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NEOCORTEX

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Many of the brain regions discussed in this volume are examples of cortical ("bark-like") structures. Taking its place alongside the archicortex (hippocampus) and paleocortex (olfactory bulb) is the neocortex, which is the most recent arrival in evolutionary history and is arguably the most impressive example of the genre. It has certainly impressed paleontologists whose research on the fossil record of hominids has demonstrated that the size of the hominid brain has trebled over the past 3 million years. Endocasts of the fossil hominid skulls indicate that this increase in size is largely due to the expansion of the neocortex and its connections. The massive and rapid changes in the size of the neocortex are paralleled in the phylogenetic differences we see in contemporary mammalian brains (Fig. 12.1). Of land mammals, the primates have the largest brains in proportion to their body weight. However, the human brain is three times as large as might be expected for a primate of equivalent weight (Passingham, 1982). Furthermore, the human brain is not simply a scaled-up version of our closest primate relative, i.e., the Bonobo chimpanzee. The greatest expansion is in the cortical structures, particularly the cerebellum and neocortex. Within the neocortex itself, the expansion is uneven. In comparison with nonhuman primates of equivalent body weight, the association and premotor areas have expanded relative to the sensory areas. When added together, the neocortex and its connections form a massive 80% by volume of the human brain (Passingham, 1982).

In all mammals the neocortex consists of a sheet of cells, about 2 mm thick. Conventionally it is divided into 6 layers, but in many regions more than 6 laminae are in evidence (Fig. 12.2). Each cubic millimeter contains approximately 50,000 neurons. The study of the laminar organization of these cells in the neocortex began in the early part of the 20th century and became known as *cytoarchitectonics*. In conjunction with studies of the organization of myelinated fibers, called *myeloarchitectonics*, cytoarchitectonics was applied by Campbell in England and by Vogt and Brodmann in Germany, to divide the neocortex into about 20 different regions. Although many more areas have since been identified, there are three major cytoarchitectural divisions of the neocortex. The *koniocortex*, or granular cortex of the sensory areas, contains small, densely packed neurons in the middle layers. These small neurons are large absent in the *agranular* cortex of the motor and premotor cortical areas. The third type of cortex has varying populations of granule cells and is called *eulaminate* or *homotypical*

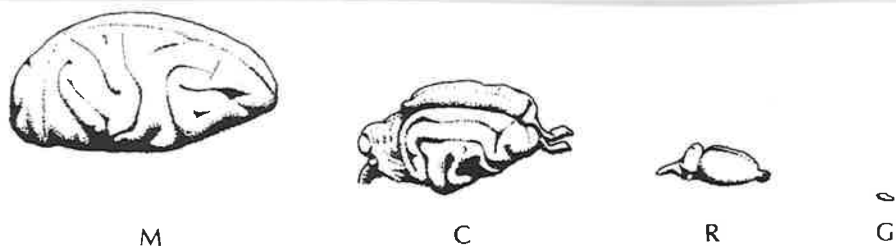

Fig. 12.1. Brains of modern vertebrates: goldfish (G), rat (R), cat (C), and Old World monkey (M). Scaled to body weight, the neocortex and its connections form an increasingly greater proportion of the brain volume. The neocortex in monkey completely envelops all other brain structures.

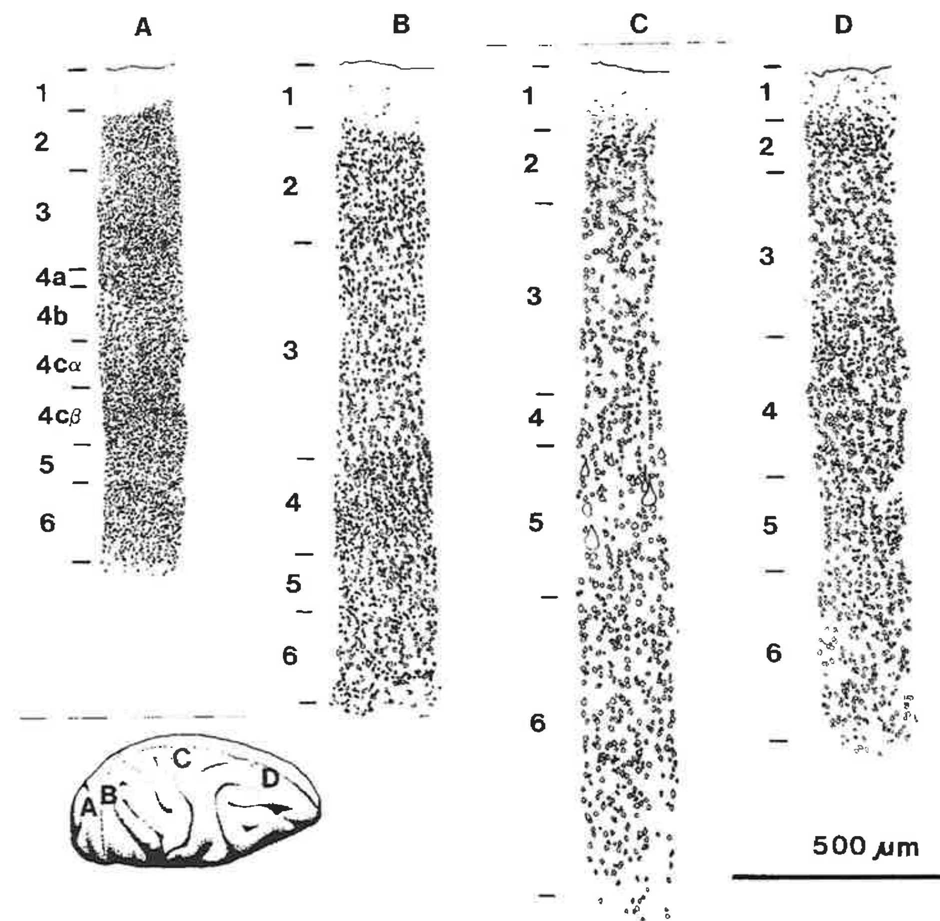

Fig. 12.2. The laminar organization of neurons in different cortical areas of the macaque monkey cortex (inset). **A:** Area 17 (striate visual cortex). **B:** Area 18 (extrastriate cortex). **C:** Area 4 (motor cortex). **D:** Area 9 (frontal cortex). A basic six-layered structure can be identified in all areas. The pia covers layer 1; the white matter is below layer 6. Note the marked difference in cell size and density among the different areas, but additional layers are apparent in some areas (e.g., Area 17). The giant neurons in layer 5 of area 4 are the Betz cells. (Celloidin-embedded brain, cut in 40 μm thick parasagittal sections, stained for Nissl substance, uncorrected for shrinkage.)

cortex. It includes much of "*association cortex*," which is a convenient description for cortex whose function has yet to be discovered (Fig. 12.2). Within each of these areas there are many subdivisions, both functional and anatomical. Some are clearly delimited by their cytoarchitectonic structure, as in the case of area 17, the primary visual cortex, or by myeloarchitectonics, as in the case of the middle temporal visual area (MT). Other areas, such as area 18 in the monkey, can only be subdivided by more elaborate immunochemical, histological, or physiological methods.

In a planar view the map of these architectonically defined areas looks like a patchwork quilt. The functional properties and subdivisions of these have been mapped most extensively in the monkey cortical areas concerned with vision. The exponential growth of functional imaging studies in humans means that more and more is becoming known about the equivalent subdivisions of the human brain. In addition to the basic sensory and motor functions, the human cortex appears to be particularly involved in high-level functions, such as speech production and comprehension. Indeed, the concept of cortical localization of function derives from studies in the last century that correlated damage of specific areas of human cortex with specific deficits in speech production. Similar modern case studies of aphasias have become celebrated in the popular culture of books, television, and films. With the advent of functional imaging studies with positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG), there has been a rapid increase in our knowledge of the functional and anatomical map of human cortex. These techniques, however, do not attempt to identify the the mechanisms or neuronal circuits responsible for these functions. Thus, the challenge is to discover what is actually happening when different regions of the cortex are activated under different sensory or behavioral tasks. Fundamental to this central endeavor is an understanding of the structure and function of the microcircuits of the neocortex and their components.

NEURONAL ELEMENTS

Nearly 100 years ago, Ramon y Cajal outlined the basic approach to studying the elementary pattern of cortical organization (Cajal, 1911). The method is to reveal the complete structure of neurons, including their axons, and then piece together these components in a jigsaw-puzzle fashion to produce circuits. He, and many since, studied the morphology and circuitry of the neocortex with the silver impregnation technique discovered by Golgi. Although this techniques has been superseded by much more sophisticated modern techniques, the basic classes of neurons revealed by the Golgi technique used by Ramon y Cajal have remained largely unaltered. All three cytoarchitectural divisions of the neocortex contain the same two basic types of neurons: those whose dendrites bear spines (the stellate and pyramidal cells, Fig. 12.3) and those whose dendrites are smooth (smooth cells, Fig. 12.4). Occasionally, *sparsely spiny cells* have been described, but these neurons form a very small subclass of cortical neurons.

Modern electron microscopic and immunochemical techniques have been used to determine the proportion of the different types in the different regions of cortex. These studies have shown that while the different types may be differentially distributed between laminae within a single cortical area, the overall proportions of a given neuronal type remain approximately constant between different areas. The pyramidal cells form

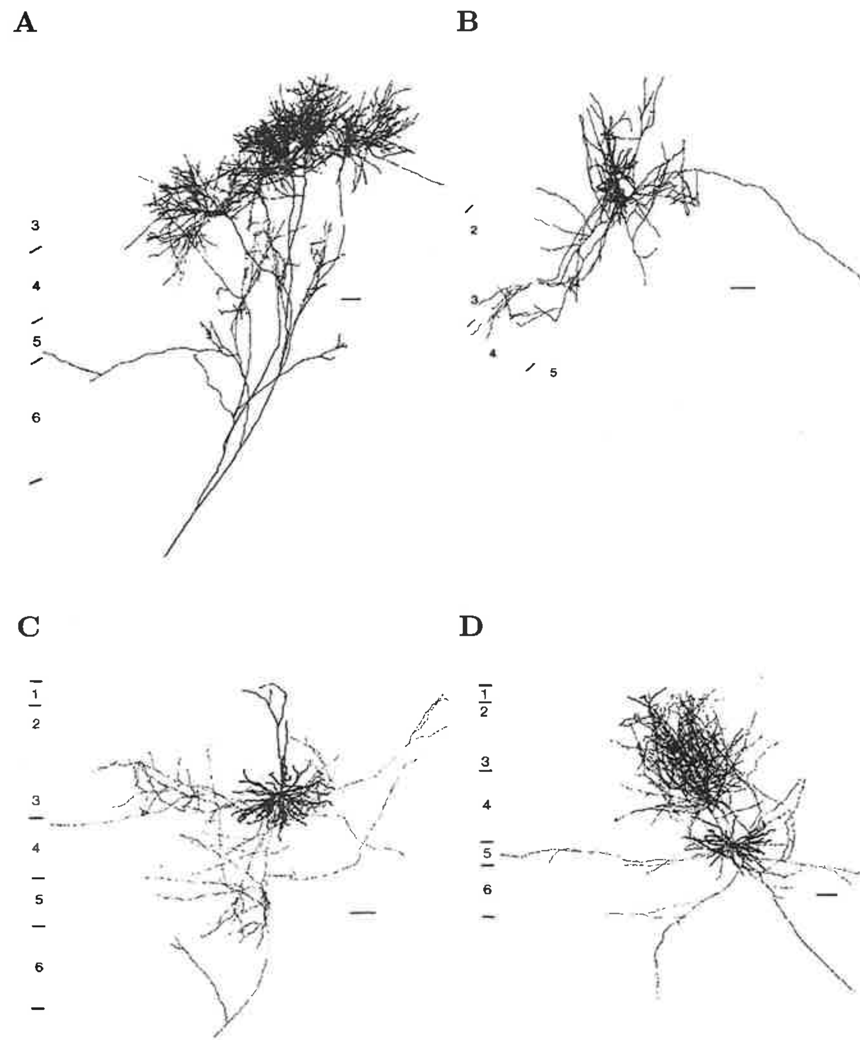

Fig. 12.3. Thalamic afferent and several spiny neurons from cat visual cortex. **A:** Y-type thalamic afferent. Note extensive but patchy arbor in layer 4. This axon formed over 8000 boutons. **B:** Spiny stellate neuron of layer 4. **C:** Pyramidal neuron of layer 3. Note characteristic apical dendrite extending to layer 1. Many collateral branches arise from the main axon before it leaves the cortex (below). **D:** Pyramidal neuron of layer 5. Note the very rich axon collateral arbor in the superficial layers. This neuron did not project out of area 17. The thalamic afferent and neurons were filled intracellularly in vivo with horseradish peroxidase. Cortical layers are as indicated. Bars = 100 μm.

about 70% of the neurons (Sloper et al., 1979; Powell, 1981) and the smooth cells form about 20% of the neurons (Peters, 1987) in all cortical areas examined. These morphological differences in the dendritic structure are only one of many differences between these two basic types. For example, the spiny cells are excitatory, whereas the smooth neurons are inhibitory. Spiny neurons use quite different neurotransmitters from

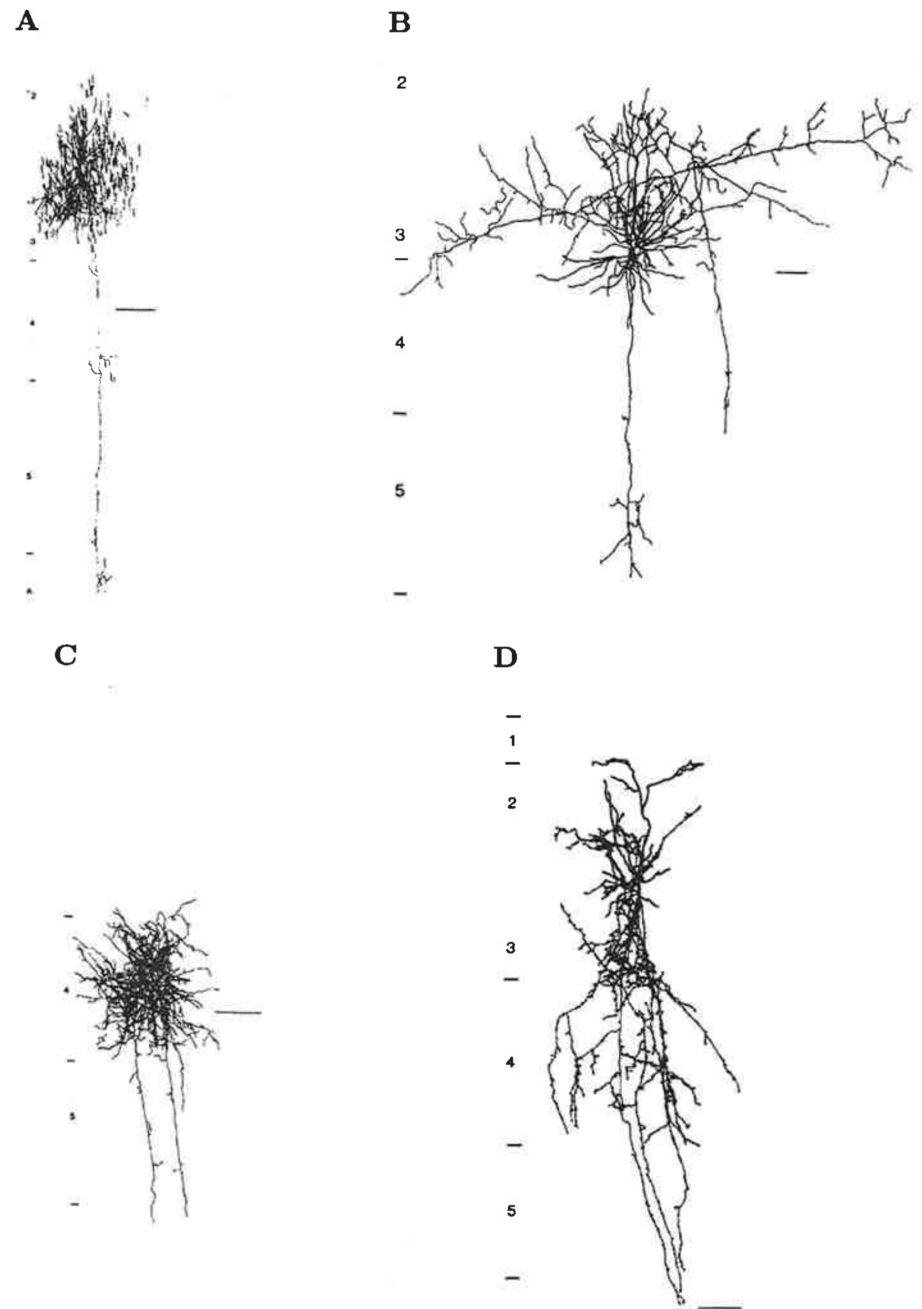

Fig. 12.4. Smooth neurons from cat visual cortex. **A:** Chandelier cell. **B:** Large basket cell of layer 3. Note lateral axon collaterals. **C:** Small basket cell of layer 4. The major portion of the axon arbor is confined to layer 4. **D:** Double bouquet cell. The axon collaterals run vertically. Cortical layers are as indicated. Bars = 100 μm.

smooth neurons; their respective synapses are associated with a quite different set of receptors and this is reflected in the morphology of the synapses.

