiological and anatomical evidence suggests that part of this process of spatial integration occurs at the level of the primary visual cortex. The relevance of this "early stage" modulation for further

visual processing is exemplified by links to perceptual phenomena. It has been known since the work of the Gestalt psychologists that certain grouping criteria, such as neighborhood, color, direction of motion, velocity, orientation, and colinearity, make contours perceptually more salient (Wertheimer, 1938; Grossberg and Mignolla, 1985; Field et al., 1993). The topology, excitatory nature, and receptive field properties of the interconnected neurons make long-range intrinsic connections ideally suited to serve as a substrate for perceptual grouping by enhancing the saliency of adjacent, colinear, and similarly orientated contours that are processed by distributed neurons with nonoverlapping classical receptive fields. The following example demonstrates how the Gestalt criterion of colinearity supports perceptual grouping.

Figure 10.9 illustrates that our visual system tends to group contour segments into one coherent figure if they have the same orientation and are additionally colinearly aligned along the contour path rather than orthogonal to it (Field et al., 1993; Polat and Sagi, 1993, 1994; Kapadia et al., 1995; Schmidt et al., 1997b). To achieve this, neuronal responses to colinearly aligned contours must be distinguished from physically identical but noncolinearly arranged contours in a context-dependent way. Obviously, both the perceived location and the form of the individual contour elements are not influenced by the context. The only information that can be used for the context-dependent processing is the topological relation between the location and orientation of the contour elements. Selection of elements composing the object, therefore, must be done at a level of visual processing where neurons have orientation-selective receptive fields whose size is equal to or smaller than that of the constituting elements of the picture. Such receptive fields are present in early visual areas such as area 17 (V1) and area 18 (V2). Long-range intrinsic connections in those areas are well suited to perform

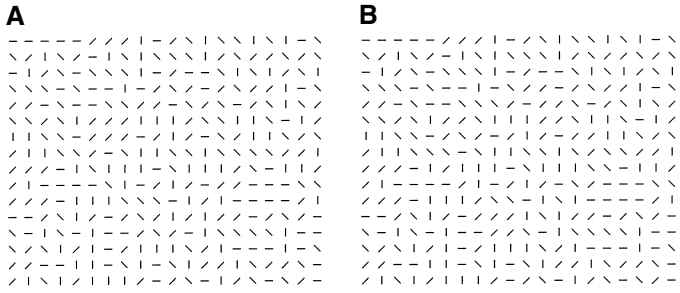

FIGURE 10-9. An example of perceptual grouping on the basis of colinearity. The colinearly arranged line segments in **(A)** that define the edges of a rhombus are grouped together and stand out from the randomly distributed line segments of the background. **(B)** The line segments are arranged in the same way as in **(A)** except those that defined the outline of the rhombus, which are now parallel to each other and hence orthogonal to the corresponding segments in **(A)** (Modified from Schmidt et al. [1997b]. The perceptual grouping criterion of colinearity is reflected by anisotropies of connections in the primary visual cortex, *European Journal of Neuroscience,* with permission from Blackwell Science Ltd.)

the context-dependent grouping operations given their functional architecture. Because they extend between neurons of similar orientation preference and colinearly aligned receptive fields, they could selectively enhance the saliency of neuronal responses to distributed elements of an object such as that shown in Fig. 10.9, according to criteria such as colinearity and orientation.

In a similar way, long-range intrinsic connections could be thought as being the substrate of other psychophysical phenomena in which perception is strongly influenced by the context in which objects are embedded (Gibson and Radner, 1937; Westheimer et al., 1976; Badcock and Westheimer, 1985; Westheimer, 1986; Polat and Sagi, 1993, 1994). They could enable the visual system to identify simple features from a noisy background (Wertheimer, 1938; Dresp, 1993; Grossberg and Mingolla, 1985; Field, et al., 1993; Kapadia et al., 1995) at an early level of cortical visual processing. In principle, long-range intrinsic connections can also contribute to the emergence of illusory contours and mediate perceptual filling-in of artificial or real scotomas (Kanizsa, 1979; Yarbus, 1957; Krauskopf, 1961; Crane and Piantanida, 1983; Ramachandran and Gregory, 1991). At present, however, the importance of long-range connections for the latter psychophysical phenomena is purely speculative. Many aspects of scene segmentation are probably also influenced by feedback connections from so-called higher cortical areas in which receptive fields are usually larger than in V1. It is likely that scenes are segmented as a result of a dynamic interplay of sensory input and intrinsic and feedback projections. In particular, when ambiguities in a visual scene cannot be solved by evaluating the local relations of an object's elements, feedback from areas with larger receptive fields is likely to play an important role.

