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NEURONAL CIRCUITS OF THE NEOCORTEX

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■ **Abstract** We explore the extent to which neocortical circuits generalize, i.e., to what extent can neocortical neurons and the circuits they form be considered as canonical? We find that, as has long been suspected by cortical neuroanatomists, the same basic laminar and tangential organization of the excitatory neurons of the neocortex is evident wherever it has been sought. Similarly, the inhibitory neurons show characteristic morphology and patterns of connections throughout the neocortex. We offer a simple model of cortical processing that is consistent with the major features of cortical circuits: The superficial layer neurons within local patches of cortex, and within areas, cooperate to explore all possible interpretations of different cortical input and cooperatively select an interpretation consistent with their various cortical and subcortical inputs.

INTRODUCTION

The enormous strides made in understanding the formation and operation of the neocortical circuits have been matched by the detailed analyses of the cellular and synaptic physiology of the elements that make up the neocortical circuits. Rapid advances in theory have also begun to clarify the nature of the computations carried out by the neocortical microcircuits. There are now many different models of cortical circuits, based on experimental data or theoretical considerations. Perhaps unsurprisingly, given their different explanatory and descriptive purposes, these model circuits differ greatly in form and content. For historical reasons, most biologically defensible circuits rely heavily on data from cat and primate visual cortex, but cell types and patterns of connections have also been described in many other cortical areas, with the contribution from rodent somatosensory cortex being perhaps the most prominent in recent years.

Here we explore to what extent the neocortical circuits discovered in primary sensory areas generalize, i.e., to what extent can neocortical neurons and the circuits they form be considered as canonical? A similar question has been applied to every aspect of the vertebrate brain and spinal cord, and it is especially relevant to questions of evolution, development, and homology of form and function. Most reasonable people would agree that evolution has been conservative, so one is not

surprised to find close similarities in basic organization across vertebrate brains. At another level, one is not surprised to find that the neocortices of different mammals contain recognizably similar cell types (Ramon y Cajal 1911), or that many measures of neocortical anatomy scale with brain size. Even within single brains, there are systematic changes at the microstructural level, for example, from posterior to anterior cortical areas in primate the pyramidal cells increase in size, complexity of dendritic branching, and number of spines (Lund et al. 1993, Elston & Rosa 1998, Elston et al. 1999, Elston 2003). However, it might reasonably be argued that the similarities and regularities are incidental to the many different mappings of input to output that are evident in the different neocortical areas and across species, and that the specific functional requirements of a given area generate an experience-dependent circuit adapted for that requirement. Can general lessons really be learned from the neocortical circuits? The answer we give is an unequivocal yes. It does not require the eye of faith to be struck, as the early anatomists were, by features of the three-dimensional circuits that are common across neocortex.

LAMINATION

Despite its evident idealization, the notion of mammalian neocortex as a six-layered structure is widely accepted and widely used as the reference for describing a wide range of anatomical and physiological data. This is significant because the six layers provide perhaps the only commonly agreed upon framework with which to explore models of cortical circuits. From early on, the lamination has prompted thoughts as to its function. Application of the Golgi-staining technique had shown laminar-specific projections of cortical neurons and presumed afferents (Ramon y Cajal 1911). Based on studies of brains of patients and experimental material from animals, Campbell & Bolton (Bolton 1910, Campbell 1905) believed that the superficial cortical layers were principally concerned with "receptive and associative" functions, whereas the deep layers had "corticofugal and commissural" functions. [It was Campbell who studied the detailed histology of the brains of two chimpanzees and an orangutan, whose motor cortices had been mapped electrophysiologically by Grünbaum & Sherrington (1901)]. Although many electrophysiological and degeneration methods had shown that cortical afferents terminated in particular layers and projection pathways had their origins in particular layers, the fine degree of laminar organization of the projection pathways was only fully appreciated with the introduction of retrograde tracers, such as horseradish peroxidase or fast blue. Applied to many cortical areas in different species, these techniques show clearly the detailed laminar specificity of the cells of origin of the efferent fiber systems (e.g., Gilbert & Kelly 1975, Jones & Wise 1977, Lund et al. 1975, Wise 1975). Thus, all the players in the cortical circuitry—afferents, intrinsic neurons, and projection neurons—organize themselves with respect to laminae. Not only that, but rules by which the afferents and efferents organize seem to be

universal for all neocortical areas (Creutzfeldt 1993, Jones 1999, Powell 1973, Powell 1981).

Unlike cortical structures, such as hippocampus or cerebellum, neocortex has its "crowning mystery," layer 1 (Hubel 1982), which consists mostly of the distal tufts of pyramidal cell apical dendrites, a sprinkling of GABAergic neurons, and many axon terminations. This layer is one major target of "feedback" connections between cortical areas and also receives input from subcortical nuclei. Why this layer has specialized for the connection between distal dendrites and cortical and subcortical inputs is one of its mysteries, but the existence of layer 1 points to a general purpose of cortical lamination, which is to generate a scaffold that constrains the way in which neurons can connect. This principle alone may be the reason why the brain makes such extensive use of cortical structures. A corollary of this is that cortical structures may allow neurons to connect with each other with the minimum use of wire (Chklovskii et al. 2002, Mead 1990, Mitchison 1991). Mitchison has shown theoretically that if there were but one cortical area instead of hundreds, the volume of cortex required to form the same circuits would be an order of magnitude larger (Mitchison 1991, Mitchison 1992).

If lamination is to be the means of defining the cortical circuits, then the axons of cortical afferents and neurons must not distribute randomly through the layers, but must show biases, preferably strong biases, for particular laminae. Vertical asymmetries in the dendrites can add a further degree of specificity. The laminar preferences of axons and dendrites were exploited in most early models of cortical circuits, which were based on the premise that where dendrites and axons overlap, there must be synaptic connections between them. Ramon y Cajal's solutions of the circuits of laminated structures, such as the retina, cerebellar cortex, hippocampus, and olfactory bulb, recommends this assumption. However, applied to the cortex, this method was evidently hindered by the plethora of different cell types found in cortex, which formed "impenetrable thickets" (Ramon y Cajal 1937) of connections. Thus, even in the neoclassical era of Golgi studies of neocortex, few attempts were made to use the data to develop circuits. One exception was Szentágothai (Szentágothai 1978) who produced several axonometric drawings of the cortical column showing the connections between different cell types inferred from data from electron microscopy and Golgi-stained material.

EXCITATORY CIRCUITS

Fundamental Intrinsic Circuits

Gilbert & Wiesel provided one of the first functional interpretations of a defined anatomical circuit (Gilbert 1983, Gilbert & Wiesel 1983) based on their intracellular recordings and reconstructions of individual cells filled with horseradish peroxidase (HRP) in cat visual cortex. The completeness of the axons revealed with intracellular injections of HRP was a revelation for eyes used to the immature or incomplete adult structures offered by the Golgi-stains. Here the laminar

preferences of the axons of different types of neurons were revealed unambiguously. By using the simple rule that axons connected to neurons whose somata were located in the layer to which the axons project, Gilbert & Wiesel developed a simple circuit for cat area 17 (V1) that was consistent with the hypothetical circuits developed by Hubel & Wiesel (Hubel & Wiesel 1962) two decades earlier on the basis of receptive field structures. Obviously, Gilbert & Wiesel's simplification is not strictly correct: If instead of taking the target neurons to be a point, the full dendritic tree of the target neuron is considered, the spatially separated apical and basal dendrites come into play as extended connecting elements and more elaborate circuits are generated. However, because the basal dendrites radiating from the cell body form about 90% of the dendritic length of any cortical pyramidal neuron (Larkman 1991), statistically at least, their circuit shows the majority view.

In Gilbert & Wiesel's circuit (see Figures 1 and 2), the thalamic input arrives in layer 4. The excitatory cells in layer 4 project to the superficial layers. The superficial pyramidal neurons project to layer 5, which in turn projects to layer 6, and the loop is closed by a projection from layer 6 to the input layer 4. This was a landmark achievement that has yet to be matched for any other cortical area.

The other great simplification offered by the Gilbert & Wiesel circuit is that it inferred only the connections of the spiny, excitatory neurons, thus eliminating at a stroke the complications offered by the different types of smooth neurons. The spiny neurons as a class provide most of the inter-laminar connections within a cortical area, whereas the axons of smooth neurons principally arborize locally within their layer of origin. Overall, the spiny cells provide the basic framework of long-distance excitation in both the vertical and lateral dimensions, which is then moulded by local inhibitory neurons.