SPINY NEURONS

Spiny neurons are called this because their dendrites bear small processes called spines. Spines are usually club shaped, with a head of about 1 μm diameter and a shaft, or *neck*, of about 0.1 μm diameter. The length of the neck varies greatly, from virtually nothing as in "stubby" spines, in which the head attaches directly to the dendritic shaft, to necks that are several micrometers long (Jones and Powell, 1969c). At the high magnifications achieved with the electron microscope, spines can be distinguished from other dendritic elements in the neuropil by the presence of a characteristic *spine apparatus*, which is composed of a calcium-binding protein, and this has been an important marker for spines in quantitative electron microscopic studies (cf. Chap. 7, Fig. 7.6A) although similar structural elements are found in dendritic shafts.

Pyramidal Neurons. The major subtype of spiny neurons are the pyramidal cells (Fig. 12.3C,D), which constitute about two-thirds of the neurons in the neocortex. Pyramidal neurons are found in all cortical layers except layer 1. Their most prominent feature is an apical dendrite that may extend through all the layers of the cortex above the soma. Pyramidal cells are the major output neurons of the neocortex. They participate both in connections between the different cortical areas and to subcortical structures such as the thalamus and superior colliculus. However, they also are a major provider of excitatory input to the area in which they are found: each pyramidal neuron has a rich collateral network that forms part of the local cortical circuitry.

The proximal shafts of the dendrites of the spiny cell types are nearly devoid of spines. The spine density varies considerably between different types of neurons. At one extreme is the sparsely spiny neuron, which may bear fewer than 100 spines over the entire dendritic tree. These neurons form a small subclass of the inhibitory neuron population. At another extreme are neurons such as the *Betz cell*, a large pyramidal cell that is found in the motor cortex (area 4) and bears about 10,000 spines. Each spine forms a type 1 synapse with a presynaptic bouton. Thus, simply counting spines gives a lower limit on the number of type 1 synapses. However, because not all type 1 synapses are formed on spines, the degree of underestimation can only be determined by quantitative electron microscopy of the dendrites of identified neurons. Due to this methodological bottleneck, accurate estimates of the number and positions of synapses onto particular neuronal types are unfortunately extremely rare.

Relatively little attempt has been made to divide up the spiny neurons into different classes and they are usually defined according to the lamina in which their soma is located. However, many types can be distinguished on the basis of their dendritic morphology. The clearest distinction is that some spiny neurons have an apical dendrite (*pyramidal cells*) and some do not (*spiny stellate cells*). Many subgroups of the pyramidal cells can be distinguished on the basis of their morphology or functional characteristics and in each layer pyramidal cells can be found whose morphology and axonal projections are exclusive to that layer. For example, in layer 4, Lorente de Nó identified "star" pyramids, which got their name because of their symmetric and radially orientated basal dendrites. The most prominent pyramidal cells in the neocortex are the Betz cells of area 4, the *motor* cortex. The Betz cells are very large pyramidal cells located in layer 5 (see Fig. 12.3D). Their axons form part of the pyramidal tract that descends to the spinal cord. The primary visual cortex also has a distinct set of exceptionally large pyramidal neurons, called the *solitary cells of Meynert*. These pyramidal cells, which are found in the deep layers (5 or 6, depending on species), project to other cortical areas and down to the midbrain structures such as the superior colliculus and the pons. Within layer 5 in the visual cortex two distinct types of pyramidal cells have now been distinguished on the basis of a correlated structure–function relationship. One type has a thick apical dendrite that ascends to layer 1 where it forms a terminal tuft. These neurons have a bursting discharge of action potentials in response to a depolarizing current. The other type has a regular discharge and their apical dendrite is thin and terminates without branching in layer 2 (Chagnac-Amitai et al., 1990; Mason and Larkman, 1990). This observation has led to theoretical work suggesting that the shape of the dendritic tree itself is a major factor in controlling the pattern of spike output from the neurons (Mainen and Sejnowski, 1996).

Spiny Stellate Neurons. A second group of spiny neurons, the spiny stellate neurons, are found exclusively in layer 4 of the granular cortex (Cajal, 1911). These also have spiny dendrites, but do not have the apical dendrite that is the characteristic of the pyramidal cells. Instead, dendrites of approximately equal length radiate out from the soma and give these neurons a star-like appearance, hence their name. Occasionally these neurons do project to other areas, but most have axonal projections confined to the area in which they occur. It has been proposed that these neurons are simply pyramidal neurons without an apical dendrite. However, they differ in a number of important respects from pyramidal cells, e.g., they have much lower spine densities and many more excitatory synapses on their dendritic tree (Anderson et al., 1994). They should be considered as a distinct cell type confined to layer 4 of sensory cortex. Previously the spiny stellate cells were thought to be the sole recipients of the thalamic input to the sensory cortices, but it is clear that although they probably are the major recipient, thalamic neurons also connect to the pyramidal cells and smooth cells (Hersch and White, 1981; Hornung and Garey, 1981; Freund et al., 1985; Ahmed et al., 1994).

SMOOTH NEURONS

The class of neurons with spine-free dendrites is frequently referred to as smooth stellates, but since their dendritic morphology is rarely stellate, a more accurate term is simply *smooth neurons.* They tend to have elongated dendritic trees, both in the radial and the tangential dimension. Their dendritic morphologies have been described as multipolar, bipolar, bitufted and stellate, but the most useful discriminator of the different types has been the axonal arbor. At least 19 different types of smooth neurons have been described (Szentágothai, 1978; Peters and Regidor, 1981) but the basket cell, first described by Ramón y Cajal, appears to be the most common. These smooth neurons do not just have morphologically distinct axonal arbors, they also form quite specific synaptic connections, as will be described below.

The most prominent smooth neuron is the cortical *basket cell.* As with basket cells in the cerebellum (Chap. 7) and hippocampus (Chap. 11), the axons of the basket cells form nests or baskets around the somata of their targets, usually pyramidal cells. How-

ever, modern studies have shown that basket cell boutons form most of their synapses on the dendrites and spines of pyramidal cells. In superficial and deep layers, the main feature of the basket cell axonal arborization is the lateral extension of the axon (Fig. 12.4B). In the middle layers, the basket cells have much more compact axonal arbors (Fig. 12.4C). As with the well-studied patterns of thalamic afferents to the visual cortex (see below), which underlie the functional ocular dominance columns, these differences in the axonal arborizations most probably relate to the functional architecture of the piece of cortex in which they are located.

As with the spiny cells, some morphological types of smooth neurons are found only in particular layers. Layer 1, for example, has two types that are not found in other layers: the *Retzius-Cajal neuron*, which has a horizontally elongated dendritic tree, and the *small neuron of layer 1*, which has highly localized dendritic and axonal arbors. Many of the smooth types have descending or ascending axon collaterals in addition to their lateral extensions. Most notable of these is the *double bouquet cell* of Ramón y Cajal (Fig. 12.4D), which is characterized by elongated dendrites extending radially above and below the somata, and an axon that forms a cascade of vertically orientated collaterals. Another neuron with a vertical organization is the Martinnoti cell, whose soma is located in layer 6, but whose axon processes span all layers. Perhaps the most evocative description of a smooth cell was given by *Szentágothai* to the *chandelier cell*, so named because its axonal boutons are arranged in a series of vertical "candles" which give the whole axonal arborization the appearance of a chandelier (Fig. 12.4A).

Histochemical methods have revealed the existence of a further smooth neuronal type, which is sparse in the gray matter, but which forms a distinct layer at the border of the gray and white matter. These neurons stain positively for the enzyme NADPH-diaphorase, which is a synthetic enzyme for nitric oxide gas. Although they are few in number, their axonal ramifications are immense and provide a rich plexus of axons throughout the gray matter.

AFFERENTS

Thalamus. The thalamus projects to all cortical areas and provides input to most layers of the cortex. The densest projections are to the middle layers, where they form about 5–10% of the synapses in those layers (LeVay and Gilbert, 1976; White, 1989; Ahmed et al., 1994). The main feature of this input is that it is highly ordered. The sensory inputs are represented centrally in a way that their topographic arrangement in the periphery is preserved. This mapping is achieved by preserving the nearest-neighbor relationships of the arrangements of the sensory or motor elements in the periphery. Such topographic projections are a ubiquitous feature of the cortex. The precision of the mapping does vary between areas, however. The primary sensory and motor areas usually preserve the highest detail of the topography, which degrades progressively through secondary and tertiary and higher order areas of cortex.

An important transform in the topography from the periphery to the center is that the regions of highest receptor density have the largest representation in the cortex. This transformation is described as the *magnification factor* of the projection (Daniel and Whitteridge, 1961). In the visual system of the primate, the fovea of the retina contains the highest density of photoreceptors and the primary visual cortex represents this by devoting cortex in the ratio of 30 mm per degree of visual field to this representa-

tion. In the far periphery of the visual field the ratio falls off to about 0.01 mm/degree of visual field. In the somatosensory system the hand and face have high densities of touch receptors and these parts have a magnified representation in the primary somatosensory cortex. One of the most remarkable cortical representations is that of the whiskers of rats and mice. Each whisker has a separate representation in the cortex, which appears as a barrel when looked at in a tangential section of the cortex (Woolsey and Van der Loos, 1970). The centers of the barrels are formed by clusters of thalamic afferents that convey impulses from each whisker. The cortical map of the whiskers forms a representation that is topologically equivalent to the arrangement of whiskers on the face of the rat or mouse. This whisker map dominates the representation of the somatosensory surface of the rodent.

In the cat visual cortex, the terminal arbors of each individual thalamic afferent may extend over 1–5 mm of the cortical surface so that each point in layer 4 is covered by the arbors of at least 1000 separate thalamic relay cells (Freund et al., 1985). Thus, the dendritic tree of an average layer 4 neuron, which extends for 200–300 μm, could receive input from many more thalamic afferents. However, the connections are not made randomly between the geniculate afferents and the cortical neurons. Selectivity is revealed in several ways. For example, there is a high degree of precision in the visuotopic map recorded in the first-order cortical neurons in the input layer, i.e., those receiving monosynaptic activation by the thalamic afferents. This clustering is made according to the eye preference of the arbors. Those thalamic relay neurons that are driven by the right eye cluster together in regions about 0.5 mm in diameter and are partially segregated from the afferents that are driven by the left eye. This segregation forms the basis of ocular dominance columns. In addition there is some clustering of the afferents according to whether they are ON or OFF center. This clustering of inputs forms the basis of the ON and OFF subfields of the simple cells. In the somatosensory pathway there are segregations according to the modality of the sensory information, e.g., light touch is segregated from deep pressure and so on (Powell and Mountcastle, 1959).

Other Subcortical Regions. Although the thalamus is a major source of input to the neocortex, it is not the only one. More than 20 different subcortical structures projecting to the neocortex have been identified (Tigges and Tigges, 1985). These structures include the claustrum, locus coeruleus, basal forebrain, the dorsal and median raphe, and the pontine reticular system. As has been pointed out in many earlier chapters, these pathways have distinct neurochemical signatures, which has made the analysis of their cortical targets more tractable. The contributions of these different pathways vary from one cortical area to the next and among species for a homologous cortical area. There are also wide differences in the laminar projections of the terminals of these neurons between areas and in very few cases have the synaptic targets of these projections been identified. Thus, it is as yet not possible to offer a simple schematic of these pathways, but there are a few whose role in plasticity and development have been examined.

Because of their relative ease of identification, the monoaminergic innervation of the cerebral cortex has been studied most intensively. These systems are generally thought to be diffuse and nonspecific, both in terms of the information they carry and in terms of their lack of spatial specificity and anatomical organization. Physiological

examinations of these neurons are rare, but closer examinations of the anatomy have generally revealed a higher degree of specificity (Parnevelas and Papadopoulos, 1989). Three main types of monoamine-containing cortical afferents have been described: the dopamine-positive fibers arising from the rostral mesencephalon, the noradrenaline-containing axons originating from the locus coeruleus, and the serotonin (5-HT) fibers that originate from the mesencephalic raphé nuclei. There has been some doubt as to the mode of release of the transmitter, because early studies failed to find clear ultrastructural evidence of synapses. This was consistent with an older concept of the brain as a complex neuroendocrine organ where neurosecretion was the means by which brain activity was modulated. However, it is now clear that monoaminergic fibers in the neocortex do form conventional synapses and can show a high degree of anatomical specificity, both for particular cortical areas and for particular laminae within a single cortical area.

The projections of the locus coeruleus, which lies in the dorsal pons, have been relatively well studied. The nucleus is small, but projects to most of the neocortex in a roughly topographic arrangement (Waterhouse et al., 1983). Neurons in the dorsal portion project to posterior regions of the neocortex, such as the visual regions, whereas neurons in the ventral portion project to frontal cortical areas. In primates, the strongest projections are to the primary motor and somatosensory cortices and their related association areas in frontal and parietal lobes (Tigges and Tigges, 1985). The fine, unmyelinated, axons ramify horizontally, most prominently in layer 6, and form synapses with spine shafts and somata (Papadopoulos et al., 1987). The neurons synthesize norepinephrine, which is thought to be involved in the development and plasticity of thalamocortical projections in the visual cortex. These fibers develop early and their removal by neurotoxins prevents plasticity of the columns formed by the thalamic afferents arbors driven by the left and right eye (Daw et al., 1983; Pettigrew, 1982). Activity in locus coeruleus neurons correlates with changes in the EEG, which suggests that it is involved in the arousal response induced by sensory stimuli.