Taken together, available evidence supports the hypothesis that long-range intrinsic connections in primary visual cortex are the anatomical substrate of context-dependent modifications and thus are important for visual scene analysis. It follows that the criteria for perceptual grouping might be partially determined by the functional architecture of these connections. Evidence in favor of this hypothesis comes from investigations in strabismic cats in which the changed perceptual capabilities are associated with both a change in the layout of the long-range intrinsic network (Löwel and Singer, 1992; Schmidt et al., 1997a) and modified neuronal interactions (König et al., 1993; for a review see Löwel and Singer, 2000).

Several electrophysiological findings in V1 have been attributed to intrinsic excitatory and inhibitory connections.

1. Besides the thalamocortical and vertically running intracortical circuits, they have been ascribed to contribute to orientation and direction selectivity (Eysel et al., 1987, 1990; Crook et al., 1997, 1998).
2. Mirroring spatial integration on the physiological level and hardly explainable by other cortical circuits are the generation of large composite receptive fields within V1 under certain circumstances (Singer and Tretter, 1976; Gilbert an Wiesel, 1985; Bolz and Gilbert, 1990; Schwarz and Bolz, 1991).

3. Also in this regard are the direct inhibitory and substreshold excitatory effects from beyond the classical receptive field (Blakemore and Tobin, 1971; Nelson and Frost, 1978; Morrone et al., 1982; Allman et al., 1985).
4. Similarly, orientation specific intrinsic connections are also a likely candidate for the synchronization of responses of spatially separated neurons as a function of stimulus coherence (Gray et al., 1989).
5. They may also be responsible for adaptive topographic reorganization of cortical maps after deafferentiation where the effects are too large to be mediated by rearrangements of the thalamocortical input (Kaas et al., 1990; Heinen and Skavenski, 1991; Gilbert and Wiesel, 1992; Darian-Smith and Gilbert, 1994; see also Florence et al., 1998).

PLASTICITY OF LONG-RANGE CONNECTIONS IN THE ADULT

The functional role of intrinsic connections in a particular situation may vary depending on the time course of the mediated function and the modifiability of the connections. Perceptual decisions probably operate on a millisecond time scale. The filling-in of an artificial scotoma requires longer time periods and might be followed by processes summarized by the term *learning.* Complete removal of the visual input leads to larger scale topographic changes in cortical maps with a delay of days to weeks.

During postnatal development intrinsic long-range connections are modifiable, whereby both spontaneous neuronal activity and sensory experience have been shown to play crucial roles in shaping the network (Callaway and Katz, 1991; Katz and Callaway, 1992; Ruthazer and Stryker, 1996; for review see Schmidt et al., 1999; Löwel and Singer, 2000). Unexpected just a few years ago, anatomical evidence now shows that these connections also remain plastic during adult life. Learning-induced or use-dependent changes may be mediated not only by long-range intrinsic connections but also by thalamocortical, local, feedforward, and feedback interareal connections. However, as outlined in the previous sections, their extent and characteristic functional topography make long-range intrinsic connections well suited to transmit feature-specific information over a large region of visual space in primary visual cortex. The next section reviews anatomical and physiological evidence indicating that long-range intrinsic connections in primary sensory cortices mediate both short-term dynamics and long-term modifications (of receptive fields) involving permanent reorganization of cortical representations.