Their excitatory circuit for the cat now has to be modified by the addition of several pyramidal cell types in the deep layers (see Figure 1). A class of layer 5A pyramidal cells project to the superficial cortical layers, as shown by Lund et al. in their Golgi study (Lund et al. 1979) and confirmed by intracellular injections of HRP (Martin & Whitteridge 1984). Other modifications include a class of layer 6 pyramidal cells that project principally to layer 3 (Hirsch et al. 1998), as in the tree shrew striate cortex (Usrey & Fitzpatrick 1996), and a class of layer 6 pyramidal cells that project within layer 6 (Katz 1987). Many elements of this same basic cat pattern of excitatory circuits have been identified in area 17 of macaque monkey (Anderson et al. 1993, Blasdel et al. 1985, Callaway 1998, Fisken et al. 1975, Fitzpatrick et al. 1985, Lund et al. 1979). This same pattern is repeated in other primate cortical areas, for example, auditory cortex (Ojima et al. 1991, Ojima et al. 1992) and motor cortex (Ghosh et al. 1988, Ghosh & Porter 1988, Huntley & Jones 1991).

Data regarding the pattern of inter-laminar projections of the rodent barrel cortex is more limited than in the cat, tree shrew, or monkey visual cortex. Nonetheless, the basic pattern of projections of the spiny neurons in the barrel cortex follows that of the cat and monkey visual cortex (Bernardo et al. 1990a,b; Chapin et al. 1987; Hoeflinger et al. 1995; Gottlieb & Keller 1997; Schubert et al. 2003; Zhang

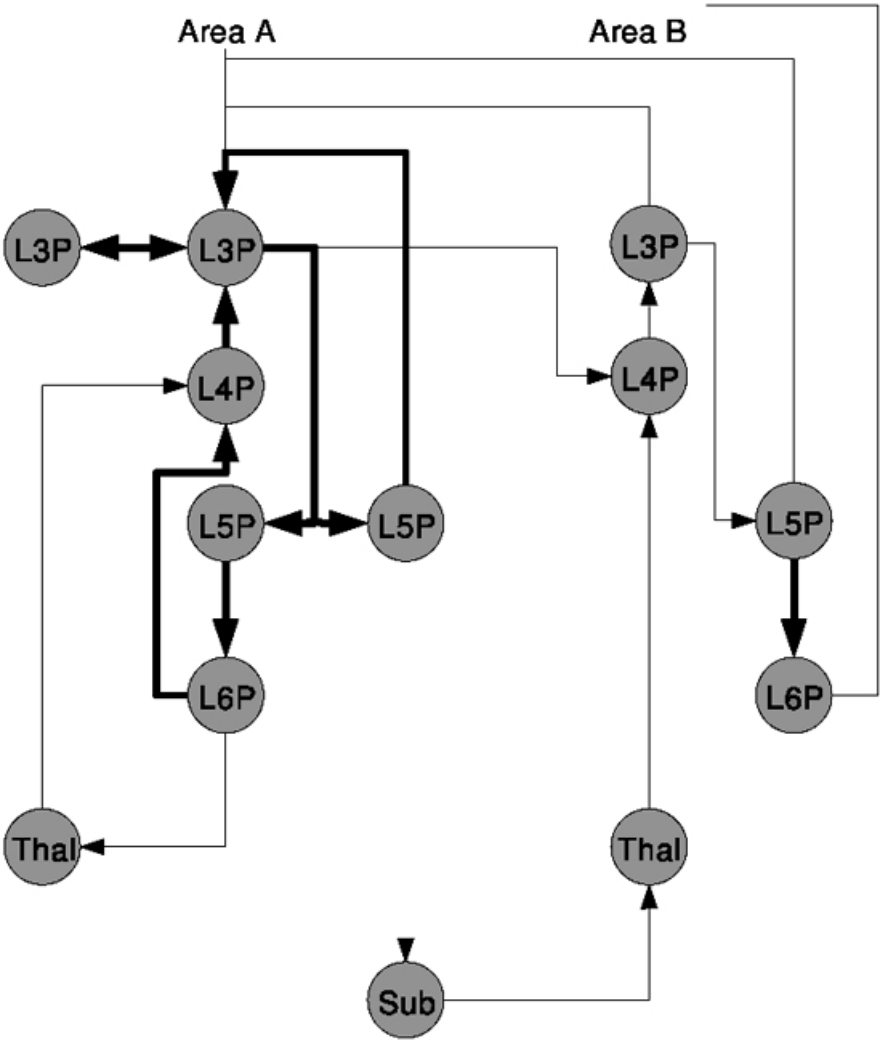


Figure 1 Graph of the dominant interactions between significant excitatory cell types in neocortex and their subcortical relations. The nodes of the graph are organized spatially; vertical corresponds to the layers of cortex and horizontal to its lateral extent. Directed edges (*arrows*) indicate the direction of excitatory action. Thick edges indicate the relations between excitatory neurons in a local patch of neocortex, which are essentially those described originally by Gilbert & Wiesel (Gilbert & Wiesel 1983, Gilbert 1983) for visual cortex. Thin edges indicate excitatory connections to and from subcortical structures and inter-areal connections. Each node is labeled for its cell type. For cortical cells, *Lx* refers to the layer in which its soma is located. *P* indicates that it is an excitatory neuron (generally of pyramidal morphology). *Thal* denotes the thalamus and *Sub* denotes other subcortical structures, such as the basal ganglia.

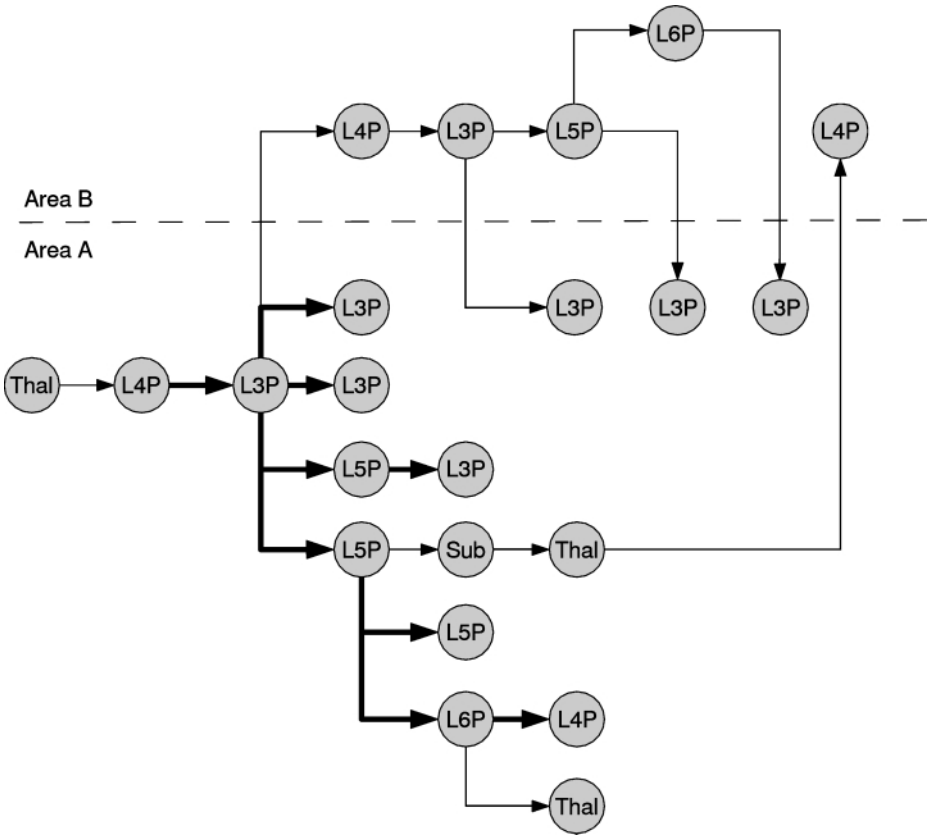


Figure 2 Graph of the temporal interactions between the cell types shown in Figure 1. Time unfolds toward the right. Each edge represents one synaptic delay. A temporal path ends when it is no longer unique; that is, further possible paths from that end node can be traced by selecting other nodes in the graph of the same cell type. For additional description, see Figure 1.

& Deschenes 1997). The one interesting variant on the vertical circuit seen in cat and monkey visual cortex is a projection from layer 6 to the upper tier of layer 5 of barrel cortex (Zhang & Deschenes 1997).

Matching of Thalamic and Layer 6 Pyramidal Arborizations

The tree shrew has been an invaluable model system for studying the intrinsic excitatory connections in neocortex. Fitzpatrick (1996) has noted that the stratification of intrinsic axonal arbors in the tree shrew visual cortex reflects the organization of parallel functional streams and that in the tree shrew it seems to do so more

emphatically than in most species. Thus, the intrinsic interlaminar connections match with an exquisite sublamination the different afferent and efferent projections and their functional properties (e.g., magno-, parvo-, and koniocellular thalamic inputs; On and Off pathways; and binocular and monocular). Matching these stratified patterns of thalamic afferent input to the middle layers are the stratified arbors of the axons of subtypes of the layer 6 pyramidal cells, most of which form axonal arborizations into the middle layers. Outside layer 4 and 6, the tree shrew also shows an interesting sublamination. The interlaminar projection from upper layer 3 pyramidal cells is to lower layer 5, whereas the pyramidal cells in the lower part of layer 3 arborize in the upper tier of layer 5 (Fitzpatrick 1996, Fitzpatrick & Raczkowski 1990, Muly & Fitzpatrick 1992, Usrey et al. 1992, Usrey & Fitzpatrick 1996).