The raphé nuclei and pontine reticular formation are a complex of nuclei that contain the highest density of neurons that synthesize serotonin. These neurons project to all cortical areas with varying degrees of laminar specificity (Tigges and Tigges, 1985; Mulligan and Tork, 1988). There are clear differences between projections to the homologous areas in different species that make generalizations impossible, e.g., the strongest projections in the monkey are to the thalamorecipient layers of area 17, whereas these layers are relatively poorly innervated in the adult cat. In the kitten, however, there is a transient surge of serotonergic innervation of the thalamorecipient layer 4, which may indicate a relationship to the critical period (Gu et al., 1990).

The third monoamine projection to cortex is the dopaminergic pathway. It has been suggested that a dysfunction of the dopaminergic innervation of the prefrontal cortex is one of the factors in the pathogenesis of schizophrenia. The dopaminergic projection to the frontal cortex originates from the ventral tegmental area, the rostral mesencephalic groups, and the nucleus linearis. They form symmetric synapses with the dendrites of pyramidal cells and with GABAergic smooth neurons (van Eden et al., 1987; Verney et al., 1990; Smiley and Goldman-Rakic, 1993). All layers except layer 4 receive dopaminergic input. Dopaminergic projections are strongest to the rostral cortical areas, especially the prefrontal cortex. Here they target pyramidal cells, particularly spines, which they share with an excitatory synapse.

Although there are intrinsic sources of acetylcholine from neurons within the cortex, the major sources of the acetylcholinergic fibers in the cortex are extrinsic. These fibers originate from the nucleus basalis of Meynert and the diagonal band of Broca, which constitute the nuclei of the basal forebrain. These cholinergic projections to the neocortex have been of particular interest because of their possible involvement in the pathology of Alzheimer's disease. The terminals of the acetylcholinergic fibers distribute through all cortical layers, with the densest innervation in layer 1 and relatively sparse innervation of the deep layers (de Lima and Singer, 1986; Aoki and Kabak, 1992). They form synapses with dendritic shaft and spines but show some bias for the GABAergic neurons.

Although it was previously thought that all GABAergic synapses were derived from intrinsic sources in the cortex, it has now been demonstrated that there are GABAergic projections from subcortical nuclei to the cortex. These afferents arise from the basal forebrain, the ventral tegmental area, and the zona incerta. The GABAergic neurons of the zona incerta project to sensory and motor cortex, but not to the frontal cortex. As with the acetylcholinergic fibers from the same source, the GABAergic neurons of the visual cortex are a major target of the GABAergic afferents of the basal forebrain (Beaulieu and Somogyi, 1991).

The claustrum is also a nucleus of the basal forebrain. It connects reciprocally and topographically with the cerebral cortex (LeVay and Sherk, 1981; Tigges and Tigges, 1985). However, the reciprocal connections do not form a single continuous map, but are segregated into function specific divisions. Thus, the claustrum is not strictly multimodal, although it contains representations of visual, auditory, somatosensory, limbic and perhaps motor functions. These functions are represented separately in the nuclear mass of the claustrum and there is no evidence of integration of the different modalities. In this respect, the claustrum follows the principle of separate representation of these modalities adopted by the neocortex and thalamus. In the case of the visual system it is clear that many, perhaps all, of the retinotopically organized visual areas converge on the claustrum and it in turn projects divergently back to them. In the primary visual cortex the projection to the claustrum arises from a subset of the layer 6 pyramidal cells. The claustrum sends a sparse projection back to all layers of visual cortex where it forms excitatory connections mainly with the spines of excitatory neurons, except in layer 4 where synapses with dendritic shafts form about half the targets (LeVay and Sherk, 1981).

Cortico-Cortical Connections. Although anatomists have emphasized the long fiber tracts between the neocortex and their subcortical targets and suppliers, the major input to any cortical area is from other cortical areas. Braitenberg and Schüz (1991) have calculated that only 1 in 100 or even 1 in 1000 fibers in the white matter is involved in subcortical projection. Most of the fibers in the white matter are involved in the intrahemispheric connections and interhemispheric connections. Over the past 20 years these connections have been intensively studied, particularly in the primate visual cortex. The pattern that has emerged is that the pyramidal cells of the superficial layers project to the middle layers (principally layer 4) of their target area, whereas the deep

layer pyramidals project outside the middle layers to superficial and deep layers. These patterns have been used to classify patterns as *feedforward* (projecting to layer 4), or *feedback* (projecting outside layer 4) (Felleman and Van Essen, 1991; Kennedy et al., 1991). All cortical areas are reciprocally connected by these feedforward and feedback pathways. In the face of multiple parallel pathways projecting to and from cortical and subcortical areas such simple classifications of feedforward and feedback may not translate into functional significance. However, it is clear that the substantial majority of the neuronal targets of these corticocortical connections are pyramidal neurons.

One of the most important principles in cortical circuitry is the need to save "wire," i.e., reduce the length of the axons that interconnect neurons (Mead, 1990; Mitchison, 1992). The dimensions of this problem are evident in the statistics of the amount of wire involved. Each cubic millimeter of white matter contains about 9 m of axon, and an equal volume of gray matter contains about 3 km of axon. The volume occupied by axons would be greatly increased if each neuron had to connect to every other neuron in a given area, or if every neuron were involved in long-distant connections between cortical areas. Instead, the design principles of cortex are that neurons are sparsely connected, that most connections are local, and only restricted subsets of neurons are involved in long-distance connections.

The constraint on volume can also lead to multiple cortical areas. If separate areas are fused into a single area that preserves the total cortical thickness of 2 mm, then the components of the original areas must spread over a larger area (Mitchison, 1992). The original connections between neurons now have to span larger distances and so contribute to a larger volume for the same number of neurons. Mitchison has shown that fusing 100 cortical areas leads to a 10-fold increase in the cortical volume. Of course, if all the cortical areas are fused into one area, then much of the white matter can be eliminated. However, the increase in the volume of the *intra*areal axons far exceeds the reduction of the *inter*areal axons. Similar arguments can be raised for the patchiness of connections within a cortical area that are a cardinal feature of cortical organization. A given cluster of neurons projects to a number of sites within a given cortical area. These clusters tend to link areas of common functional properties. The size of the clusters—about 400 μm—is remarkably uniform between cortical areas. This size is similar to the spread of the dendritic arbor. Malach (1992) has shown theoretically that such an organization increases the diversity of sampling across a cortical area that has a nonuniform distribution of functional properties.

SYNAPTIC CONNECTIONS

Types

Gray used the electron microscope to make the fundamental observation that there are two basic types of synapses in the neocortex, which he called *types 1 and 2* (Gray, 1959). The synapses made by the vast majority of the cortical spiny neurons and by some of the subcortical projections, such as the thalamic and claustral afferents, are type 1. Type 2 synapses are made by smooth neurons and some of the subcortical projections, such as the noradrenergic fibers. His classification was based on the appearance of the electron-dense staining adjacent to the pre- and postsynaptic membranes. The type 1 synapses have a thicker postsynaptic than presynaptic density, giving them an *asymmetrical* appearance. The type 2 synapses have equally thick pre- and postsynaptic densities, which given them a more *symmetrical* appearance. There are additional morphological criteria that have been used to classify the synapses (see Chap. 1). The synaptic cleft of the type 1 synapses is wider than that of type 2 synapses; the vesicles associated with type 1 synapses tend to be round, while the type 2 synapses are pleomorphic (Colonnier, 1968). Significantly, these morphological distinctions correlate with the physiological divisions, excitatory in most cases being type 1 and inhibitory, type 2 synapses.

Both types of synapses are found throughout the cortex in approximately constant proportions. In each cubic millimeter of neocortex there are 2.78×10^8 synapses, 84% of which are type 1 synapses and 16% are type 2 (Beaulieu and Colonnier, 1985). Both types are found on all cortical neurons, but their locations on the dendritic trees of the different types differ (Fig. 12.5; Gray, 1959; Szentágothai, 1978; White and Rock,

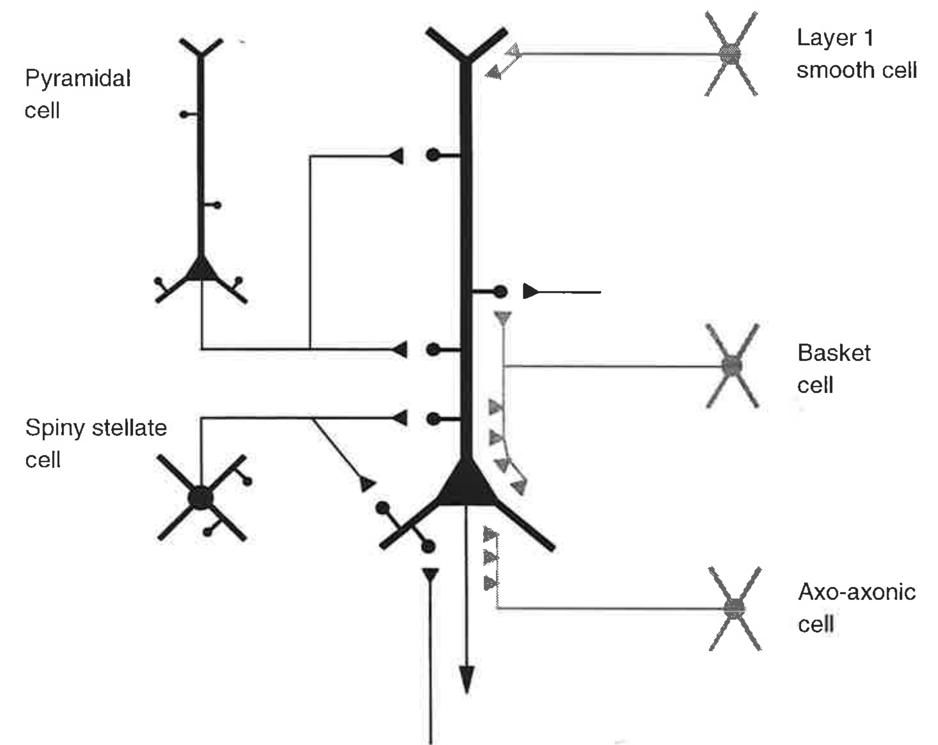

Fig. 12.5. Synaptic connections in neocortex. Configurations of excitatory and inhibitory connections made onto a typical pyramidal neuron (center). The excitatory (spiny) cells (black, left) and thalamic afferents (black, bottom) form synapses with the spines of the target pyramidal cell. Layer 6 pyramidal cell (not shown) are the exception to this rule. They form synapses mainly with the dendritic shafts of target spiny cells. There are a number of different classes of inhibitory (smooth) cells (gray, right), each with a characteristic pattern of connection to the pyramidal cell. Three classes are shown here. Each smooth cell makes multiple synapses with its target. The superficial smooth cell synapses with the apical tuft. The basket cell synapses with the soma, dendritic trunk, and dendritic spines. The chandelier cell synapses with the initial segment of the axon.

1980; Beaulieu and Colonnier, 1985; White, 1989). Pyramidal cells receive few type 1 synapses on their dendritic shafts and none at all on their somata or initial segment of the axon. Conversely, type 2 synapses are found on the proximal dendritic shafts, on the somata, and on the axon initial segment of pyramidal cells. Nearly every spine of pyramidal cells forms a type 1 synapse, but only about 7% of spines form an additional type 2 synapse. Similar distributions have been reported for the spiny stellate cells of the mouse somatosensory cortex, but the pattern for the spiny stellate cells in layer 4 of the primary visual cortex is different. About 60% of the type 1 synapses are formed with the proximal and distal dendritic shafts, the remainder are formed on the heads of the dendritic spines (Ahmed et al., 1994; Anderson et al., 1994). Type 2 synapses are found on the somata, but synapses are rarely found on the axon initial segment. Although the type 2 synapses are clustered in higher density on the proximal dendrites, about 40% of the type 2 synapses are on distal portions of the dendrites (i.e., more than 50 μm from the soma).

The smooth neurons by definition do not bear spines, so both type 1 and type 2 synapses are formed on the beaded dendrites that are a characteristic feature of smooth neurons. The beads themselves are the sites of clusters of synaptic inputs. The pattern of input to the smooth neurons is quite different from that of the spiny neurons: both types of synapses cluster on the proximal dendrites and somata at about 2–3 times the density found for spiny dendrites. The type 2 synapses are rarely found on the distal regions of the dendritic tree and the density of type 1 synapses on the distal dendrites is less than on the proximal dendrites. The initial segment of the axon of smooth neurons does not form synapses.

SPINY NEURONS

The axons of the spiny neurons form the vast majority of the synapses in the cortex. The synapses they form are type 1 in morphology and almost all are on spines (80–90% of targets) (Sloper and Powell, 1979a; Martin, 1988). One type of spiny neuron, a layer 6 pyramidal neuron, is the exception to this general rule: it forms most of its synapses preferentially with the shafts of spiny neurons in layer 4 (see White, 1989). Some synapses of the spiny stellate or pyramidal neurons are formed with dendrites or somata of smooth neurons, but these constitute only about 10% of their output. A feature of the output of the spiny neurons is that they contribute only a few synapses to any individual postsynaptic target. Conversely, any single neuron receives its excitatory input from the convergence of many thousands of neurons, most of which are in the same cortical area. The thalamic afferents, which provide the principle sensory input to cortex, form about 10% or less of the synapses in layer 4, the main thalamorecipient layer (White, 1989; Ahmed et al., 1994; Fig. 12.6).

SMOOTH NEURONS

The synaptic connections of the smooth neurons differ in a number of significant respects from the spiny neurons. Their axons are less extensive than those of the spiny neurons and they make multiple synapses on their targets. This means they contact many fewer targets on average than spiny neurons. Whereas the spiny neurons generally form synapses with dendritic spines, the smooth neurons target a variety of sites. In addition, different smooth neuron types form synapses specifically with different

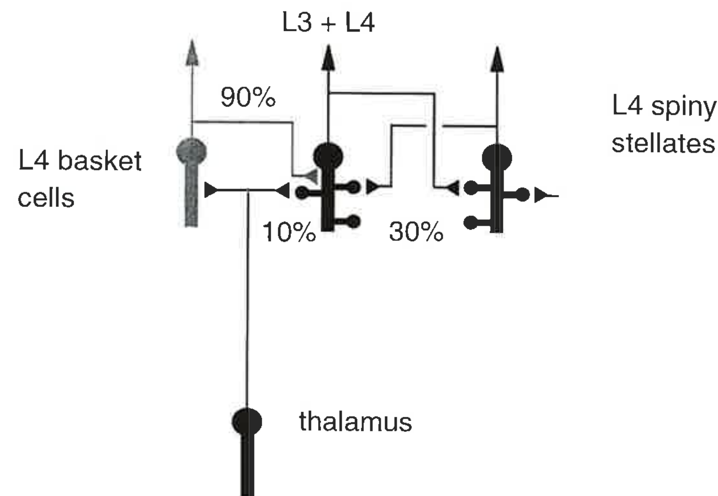

Fig. 12.6. Fractions of synaptic connections onto spiny stellate neurons in layer 4 of cat striate cortex (Ahmed et al., 1994). Only about 10% of the excitatory synapses are derived from the lateral geniculate nucleus. Thirty percent arise from other spiny stellate neurons in layer 4, and a further 40% from the layer 6 pyramidal cells (not shown). Ninety percent of the inhibitory inputs arise from layer 4 basket cells.

portions of the neuron (Fig. 12.5). The major output of the smooth neurons, however, is to spiny neurons. The smooth neurons form no more than 15% of the targets of the spiny neurons.