SHORT-TERM DYNAMIC CHANGES OF RECEPTIVE FIELD SIZE AND LOCATION

Based on a number of studies showing that receptive fields can change within minutes to hours, the receptive field of a neuron is understood as a highly

dynamic rather than a fixed neuronal property. Pettet and Gilbert (1992) stimulated primary visual cortical neurons with an artificial scotoma (a mask) covering their receptive field. The surround of the visual stimulus consisted of moving oriented bars. In cases in which the orientation of the bars matched the orientation preference of the neuron, the original receptive field size expanded up to fivefold within minutes and collapsed again when the center of the scotoma was stimulated with a small oriented stimulus. Because an important prerequisite of the receptive field expansion was the stimulation of the surround, it was concluded that dynamic changes of receptive field properties are context-dependent. The dynamic receptive field expansion of a binocular neuron can also be induced by stimulation of the nonconditioned eye (Volchan and Gilbert, 1995). Because afferents of the two eyes first converge onto single cells in the primary visual cortex, this was assumed to be the neural site of the dynamic changes. Also, because the effect was dependent on stimulus orientation, long-range intrinsic connections were discussed as a likely candidate to mediate the contextual influences.

To test whether dynamic short-term plasticity indeed involved lateral connections Das and Gilbert (1995a) quantified the strength of intracortical connections between two conditioned neurons. In their experiment, a mask covered the receptive fields of two neurons with similar response properties. Cross-correlograms were computed from spike trains evoked by a moving bar covering a common part of both receptive fields. Concomitant with the expansion of receptive field sizes, the effective connectivity between the coconditioned neurons increased and returned to baseline when the region of the artificial scotoma was visually stimulated. Other receptive field parameters such as orientation preference did not change. No significant cross-correlation developed between neurons that did not correlate before conditioning either because of a large spatial separation or a large difference in orientation preference. These data indicate that the observed modifications occurred within the existing framework of intrinsic long-range connections and are probably based on changes in synaptic efficacy initiated by phenomena such as long-term potentiation (LTP) or long-term depression (see page 415).

LONG-TERM CHANGES OF RECEPTIVE FIELDS AND CORTICAL MAPS

First evidence for adult cortical plasticity came from studies of the somatosensory system by Merzenich and colleagues. Cutting the median nerve in a monkey lead to expansion of the representation of surrounding skin surfaces into the regions formerly representing the denervated parts (Merzenich et al., 1983a, 1983b). Thereby, the cortical territory receiving input from the remaining intact skin parts adjacent to the deafferented field was expanded. The representation of some skin surfaces were even shifted to completely new locations. At the same time, the receptive field sizes decreased as if to compensate for the magnification factor of the newly gained representation. Similarly, in the motor cortex, amputation of one digit led to occupation of the initially silenced cortical region by inputs from adjacent digits (Merzenich et al., 1984).

Further experiments demonstrated that representational plasticity did not necessarily require amputation. Artificially fusing two independent fingers (syndactyly) so that they could only be used together caused the border of representations to smear. In addition, responses to movements of either digit could be elicited in both of the formerly strictly separated cortical representations (Clark et al., 1988). When adult owl monkeys were trained to use a particular digit repetitively for a behavioral task that was repeated several thousand times, the cortical representation of that digit expanded at the cost of the other, less often used digits (Jenkins et al., 1990). Thus, practice alone was sufficient to enlarge the region of cortex containing neurons that were activated during the repetitive behavioral task. This emphasizes the highly dynamic nature of cortical representations, even in the adult brain. Moreover, the observations indicate that perceptual processes themselves must be based on and supported by dynamic neuronal circuitries. In summary, basic features of somatosensory and motor cortical maps, such as receptive field sizes, representation of skin surfaces, and the boundaries between different submodalities, are dynamically maintained throughout life in a use-dependent way.

In the visual system of cats, adult plasticity was first observed in the lateral geniculate nucleus (LGN). Receptive fields of neurons located in the part of an LGN-layer corresponding to a monocular retinal lesion were displaced compared to the normal topography in the other (intact eye's) layer (Eysel et al., 1980, 1981). About a month or more after lesioning, the silenced geniculate cells shifted their receptive field center up to 5° of visual field angle into the immediate surround of the retinal lesion, depending on the eccentricity of the lesion. Excitatory spread within the retina from intact to lesioned areas was histologically excluded. The visual cortex as the origin of a new input via corticofugal connections could also be discarded on the basis of latency measurements and the nature of the responses. However, the optic tract fibers displayed considerable overlap within a LGN layer. Therefore, the lateral spread of activity accounting for the changes was assumed to result from intralaminar reorganization within the LGN. As a possible mechanism, an unmasking of previously ineffective excitatory inputs and/or intralaminar collateral sprouting was considered (Eysel et al., 1980).