The variants in the pattern of thalamic afferent input and the matching variants in the axonal arborizations of the layer 6 pyramidal cells seen in the tree shrew are also present in macaque monkey area 17. There are stratified patterns of arborizations formed by the pyramidal cells of layer 6, which, as in the tree shrew, follow the pattern of afferent input stratification. In all, eight different subtypes of layer 6 pyramidal cells have been distinguished in the macaque monkey area 17 (Briggs & Callaway 2001). Two of the subtypes, called class I, have axons that arborize mainly in layer 6. The other six subtypes, called class II, have axons arborizing in various subdivisions of layer 4 (Wiser & Callaway 1996). In both classes, the apical dendrite formed more side branches in the same layer as the axonal arborization. Despite their apparent diversity, these eight subtypes of layer 6 pyramidal cells are only variations on the same two morphological themes seen in other species.

In the cat visual cortex (Katz 1987) and rat barrel cortex (Zhang & Deschenes 1997), layer 6 pyramidal cells form two basic types: One forms an axonal arbor in the middle layers, principally layer 4. In the cat, many of this type project back to the lateral geniculate nucleus. The other has a laterally extending axon that aborizes in layers 5 and 6. In the cat, these cells also project to the claustrum. The output of layer 6 is also expressed in the position of the cell somata. In monkey area 17, the pyramidal cells that project back to the magnocellular layers of the lateral geniculate nucleus (LGN) are located in the lower part of layer 6, whereas the pyramidal cells that project to the parvocellular layers of the LGN tend to be concentrated in the upper parts of layer 6, with some also in the lower tier. Pyramidal cells whose somata form the middle of layer 6 do not project to the LGN (Fitzpatrick et al. 1994). In the rat somatosensory cortex, the pyramidal cells that project to the ventral posteromedial nucleus (VPm) alone are concentrated in the upper part of the lamina, whereas those that project to VPm and the posterior group (Po) are concentrated lower in the lamina. Layer 6 pyramidal neurons that project to other cortical regions are found in far larger numbers in the rat than in cat or monkey area 17, and they are distributed through the lamina (Zhang & Deschenes 1997).

The examples of the macaque monkey and the tree shrew indicate an elaboration of the somewhat simpler patterns seen in ferret, rat, or cat. The elaboration seems

to correlate best with an increased segregation in some input stream, although this may not be the sole reason for the differences between primate and tree shrew on one hand, and ferret, cat, and rat on the other. One desirable consequence of the increased stratification or sublamination is that it allows a higher selectivity in both the inputs that a particular neuron receives and ipso facto, a greater diversity of what is passed on to other brain regions (see the related argument of Malach below).

However, we should emphasize again that the differences seen between cat and monkey, for example, are like the differences between a grandfather clock and a Swiss chronometer. If more precision is required for functional streaming, or if the outputs need to be diversified, then Nature's solution has not been to build entirely different circuits, but rather to focus axonal and dendritic arbors into a sublamina and duplicate or triplicate the same basic pattern of interlaminar excitatory connections.

Static Connectivity

While it is a modest achievement to construct a simple diagram of the basic interlaminar connections, constructing a circuit based on a quantitative assessment of the numbers of neuronal types and their synaptic connections is much more difficult. Missing from the literature are quantitative estimates of the proportion of synapses any given class of spiny neurons contributes to a particular lamina. This missing factor makes the interpretation of connections on the basis of functional assays especially difficult. For example, in the cat, layer 5 pyramidal cells and layer 4 spiny stellate cells can both be activated monosynaptically by electrically stimulating the Y-type thalamic afferents, which form arbors principally in layer 4 with an additional collateral projection to layer 6 (Bullier & Henry 1979, Martin & Whitteridge 1984). It seems likely from simple geometric considerations that many more Y-type synapses are formed with the spiny stellate dendrites than on the layer 5 pyramidal neurons (Freund et al. 1985), which have only a short segment of their apical dendrite in the zone of thalamic termination. Yet the relative difference in connection strength is not differentiated by a simple electrical stimulus.

Callaway's study with caged glutamate in the rat (Callaway 2002) shows that glutamate stimulation apparently does reveal stronger or weaker projections. For example, glutamate stimulation of layer 4 provides more activation in layer 3 than it does in layer 5. This may indicate that there are numerically many more layer 4 neurons than layer 5 neurons projecting to layer 3. Alternatively, the results may indicate that uncaging glutamate in layer 4 activates both layer 5 neurons (e.g., via their apical dendrites) and layer 4 neurons, so that the net excitatory effect on layer 3 pyramidal cells is the sum of layer 4 and 5 effects.

Another interpretation for differences in strengths of the activation is that different types of excitatory neurons engage in two distinctly different operations, one being a driving function, the other modulating. The proposal for two basic excitatory connections, termed drivers and modulators, has come from a

consideration of the long-distance synaptic projections from cortex to thalamus (Crick & Koch 1998, Sherman & Guillery 1996). The driving inputs are defined by their ability to affect the qualitative aspects of the receptive field. For example the center-surround organization of dLGN neurons is given by driving retino-thalamic inputs. The modulating inputs, however, alter the quantitative aspects of the response of their target neurons, not the qualitative structure of the receptive field. They (Crick & Koch 1998, Sherman & Guillery 1996) also propose that there are direct morphological correlates of the two functional types. The axons of the drivers form terminals with thick branches and grape-like clusters of large boutons and usually originate from layer 5 pyramidal cells, whereas the modulators form thin axons with tiny terminal boutons protruding from the main branch and usually originate from layer 6 pyramidal cells. According to Sherman & Guillery these two types of corticothalamic boutons are likely to occur in all thalamic nuclei, indicating that they form part of a stereotyped output from neocortex (Sherman & Guillery 2001). The driving projections to thalamus would thus provide a significant alternative path for inter-areal communication. It should also be noted, however, that the same two morphological types are also seen in the direct inter-areal projections in the primate visual cortex (Rockland 1996), but their possible functional roles remain unexplored.

The pattern of activation following the uncaging of glutamate indicates that the target layers that are maximally activated are largely those expected from the laminar pattern of connections. The one major anomaly is the lack of strong activation of layer 3 pyramidal cells from their neighbors, but this is simply explained by the difficulty of preventing the artifact of direct activation of the recorded neuron by nearby photo-stimulation. Thus the functional maps derived from the glutamate uncaging do not accurately reflect the extent of the contribution of neighboring neurons.

What has yet to be established is whether the varying strengths of the activation patterns revealed by methods such as photo-stimulation quantitatively reflect the anatomy or whether there are other factors, such as those suggested by Sherman & Guillery, that are crucial to understanding the basic functional interactions between the components of the circuits. If the numerically superior projections predominate in the responses evoked by electrical stimulation or uncaging glutamate, then it is clear that our understanding of the physical connections needs to be leavened with our knowledge of the functional consequences of the projection. It seems clear already that numerically small projections need not necessarily reflect functional impotence. On the contrary, it is the numerically small projections, such as the thalamic afferents or afferents from other cortical areas, that are thought to dominate or strongly modulate the response properties of their target areas in many instances. For example, synapses from the lateral geniculate nucleus form less than 10% of the excitatory synapses in layer 4 of area 17 in cats and monkeys (Ahmed et al. 1994, Garey & Powell 1971, Latawiec et al. 2000, Winfield & Powell 1983), yet they clearly provide sufficient excitation to drive the cortex. Similarly, the inter-areal projections also form a few percent of the synapses in their target

layers, yet both the feedforward and feedback inter-areal circuits are thought to be functionally powerful.

There are various explanations for this apparent disparity between functional efficacy and actual numbers of synapses. One possibility is that there are large variations in synaptic strength, so that the thalamic synapses formed with layer 4 neurons, for example, have very strong synapses relative to the 10- or 20-fold more numerous excitatory synapses deriving from cortical neurons. This seems not to be the case: While thalamocortical synapses do appear exceptional in having a very low quantal variance (Bannister et al. 2002, Gil et al. 1999, Stratford et al. 1996, Tarczy-Hornoch et al. 1999), the peak amplitudes of the excitatory postsynaptic potentials (epsp's) are at most a factor of 2 greater than say, spiny stellate excitatory synapses. In fact, across all species, the peak amplitudes of epsp's or inhibitory postsynaptic potentials (ipsp's) evoked by single presynaptic neurons are small, despite a wide variety of target neurons and sites of synapse. One solution to this apparent discrepancy between structure and function is that the relatively small inputs from the thalamus or from inter-areal connections are amplified by recurrent circuits (Douglas et al. 1989). Thus, numerically small inputs with moderate synaptic strengths could, through the actual configuration of the recurrent cortical microcircuits, play a key role. The interpretation of the physical and functional anatomy thus depends crucially on an understanding of configuration of the circuits themselves.