Basket cells (Fig. 12.4B) are the most frequently encountered smooth neuron in Golgi preparations and in intracellular physiological studies. Kisvárday (1992) has estimated that they form at least 20% of all GABAergic neurons. They have a very characteristic axon that forms the most extensive lateral connections of any of the smooth cell types. The basket cells of the superficial and deep layers have axons that radiate from the soma up to distances of 1–2 mm. In layer 4 the small basket cell (also called a *clutch cell*, in this context; see Fig. 12.4C) axon is more localized and extends about 0.5 mm laterally in most cases (Mates and Lund, 1983; Kisvárday et al., 1985). Each basket cell forms multiple synapses with about 300–500 target neurons and makes about 10 synapses on average with each target. Ramón y Cajal originally provided the descriptive name "basket" cells because in the Golgi preparations the axons of the basket cells form pericellular "nests," or baskets, around the soma of the pyramidal cells (Cajal, 1911). Modern light and electron microscopic studies on the axonal boutons of intracellularly labeled basket cells have revealed, as noted above, that the major targets of the basket cell axons are the dendritic shafts and spines of pyramidal and spiny stellate cells (Somogyi et al., 1983; Kisvárday, 1992). The "basket" seen by Ramón y Cajal is formed by the convergence of about 10–30 basket cells each contributing a twiglet to the perisomatic nest. Superficial and deep basket cells and clutch cells make about 20–40% of their synapses with spines, 20–40% with dendritic shafts, and the remainder with the somata.

The chandelier cell (Fig. 12.4A) is rarely encountered in Golgi preparations and in intracellular recordings in vitro and in vivo. However, they have been a focus of in-

terest because their sole output is to the initial segment of the axons of pyramidal cells. Such specificity is not seen with any other neocortical cell although it is common elsewhere in the brain (see earlier chapters). The chandelier cells seem to be found only in the superficial layers and layer 4, but some have a descending axon collateral that innervates the deep layer pyramidal cells. Correspondingly, electron microscopic examination of the initial segments of the pyramidal cells has indicated that there are about three times as many synapses along the initial segment of the axon of superficial layer pyramidal cells as compared with deep layer pyramidal cells (Somogyi, 1977; Sloper et al., 1979; Peters, 1984). In the superficial layers, the axon initial segment forms about 40 type 2 synapses with the boutons of the chandelier cell. Each pyramidal cell receives input from 3 to 5 chandelier cells and each chandelier cell forms synapses with about 300 pyramidal cells over a surface area about 200–400 μm across (Somogyi et al., 1982; Peters, 1984).

Double bouquet neurons (Fig. 12.4D) are smooth neurons found in the superficial layers and having a bitufted axonal system that spans several layers (Cajal, 1911; Somogyi and Cowey, 1981). In contrast to the laterally directed axons of the basket cell, the predominant orientation of the double bouquet cell's axon is vertical. For this reason, it was originally thought that the vertically oriented apical dendrites of the pyramidal cells were the major target of multiple synapses from the pallisades of double bouquet axons. There is no clear evidence of multiple synapses between double bouque axons and apical dendrites, but the pyramidal cells are nevertheless major targets. About 40% of the type 2 synapses of double bouquet cells are formed with dendritic shafts and most of the remainder are formed with dendritic spines (Somogyi and Cowey, 1981).

The synaptic connections formed by the axons of layer 1 neurons have been studied rarely. The small neurons of layer 1 have as their major target the spines and dendritic shafts of pyramidal cell apical dendritic tufts that form most of the neuropil of layer 1. The connections made by the Cajal-Retzius cells are unknown. Similarly, the connections made by other smooth neurons of the neocortex have yet to be determined.

BASIC CIRCUIT

An article of faith among neuroanatomists from the beginning of the study of the cortical circuits was that there was an elementary pattern of cortical organizations. Anatomists studying Golgi stained material were generally convinced that there were structural details that remained constant despite variations in cell number, form, size, and type of neurons. This constant, according to Lorente de Nó, was the "arrangement of the plexuses of dendrites and axonal branches," by which he meant the synaptic connections between cortical neurons. However, subsequent examination of the details of cortical circuitry still leaves considerable leeway in interpretation of the pattern of connections. Any attempt to suggest a common basic pattern of connections necessarily will be open to the criticism that such models are based on the intensive study of a very small number of areas, mainly primary sensory areas at that (White, 1989). Nevertheless, the great advantage of having some hypothetical circuit is that it focuses ideas and gives form to otherwise simply descriptive accounts of cells and connections within a given area that have been the standard works in the anatomical field.

Most modern models of cortical circuits are derived from functional studies. In contradistinction to the great diversity of cell types and interconnections that characterize the anatomical descriptions, the circuits derived from physiological experiments strip off all the embellishment and detail: simple circuits of excitatory cells make up the core of these models. The Hubel-Wiesel models of the local circuits of visual cortex are the best-known examples (Hubel and Wiesel, 1977). In these circuits, the inhibitory neurons are added as a means of providing the lateral inhibition that is such a feature of sensory processing at all levels. Two basic designs have emerged. In the dominant model, the processing is strictly serial: input arrives in the cortical circuit, it is fed forward through a short chain of two or three neurons within the local area, and then it is transmitted to other areas by the output neurons. This feedforward model follows from the simple idea that sensory input must pass through several processing stages in the neocortex before it arrives at a motor output.

An alternative view was first given form by Lorente de Nó. He supposed that the rich interconnections between the different cortical layers made the cortical circuit a unitary system, with no clear basis for a distinction between input, association, and output layers. In his view, impulses circulate through these recurrent circuits and the activity in the cortical circuit is modified by the action of the association fibers arriving at critical points within the circuit. In turn, the effect of the incoming input depends on the activity in the circuit at that point in time.

Both the feedforward and the recurrent recurrent model agree, however, that the processing that occurs in the neocortex is essentially local and vertical. In this arrangement, the anatomy and the physiology agree. In most cortical areas the function being represented is laid out topographically, as in the retinotopic maps of the visual cortex or the motor maps in the motor cortex. For example, portions of the sensory surface that will receive related input are nearest neighbors in their cortical representation. The vertical connectivity within the cortex is similarly local. The axons of cortical neurons do not extend more than a few millimeters laterally in any area. Thus the monosynaptic connections at least are local. This corresponds with the physiological findings of Mountcastle, Hubel and Wiesel, and others who discovered that neurons with similar functional properties are organized in "columns" that extend from the cortical surface to the white matter (Powell and Mountcastle, 1959; Hubel and Wiesel, 1977; Fig. 12.7).

In fact, with few exceptions, most arrangements of neurons are only strictly columnar when viewed with the one-dimensional tool of the microelectrode. The clearest view arises from optical imaging in which the activity of large numbers of nerve cells can be viewed indirectly by measuring the changes in the oxygenation of hemoglobin that occur during the increased oxygen demand of neural activity. Such imaging techniques have been used to show that in the lateral dimension, the different functional maps take the form of slabs or pinwheels. The widths of the slabs vary according to the particular property being mapped, but are of the order of 0.5 mm in the case of the best-studied system—the ocular dominance system of the primary visual cortex. In this system, the afferents of the lateral geniculate nucleus representing left and right eye map into a series parallel slabs that look like a zebra's stripes when viewed from the surface. Such segregation and patchiness are seen at the level of single axonal arbors and appear to be the means by which the cortex maps multiple processes into a single area. In the few cases in which it has been examined, the rule of connectivity between

patches is that "like" connects to "like." For example, a number of different functional dimensions are represented within the retinotopic map of the primary visual cortex of primates. These dimensions are seen physically in the ocular dominance and orientation slabs and the cytochrome oxidase columns, which are called "blobs" because of their appearance when viewed in tangentially cut sections of the cortex (Hendrickson et al., 1981; Horton and Hubel, 1981; Wong-Riley and Carroll, 1984; Fig. 12.7). In each of these systems, neurons of like function interconnect.

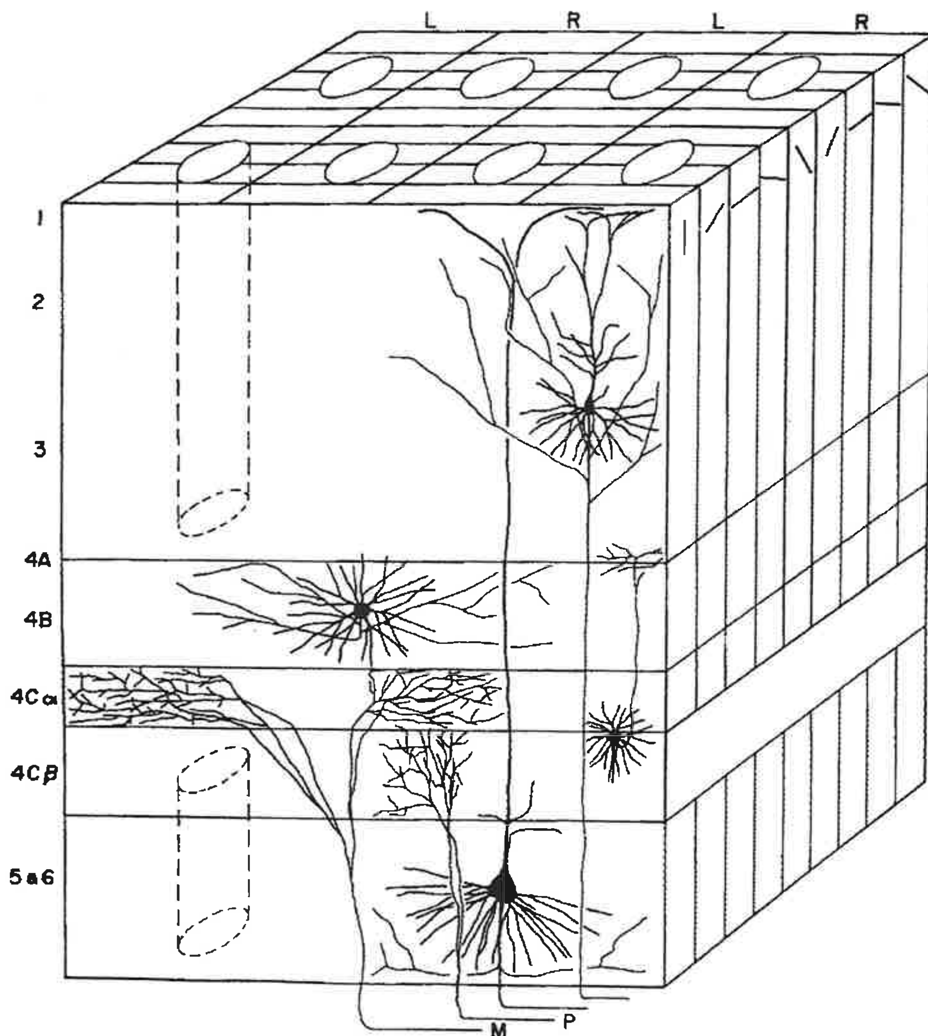

Fig. 12.7. "Ice cube" model of visual cortex in the macaque monkey devised by Hubel and Wiesel. L and R indicate ocular dominance "columns" or "slabs." The narrower orientation columns run orthogonally. The cytochrome oxidase rich "blobs" appear as cylinders in the center of ocular dominance columns. M, P: Thalamic afferents originating from the magno and parvocellular layers of the lateral geniculate nucleus, respectively, and terminating in separate subdivisions of layer 4, within appropriate ocular dominance slabs.

CORTICAL OUTPUT

All projection neurons have recurrent collaterals that participate in local cortical circuits, so there are no layers that have exclusively output functions. The output neurons from the cortex are generally pyramidal cells. These same cells, however, may also be *input* neurons in that they may receive direct input from the thalamus. There is a laminar-specific organization of the output according to the location of their targets. A simplified view of the laminar organization is provided in the summary figure Fig. 12.8. The general rule-of-thumb is that cortico-cortical connections arise mainly from the superficial cortical layers and the subcortical projections arise from the deep layers. Within the deep layers, there is an output to regions that have a motor-related function, e.g., the superior colliculus, basal ganglia, brainstem nuclei, and spinal cord. These regions receive their cortical output from a relatively small number of layer 5 pyramidal cells. There is also an output to the subcortical relay nuclei in the thalamus, which are the source of the primary sensory input to the cortex. This cortico-thalamic projection generally arises from the layer 6 pyramidal cells. However, there are clear exceptions to this rule of thumb. In area 4, the projections into the pyramidal tract, which supplies the spinal cord and cerebellum, arise from both layer 5 and from layer 3 pyramidal cells. The cortico-cortical connections may also arise from neurons in the deep layers. However, the simplifications are not extreme and offer a useful constraint on the connections that can be made within the basic circuits. For example, if a circuit in cat visual cortex requires an output to the eye-movement maps of the superior colliculus, then it necessarily will have to connect to the output pyramidal cells of layer 5. Although particular laminae are the source of the outputs to these different cortical and subcortical regions, the set of output neurons within a given lamina may not be uniform. Thus, within layer 6, the pyramidal cells that give rise to the cortico-thalamic projection are morphologically different from those that give rise to the cortico-

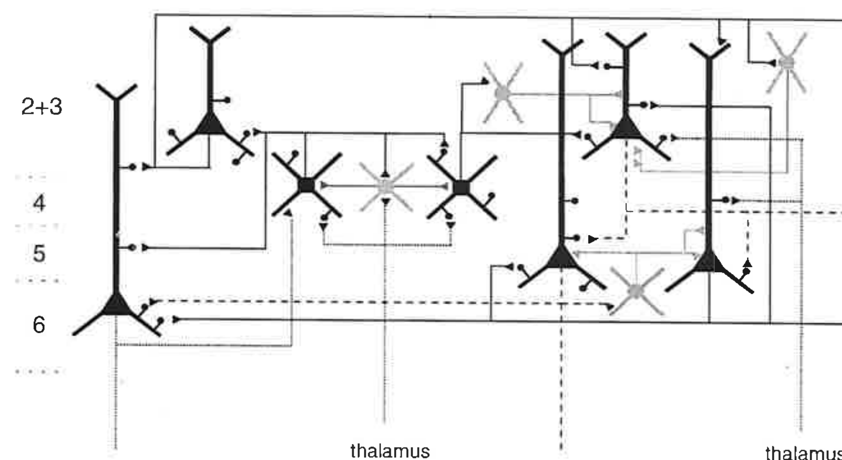

Fig. 12.8. Basic circuit for visual cortex. Smooth, GABAergic, neurons and their connections are indicated in gray. Spiny neurons and their connections are indicated in black. Cortical layers as indicated.

claustral projection (Katz, 1987). These two groups of pyramidal cells also have different local projection patterns: the cortico-thalamic pyramidal cells have a rich projection to layer 4, whereas the cortico-claustral cells project within layer 6 itself. The receptive fields of the cortico-thalamic neurons are significantly smaller than those of the cortico-claustral neurons (Grieve and Sillito, 1995).