It is now well established that representations in the primary visual cortex can also be reorganized reversibly as well as permanently after visual conditioning, restricted deafferentiation, or electrical stimulation. Visual cortical map reorganization was first demonstrated after retinal lesions in both monkey V1 and cat area 17. When V1/area 17 neurons were deprived of all their normal feedforward input by binocular lesions affecting corresponding retinal loci, they acquired new (or modified) receptive fields driven by inputs from intact retinal regions surrounding the lesions (cat: Kaas et al., 1990; Gilbert and Wiesel, 1992; Chino et al., 1992, 1995; Darian-Smith and Gilbert, 1995; monkey: Heinen and Skavenski, 1991; for review, see Kaas, 1991; Buonomano and Merzenich, 1998; Gilbert, 1998). Other reports demonstrated that reorganization also occurs after monocular lesions, indicating that both eyes are capable of inducing cortical plasticity independently

(Schmid et al., 1996; Calford et al., 1999). Rearranged fields typically appeared at the edge of the scotoma.

In the primary visual cortex of cats, substantial reorganization on a small spatial scale occurred within hours after the lesions (Chino et al., 1992; Gilbert and Wiesel, 1992), similar to observations in the somatosensory system (Calford and Tweedale, 1988; Kaas, 1991; Kelahan and Doetsch, 1984; Merzenich et al., 1983a, 1983b; Wall and Cusick, 1984), whereby receptive fields adjacent to the lesion boundary increased in size and shifted their location, but neuronal responses were sluggish and fatigued easily (Darian-Smith and Gilbert, 1995). After longer recovery periods of more than 2 to 3 months, between about 50% (Heinen and Skavenski, 1991) and 100% of all neurons located in an initially silenced cortical region (measuring up to 6–10 mm in diameter) acquired new receptive fields if the retinal lesion covered a visual field angle smaller than 5° (Chino et al., 1995; Darian-Smith and Gilbert, 1995). In the long run, orientation and direction selectivity recovered to normal levels, but maximal response amplitudes and contrast thresholds (= responsiveness) remained reduced (Chino et al., 1995). In addition, recovered receptive fields were sometimes larger and less defined (Heinen and Skavenski, 1991; Gilbert and Wiesel, 1992).

As originally shown in monkey and human motor cortex (Clark et al., 1988; Jenkins et al., 1990; Karni et al., 1995), representational plasticity in the visual system can also be produced by long-lasting activity changes without peripheral (retinal) lesions. Sugita (1996) fitted adult monkeys with prisms reversing the visual field. After a few months, neurons in the primary visual cortex developed novel receptive fields in the ipsilateral hemifield that normally only activates neurons in the contralateral cortex. These results indicated that (1) visual cortical neurons can acquire new inputs from distant areas (probably involving callosal connections) as well as from neighboring retinal areas and (2) visual input changes—not necessarily lesions—are sufficient to induce rearrangements in the visual field map.

WHERE DOES REORGANIZATION TAKE PLACE?

One of the most interesting questions resulting from these studies is: Where in the brain does reorganization take place? In the case of retinal lesions that cover all layers including the ganglion cell layer, a modification at the retinal level is unlikely to contribute to large-scale cortical rearrangements. There is limited evidence for a contribution of thalamic nuclei and spreading corticothalamic connections to cortical reorganization in the adult somatosensory and motor system (Rasmusson and Nance, 1986; Wells and Tripp, 1987; Garraghty and Kaas, 1991). After ligating the ulnar and median nerve in a squirrel monkey, Garraghty and Kaas (1991) observed a reorganization in the ventrobasal complex of the thalamus corresponding to the cortical changes. On the other hand, a more recent study demonstrated that a large part of thalamic plasticity in the somatosensory system is cortically mediated (Krupa et al., 1999; for a review see Kaas, 1999). In the "visual" thalamus, the lateral geniculate nucleus, the actual scotoma remained silent even months after the