Lateral Connections

INTRA-AREAL It is clear that the interlaminar connections not only have characteristic patterns but that for the most part, the contribution of a particular spiny neuron to the interlaminar connections exceeds that of its intralaminar connections. For example, most layer 5 and layer 6 pyramidal cells connect outside their layer of origin. While some layer 4 spiny neurons do arborize extensively within layer 4, the major projection of layer 4 spiny neurons is to layer 3. It is only in the superficial layers that the pyramidal cells make extensive arborizations within the same layers, so monosynaptic recurrent connections between layer 2 and 3 pyramidal cells are likely to predominate more than in any other layer. It is these intralaminar connections that are of particular interest for our consideration of lateral excitatory connections.

We know more of the pattern of lateral connections of the superficial layer pyramidal cells than for any other layer. Early evidence from retrograde labeling indicated that discrete patches of neurons projected to a single point (e.g., Jones & Wise 1977). Evidence of "patchy" local axonal connections was most clearly seen in reconstructions of individual pyramidal cells filled intracellularly with a label in cat and monkey, or after bulk injections of tracers into the superficial layers in cat (Gilbert & Wiesel 1989, Kisvarday & Eysel 1992, Lowel & Singer 1992); tree shrew (Chisum et al. 2003, Rockland et al. 1982); or monkey somatosensory, motor, and visual areas (Huntley & Jones 1991, Juliano et al. 1990, Levitt et al.

1993, Lund et al. 1993, Malach 1992, Rockland & Lund 1983, Yoshioka et al. 1992), and prefrontal cortex (Kritzer & Goldman-Rakic 1995, Melchitzky et al. 1998, Pucak et al. 1996, Selemon & Goldman-Rakic 1988). Interestingly, similar injections into the rat visual and somatosensory cortex did not generate the same patchy connections (Lund et al. 1993), although Burkhalter & Charles (Burkhalter 1989, Burkhalter & Charles 1990) have described periodicities in the density in layers 2–6 after bulk injections of tracers in rat V1.

The interpretation of the patchy labeling is not straightforward. The tracers commonly used (HRP, biocytin, phaseolus vulgaris lectin, biotinylated dextrose amine) are taken up by cells that project from the injection site and by distant cells that send their axons to the injection site. The result is that the labeled patches are a mix of cells and axons, with some axons belonging to local cells and others coming from neurons at distant sites, including the injection site. One implication of the observation that cells and axons are colocalized is that patches or stripes of the superficial layer neurons, 200–500 microns in diameter or width, make reciprocal connections with each other.

In a comparative study, Lund et al. made similar-sized injections in visual area V1, V2, and V4; somatosensory areas 3b, 1, and 2; motor area 4, and prefrontal cortical areas 9 and 46 (Lund et al. 1993). In all the areas studied, there was a dense central core of labeled axons and cells at the injection site surrounded by fingers of label that separate into isolated patches at the furthest distances from the injection site. Comparing the patterns in the different areas of macaque monkey indicated that layer 3 was the major source of the label, with a lesser contribution from layer 2 neurons. The average size of a patch or stripe and the spacing between them varied from area to area, but a close correlation was found between the patch size and the spacing between them (Figure 3); this was true also for cat and tree shrew visual cortex. For all three species, the inter-patch spacing was roughly double that of the patch diameter in a given area. Injections into area TE in the macaque inferotemporal cortex also showed patches that were larger and less orderly than those seen in area 17 (Fujita 2002, Fujita & Fujita 1996).

Obviously, these lateral connections are not generated without regard to the functional architecture of the particular area in which they are found. Quite what the clusters relate to and how they develop has been a question avidly pursued by experimentalists and theorists alike since the layer 3 patches were first analyzed in tangential sections (Callaway & Katz 1990, Koulakov & Chklovskii 2001, Lowel & Singer 1992, Mitchison & Crick 1982, Rockland et al. 1982, Rockland & Lund 1983, Swindale 1992). In macaque area 17, Livingstone & Hubel (1984) showed that neurons located in the cytochrome oxidase–rich blobs formed reciprocal connections. Similarly, the cytochrome oxidase–poor compartments also formed reciprocal clustered connections. In the macaque monkey, Malach et al. (1993) found that domains with like eye dominance (monocular versus binocular) tend to be linked, as were domains with like orientation preference. The same trend was noted by Yoshioka et al. (1996). In both studies, the intensity of the label tailed off with distance from the injection, suggesting that neurons in neighboring

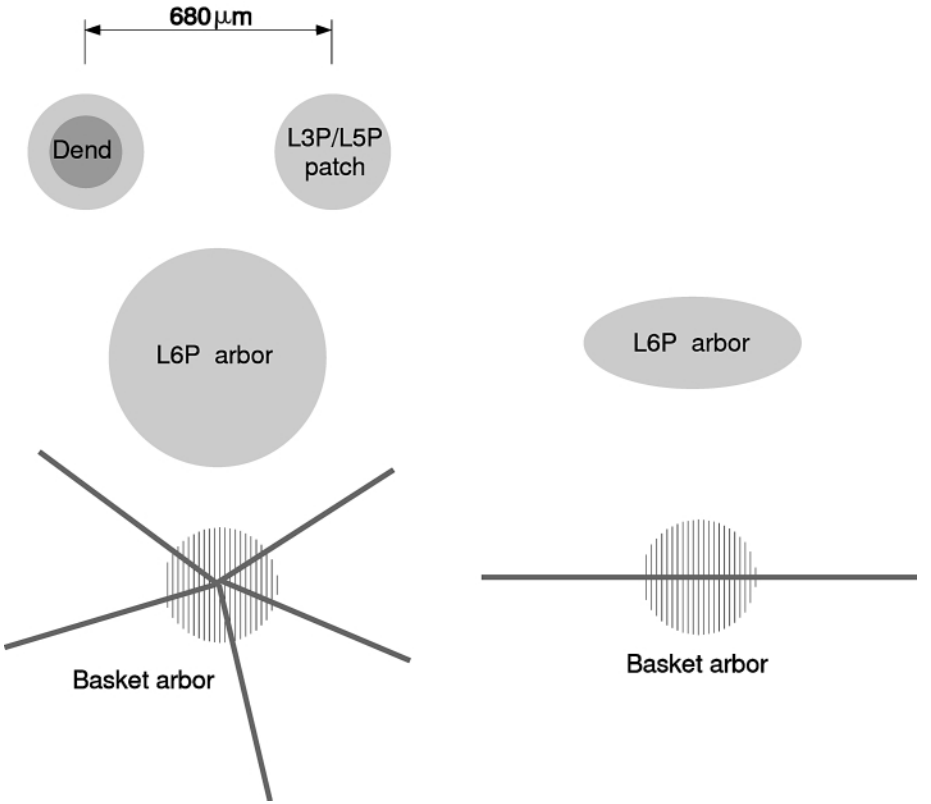


Figure 3 Approximate sizes of some important axonal arborizations, shown in tangential (*left*) and vertical (*right*) sections. Top: Diameter of layer 3 (or layer 5) patches (*light gray disk*, 320 μm diameter), compared with that of the basal dendrites of a layer 3 pyramidal cell (*dark gray disk*, 200 μm diameter). The inter-patch distance is 680 μm. Patch data were averaged over multiple animals and cortical areas (derived from Amir et al. 1993, Blasdel 1992, Burkhalter 1989, Fitzpatrick et al. 1998, Fujita & Fujita 1996, Kaas et al. 1989, Kisvárday et al. 1997, Kisvarday & Eysel 1992, Levitt et al. 1994, Luhmann et al. 1986, Lund et al. 1993, Malach et al. 1997, Rockland et al. 1982, Yoshioka et al. 1992). Middle: Diameter of layer 6 pyramid axonal arborization (*light gray*, 590 μm diameter) in layer 4. (Data derived from Hirsch et al. 1998, Martin & Whitteridge 1984, Usrey & Fitzpatrick 1996, Wiser & Callaway 1996, Zhang & Deschenes 1997.) Bottom: Diameter of perisomatic arborization (*vertical hatched disk*, 280 μm diameter) and approximately 5 long radial branches (*dark gray lines*, 650 μm radius) of large L3 basket cell. (Data estimated from Kawaguchi & Kondo 2002; Kisvárday et al. 1987, 1997, 2002; Somogyi et al. 1983.)

patches are more strongly connected than distant ones. Eye dominance specific connections of layer 3 pyramidal cells are not seen in normal cats, but are seen in strabismic cats (Schmidt et al. 1997, Trachtenberg & Stryker 2001). Like-to-like connections are only seen at some distance from the injections site (400–1000 microns) (Kisvárday et al. 1997, Malach et al. 1993, Stettler et al. 2002). At short range, the correlation breaks down and the axons freely innervate regions with quite diverse functional properties.