As with the local intra-areal connectivity, the output neurons that project to other cortical areas also appear to be organized in patchy systems. One of the most elaborate discovered so far is the output from primary (V1) to the secondary visual area (V2), which arises from at least three specific subgroups of neurons in V1. These neurons project to another stripe system in area V2 in the monkey. These pathways may be visualized by the pattern of cytochrome oxidase staining (Gilbert and Kelly, 1975; Gilbert and Wiesel, 1979). Neurons located in the cytochrome oxidase blobs in V1 project to a series of thin cytochrome oxidase blobs in V2. The neurons in layer 3 outside the blobs project to pale stripe (interstripes) in V2, while the third group of projection neurons located in layer 4B of V1 project to a series of thick cytochrome stripes in V2. The stripes formed by these projections themselves reveal the organization of output from V2 to other cortical areas: the thin cytochrome stripes project to visual area 4 (V4), the interstripes to V3 and V4, and the thick stripes to area MT.

SYNAPTIC ACTIONS

Release of neurotransmitter at synapses is triggered by the membrane depolarization associated with the arrival of an action potential. Consequently, the pattern of arrival of APs at the end terminal is one of the fundamental factors governing the interaction of pre- and postsynaptic neuron. It is usually assumed that the pattern of action potentials seen by the presynaptic terminal is exactly the pattern that was generated at the beginning of the presynaptic axon. That is, we assume that the axon acts as a simple transmission line for action potentials, and that there are no factors that selectively alter its transmission characteristics over moderate time intervals. The presynaptic axon begins at the initial segment, which is also the site at which the axonal action potential transmission begins. The initial segment is electrotonically close to the soma, and therefore we assume the electrical events of the initial segment can be recorded from the soma, which is the most probable site of impalement by intracellular electrodes. Most of our knowledge about interneuronal communication rests on interpretations of electrical events in the soma, and in particular, on the assumption that the action potentials that we observe in the soma will ultimately affect postsynaptic targets.

NEURONAL EXCITABILITY

In considering the action of synapses, there are two key issues. One is the effect of the synapses on the neuron at the site of the synapses; the other, the response of the whole neuron to the local synaptic actions. The latter issue includes the attributes of the neuron, such as its membrane properties, the ionic currents involved, and the shape and cable properties of the neuron.

Sodium Currents. Action potential generation entails regenerative depolarization followed by a restorative repolarization. In cortical neurons, as in most other neurons, these two phases are mediated by a fast, voltage-dependent, inactivating sodium current (Connors et al., 1982), and a delayed, voltage-dependent potassium current (Prince and Huguenard, 1988), respectively. In addition to the inactivating sodium current, cortical neurons also exhibit a non-inactivating, voltage-dependent sodium current (Stafstrom et al., 1982, 1984) similar to that observed in cerebellar Purkinje cells (Llinás and Sugimori 1980a,b; see Chap. 7) and hippocampal pyramidal cells (Hotson et al., 1979; Connors et al., 1982; see Chap. 11), and analogous to the slow inward calcium current (I_i) seen in spinal motoneurons (Schwindt and Crill, 1980; see Chap. 4). In cortical neurons this "persistent" sodium current (I_{NaP}) is activated about 10–20 mV positive to the resting potential and attains steady-state conductance within about 4 ms. It remains persistent and large up to at least 50 mV above resting potential (Stafstrom et al., 1984). These properties suggest that I_{NaP} can be activated by EPSPs, and that I_{NaP} acts as a current amplifier for depolarizing inputs. Indeed, I_{NaP} can itself provide regenerative depolarization that is able to drive the membrane to the level where the larger spike generating sodium current is activated (Stafstrom et al., 1982). The difference in kinetics between these two regenerative sodium currents is probably responsible for the indistinct transition between the subthreshold rise of membrane potential and the rapid initial rise of the action potential (Stafstrom et al., 1984).

By recording directly from the apical dendrites of the pyramidal cells (Stuart and Sakmann, 1994), it has been shown that the dendrites contain active sodium conductances. However, they appear to be at a much lower density than at the soma or axon initial segment, which has the highest density and is the main site of initiation of the action potential, as was originally proposed from recordings from the motoneuron (Fuortes et al., 1957; Eccles 1957).

Potassium Currents. The inward sodium currents that accompany spike depolarization are opposed by an increase in outward potassium currents, and these currents ultimately restore the neuronal membrane to its resting level. The classical action potential mechanism provides a restorative outward current by just one delayed voltage-dependent potassium conductance, but the restorative outward current of cortical neurons is enhanced by several additional potassium currents. These currents affect the dynamics of membrane during postspike recovery and also during the subthreshold response to depolarizing inputs. Consequently, they affect the neuron's repetitive discharge behavior.

In the simplest case, a suprathreshold sustained depolarizing input current will evoke a train of action potentials. Each action potential ends with a repolarization that drives the membrane potential below threshold. The subsequent interspike interval will depend on the rate of postspike depolarization, since this will determine the interval to the next threshold crossing. If the time constants of the membrane currents are all short (i.e., of the order of an action potential duration), then the interspike intervals will be of equal duration and the neuron will exhibit sustained regular discharge. But some of the potassium conductances have much longer time constants and so their outward currents can be active throughout successive interspike intervals. Since these outward potassium currents oppose the depolarizing input currents, they retard threshold crossing and so increase the interspike interval. These interactions are the basis of adaptation, often re-

ferred to as *spike-frequency adaptation*, the progressive lengthening of interspike interval that occurs during a sustained depolarizing input to some cortical neurons. The process of adaptation in cortical cells is interesting because it imposes an intrinsic restriction on their discharge. It is calcium-dependent, it can be modified by neurotransmission, and adaptation characteristics correlate with morphological cell type.

The outward potassium currents that underly the impulse afterhyperpolarizations (AHP) are seen in cortical neurons both in vivo and in vitro (Connors et al., 1982). Three separate AHPs have been identified in layer 5 neurons of sensorimotor cortex: a fast, medium, and slow AHP (Schwindt et al., 1988b). The fast AHP has a duration of milliseconds, and follows spike repolarization. It is often followed by a transient delayed afterdepolarization (ADP). The medium AHP follows a brief train of spikes. It has a duration of tens of milliseconds, and its amplitude and duration are increased by the frequency and number of spikes in the train. The slow AHP (sAHP) is evoked by sustained discharge, and has a duration of seconds. All three hyperpolarizations are sensitive to extracellular potassium concentration, but they have different sensitivities to divalent ion substitutions and pharmacological manipulations (Schwindt et al. 1988a,b). This suggests that they are mediated by at least three distinct potassium conductances. However, the individual potassium conductances have not been identified completely. This is partly because of the difficulty in comparing the characteristics of the many potassium conductance types found in various excitable cells, the many different regimes of investigation, and inconsistent nomenclature.

There is evidence that neocortical cells have at least four potassium conductances: a delayed rectifier, a fast, transient, voltage-dependent (A-like) current; a slow, calcium-mediated (AHP-like) current; and a slow, receptor-modulated, voltage-dependent (M-like, mAHP) current (Connors et al., 1982; Schwindt et al., 1988a,b). Thus, the potassium currents of neocortical neurons appear qualitatively similar to those reported in hippocampal neurons of archicortex (see Chap. 11). But the situation is rather more complicated than this, as the following examples illustrate. The transient fast current of cortex is TEA sensitive (Schwindt et al., 1988a). The mAHP current is due to a calcium-mediated potassium conductance and so is superficially similar to AHP currents seen in hippocampal neurons. But the cortical conductance mechanism is not sensitive to TEA whereas the hippocampal current is. The cortical conductance is sensitive to apamin, whereas the hippocampal current is not (Schwindt, 1992). Muscarine and beta-adrenergic agonists abolish the sAHP but have no effect on the mAHP (Schwindt et al., 1988), whereas in hippocampus acetylcholine affects both the M and AHP currents (Madison and Nicoll 1984). These and other conductance differences may be due to important functional constraints on the discharge of neocortical neurons that are different from the discharge requirements of hippocampal neurons. An alternative view is that the differences have less to do with unique discharge requirements than with the variations of parallel evolution.

Some outward current conductances can be modulated by neurotransmitters. The outward potassium M current of cortical pyramids is reduced by activation of muscarinic receptors (Brown, 1988; McCormick and Prince, 1985). Since the outward current is reduced, the effect of depolarizing currents is enhanced. The slow Ca^{2+}-activated potassium (AHP) current of cortical pyramids is also decreased by acetylcholine (McCormick and Prince, 1986b). These modulations of slow outward currents are the

means whereby acetylcholine enhances discharge frequency and decreases adaptation. Similar effects have been noted in hippocampal neurons (Benardo and Prince, 1982; Cole and Nicoll, 1984; Madison and Nicoll, 1984). Neurotransmitters may also modulate currents that interact with the slow hyperpolarizing potassium currents. Schwindt et al. (1988b) have shown that low concentrations of muscarine abolish the sAHP, but at higher concentrations the sAHP is replaced by a slow after-depolarization (sADP) that is not potassium sensitive, nor is it sensitive to the sodium channel blocker TTX. The mechanism of the sADP is unknown.

In addition to the above effects, acetylcholine also evokes a transient early inhibition of pyramidal neurons. However, two findings indicate that this inhibition is probably an indirect effect of the excitation of inhibitory interneurons. First, the inhibition is mediated by a chloride conductance similar to that activated by GABA. Second, ACh has a rapid excitatory effect on the fast-spiking (presumably GABA-ergic) cortical neurons (McCormick and Prince, 1985, 1986b), and smooth cells are known to have cholinergic afferents (Houser et al., 1985).

Calcium Conductances. Calcium currents also contribute to the dynamics of cortical neurons. Somatic recordings from antidromically activated pyramidal tract neurons in vivo indicated the existence of fast prepontentials (Deschênes, 1981). Blocking the sodium channel blocker with QX-314 left these prepotentials intact, suggesting they were mediated by calcium channels in the dendrites (Hirsch et al., 1995).

These currents may affect the dynamics directly by contributing to the electrical behavior of the membrane, or indirectly by changing the internal calcium concentration, which in turn affects potassium conductance (described above). Where calcium currents are voltage-dependent, they operate as sodium currents do and so could contribute to spike generation. However, the calcium currents appear to be relatively small in cortical neurons, and must be unmasked by both blocking the sodium currents and depressing the potassium currents. Under these conditions, a Ca^{2+} spike can be elicited from some cortical neurons (Connors et al., 1982; Stafstrom et al., 1985). The threshold for this spike is about 30–40 mV positive to the resting potential, and therefore well above the activation thresholds for the sodium currents, I_{NaP} and I_{Na}.

Calcium spikes have been observed in hippocampal pyramidal cells (see Chap. 11) and elsewhere, and in these cases, they can be evoked after blockade of the sodium currents alone (Schwartzkroin and Slawsky, 1977; Wong et al., 1979). In order to initiate a calcium spike the conductance for calcium must be much larger than that for potassium. Presumably, g_K is large in cortical cells, and must be depressed in order to obtain a conductance ratio favorable for calcium spike initiation. Therefore, the need to depress the potassium conductance in cortical cells implies either that g_K is larger in cortical neurons than other calcium-spiking cells, or that the calcium conductance is smaller. An alternative explanation is that the site of the calcium conductance is located in the dendrites, electrotonically distant from the soma. In this case, a depolarization large enough to drive the distant site to the activation threshold of the calcium conductance would also strongly activate the more proximal voltage dependent potassium conductances. The resulting increase in potassium conductance would shunt depolarizing current injected into the soma, and so prevent the dendritic membrane from reaching the threshold for calcium current activation.

Stafstrom et al. (1985) suggest that there are two calcium conductances in cortical neurons, and that these are distributed along the soma-dendrite. The somatic calcium conductance is slow and small and has a high threshold. The dendritic conductance is both faster and larger than its somatic counterpart. Its threshold is also high, but this may be partly due to electrotonic distance from the soma, which makes it relatively difficult to activate from an electrode in the soma. Both somatic and dendritic currents contribute to the calcium spike. Somatic depolarization activates the somatic calcium current and that in turn activates the more distal dendritic calcium conductance that powers the calcium spike. Both currents are probably persistent and so they require activation of an outward current to effect the recovery phase of the spike. This outward current is provided by the slow potassium (AHP) current that is activated by the influx of calcium in cortical (Hotson and Prince, 1980) and hippocampal (Madison and Nicoll, 1984; Lancaster and Adams, 1986) neurons.

Direct evidence for the existence of dendritic voltage-sensitive calcium channels has come from membrane patches of apical dendrites (Huguenard et al., 1989) and by calcium imaging of the dendrites (Yuste et al., 1994). The imaging studies showed that the dendritic accumulation of calcium took place immediately after calcium spikes were triggered, followed by a slower diffusion of intracellular calcium. Confocal and two-photon microscopic imaging of calcium has revealed the sites of calcium channels in the dendritic shaft (Markram and Sakmann, 1994) and in spine heads (Yuste and Denk, 1995). It appears that calcium channels are distributed over the whole dendritic tree. The in vivo study of Hirsch et al. (1995) indicated that calcium spikes may be initiated in cat visual cortex in the absence of sodium spikes. However, Svoboda et al. (1997) found that sodium spikes were required to activate calcium spikes in rat barrel cortex.

The issue of the role of spines in the compartmentalization of calcium has also been addressed by a number of studies, unfortunately none as yet in neocortical pyramidal cells. The first studies that used optical methods to image the spines in hippocampal pyramidal cells indicated that individual spines could have quite different calcium dynamics from their parent dendrites (Muller and Connor, 1991; Guthrie et al., 1991). However, further studies in the hippocampal pyramids in which two-photon microscopy was used to image the spines of hippocampal pyramidal cells loaded with a Ca-sensitive dye indicate that individual spines are only activated under subthreshold conditions. If the neuron fires an action potential, then calcium enters the spines (Denk et al., 1996). Neocortical pyramidal cells have similar dimensions to those of the hippocampal pyramidal cells and it is likely that similar phenomena will be observed. Theoretically, the restriction of calcium in the spine during subthreshold synaptic activation could serve to segregate the potential that occurs on spines during coactivation of pre- and postsynaptic neuron (Rall, 1974a).

Repetitive Discharge. The repetitive discharge properties of neocortical cells has been investigated both in vivo (e.g., Calvin and Sypert, 1976) and in vitro (e.g., Ogawa et al., 1981). McCormick et al. (1985) originally reported three electrophysiological cell types in neocortex: fast-spiking, regular spiking, and bursting cells. The fast-spiking cells were sparsely spiny or aspiny neurons. These "smooth cells" are the GABA-containing, inhibitory neurons of cortex. The regular and bursting cells were both pyramidal neurons. "Regular firing" which is somewhat of a misnomer, refers to the adapting pattern of discharge in response to an injection of constant current into the soma. This was the predominant behavior of most pyramidal cells. Only a small percentage of these pyramidal cells exhibited a bursting discharge and they were located mainly in the deep cortical layers (Connors and Gutnick, 1990). However, it is now clear that there are exceptions to the general function–structure relationships described and smooth neurons are found that have the adapting pattern that was thought to be a characteristic of pyramidal cells. Kawaguchi (1995), for example, has found chandelier cells, double bouquet cells, and neurogliaform cells with adapting patterns of discharge that are more commonly associated with spiny neurons.

The discharge of regular spiking neurons showed various degrees of adaptation, and the presence of both AHP and M currents could be demonstrated in these cells. A transient, fast voltage-dependent (A) current is present in pyramids and this may contribute to their adaptation (Schwindt et al., 1988a). The structure–function correlations of the burst/nonburst firing pyramidal cells of layer 5 have been determined (Chagnac-Amitai et al., 1990; Connors and Gutnick, 1990; Mason and Larkman, 1990; Kim and Connors, 1993). The regular firing pyramids have thin apical dendrites that do not branch extensively in layer 1. The burst-firing pyramids by contrast have thick apical dendrites and an extensive tuft in layer 1. Multipolar and bitufted neurons with bursting patterns have been described by Kawaguchi (1995) who called them *low-threshold spike cells*. These neurons would respond with a burst of action potentials when the neuron was depolarized from a hyperpolarized potential. Their dendrites had few spines.