retinal lesion and thus at a time at which cortical reorganization was already completed (Gilbert and Wiesel, 1992; Darian-Smith and Gilbert, 1995). Anatomical analysis demonstrated that the thalamocortical afferents did not sprout into the cortical scotoma (Darian-Smith and Gilbert, 1995). Because the physical extension of geniculate arbors within the cortex is in the range of 1 to 3 mm (Humphrey et al., 1985), these arbors may account for short-term changes, which are in the range of 3 mm (Chino et al., 1992). Although the lateral geniculate nucleus itself exhibits a limited increase of its lateral excitatory spread in response to removal of visual input (up to 250 μm beyond normal; Eysel et al., 1980), this fact alone cannot explain cortical changes observed after long-term deafferentiation.

Neurons in the cortical scotoma can display new receptive fields separated by 6 to 10 mm in cortical distance from their original position (Kaas et al., 1990, Gilbert and Wiesel, 1992; Darian-Smith and Gilbert, 1995). Deafferentiating the upper limb in a monkey also led to cortical reorganization over more than 10 mm (Pons et al., 1991). The only known system that could mediate these large-scale modifications are the long-range intracortical connections (Gilbert and Wiesel, 1979, 1989, Luhmann et al., 1991; Katz and Callaway, 1992; Kisvárday et al., 1992, 1997; Galuske and Singer, 1996; for review see Löwel and Singer, 2000). Some of the characteristics displayed by reorganized receptive fields match features of the functional layout of these connections. Two remote parts of one receptive field that were separated by 10° of visual field angle by the scotoma displayed the same orientation and spatial frequency tuning (Chino et al., 1995). Similar observation were made by Das and Gilbert (1995b) using optical imaging of intrinsic signals to determine long-term adaptive changes after retinal lesions. The area of cortex that remained silent in the optical images immediately after the lesion recovered after 5 months. At that time, receptive fields of the neurons in the initially silenced area had shifted their receptive fields to outside the scotoma, but the orientation preference map within the cortical scotoma resembled the map recorded before lesioning the retina. Because neurons in this part of the cortical map do not receive feed-forward input (input from the retina), the recorded responses must be mediated by cortical inputs. The pattern of reorganization reflecting the extent and specificity of long-range horizontal connections suggests that they are the neuronal substrate of the plastic modifications. It cannot be excluded that feedback connections also take part in the reorganization of primary visual cortex; however, the observations that (1) most of the reorganized neuronal responses, although sluggish, were typical for V1 receptive fields and (2) feed-forward input to higher cortical areas is silenced at topographical locations corresponding to the scotoma site make this possibility rather unlikely.

SHORT-TERM CELLULAR MECHANISMS AND LONG-TERM REARRANGEMENTS OF LONG-RANGE INTRINSIC CONNECTIONS

Short-term plastic changes may be triggered by dynamic adjustments of excitation and inhibition and are most probably achieved by rapid modulations of the

effectiveness of preexisting connections, whereby subthreshold excitatory inputs may become suprathreshold by either suppressing inhibitory or potentiating excitatory connections (Chino et al., 1992; Gilbert and Wiesel, 1992). The efficacy of existing synapses can be strengthened by mechanisms such as LTP in a use-dependent manner according to Hebbian rules (Hebb, 1949). On a longer time scale, new synapses can be formed, thereby establishing entirely new connections.

Immediately after a retinal lesion, excitability in a local region surrounding the cortical scotoma was increased (Eysel et al., 1999b), whereas an imbalance between excitation and inhibition was observed 2 weeks later (Rosier et al., 1995; Arckens et al., 1997). These rather acute changes disappeared after longer postlesion periods. Cortical lesions evoke qualitatively similar rearrangements in the cortical region outside the lesion as peripheral deafferentiation (Eysel and Schweigart, 1999). Specifically, NMDA receptor-mediated excitatory postsynaptic potentials, known to be involved in synaptic plasticity, were increased in the region surrounding the scotoma (Mittmann et al., 1994). LTP involving NMDA receptors has been demonstrated in visual cortical slices of both cats (Hirsch and Gilbert, 1993) and rats (Artola and Singer, 1987; Artola et al., 1990; Kirkwood and Bear, 1994).