The view that the patches link neurons having similar functional characteristics invites a tempting simplification: Like connects to like. This pattern is explained by the equally beguiling slogan: Cells that fire together, wire together. But this interpretation is not entirely convincing, because it neglects the spatial organization of the dendritic trees of the target neurons. It turns out that the patch diameter correlates closely with the spread of the basal dendrites of the layer 3 pyramidal cells (Luhmann et al. 1986, Lund et al. 1993, Rockland et al. 1982). Thus, the largest patches were found in the macaque motor cortex (481 microns diameter), which also has the largest pyramidal cells. Malach (Malach 1992) has explored the significance of this scaling of patch and the size of individual cell dendrites. His idea is that the matching of size maximizes the diversity of a neuron's connections. Thus, assuming there is no selection of inputs, only neurons located in the middle of patches will have a pure sample of the patch inputs (see Figure 3), whereas those lying in the middle of a nonpatch receive pure nonpatch inputs. Neurons in-between have mixed inputs. This model generates a simple continuum from pure patch properties to pure nonpatch properties, so that more often, like does not connect to like. His model provides a convenient hypothesis to explain the size matching of patch and dendritic arbor, assuming equal sampling of inputs and unbiased dendritic arbors. His assumption of no dendritic bias seems to be valid for most neurons in cat area 17 (Anderson et al. 1999) but may not hold for some neurons in layer 4 of macaque area 17 (Katz et al. 1989) and the layer 4 of rat barrel cortex (Petersen & Sakmann 2000).

Questions of the meaning of the lateral connections extend to the overall distribution of the patches, which usually shows some degree of bias. In area 17 of New World monkeys, for example, the distribution of patches is roughly ellipsoid, with the long axis extending 1.7 times further from the injection site than the minor axis (Sincich & Blasdel 2001). The interpretation of the bias depends obviously on how much is known of the functional architecture of the cortical area concerned. For example, the layer 3 projections in area MT of the owl monkey are ellipsoid and asymmetrical relative to the injection site, but apart from a tendency for domains of similar orientation preference to be connected, the overall pattern of patches in area MT do not correlate with any obvious feature of the functional architecture (Malach et al. 1997). In inferotemporal cortex, adjacent injections in area TE gave rise to irregular patches that either were not adjacent to each other or overlapped extensively, which suggested that the underlying functional map is itself patchy (Fujita 2002, Fujita & Fujita 1996). A similar pattern is seen in prefrontal cortex (Lewis et al. 2002).

Even in a functionally well-defined area like macaque area 17, where the maps of functional properties are continuous, attempts to map the overall biases in the distribution of the lateral patches onto some functional attribute such as orientation have had mixed fortunes. The early papers on macaque referred to above did not detect any correlations with receptive field properties, such as orientation selectivity, and suggested that the bias reflected the anisotropy in the visual field map (Yoshioka et al. 1996). Indeed, the anisotropy of the retinotopic map in macaque area 17 is considerable. Most studies find a ratio of 1.6:1 for the magnification factor measured parallel and perpendicular to the V1/V2 borders, which represents the vertical meridian (Tootell et al. 1988, Van Essen et al. 1984). Blasdel & Campbell (2001) have shown by functional imaging that this anistropy is most likely generated by the ocular dominance columns, which would mask any correlations of the bias in lateral connections with the functional architecture. In the tree shrew, ocular dominance columns are absent, the visual field map is quite isotropic, the receptive field sizes are very large, and here the lateral projections of the layer 3 pyramidal cells do show a striking extension along the axis of the map of visual space that corresponds to preferred orientation of the pyramidal cells (Bosking et al. 1997, Chisum et al. 2003). Subsequently, a similar but much weaker bias was found for the pattern of lateral connections in area 17 of New World monkey (Sincich & Blasdel 2001). In general, the lateral projections of layer 3 pyramidal cells in Old and New World monkey area 17 cover only a few degrees of the visuotopic representation compared to the 5–20 degrees covered in cat and tree shrews.

Biases accepted, the question remains, what are lateral connections there for, and why do they seem so similar across cortex? In the visual cortex, one answer is that they are responsible for the physiological effects expressed in the "nonclassical" receptive field (see Fitzpatrick 2000). For example, a bar presented outside the classical receptive field can facilitate the response of a bar presented to the classical receptive field. This notion that the lateral connections mediate contextual interactions is an attractive hypothesis. But even here it is still not clear to what extent the lateral projection in visual cortex provides a catchment area that is larger than anticipated from the dimensions of the classical receptive field. On one hand, there is the claim that the lateral connections in macaque area 17 extend eight times the size of a classical receptive field (Gilbert 1992, Stettler et al. 2002); however, Yoshioka et al. (1996) and Sincich & Blasdel (2001) claim that the dimensions of the labeled patches match the extent expected from the classical receptive field size. All these estimates consider only the extent of the monosynaptic connections within layer 3 and, of course, neglect the possible role of intra- and inter-areal connections in providing additional contextual information. The question of what they are for remains largely unanswered. It is clear that yards of ignorance remain at even the most basic level; e.g., it remains to be discovered what determines the number of patches, the extent of their distribution, how individual neurons contribute to the input to these patches, and where the neurons that constitute a patch send all their outputs.

INTER-AREAL The layer 3 pyramidal cells are also the main source of the feedforward projections to other cortical areas, where they terminate in the middle layers, much as the thalamic afferents do. The feedback projections, by contrast, originate mainly in layers 5 and 6 and terminate outside layer 4 (Rockland & Pandya 1979). This has proved an invaluable simplification in generating an anatomical hierarchy of visual areas (Felleman & Van Essen 1991). However, the hierarchies generated by this method are very under-constrained, and enormous numbers of equally plausible hierarchies can be generated (Hilgetag et al. 1996). One invaluable means of constraining the solution has proved to be the quantitative measure of the proportion of layer 2 and 3 neurons that contribute to the feedforward and feedback pathways. Surprisingly, these proportions change in a regular manner from area to successive area and so suggest the existence of a "distance rule" (Kennedy & Bullier 1985, Rockland 1997, Barone et al. 2000). In this rule, the higher the proportion of superficial layer neurons (SLN%) of the total neurons that contribute to a projection to another area, the closer are the areas in the hierarchy. For example, after injections into area V4, 100% of the labeled neurons in V1 (area 17) are in layers 2 and 3, compared to 93% in V2 and 60% in V3A. By ranking the areas according to the SLN%, a single hierarchy emerges. Interestingly, it shows some striking differences from previous hierarchies. For example, the area called frontal eye field (FEF) lies at level 8 of the Felleman–Van Essen hierarchy. With the SLN% ranking it lies only at level 4, together with areas V3 and V3A, which again lie on different levels in the Felleman–Van Essen hierarchy.

The functional significance of these revisions of the cortical hierarchy have yet to be explored. Nevertheless, the evidence from the study of areal connections in the macaque visual cortex indicates that the superficial and deep layers of the cortex vary inversely in their projections to any other cortical area and thus in their respective influences on the local circuits in their target areas. The distance rule governing the hierarchical relationships of cortical areas may well be an organizing principle of monkey neocortex. Evidence supporting this view comes from the laminar organization of afferents in the frontal lobe (Barbas 1986) and the somatosensory cortex (Batardiere et al. 1998). These results have potentially important consequences for how we view the influence and role of the inter-areal connections to the local cortical circuits. These issues are considered in the final section.

INHIBITORY CIRCUITS

Smooth neurons may not be well-endowed with dendritic spines, but they are richly endowed with names. Almost all types individually bear more than one name, and as a group they are referred to exchangeably (albeit not always completely accurately) as aspiny, nonpyramidal, inhibitory, GABAergic, or inter-neurons. Following Ramon y Cajal, the neoclassical school of anatomists have generally preferred the evocative descriptive images of "double-bouquet," "basket," or

"chandelier," based chiefly on the gestalt of the axonal arbor, but the modern trend is toward multivariate classification schemes in which factors such as morphometrics, biophysics, synaptic dynamics, synaptic targets, and neurochemical markers are employed to subdivide ever more finely, if arbitrarily, the population of smooth neurons.

The time constant of cortical evolution being somewhat longer than that of scientific nomenclature, the morphology of the smooth neurons has been remarkably conserved. For example, the smooth neurons in the primary visual cortex of marsupials and macaques are recognizably similar (Tyler et al. 1998) even though the two principal marsupial lines diverged from the eutherian line over 135 million years ago. Although from Ramon y Cajal onward there have been claims for neuronal types that are unique to the neocortex of humans or great apes [most recently from Nimchimsky et al. (1999)] there is nevertheless a great similarity in the proportion of the GABAergic neurons and their patterns of connection across cortical areas that have widely different functions. Remarkable too is that while the proportion of GABAergic neurons in a given area varies, between 10%–20% of the synapses found in any neocortical area in all species examined are the symmetric variety formed by GABAergic boutons. In one recent count of neocortical areas as different as human anterolateal temporal cortex and the hindlimb area of rat somatosensory cortex, symmetric synapses formed 11.5% and 10.7% of the population, respectively (DeFelipe et al. 2002). Generally, the ratio of symmetric to asymmetric synapses is remarkably constant, despite large regional variations in the average number of spines (the main site of asymmetric synapses) born by a pyramidal cell (Elston et al. 2001; Elston & Rosa 1998, 2000). While some morphological features, such as spine numbers on pyramidal cells, can vary widely from area to area or species to species (see Elston 2002), other parameters, such as the overall density of synapses, shows remarkably little variance from area to area in different species (Cragg 1967, O'Kusky & Colonnier 1982, Rakic et al. 1986, Schuz & Palm 1989).