Bursting neurons (Connors et al., 1982; McCormick et al., 1985; Kawaguchi, 1995) respond to depolarization by generating a short burst of about three spikes. McCormick and Gray (1996) have reported another class of bursting cell, which they called a *chattering cell*. This cell produces a series of bursts during sustained depolarization. The exact mechanism of bursting in cortical neurons is unknown, but it has been explained by various mechanisms, including the activation of low- and high-threshold calcium currents (McCormick et al., 1985; Jahnsen, 1986a; McCormick and Gray, 1996), by a calcium-dependent potassium current (Berman et al., 1989), and most recently by the distribution of sodium channels in the dendritic tree (Mainen and Sejnowski, 1996). In theory, it is possible to achieve a short burst in a neuron that has limited fast outward current and a dominant AHP current (Berman et al., 1989). The reduced fast-outward current encourages a short interspike interval and consequently a rapid discharge. The discharge would be terminated by the growing AHP current. Thus, variations in the parameters of the same outward current conductances could determine whether a pyramidal neuron discharges in regular or burst mode. In the model of Mainen and Sejnowski (1996), the dendritic sodium conductances promote propagation of the somatic action potential back into the dendrites. When the soma has repolarized, current returns from the dendrites to produce a late depolarization and some maintained action-potential discharge. This effect was enhanced by high-threshold, voltage-gated Ca^{2+} channels. Schwindt et al. (1988a) have shown that reduction of the transient fast potassium conductance converts normal firing into burst firing, whereas specific reduction of mAHP increases the instantaneous discharge rate but does not affect adaptation (Schwindt, 1992).

The fast-spiking cells encompass a variety of smooth neuron types (Kawaguchi 1995). The action potentials of fast-spiking cells are brief by comparison with pyra-

midal neurons. The repolarization phase of the action potential is rapid and followed by a significant undershoot. This indicates the presence of an unusually large and fast repolarizing potassium current. Indeed, Hamill et al. (1991) were able to demonstrate that fast-spiking cells have a higher density of "delayed rectifier" potassium currents than do pyramidal cells. The spike repolarization is followed by a transient afterhyperpolarization. These cells showed little or no adaptation. The initial slopes of their current-discharge relation were steeper and their maximum discharge frequencies were higher than those of pyramidal neurons. There was no evidence of either the AHP or M potassium currents in these neurons; the absence of these longer time-constant outward currents in fast-spiking cells would explain their lack of adaptation.

Long-Term Potentiation. Brief tetanic stimulation of a set of input fibers potentiates synapses in hippocampal excitatory synapses for many hours (Bliss and Lömo, 1973). The mechanisms of this process have been extensively studied in the brain (see Chaps. 10 and 11) and the same processes are found in neocortical neurons. Homosynaptic (specific to the stimulated pathway) long-term potentiation (LTP) was first seen in neocortex in vivo, along with the converse phenomenon of heterosynaptic (affecting nonstimulated pathways) long-term depression (LTD), in which the synapses become weaker (Tsumoto and Suda, 1979). Subsequent investigation in vitro confirmed the presence of both LTP and LTD in neocortical neurons of young rats and kittens (Komatsu et al., 1981; Artola and Singer, 1987; Bindman et al., 1988; Artola et al., 1990; Aroniadou and Teyler, 1992). However, while LTP could be readily induced in neocortical neurons that showed bursting behavior (Artola and Singer, 1987), LTP was only induced in other cortical neurons in the presence of bicuculline, the GABAa antagonist (Artola and Singer, 1987).

LTP of inhibitory synapses has also been observed in visual cortex of developing rat (Komatsu and Iwakiri, 1993). Tetanic stimulation of an inhibitory pathway onto layer 5 pyramidal cells leads to a long (more than 1 hr) potentiation of the IPSPs. Weaker stimuli led to a short-term potentiation. The effects were specific to the stimulated pathway.

Artola et al. (1990) provided evidence that identical stimulation could produce either LTD or LTP, depending on the level of depolarization of the postsynaptic neurons. They suggested that if the EPSPs produced a depolarization that exceeds a certain level but remains below the threshold for activation of the NMDA receptor, then LTD results. If, however, the threshold for the NMDA receptor is reached, then LTP results. This is essentially the theoretical model of Bienenstock et al. (1982). Kimura et al. (1990) found that tetanic stimulation that would otherwise produce LTP will produce LTD if postsynaptic calcium ions are chelated. This indicates that the prevailing calcium concentration may be important for the production of LTP or LTD. Kirkwood et al. (1993) showed that one of the most effective means of producing LTD is by low-frequency (1 Hz) stimulation and that the induction of LTD was dependent on NMDA receptors. This suggests that the actual level of calcium might be critical for determining whether LTP (high postsynaptic calcium) or LTD (low postsynaptic calcium) is induced. However, a recent study (Neveu and Zucker, 1996) indicates that this is not the simple solution.

The precise roles of LTP and LTD in the neocortex remain a matter of speculation; the widely held belief that they have something to do with memory remains the central dogma. However, the existence of a clear *critical period* of development in the sensory cortex, in particular, has led to the obvious hypothesis that these synaptic processes are part of the cascade that leads to the formation and modification by experience of nerve connections. Investigations of mouse barrel cortex and rat visual cortex of the rat have indicated that LTP, induced without the aid of GABA antagonists, has a critical period. For example, in barrel cortex, it was possible to potentiate the thalamo-cortical synapses during the first week of life, but not the second (Crair and Malenka, 1995). This matches approximately the time course of structural plasticity of the thalamocortical afferents (Schlaggar et al., 1993). The LTP was dependent on NMDA-receptor activation and on increases in postsynaptic calcium.

In rat visual cortex, Kirkwood et al. (1995) also demonstrated that there is a critical period for LTP that corresponds to the falling phase for the plasticity of left and right eye inputs to cortex (ocular dominance plasticity). LTP was evoked in layer 3 by tetanic stimulation in the white matter. Unlike in adult rat cortex (described above), the LTP could be induced without blocking the GABA receptors. LTP could, however, be preserved beyond the normal end of the critical period by dark-rearing the pups. This procedure is known to delay the critical period in cats (Cynader and Mitchel, 1980) and appears to have some effect in rats. This dark-rearing paradigm has also been used to study the model of Bienenstock et al. (1982), which predicts that synapses that are used a lot will be more prone to LTD, while synapses that are used less will potentiate more readily. The history of synapse use therefore is an important factor in deciding whether a particular stimulation will lead to LTD or LTP. Kirkwood et al. (1996) found that in dark-reared rats, LTP was enhanced, whereas LTD was hard to evoke. The effect was reversed after dark-reared rats were exposed to light after just two days.

The processes of LTP and LTD have been studied in a number of different cortical areas. In the motor cortex (area 5a) of young adult cats, brief tetanic stimulation of the same area or area 1 and 2 could evoke LTP (Keller et al., 1990). This study was one of few to examine the phenomenon in vivo and to identify the neurons being recorded. They found that LTP could be evoked in both spiny (pyramidal cells) and smooth neurons. However, LTP was induced only in those neurons that produced monosynaptic EPSPs in response to stimulation. Thalamic input to the motor cortex could also be potentiated in vivo by coactivation with the cortico-cortical pathway (Iriki et al., 1991). Tetanic stimulation of the ventrobasal thalamus alone did not product LTP.

There are, however, some differences in the plasticity seen in rat sensory (granular) cortex and motor (agranular) cortex in vitro (Castro-Alamancos et al., 1995). Although both cortical areas could reliably generate homosynaptic LTD, LTP was more reliably generated in sensory cortex than in motor cortex, unless inhibition was reduced by application of GABA receptor antagonists. In both areas, the application of NMDA antagonists blocked the induction of both LTP and LTD. However, the kainate/AMPA receptor-mediated responses are also potentiated (Aroniadou and Keller, 1995) in rat motor cortex in vitro.

EXCITATORY SYNAPSES

In the neocortex the main excitatory neurotransmitter is the amino acid glutamate. The postsynaptic membrane of glutamate synapses contains a collection of different receptor types. The amino acid sequences of many of these receptor proteins have now

been identified and specific antibodies have been raised that recognize subunits of the receptors (see Chap. 2). Although additional species of glutamate receptor may well be identified, the immediate goal is to discover the role of these different receptor subtypes in the different cortical circuits.

The glutamate receptors have been divided into three major types on the basis of their amino acid sequences and agonists. These three are the AMPA/kianate receptor, the NMDA receptor, and a more recently discovered class of metabotropic receptor. Of these, the ionotropic NMDA and AMPA/kianate receptors have been best studied. The AMPA receptor is ligand gated and unlike the NMDA receptor, is not voltage-dependent. Both receptors are involved in fast synaptic transmission, although the activation of the NMDA receptor is relatively slow compared with the AMPA receptor and contributes minimally to the peak amplitude of unitary EPSPs (see Chap. 2).

Activation of the AMPA receptor in cortical neurons evokes a short-duration conductance change to sodium and to a lesser extent, potassium (Hablitz and Langmoen, 1982; Crunelli et al., 1984). The permeability of the AMPA receptors to calcium is low. Activation of the NMDA receptor evokes a long-duration conductance change (tens of milliseconds), during which cations flow through the channel. Although a significant flux of calcium can occur through the NMDA channels, they are much less conductive to calcium than the voltage-sensitive calcium channels. Consequently, most of the current is carried by sodium and potassium ions. However, the entry of calcium through the NMDA receptor appears to be important for the activation of the CaM kinase II and protein phosphorylation of the AMPA receptors that is important for potentiation.

Although the current–voltage relationships for the NMDA channel have been studied in vitro, they have yet to be done in vivo. In vitro, the resting potential of the membrane is sufficiently negative that the channel is probably blocked by magnesium, thus endowing the channel with its voltage sensitivity. However, because neurons are spontaneously active in vivo, it is likely that they are much closer to the firing threshold. Thus, in vivo the NMDA receptors may be released from their magnesium block under resting conditions and their current–voltage behaviour may resemble more that of conventional AMPA receptors. Thus, the notion derived from experiments in hippocampal slices in vitro (e.g., Collingridge et al., 1983a,b) that NMDA receptors only contribute to synaptic excitation during high-frequency stimulation, or after a reduction in inhibition, is probably not true for neocortex. In vivo evidence from visual cortex (Fox et al., 1990) and rat barrel cortex (Armstrong-James et al., 1993) suggests that, although there may be laminar differences in the involvement of NMDA receptors, they are clearly involved in synaptic responses to natural stimuli.

As with the ionotropic glutamate receptors, the metabotropic glutamate receptors (mGluR) are widely distributed through the brain. They are found on pre- and postsynaptic sites. They are coupled to G-proteins and their action is slower than that of the slow ionotropic receptor, NMDA. The time course of the metabotropic receptors depends on the particular set of subunits involved in a given receptor. The slowly developing depolarization of Purkinje cells induced by low-frequency stimulation of the parallel fibers can be blocked by RS-α-methyl-4-carboxyphenylglycine (MCPG) the competitive antagonist of the group I and II mGluRs.

In the neocortex, studies of the action of metabotropic receptors in the neocortex are in their infancy and have mainly addressed issues of development and plasticity. Few

have considered their functional roles. The direct action of the mGluR on pyramidal cells, after blocking AMPA and NMDA receptors, was to produce a slow depolarization after evoked spikes (Greene et al., 1994). In burst-firing neurons that project to the superior colliculus or pons, application of mGluR agonists inhibited the burst firing and changed the neurons to a tonic mode of firing (McCormick et al., 1993; Wang and McCormick, 1993). This effect is mediated by a decrease in a potassium conductance. In isolated neocortical neurons, Sayer et al. (1992) found that mGluR activation reduced the high-threshold Ca^{2+} current mediated by L-type calcium channels.

In slices of frontal cortex of immature rats, Burke and Hablitz (1995) provided evidence that mGlu receptors are located on both pre- and postsynaptic terminals. It appeared from their pharmacological dissection that different receptor subtypes were localized at the pre- and postsynaptic sites. When $GABA_A$ receptors were blocked, mGluR agonists increased epileptiform discharges, whereas the antagonist MCPG suppressed epileptiform activity. Ionophoretic application of mGluR agonists in rat barrel cortex in vivo produced disinhibition in response to natural stimulation of the vibrissae, whereas application of the antagonists reversed these disinhibitory effects (Wan and Cahusac, 1995). The effect might be mediated by a presynaptic receptor that depresses the release of GABA.

Locations of Excitatory Synapses. The major fraction (65–85%) of excitatory synapses made on pyramidal cells are on their spines, the remainder being on dendritic shafts. No excitatory synapses are made on the somata of pyramidal cells. It was previously supposed that spiny stellate cells followed the pattern of innervation of pyramidal cells. This is true for spiny stellate cells of the mouse barrel cortex (White, 1989), but it is not true for spiny stellates of layer 4a in area 17 of the cat (Ahmed et al., 1994; Anderson et al., 1994). It also may not be true for monkey spiny stellates. In the cat, about 60% of the excitatory input arrives on shafts of dendrites. The excitatory inputs to smooth neurons are onto both the dendritic shafts and the soma. In the case of the cat, at least some of the layer 4 smooth neurons form somatic synapses with the thalamic afferents (see Synaptic Connections, above).

The strength of the excitatory synaptic coupling between excitatory neurons has been studied in a variety of cortical areas in rat and cat. Mason et al. (1991) made the first recordings from pairs of pyramidal neurons in the superficial layers of the rat visual cortex. They reported that the synapses produced small-amplitude EPSPs, about 0.1–0.4 mV as recorded in the soma. Thomson et al. (1993) studied the connections between pyramidal cells in the deep layers of the rat's motor cortex. They found that synaptic transmission was mediated by both NMDA and non-NMDA glutamate receptors. These synapses produce an EPSP with an amplitude of 1–2 mV, recorded in the soma, which was depressed by repetitive stimulation. Similar findings have been made by Markram and Tsodyks (1996) recording from pairs of neighboring layer 5 pyramidal cells in rat somatosensory cortex.

Stratford et al. (1996) examined the excitatory input to spiny stellate neurons in layer 4 of cat visual cortex. The advantage of the spiny stellate neuron for these studies is that its dendritic tree is symmetrical and electrotonically compact. Thus variations in amplitude and time course of the EPSPs are more due to synaptic properties than to the cable properties of the dendrites. The intracortical sources of excitation were spiny

stellate neurons similar to the target, and also layer 6 pyramidal cells. These two types of cortical neuron had very different synaptic physiologies. The spiny stellate to spiny stellate synapse produced EPSPs with an amplitude recorded in the soma of about 1.5 mV, which depressed slightly with repetitive stimulation. The layer 6 pyramid synapses produced comparatively small-amplitude EPSPs (0.4 mV), which showed strong facilitation with repetitive stimulation. In addition they were able to demonstrate large-amplitude (2.0 mV) EPSPs from putative single thalamic fiber inputs to these same spiny stellate cells. Unlike the EPSPs of cortical origin, these putative thalamic EPSPs showed remarkably little variance in amplitude from trial to trial, and only slight depression with repetitive stimulation. Thus, the excitatory synapses formed with a single type of neuron can show a variety of static and dynamic properties, according to their source.