A number of findings link the phenomenon of synaptic plasticity at the cellular level with that of topographical reorganization at the cortical map level. In cat visual cortex, a variety of conditioning paradigms (pairing protocols) demonstrated that use-dependent synaptic changes can be elicited in vivo. The orientation selectivity of visual cortical neurons was shifted by pairing the presentation of oriented bars with either iontophoretically applied currents (Frégnac et al., 1988, 1992), direct glutamate application (Greuel et al., 1988), or, more recently, with electrical stimulation of the reticular formation (Galuske et al., 1997). Moreover, coupling strength measured as the cross-correlation peak between neurons with nonoverlapping receptive fields was also enhanced by pairing visual stimulation with electrical stimulation of the reticular formation, which is known to increase cortical acetylcholine levels and facilitate use-dependent synaptic gain changes (Herculano-Houzel et al., 1999). Modifications of orientation preference maps in adult cats were induced by pairing the presentation of oriented wholefield gratings with reticular stimulation (Galuske et al., 1997). Within hours, isoorientation domains preferring the conditioned orientation expanded at the cost of nonconditioned domains, whereas conditioning without pairing induced only large-scale habituation. Similar changes in orientation maps were observed after intracortical microstimulation (Godde and Dinse, 1998, 1999). Although, the majority of these changes were within the range of the local connectivity, the involved mechanisms might also apply for long-range synaptic gain changes.

One possibility to translate short-term synaptic gain changes into long-term alterations of cortical topography is the outgrowth of new connections, a characteristic phenomenon of early postnatal development (for review see Schmidt et al., 1999; Löwel and Singer, 2000). As early as 1960, experiments in adult rabbits demonstrated the ingrowth of horizontal fibers into destroyed cortical laminae

that were devoid of surviving cells (Rose et al., 1960). More than 30 years later, morphological changes of long-range intrinsic connections were demonstrated in adult cats by using extracellular biocytin injections into cortex just outside the boundary of the original cortical scotoma induced by binocular retinal lesions. The comparison of the density of lateral projections into reorganized and nondeprived visual cortex revealed that axon collaterals from cortical neurons surrounding the visual cortical scotoma predominantly branched into the deprived as opposed to the normal cortical area (Darian-Smith and Gilbert, 1994, 1995). Axon fibers were 57–88% denser within reorganized than within normal cortex. The increase in connectivity was accompanied by a reduced bouton density per single axon in the reorganized region. Because the newly grown fibers did not extend beyond 4 mm, it was concluded that reorganization is mediated by modifications in the preexisting framework of long-range intrinsic connections rather than by an extension of fibers beyond their normal level (Darian-Smith and Gilbert, 1994). Similarly, functional reorganization in the rat motor cortex was mediated and constrained by the given layout of intrinsic connectivity (Huntley, 1997). However, a recent study in the somatosensory system indicated that sprouting may occur beyond the framework of pre-existing connections. By analyzing the distributions of thalamic and cortical connections in macaque monkeys with long-standing accidental trauma to a forelimb, it was shown that thalamocortical projections were relatively normal, whereas connections in the somatosensory cortex (area 3b and 1) were markedly more widespread than in normal animals (Florence et al., 1998).

Thus outgrowth of new connections, previously thought to be restricted to so-called "critical periods" in early life, also occurs in the adult brain and most probably mediates long-term long-range representational plasticity in the cortex.

CONCLUSIONS

1. The majority of long-range intrinsic connections of excitatory cortical neurons in the primary visual cortex of cats link neurons with similar response properties (e.g., orientation preference and possibly also direction preference) according to the rule: "like connects to like."
2. There is extensive cross-talk between different orientation domains.
3. There are clear differences in the layout of long-range excitatory and inhibitory connections.
4. The selectivity of the long-range connections may depend on the relative position of a neuron within a functional map (e.g., projections extending from pinwheel centers are less orientation selective than projections originating from linear zones of an orientation preference map).
5. Both the selectivity and maximal lateral extent of long-range connections depend on the layer (layer IV connections are probably less orientation-selective than supragranular and infragranular projections and much shorter, about 50%, than layer III connections).