Morphological Types of Smooth Neurons

There seems to be broad agreement over time and place that about ten morphologically distinct varieties of smooth neurons can be distinguished and that examples of the basic forms are found in all species. Although there are claims that the proportion of double bouquet cells greatly increases in primates, double bouquet cells are certainly seen in other species, including cat (Peters & Regidor 1981, Somogyi & Cowey 1981, Szentágothai 1973) and rodent (Connor & Peters 1984, Kawaguchi & Kubota 1997, Peters & Harriman 1988). In the monkey, double bouquet and bipolar cells have been lumped together by Lund & Wu on the grounds that their axon collaterals form narrow columns regardless of whether the dendritic morphology is bipolar or multipolar (Lund & Wu 1997).

DeFelipe (2002) has conveniently divided the smooth neurons into just three basic groups on the basis of the clustering of the axon. Those neurons that have local

arbors include the neurogliaform (also called spider web); small basket (also called clewed, or clutch); chandelier cell (also called axo-axonic); and common type, i.e., a type with no particularly distinguishing features. Those forming vertically oriented axons include the neurons with axonal arcades, Martinotti cells, bipolar cells, and double bouquet cells. Only the large, or wide arbor basket cells, and the medium arbor cells have axons that extend horizontally. Large basket cells have the most extensive horizontal axons, but the extensions typically consist of 4 or 5 long branches that extend a few 100 microns laterally from the cell body but, unlike the horizontal projections of pyramidal cells, do not form dense bouton clusters (Figure 3). Thus, the diversity of the GABAergic neurons, currently much emphasized, is perhaps no greater than that of pyramidal cells, e.g., there are eight morphological variants alone of layer 6 pyramidal cells in the macaque area 17 (Wiser & Callaway 1996).

Immunoreactivity of Smooth Neurons

All GABAergic cells show immunoreactivity to calcium-binding proteins, as well as to neuropeptides, such as cholecystokinin, somatostatin, vasoactive intestinal polypeptide, neuropeptide Y, and corticotropin-releasing factor (Demeulemeester et al. 1988, 1991; Hendry et al. 1984; Schmechel et al. 1984; Somogyi et al. 1984). The profile of immunoreactivity expressed by a neuron depends on its laminar location and morphological type. There is considerable overlap in expression of a particular peptide or calcium-binding protein between cell types, and the profile depends also on the cortex's state of embryological development. Nevertheless, the immunoreactivity of cells to these markers provides another basis for the classification of smooth cell subtypes (e.g., Wang et al. 2002). VIP and substance P are also associated with cholinergic axons (Eckenstein & Baughman 1984, Vincent et al. 1983). Some spiny neurons also express immunoreactivity for calbindin, cholecystokinin, and somatostatin, but their immunoreactivity for these molecules is weaker, particularly in more mature animals, and the expression of different peptides may vary over development.

Although the proportion of neurons expressing a particular calcium-binding protein differs widely between areas, even in the same species, the basic laminar pattern of the neurons that express the calcium-binding proteins is conserved. For example, the pattern of calbindin immunoreactivity is similar for all cortical areas in species as diverse as rat, cat, and monkey. In the macaque somatic sensory, auditory, and extrastriate visual cortex, most immunoreactive cell bodies are in layer 2 and the upper part of 3, with a lower density in layer 5. One variant occurs in area 17, where there is an additional tier of neurons in layer 4. Curiously, the macaque motor cortex has few calbindin-immunoreactive cells (DeFelipe et al. 1990), whereas in the rat (Sun et al. 2002) and cat motor cortex (Porter et al. 2000), the calbindin immunoreactive cells have a similar distribution to macaque somatosensory, auditory, and extrastriate areas. The majority of immunoreactive synaptic boutons are distributed in the superficial layers with only a sparse

distribution in the deep layers. In macaque the synapses formed in the somatic sensory areas (1, 2, 3a, 3b) are 40% on spines and 60% on small-caliber dendritic shafts, thought to be the distal portions of the basal and apical dendritic branches of pyramidal cells (DeFelipe et al. 1989a). Similar proportions and targets were found for the output of tachykinin-positive double bouquet cells in the macaque auditory cortex (DeFelipe et al. 1990).

Proportions of Morphological Types

One difficult question, only partially answered, is how many basket cells, chandelier cells, double bouquets, etc. are there in a given area? One attempt at an answer has come by correlating morphological features of the smooth neurons with the expression of various peptides and calcium-binding proteins. Unfortunately, because there is no one-to-one correlation of morphology with immunochemical identity, quantitative estimates of the proportions of different morphological types of smooth neurons are difficult to obtain. For example, the most widely used immunochemical markers for subdividing the smooth neurons are the three calcium-binding proteins (parvalbumin, calbindin, calretinin), which between them label virtually all the variants of GABAergic neurons. This means that no single morphological type can be identified and counted exclusively on the basis of its expression of a particular calcium-binding protein. As a means of classifying different types of smooth neurons, calcium-binding protein and peptide immunochemistry needs to be interpreted judiciously because the expression of these markers in a particular morphological type varies across areas and species (DeFelipe 1993).

Parvalbumin labels small and large basket cells (Blumcke et al. 1990, Hendry et al. 1989, Van Brederode et al. 1990) and chandelier cells (DeFelipe et al. 1989b, Lewis & Lund 1990). Calretinin labels a heterogenous group of neurons (Meskenaite 1997, Rogers 1992, Rogers & Resibois 1992), which include the Cajal-Retzius cells of layer one and a morphologically heterogenous group of neurons with vertically oriented axons, among them a small group of double bouquet cells (Conde et al. 1994, Gabbott & Bacon 1996a, Meskenaite 1997). Interestingly, calretinin-positive neurons form synapses mainly with other smooth neurons (possibly calbindin-positive neurons) in layer 3, but with pyramidal cells in layer 5 (Meskenaite 1997). In an interesting parallel, the hippocampus calretinin-positive neurons also form synapses mainly with other calretinin- and calbindin-positive neurons (Gulyas et al. 1996). In the macaque visual cortex, calbindin labels mainly, but not exclusively, the double bouquet cells (Hendry et al. 1989) and in the prefrontal cortex it labels double bouquet, Martinotti, and neurogliaform cells. Similarly, in rat frontal cortex, some Martinotti cells, which also express somatostatin, are immunoreactive for calbindin, as are the double bouquet cells (Kawaguchi & Kubota 1997).

Most estimates of the proportions of the different neurons are necessarily indirect, but one useful number has come from the study of calbindin-immunoreactive neurons in macaque cortex. Calbindin is expressed in the axons as well as the cell

body and dendrites of double bouquet cells. In tangential sections of area 17 (Peters & Sethares 1997) and auditory cortex (DeFelipe et al. 1990), the tight columnar bundles of calbindin-immunoreactive axon collaterals form an apparently regular array spaced 25 microns apart. Thus under each square millimeter of surface there are 2500 vertical bundles. On average, each double bouquet cell makes more than one bundle to give a ratio of 0.7 double bouquet cells per bundle (Peters & Sethares 1997). This gives 1750 calbindin neurons in the superficial layers under each square millimeter of cortical surface. Because the number of superficial layer neurons under each square millimeter of macaque area 17 is known to be 52,000, 17% of which are GABAergic (Beaulieu et al. 1992), it follows that only 20% of the GABAergic neurons in the superficial layers are calbindin-positive. This is comparable with actual counts made in the macaque frontal cortex (Gabbott & Bacon 1996a) and cat visual cortex, where 20%–30% of the GABAergic neurons are calbindin-positive (Demeulemeester et al. 1989, Hogan et al. 1992, Huxlin & Pasternak 2001).

In macaque area 17, the majority of the GABAergic neurons must be parvalbumin-positive because the calretinin population forms only 14% of GABAergic neurons (Meskenaite 1997). The parvalbumin population consists of the chandelier cells, the large basket cells, and five or six other types, all of which have axonal arborizations that surround the dendritic tree (Jones 1975, Lund & Wu 1997). In the macaque prefrontal cortex, calretinin neurons are in the majority, forming 45% of the GABAergic neurons, compared to 24% for parvalbumin and 20% for calbindin (Conde et al. 1994, Gabbott & Bacon 1996b). The remaining 11% of GABAergic neurons did not stain strongly for any of the three calcium-binding proteins, but technical issues cannot be ruled out in accounting for these negative results.