INHIBITORY SYNAPSES

The existence of inhibition in the cortex has been demonstrated repeatedly using intracellular recording. The first recodings were made in the Betz cells of the cat motor cortex in vivo (Phillips 1959). By antidromically activating the pyramidal tract neurons, Phillips demonstrated the presence of a recurrent inhibitory pathway in the cortex. Later studies were made in visual cortex (Li et al., 1960; Pollen and Lux, 1966; Creutzfeldt et al., 1966; Krnjévic and Schwartz, 1967; Toyama et al., 1974). These confirmed Phillips's (1959) observation that every neuron received an inhibitory input. Electrical stimulation of either the subcortical thalamic nuclei or local cortical stimulation produced a long-lasting (100–200 msec) IPSP. The role and mode of operation of inhibition in generating the stimulus-specific responses of neurons in the visual cortex remain questions of intense interest (Somers et al., 1995; Douglas et al., 1995; Ferster et al., 1996).

A number of chemical substances have inhibitory effects on cortical neurons, but the most dominant inhibitor appears to be GABA. Krnjévic and Schwartz (1967) performed a direct comparison between the membrane effects of GABA and naturally occurring IPSPs in mammalian cortex. They used surface stimulation to evoke IPSPs in neurons of pericruciate cortex, and recorded IPSPs that reached peaks at about 20–30 ms, had durations of 200–300 ms, and amplitudes of about −10 mV at the resting membrane potential. These IPSPs could be reversed by current injection or intracellular Cl injection (Krnjévic and Schwartz, 1967; Dreifuss et al., 1969). Application of GABA usually hyperpolarized the cells and reduced the amplitude of the IPSPs (Krnjévic and Schwartz, 1967). The reduction in IPSP amplitude was dependent on the GABA ejection current. The highest ejection currents flattened the IPSP (Krnjévic and Schwartz, 1967), and sometimes slightly inverted them (Dreifuss et al., 1969). The applied GABA increased the input conductance, whose time course was similar to that of the IPSP voltage response, and decayed with a time-constant of about 50 ms. Direct application of GABA also gave a marked increase in input conductance, together with hyperpolarization in most instances. The reversal potentials for the direct GABA effect and the IPSP were similar. Dreifuss et al. (1969) therefore concluded that GABA was the source of the cortical IPSP. The development of a specific GABA receptor antagonist, bicuculline, allowed confirmation that cortical inhibitory processes were GABA mediated and had an important functional role in shaping cortical responses

(Sillito, 1975; Tsumoto et al., 1979). Subsequent identification of the structure of the GABA receptor (Barnard et al., 1987) has allowed specific antibodies to be developed for the GABA receptor subunits and so enabled the regional distribution of GABA receptor subunits to be mapped (Fritschy and Mohler, 1995).

Receptor Types. In their original paper on the heterogeneity of hippocampal responses to GABA, Alger and Nicoll (1982) proposed that there were two different mechanisms mediating GABA inhibition and that these two mechanisms were activated by two different GABA receptor types. However, the details of their hypothesis differed considerably from current models of GABA action in hippocampus. Alger and Nicoll (1982) suggested that there was only one hyperpolarizing mechanism, and that it was distributed throughout both soma and dendrites. This hyperpolarization was Cl-dependent. Their second mechanism was depolarizing. They were uncertain of the ion conductance involved, but it was slightly sensitive to chloride. However, the presence of both hyperpolarizing and depolarizing responses on the dendrite, and both sensitive to chloride, did not seem attractive! They proposed two species of GABA receptor, a single receptor type mediating hyperpolarization, and a second mediating depolarization. The hyperpolarizing receptor was seen as being the true (subsynaptic) receptor, whereas the depolarizing variety was extrasynaptic. They began on the assumption that both ought to be blocked by bicuculline. Thus, they ascribed their failure to block the hyperpolarizing response in dendrites to the subsynaptic location of the GABA receptors that activated the (putative chloride) hyperpolarizing conductance. In their view, the subsynaptic receptors would be relatively protected from the bicuculline and so the (chloride) depolarizing response would be more effectively blocked. They argued that this arrangement would explain why the application of bicuculline to the dendrites would sometimes unmask a hyperpolarizing response. The residual hyperpolarization arose from the subsynaptic GABA conductance, which was unopposed by the blocked extrasynaptic (depolarizing) mechanism. Thus the two receptors of Ager and Nicoll (1982) are very different from the two receptors now thought to mediate $GABA_{A/B}$, unless we interpret the depolarizing response to be $GABA_B$. But this interpretation does not fit, because they were able to show that the depolarizing response was blocked by bicuculline.

$GABA_A$. In early studies it was found that the conductance changes, reversal potential, and sensitivity to chloride of GABA ionophoresis and IPSPs were similar (Eccles, 1964), suggesting that they were both mediated by chloride channels. The GABA receptor associated with the chloride conductance is now known as the $GABA_A$ receptor. It is the receptor that also binds benzodiazepine and barbiturate (see Matsumoto, 1989). The $GABA_A$ receptor is selectively blocked by bicuculline. There are 16 known $GABA_A$ receptor subunits that may assemble in various combinations of 5 (pentamers) that form the functional chloride channels (Barnard et al., 1987; Nayeem et al., 1994). The β subunit contains the $GABA_A$ receptor site, whereas the α subunit contains the benzodiazepine receptor site. Benzodiazepines increase the effect of GABA by increasing the frequency of channel opening in the presence of GABA. Picrotoxin acts by interference with the chloride ionophore (Barker et al., 1983). At low concentrations, barbiturates prolong the duration of $GABA_A$ channel opening without affecting

conductance (Study and Barker 1981) and at concentrations of the order 50 μM they directly activate chloride channels (?). Alphaxalone has similar effects (Cottrell et al., 1987). The $GABA_A$ receptor sensitivity is reduced in the presence of the raised intracellular calcium associated with the calcium spike (Inoue et al., 1986).

$GABA_B$. The failure of the specific $GABA_A$-receptor antagonist, bicuculline, to block the long-duration IPSP in cortex (Curtis et al., 1970; Godfraind et al., 1970; Curtis and Felix, 1971) indicated the presence of another GABA-mediated response. Bowery and colleagues (Hill and Bowery, 1981; Bowery et al., 1987) discovered a second class of GABA receptor, which was not sensitive to barbiturates or benzodazipines (Alger and Nicoll, 1982; Blaxter et al., 1986; Bormann, 1988). These $GABA_B$ receptors are activated by the antispastic drug, baclofen, which is ineffective at $GABA_A$ receptors (Bowery et al., 1984). The $GABA_B$ receptor has now been cloned (Kaupmann et al., 1997). It forms part of the G-protein-coupled receptor superfamily (Bowery, 1993). The $GABA_B$ receptor is indirectly coupled to calcium and potassium channels via GTP-binding proteins and perhaps protein kinase C (Dutar and Nicoll, 1988b; Dolphin and Scott, 1986). In frontal cortex, G proteins are involved in the postsynaptic response, and the short latency of the $GABA_B$ IPSPs suggests a close coupling between receptor and ionophore (Hablitz and Thalmann, 1987). The $GABA_B$ receptors are also found presynaptically, where they activate potassium channels or inhibit calcium conductances. This may reduce the GABA released and reduce the overall level of GABA-mediated inhibition. On excitatory terminals, the $GABA_B$ receptors may also reduce the release of excitatory neurotransmitter (Thomson et al., 1993). Connors et al. (1988) showed in cortical slices that baclofen, the $GABA_B$ agonist, activated a long time-course hyperpolarization with a reversal potential around the potassium reversal potential, and similar observations were made in cat visual cortex in vivo (Douglas et al., 1988; Douglas and Martin, 1991).

Two low-potency $GABA_B$ antagonists, phaclofen and saclophen, have been used as $GABA_B$ receptor blockers (Kerr et al., 1987, 1988). They block the long-duration late component of the IPSPS in vitro in frontal cortex (Karlsson et al., 1988) and in visual cortex (Connors et al., 1988; Hirsch and Gilbert, 1991). Due to the low potency of phaclofen, its effects on orientation and direction selectivity of visual cortical neurons in vivo has proved inconclusive (Baumfalk and Albus, 1988), whereas blocking $GABA_A$ receptors with n-m-bicuculline produces a marked reduction in the selectivity of visual cortical neurons to visual stimuli (Sillito, 1975).

In addition to their role in postsynaptic inhibitory process, $GABA_B$ receptors also inhibit transmitter release in neocortical neurons via a presynaptic mechanism (Deisz and Prince, 1989). The mechanism is probably by reducing the entry of calcium into the presynaptic terminal and thus lowering the probability of transmitter release. Phaclophen is ineffective at the presynaptic $GABA_B$ sites (Dutar and Nicoll, 1988b).

ELECTRICAL PROPERTIES OF THE IPSP

Responses to GABA. There are at least three distinct responses to direct GABA applications to cortical neurons in vitro (Scharfman and Sarvey, 1987). The first response is a fast hyperpolarization; this predominated when the GABA was ejected close to the soma. It produced a large increase in the input conductance. The second was a longer-lasting depolarization, which was evoked most readily by application of GABA to the distal dendrites. It was associated with a moderate increase in the input conductance. The third was a slow hyperpolarization that appeared on the trailing edge of the depolarization. It was a prolonged response that decayed over many seconds and was associated with a moderate increase in the input conductance. The three compounds are often mixed. For example, ejection in the vicinity of soma may show early somatic hyperpolarizing response followed by a relatively late depolarization (as GABA diffuses onto dendrites and evokes a dendritic response). GABA ejected in the vicinity of proximal dendrites evokes both a somatic and a dendritic response.

The somatic response had a reversal potential of -65 mV, was chloride-dependent, and was blocked by bicuculline (Scharfman and Sarvey, 1987; Connors et al., 1988). The dendritic depolarization is probably also mediated by $GABA_A$ receptors since it is blocked by bicuculline and picrotoxin and is potentiated by benzodiazepines (Blaxter and Cottrell, 1985). The differences in the response between somatic and dendritic activation of the same receptor have been explained by possible differences in the chloride concentrations in dendrites and soma (Thomson et al., 1988). Lambert et al. (1991) have proposed that the $GABA_A$ receptors in the hippocampus mediate their dendritic responses via a different ionophore. By contrast the dendritic hyperpolarization evoked by GABA is mimicked by baclofen, the specific $GABA_B$ agonist. This hyperpolarization reverses at -90 mV (Ogawa et al., 1986; Scharfman and Sarvey, 1987; Connors et al., 1988). The GABA hyperpolarization is potassium-dependent and can be evoked alone by small doses of GABA applied to the dendrites (Wong and Watkins, 1982) or by blocking the depolarizing component with bicuculline (Inoue et al., 1985a,b). This dendritic hyperpolarization is blocked by phaclofen and thus is probably mediated by the $GABA_B$ receptor (Dutar and Nicoll, 1988b).

In neocortical slices, long and short IPSPs have been observed (Ogawa et al., 1981; Connors et al., 1982). The stimulus threshold for the late, long IPSPs mediated by the $GABA_B$ receptor is higher than for the early, short IPSPs, which are mediated by the $GABA_A$ receptors (Connors et al., 1982). In most neurons the early IPSPs were depolarizing because the resting potential of the cortical neurons was more negative than the reversal potential of chloride (Connors et al., 1982; McCormick et al., 1985).

Sites of Action of Inhibitory Synapses. Fatt and Katz (1953) found that the main effect of inhibitory input to crustacean muscle fiber was to attenuate the amplitude of end-plate potentials. The membrane potential of the muscle fiber was hardly affected by the inhibitory input, unless the membrane was polarized away from resting, in which case the effect of the inhibitory input was to drive the membrane towards the original resting membrane potential. The inhibitory input was associated with a 20–50% increase in membrane conductance. They estimated this increase in conductance from the change in the membrane time-constant as reflected in the rate of decay of the end-plate potential. Fatt and Katz did not use the term *shunting inhibition*, nor did they place particular emphasis on the interaction between the end-plate potential amplitude and the increase in conductance evoked by the inhibitory input. They were more concerned to point out that hyperpolarizing inhibition was not a sufficient explanation for the decrement in EPSP amplitude observed (it could account for only about 5%, whereas an 80% reduction was observed). They emphasized the possible interaction between the

excitatory and inhibitory neurotransmitter at the receptor, rather than analyzing the interaction of postsynaptic potentials.

The soma or the proximal dendrites are the regions where anatomical and immunocytochemical studies have revealed the major concentration of symmetric (Gray's type II), GABA-ergic synapses (LeVay, 1973; Ribak, 1978; White and Rock, 1980; Freund et al., 1983; Peters, 1987). In brain slice preparations large conductance changes occur only transiently at the onset of an electrically evoked IPSP and last for 15–25 msec. The long phase of the IPSP is associated with a small conductance change (Ogawa et al., 1981). Intracellular recordings from visual cortical neurons in vivo revealed hyperpolarization during a long period of visually evoked inhibition (Douglas et al., 1988; Ferster, 1988; Ferster and Jagadeesh, 1992) but they did not show large conductance changes that would have been expected on the basis of the in vitro studies.

It is possible that the large conductance inhibitory synapses are located more distally on the dendritic tree and would thus be more difficult to detect. Indeed, a more distal location would enhance the shunting effect of the synapse since the input conductance of the trunk dendrite decreases relative to the active conductance of the inhibitory synapse. In these peripheral sites, the degree of conductance increase could be masked by the impedance properties of the intervening dendritic tree. While this is a suitable theoretical explanation for the absence of large changes in somatic input conductance, the current neuroanatomical data (LeVay, 1973; Ribak, 1978; White and Rock, 1980; Freund et al., 1983; Peters, 1987) do not support the existence of a large population of putative inhibitory synapses located distally on the dendrites of cortical neurons.

An extreme example would have the shunting inhibitory synapse located on the spine head, or distally on the neck. Under these circumstances, a large increase in conductance evoked in the spine head would provide very specific shunting of an excitatory synapse on the spine head, but the conductance change would be masked from the soma by the high axial resistance of the spine neck. However, the present neuroanatomical data suggest that relatively few excitatory synapses could be influenced in this way: only 7% of spines have both synaptic types (Beaulieu and Colonnier, 1985). Even if this figure is an underestimate by 100%, there remain a large number of spines without inhibitory input. Since the major excitatory input to pyramidal cells is thought to arrive on spines (LeVay, 1973; Peters, 1987; Colonnier, 1968; Szentágothai, 1973); most of this input could not be selectively inhibited.

NEUROTRANSMITTERS

AMINO ACID TRANSMITTERS

The establishment of the identity of cortical neurotransmitters has been one of the most tortuous activities of the last 40 years. Hayashi (1954) first proposed the amino acids L-glutamate and L-aspartate as candidates for the excitatory neurotransmitters in the cerebral cortex. This was supported by Krnjévic and Phillis (1963) and by the superfusion studies of Jasper et al. (1965), who found that glutamate, aspartate, glycine and taurine were released during activation of the cortex. Clark and Collins (1976) showed that the release of glutamate, aspartate, and GABA were calcium-dependent. However, resistance to accepting glutamate as a neurotransmitter was strong because glutamate is distributed throughout the brain in high concentrations, a quite different picture from

the restricted location and lower concentrations of acknowledged neurotransmitters, such as acetylcholine and catecholamines.