6. It may well be that the functional specificity of long-range intrinsic connections depends on a variety of functional properties, of which only a minority have been analyzed to date.
7. Many different functions have been ascribed to long-range intrinsic connections. In particular, there is growing evidence that they are important for perceptual integration.

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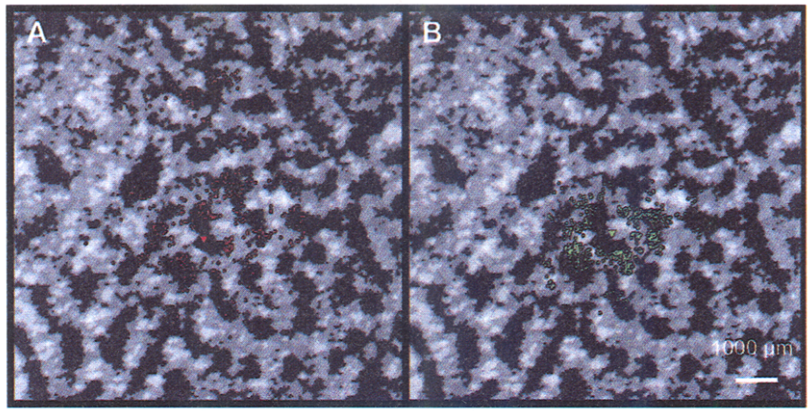

FIGURE 10-5. Superposition of retrogradely labeled neurons and 2-DG labeled horizontal orientation columns in cat primary visual cortex. **(A)** An injection of red microspheres was made into a column preferring horizontal contours. Of the labeled neurons, 54.6% (n = 414) are localized in iso-orientation domains. **(B)** Cell distribution after an injection of green microspheres in a column preferring vertical contours. Only 22% of the labeled neurons (n = 360) are localized in the 2-DG labeled horizontal orientation domains. (From Schmidt, Kim, Singer, Bonhoeffer and Löwel, 1997, *Journal of Neuroscience* 17, p5480–5492, copyright 1997 by the Society for Neuroscience.)

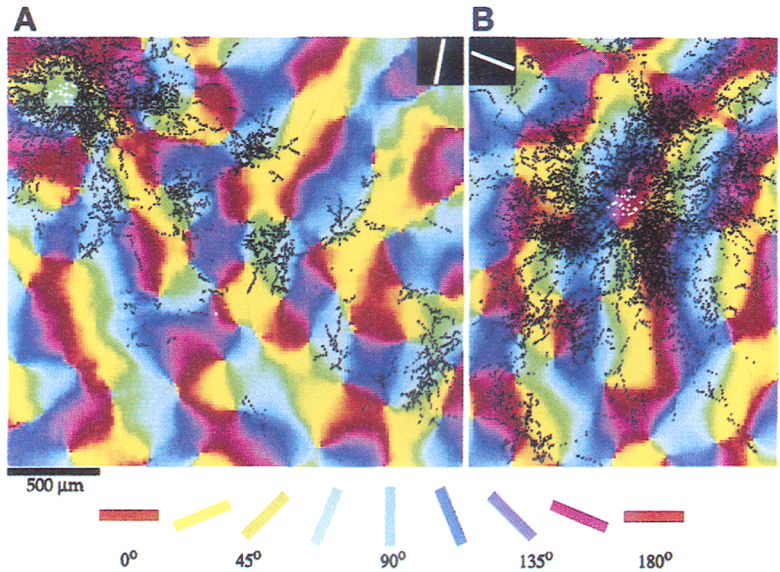

FIGURE 10-6. Topographic relationship between long-range intrinsic connections and iso-orientation domains in tree shrew primary visual cortex. The functional architecture of the cortex was visualized using optical imaging of intrinsic signals. In these maps, the preferred orientation for every region of the imaged cortex is color-coded according to the scheme below the figure (e.g., red codes for 0° and blue codes for 90° orientation preference). Biocytin was injected extracellulary into a domain preferring contours of 80° (light blue) **(A)** or 160° (red) **(B).** Both retrogradely labeled neurons (white symbols) and anterogradely labeled boutons (black dots) are superimposed with the optically recorded orientation preference map. Near the injection site, labeled boutons are found at sites with all orientation preferences, whereas at longer distances, boutons are located preferentially at sites preferring the same orientation as the injection site. (From Bosking, Zhang, Schofield and Fitzpatrick, 1997, *Journal of Neuroscience* 17, p2112–2127, copyright 1997 by the Society for Neuroscience.)