Many of these difficulties in determining the precise proportions of the different morphological types will disappear as new molecular markers are developed to differentiate the types of cortical neurons, but it seems unlikely that there will be any great surprises in the future as to the known morphological variants of the smooth neurons. Probably, the major classes will still be those revealed to us over many years through application of the traditional Golgi stain. What this method has shown us, and what subsequent techniques such as intracellular labeling, immunostaining, and electron microscopy have confirmed, is that there are two basic modes of connection of the smooth neurons (Figure 4). The first, horizontal class, exemplified by the basket and chandelier cells, are neurons with local axonal arbors that target the proximal portions of the dendritic tree of spiny cells. This targeting is very obvious in the parvalbumin immunostained material. The second, vertical class, most elegantly exemplified by the double bouquet cells, have vertically oriented axonal arbors and target the more distal portions of the dendritic trees of spiny cells, principally pyramidal cells. Because the smooth neurons are inhibitory, it is evident that these two broad divisions give rise to different functional possibilities. In the first class, the principal targets cluster around the integration and the output region of the neuron: the axon initial segment, soma, and proximal

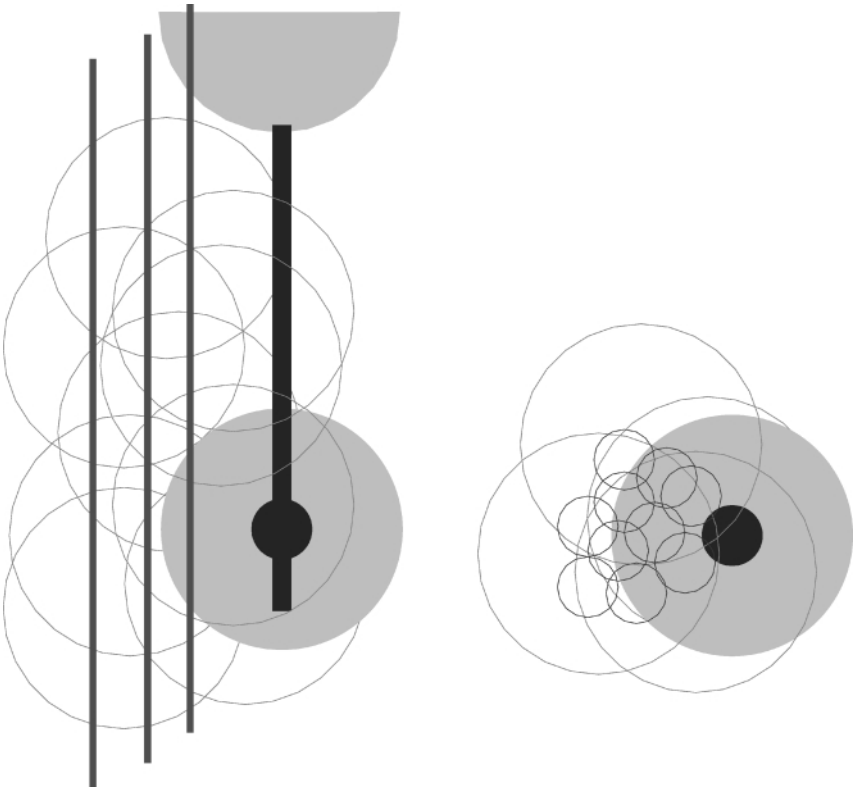


Figure 4 Schematic showing the proposed distinction between the effects of horizontal and vertical smooth cells. Vertical section through superficial layers on left; tangential section on right. The parvalbumin positive horizontal smooth cells make multiple synaptic contacts on the crucial dendritic output path (apical dendrite, soma, and initial segment; *black-gray*) of a representative superficial pyramidal neuron, whose apical and basal dendritic fields are shown as light gray regions. The dendritic fields of some overlapping neighboring pyramids are indicated as light gray circles. The trajectories of three double bouquet axons (*left*, *dark gray lines*) pass vertically through the dendritic fields, making contact with some of them at various locations ranging from proximal to distal. Typical zones of influence of some vertical double bouquet axons are shown in the tangential view (*right*, *small dark gray circles*). These zones are spaced at 25 μm (see text).

dendrites. In the second class, the targets are the main regions of excitatory input: the distal basal dendrites and branches of pyramidal cell apical dendrites.

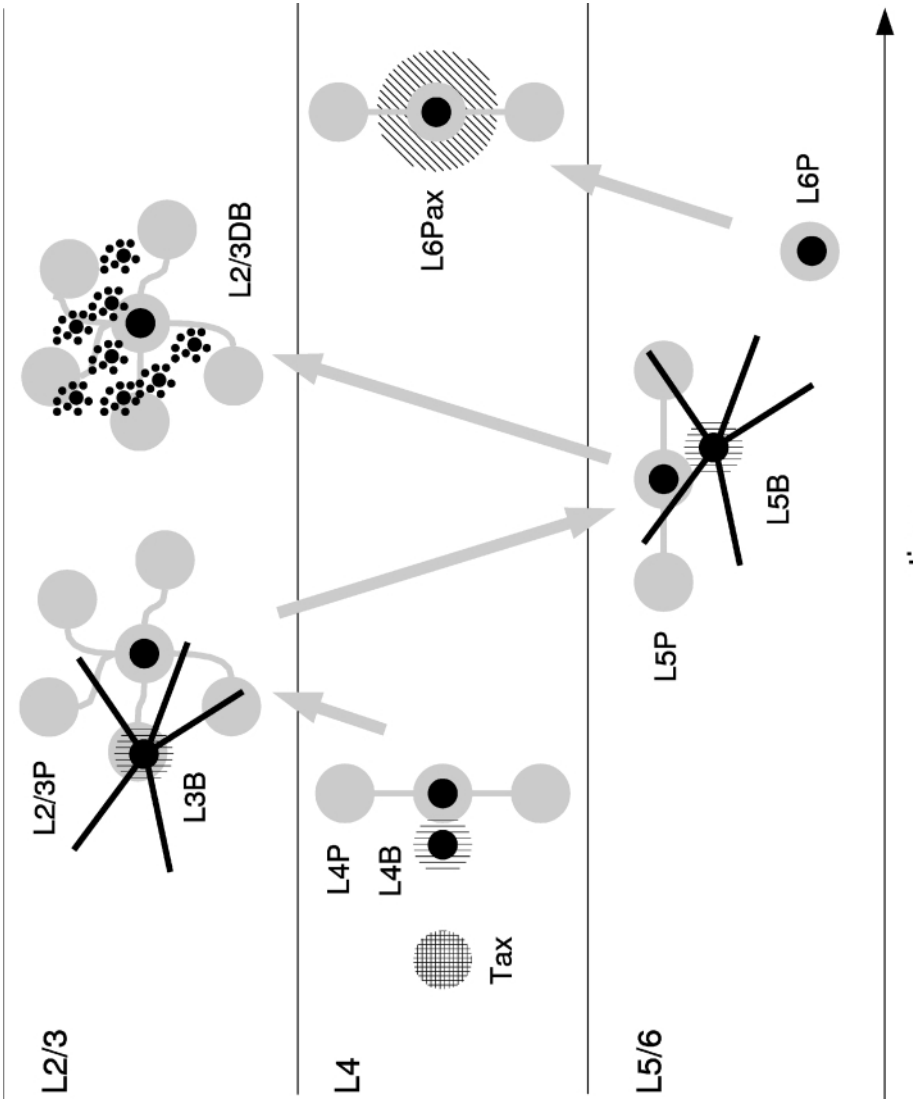
The differential laminar distribution of the various smooth cell types has an important consequence: The relative proportions of chandelier, basket cell, double bouquet cell, etc. synapses that a spiny cell receives will depend critically on its

laminar location. Thus, for example, layer 3 pyramidal cells receive far more input from chandelier cells than those of layer 6 simply because layer 3 is more richly endowed with chandelier cells (Farinas & DeFelipe 1991, Sloper & Powell 1979).

FUNCTION FROM STRUCTURE

As has long been suspected by many cortical neuroanatomists, the same basic laminar and tangential organization of the excitatory neurons of the neocortex, the spiny neurons, is evident wherever it has been sought (Figures 1, 2, and 5). The inhibitory neurons similarly show characteristic morphology and patterns of connections throughout the cortex. Here, we have simply identified the constant elements of this circuit and pointed to the existence of some of the variants in both the spiny and smooth populations. These variants, occurring across areas in the same species and between species, are unsurprising given the widely different uses of the different cortical areas and the different activities of their owners. In terms of their amino acid neurotransmitters, the spiny and the smooth neurons are monogamous. The former use glutamate, the latter GABA. Variations in the immunochemistry arise with secondary markers, such as the calcium-binding proteins and peptides. In the case of the smooth neurons, this is perhaps due to their long migration from the median eminence, as in their travels they are likely to meet with remarkably different microenvironments that could induce the expression of different genes. Nevertheless, all things considered, many crucial aspects of morphology, laminar distribution, and synaptic targets are very well conserved between areas and between species.

One of the most intriguing consistencies of neocortical structure is the presence of patchy connections made by the pyramidal cells, particularly of the superficial cortical layers. Localized injections of tracers produce labeling of 10–30 patches, usually regularly spaced and appearing as petals of a daisy (Figure 5). The axons of individual pyramidal cells form far fewer patches than the collective, indicating that within any patch there is a heterogenous cluster of pyramidal cells, which distribute their output to different subsets of the total complement of patches. The patches also receive additional excitatory input from pyramidal cells projecting from other cortical areas (Gilbert & Wiesel 1989). Double-labeling experiments (Bullier et al. 1984, Kennedy & Bullier 1985, Perkel et al. 1986) show that the axons of individual projection neurons rarely innervate more than one other cortical area, despite the fact that each cortical area connects to many other cortical areas (Zeki 1978a,b). This means that the fan-out from one patch of projection neurons to other cortical areas is organized on similar principles to the fan out to other clusters within a cortical area. Thus, pyramidal cells lying within a single patch may receive inputs from other patches in its own area, or from other areas, that are most likely quite heterogenous in functional properties. Their individual responses, even within a single patch, might be much more varied than suggested by the like-to-like simplification. What could the possible role of such an arrangement be?



An Anatomical Model of Cortical Function

A simple model of cortical processing, consistent with the major features of cortical circuits discussed in this review, is as follows (see Figure 6): A patch of superficial pyramidal neurons receive feedforward excitatory input from subcortical, inter-areal, and intra-areal sources. In addition to their interactions with their close neighbors within their patch, the members of this patch also receive feedback from a number of sources: from deep pyramidal cells immediately beneath their patch, from other close patches within the superficial layers, and from subcortical inter-areal connections. Thus, the neurons of a superficial patch, taken as a group, receive a sample of thalamic input (some preprocessed by layer 4), a sample of surrounding and remote superficial patches, and a sample of the output from their corresponding deep pyramidal neurons.

All of these inputs are processed by the dendrites of the superficial pyramids whose signal transfer properties can be adjusted dynamically by the pattern of the vertical inputs from smooth cells (e.g., double bouquet cells). The superficial

←

Figure 5 Schematic showing the laminar-temporal evolution of interactions between some important neuronal types, following an input from the thalamus. Time unfolds toward the right and has a duration of 5 synaptic crossings. Neuronal elements are shown in plan (tangential) view, but located in their laminae (*L2/3*, *L4*, and *L5/6*). The relative sizes of axonal arbors, patches, inter-patch distances, etc. conform as reasonably as possible to Figure 3. The patchy axonal arborizations of excitory neurons are shown as connected gray disks. Their dendritic arborizations are denoted as smaller black discs superimposed on the central axonal clusters. The dendritic arbors of inhibitory neurons are also shown in black, but superimposed on vertical hatching, which denotes their dominate axonal arborization. Basket cells have in addition a few thin radial axons (*radiating black lines*). Double bouquet cells have a small black dendritic arborization surrounded by black dots that denote their vertically oriented axonal arbors (see also Figures 1, 3, and 4). Excitatory interlaminar effects are indicated by gray arrows. Intralaminar effects are unmarked. Thalamic afferents (*Tax*) activate spiny stellate (*L4P*) and small basket (*L4B*) neurons in layer 4. The stellates activate pyramidal cells (*L2/3P*) and basket cells (*L3B*) in layer 3. Note the region of influence of the large basket cell (*L3B*) relative to the patches of the pyramidal cells. The primary arbor of the basket cell matches approximately the pyramidal patch size, but unlike the pyramidal patches, the basket cell's thin radial arborizations focus their longer range inhibitory effect along restricted, nearly radial paths. The superficial pyramidal cells activate the pyramidal cells of layer 5 (*L5P*), which in turn activate those of layer 6 (*L6P*). Both the superficial and deep pyramidal cells activate superficial neurons. Importantly, they also activate the vertically disposed double bouquet cells. The pattern of activation of double bouquet cells could dynamically determine the input-output relations computed by the dendrites of the various L2/3Ps that they contact (see Figures 4 and 6). The layer 6 pyramidal cells project to layer 4, where their wide arbors (*L6Pax*) combine with thalamic afferents to shape activation of layer 4 spiny stellates.

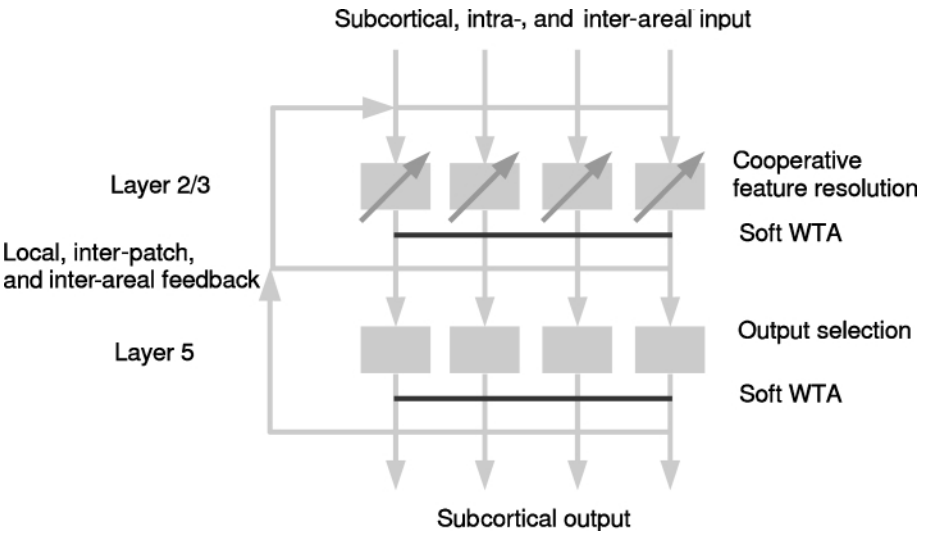


Figure 6 Simple model of cortical processing incorporating the principal features of cortical circuits. A patch of superficial pyramidal neurons receive feedforward input from subcortical, inter-areal, and intra-areal excitatory sources. They also receive recurrent input from other local superficial and deep pyramidal cells. These inputs are processed by dendrites of the superficial pyramidal neurons (*upper gray rectangles*, layer 2/3) whose signal transfer properties are adjusted dynamically by the pattern of vertical smooth cell inputs (*oblique dark gray arrows*). The outputs of the superficial pyramids participate in a selection network (e.g., soft winner-take-all mechanism) mediated by the horizontal smooth cells (*upper horizontal dark gray line*). These outputs of the superficial pyramids adjust the pattern of vertical smooth cell activation. In this way, the superficial layer neurons within and between patches, and within and between areas, cooperate to resolve a consistent interpretation. The layer 5 pyramids (*lower gray rectangles*) have a similar soft selection configuration (*lower dark gray line*) to process local superficial signals and decide on the output to motor structures.

pyramids collectively participate in a selection network, mediated by the horizontal inputs from the smooth cells that control their outputs (e.g., basket and chandelier cells). The selection mechanism is a soft winner-take-all or soft MAX mechanism, which are important elements of many neuronal network models (Maass 2000, Riesenhuber & Poggio 1999, Yuille & Geiger 2003). The outputs of the selected superficial pyramids feed back to adapt the pattern of vertical smooth cell activation. In this way, the superficial layer neurons within and between patches, and within and between areas, cooperate to explore all possible interpretations of input, and so select an interpretation consistent with their various subcortical inputs.

The superficial layers are organized to distribute and explore possible interpretations, whereas the deeper layers are organized to exploit the evolving

interpretations. The pyramidal cells of layer 5 that drive subcortical structures involved in action (e.g., basal ganglia, colliculus, ventral spinal cord) decide the output of the cortical circuits. The same layer 5 pyramidal cells influence the ongoing input by their connection to layer 6 pyramidal cells that connect to the thalamic input layers. The explorative processing in the superficial layers is constrained via the recurrent projection from other layer 5 pyramidal cells to conform to the output that has already been decided. These layer 5 pyramidal cells are also the origin of the feedback projections to the superficial layers of other cortical areas. In this way, they also provide additional contextual information to the evolving interpretations occurring in the superficial layers of other cortical areas.

Clearly, this model is a tentative hypothesis of how the generic circuits might express themselves functionally. However, its strength is that it casts antomical data in a way that is accessible to theoreticians and systems physiologists. The investigation of neocortical structure and its development has entered an exciting phase in which the detailed organization is accessible to experiment and essential to the theoretical understanding of cortical computation. It is thus a curious paradox that while molecular biology has long recognized the central importance of detailed structural studies for understanding function, the same cannot be said for contemporary neuroscience.

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