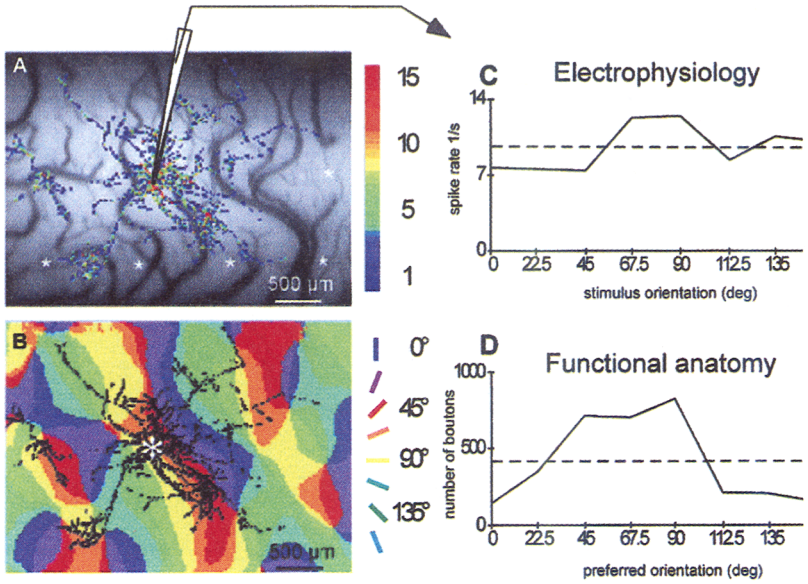

FIGURE 10-7. Relationship between a neuron's axonal projections, its receptive field properties, and the functional map in which the neuron is embedded. **(A)** Superposition of a density map of all axon terminals (colored dots) of a biocytin-filled pyramidal neuron with the vascular image containing five reference penetrations (white stars). Color scheme indicates the number of terminals per image-pixel. **(B)** Superposition of the bouton distribution (shown in black) with the optically visualized orientation map. The preferred orientation for every region of the imaged cortex is color-coded according to the scheme on the right side of the figure. Panels **(C)** and **(D)** provide a quantitative comparison between the electrophysiologically measured orientation tuning of the neuron **(C)** and the orientation distribution of all labeled boutons **(D).** (Modified from *Brain Research Protocols,* 3, Buzás, Eysel, and Kisvárday, Functional topography of single cortical cells: an intracellular approach combined with optical imaging, p. 199–208, copyright 1998, with permission from Elsevier Science.)

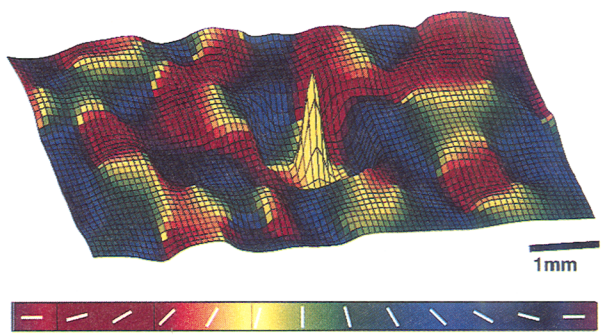

FIGURE 12-7. Connectivity of cortical circuitry in the model. The color map represents the orientation preference of each cortical mini column. The pattern of intracortical connections to cells in the central (Yellow) mini-column is represented by the surface amplitude, which codes the net (Σ Excit – Σ Inhib) strength of intracortical connections from each column to the cells of the central column. Three classes of intracortical connections are included in the model: short-range excitatory, short-range inhibitory, and long-range excitatory. Short-range connections are densest in the vicinity of the presynaptic cells and fall off with distance. Short-range excitatory connections are more numerous, but more spatially restricted than short-range inhibitory connections. Long-range excitatory connections can span the entire circuit and preferentially target cells with similar orientation biases. All connections target both excitatory and inhibitory neurons.