Other acidic amino acids also exert an excitatory effect of neurons. Some of these are more potent than the endogenous amino acids. The D-isomer of *N*-methyl aspartate is much more potent than L-glutamate (Curtis and Watkins 1963). The extraction of kainate and quisqualate from plants provided more agents that had stronger excitatory effects on neurons than L-glutamate (Shinozaki and Konishi, 1970). An antagonist, L-glutamic acid diethylester (GDEE), proved to be more effective against L-glutamate than other excitatory amino acids and indicated that there may be more than one type of excitatory amino acid receptor (Haldeman et al., 1972; Haldeman and McLennan, 1972). With the recent effort devoted to the characterization of receptor subunits, L-glutamate has emerged as the major excitatory amino acid transmitter of the cerebral cortex.

The acceptance of the amino acid GABA as the major inhibitory neurotransmitter has been as slow as that for glutamate. This occurs, despite the demonstration by Krnjévic and Schwartz (1967) that ionophoretically applied GABA profoundly inhibited cortical neurons and the evidence that GABA was released from active cortical synapses (Iversen et al., 1971). Application of n-m-bicuculline, the $GABA_A$ receptor antagonist, has a marked effect on the receptive field structure of visual cortical cells (Sillito, 1975; Tsumoto et al., 1979) and on the shape of the electrically evoked IPSP (Connors et al., 1988; Douglas et al., 1989). Antibodies directed against the synthetic enzyme for GABA, glutamate decarboxylase, or against the amino acid itself, indicate that about 20% of the neocortical neurons synthesize and contain GABA (Naegele and Barnstable, 1989).

Acetylcholine. Ionophoretic application of acetylcholine modifies the response to visual stimulation of most neurons in the cat visual cortex (Sillito and Kemp, 1983). The effect is usually facilitatory and seems to enhance the signal-to-noise ratio, rather than being generally excitatory. In deep layer pyramidal neurons, ACh induces a depolarization accompanied by an increase in resistance. The reversal potential is above that for potassium, suggesting that the action of ACh is to decrease the conductance for potassium (Krnjévic et al., 1971) by modulation of the slow outward potassium M current. The ACh response is mediated by a muscarinic receptor. The slow depolarization is preceded by a short latency hyperpolarization and a decrease in resistance that is probably due to the rapid muscarinic excitation of the inhibitory neurons (McCormick and Prince, 1985, 1986a). The inhibitory neurons are innervated by cholinergic afferents (Houser et al., 1985).

The onset of the depolarizing muscarinic excitation is slow and the response is sustained for many seconds. Some of the effects of ACh are mediated by second messengers (Stone and Taylor, 1977). Low concentrations of muscarine abolish the slow AHP (sAHP), but at higher concentrations the sAHP is replaced by a slow after depolarization (sADP) that is not mediated by potassium or sodium (Schwindt et al., 1988b; Schwindt, 1992). ACh-induced excitation can be enhanced selectively by somatostatin, although somatostatin itself inhibits spontaneous firing (Mancillas et al., 1986).

Biogenic Amines. Norepinephrine depresses the spontaneous extracellular activity of most cortical neurons (Reader et al., 1979; Armstrong-James and Fox, 1983). Some cortical cells in the deep layers are excited by low concentration of norepinephrine but inhibited by higher concentrations (Armstrong-James and Fox, 1983). Waterhouse et al. (1990) found that visual cortical cells in the rat showed enhanced responses to visual stimuli during ionophoresis of norepinephrine but depressed responses during serotonin ionophoresis.

Neuropeptides. The GABAergic neurons of the neocortex colocalize various peptides, including somatostatin (SSt), cholecystokinin, neuropeptide Y, vasoactive intestinal polypeptide (VIP), and substance P (Hendry et al., 1984; Schmechel et al., 1984; Somogyi et al., 1984; Demeulemeester et al., 1988). VIP and substance P are also associated with cholinergic axons (Vincent et al., 1983a; Eckenstein and Baughman, 1984).

The physiological role of neuropeptides remains obscure. Salt and Sillito (1984) showed that SSt could inhibit or excite cortical neurons. They were unable to demonstrate a modulatory effect on either GABAergic or cholinergic transmission. Mancillas et al. (1986) found that SSt inhibited rat cortical neurons. Cholecystokinin and VIP (Grieve et al., 1985a,b) produce mild excitation in some neurons. The difficulty in detecting effects, and the variety of effects produced, suggests that the role of these peptides is not primarily fast neurotransmission. Possibly, they are part of some cascade of effects acting over time courses of many hours or days, rather than the hour or so for conventional experiments that require receptive field mapping.

DENDRITES

The surface area of the dendrites is one to two orders of magnitude larger than that of the soma and the dendrites receive the vast majority of the synaptic inputs to the neuron. This arrangement suggests that the role of the dendrites is to integrate synaptic input, the result of which the neuron then expresses as the discharge activity of the soma. Unfortunately, in most cases the diameters of the dendrites of typical cortical neurons are too small to obtain stable recordings using available electrophysiological techniques and so most of our understanding of their electrical behaviour is derived indirectly, from recordings made from the somata and apical dendrites (Stuart and Sakmann, 1994). These methods are now being supplemented by sophisticated imaging techniques such as calcium imaging and two-photon microscopy (Denk et al., 1995).

The simplest electrical model of a dendrite is the passive electrotonic structure (Rall, 1977, 1989; Segev, 1995; Johnston and Wu, 1995). In this *cable model*, the dendrites are composed of cylindrical segments of membrane that are linked in a tree-like structure. The membranous wall of the cylinders has capacitance and linear conductance and the interior of the cylinders presents a linear axial conductance to the longitudinal passage of current. Such cylinders are electrically distributed (nonisopotential) structures and an input current injected at a point will establish voltage gradients along the dendrite. For simple cylindrical dendrites, the voltages at any point along their length is specified by the cable equation. The solution of this equation, and so the voltage profile, depends on the boundary conditions at the ends of the dendritic cylinder. These boundaries are usually approximated as either an infinite cable, a cut (short circuit) end, or sealed (open circuit) end. Rall (1959a,b) showed that the cable equation could also be solved for branching cylindrical dendrites, provided that there was a 3/2 power relationship between the parent and daughter branch diameters. When this relationship and a few other restrictions hold, then the entire dendrite can be reduced to a single equivalent cable of constant diameter.

In real neurons the synaptic voltages attenuate more rapidly toward the soma than toward the dendritic terminations. The electrical asymmetry of the dendritic tree arises because the terminations are sealed ends and little synaptic current is lost from them, whereas the somatic end has many other dendrites attached and so presents a large conductance load to the source synapse located on one of the dendrites. The voltage attenuation from dendrites to soma may be as much as a few hundred-fold. This implies that a number of EPSPs must occur within a membrane time-constant in order to displace the somatic potential across a 10–20 mV threshold. If the effect of a synapse depended only on its peak voltage, then the response of the neuron would be very sensitive to the displacement along the dendrite of the synapse. But, if the entire EPSP is considered, the situation is different. The passive dendrite behaves as a low-pass filter, and so the temporal form of the synaptic potentials becomes significantly broader as they spread from distal synaptic sites towards the soma. Although the peak synaptic voltages are attenuated, the attenuation of the time integral of the EPSP at the soma is smaller and not much affected by synaptic location. This is also true of the integral of the synaptic current at the soma (synaptic charge delivery). Since the synapses exert their effect collectively, by sustained depolarization of the somatic membrane, it is the charge delivery to the soma that best expresses synaptic efficacy (Bernander et al., 1994).

The broadening of the EPSP as it spreads centripetally has the effect of delaying the signal, and makes the response at the soma sensitive to the temporal order of synaptic events applied in the dendrites. This means that the dendrite can usefully compute functions such as direction of motion (Rall, 1964; Koch et al., 1982). Passive dendrites can also act on different time scales. For example, extensively branched distal dendrites provide a large area for charge equilibration, and so the time constant for synaptic integration is much shorter (about 0.1 τ_m) there than closer to the soma. The briefer synaptic events in the distal arbors interact as coincidence detectors, whereas the longer events closer to the soma integrate (Agmon-Snir and Segev, 1992).

The morphology of the dendritic tree is important, at least in so far as it affects the passive spread of currents from the synapses to the initial segment (Mainen and Sejnowski, 1996). Most cortical neurons are electrotonically compact, whether measured electrophysiologically (Stafstrom et al., 1985) or anatomically (Douglas and Martin, 1993). However, the apical dendrite of the pyramidal cells is a special case. The electrotonic length of the apical dendrite is about 2–3 times greater than that of the basal dendrites, and the synaptic inputs injected into the apical tuft at the distal end of the apical dendrite are greatly attenuated en route to the soma (Bernander et al., 1994). This apparent ineffectiveness of the distal apical input is counterintuitive. Important interareal projections make their synapses there, and there has been no phylogenetic trend to dispense with apical dendrites (with the possible exception of layer 4 spiny neurons). One possibility is that the apical dendrite makes use of active currents to enhance selectively signal transmission to the soma (Bernander et al., 1994). Where the

dendrites are long and narrow, and so electrotonically short, the dendrite can decompose into electrotonically separate subunits, each of which can compute a relatively independent function (Koch et al., 1982). It is unlikely that such conditions exist in cortical neurons, except possibly in the apical tufts.

ACTIVE PROPERTIES

The cable model has been extremely useful in obtaining qualitative insights into the behavior of quiescent dendrites. However, it has two significant failings that limit its application to cortical neurons. First, the approximation to a cable across the branches in a dendrite requires that a particular relationship of diameters hold between the parent and daughter segments of the branch. This relationship is only rarely true across the dendritic branches of cortical neurons. Second, it is clear that the majority of cortical neurons have many active conductances in their dendrites (Stuart and Sakmann, 1994), and so the linear cable approximation is only useful under very restricted conditions. Active dendritic conductances include voltage-dependent sodium, potassium, and calcium currents (Markram and Sakmann, 1994; Stuart and Sakmann, 1994; Magee and Johnston, 1995b). When the nonlinearities due to the active conductances are included, the dendritic models have mathematic descriptions that cannot be solved analytically. The models must then be investigated by numerical simulations of compartmental approximations to the dendrites. In these compartmental models, the dendritic segments are considered to be electrotonically short (isopotential) compartments linked by axial resistors according to the topology of the dendrite. When the dendritic quantization is sufficiently small, the compartmental description with only passive components converges to the continuous description of the cable equation. However, the important interest in the compartmental approach is not the passive cable behavior, but the effects of active conductances.

The active conductances are able to generate a variety of subthreshold nonlinearities and may cross the thresholds for calcium or sodium action potentials. The exact roles of the active dendritic conductances are unknown, but they could support a number of interesting functions. Sodium spikes are able to propagate retrogradely into the dendritic tree (Stuart et al., 1997). The action potential propagates more reliably centrifugally than it does centripetally, because in the latter case the branching dendritic tree presents a large impedance load to the small action potential currents generated in the narrow peripheral dendrites. The retrograde spikes could provide a signal to hebbian synapses that the postsynaptic cell is active. For example, Yuste and Denk (1995) have used two-photon microscopy of hippocampal pyramidal cells to show that the centrifugal action potential invades the dendritic spines and leads to a local rise in their calcium ion concentration.

The introduction of active conductances in the apical dendrite could provide amplification and linearization of synaptic inputs to the apical tuft (Bernander et al., 1994), or decompose the dendritic tree into a number of distant multiplicative subunits (Mel, 1993). The active conductances could also amplify selective combinations of input by nonlinear multiplicative interactions (Mel, 1993). Since these effects are usually associated with increases in conductance, increasing stimulation will cause the multiplicative and subregion effects to become more localized in space and time (Mel, 1993).

Dendrites with slow active currents that are partly decoupled from the fast spike generating currents at the soma can produce a wide repertoire of temporal patterns of output spikes, including bursting (Pinsky and Rinzel, 1994; Mainen and Sejnowski, 1996). Activation of dendritic potassium conductances could also offset large dendritic input currents, thus providing an adaptive mechanism to keep the dendrite in a favorable operating range (Bernander et al., 1991, 1994).

SPINES

One of the most prominent features of cortical neurons is their dendritic spines (Cajal, 1911). They are the major recipients of excitatory input, and play an important role in activity-dependent modification of synaptic efficacy such as LTD and LTP (for a review see Shepherd, 1996). Although these structures have been extensively examined by light and electron microscopy, physiological data has been more difficult to obtain because of their tiny dimensions, and so their functional role is still not entirely understood. Fortunately, recent advances in imaging techniques are making it possible to measure calcium dynamics in individual spines with high time resolution (Denk et al., 1996).

The simplest views of spine function were mechanical. They were thought to be convenient physical connections whereby *en passant* axonal boutons could more easily connect to dendrites (Peters and Kaiserman-Abramof, 1970; Swindale, 1981). More elaborate views have considered the electrical and chemical properties of the spinous connection (see Chap. 1).

ELECTRICAL MODELS

The membrane area of the spine neck is very small and consequently, little synaptic current flows through the neck membrane. Therefore most of the synaptic current injected into the spine head reaches the trunk dendrite via the spine neck. Nevertheless, the resistance to current flow through the neck is high, on the order of 100 $M\Omega$ or more (Segev and Rall, 1988). This is roughly the input resistance of a typical spiny dendrite about half a length-constant from the soma. So the spine neck will attenuate by about half the voltage applied at the spine head. Thus the neck resistance could be used to control the efficacy of the synapse (Rall, 1962) and so provide a basis for synaptic plasticity (Fifkova and Anderson, 1981). The resistance could be changed by modifying the neck diameter or length (Rall, 1974a,b), or by partial occlusion of the neck by the spine apparatus (Rall and Segev, 1987). However, attempts to correlate changes in spine dimensions in relation to, for example, LTP induction have been unconvincing (Fifkova and van Harreveld, 1977; Andersen et al., 1987; Desmond and Levy, 1990).

The *twitching spine* hypothesis of Crick (1982) proposed that a change in spine length could be achieved quickly, by calcium activation of myosin and actin localized in the spine neck (Fifkova and Delay, 1982; Markham and Fifkova, 1986). In theory, a burst discharge of the excitatory afferent could raise the free calcium concentration in a spine to the level required to activate the actin (Gamble and Koch, 1987). The twitching spine hypothesis is one of the interesting suggestions that could soon be tested by the new imaging techniques.

Saturating Spines. The flow of synaptic current through the spine input resistance will shift the spine head potential toward the EPSP reversal potential and reduce the driving potential for the synaptic current. For small synaptic conductances the synaptic current saturates. This interdependence gives rise to a sigmoidal relationship between synaptic conductance and synaptic current (Fig. 12.9). We do not know exactly where on this relationship the operating range of the neocortical synapse lies.

That spines generally receive only one excitatory synapse can be interpreted in two opposing ways, in this context. It may reflect the need to avoid saturating the synapse, or it may indicate that a single synapse on a spine always saturates the synapse, so that additional inputs would be redundant. If the synapse is driven into saturation, then the spine potential will be relatively insensitive to the exact amount of neurotransmitter delivered to the synapse. The spine head will simply turn on to a repeatable voltage level. Moreover, because the spine neck resistance is at least as large as that of the parent dendritic trunk, the spine approximates a constant current source attached to the dendrite. The synapse on the spine head is less susceptible to changes in the dendritic input resistance than is a synapse located on the dendritic trunk.

Spine Action Potentials. A special case of saturation behavior arises if the spine head membrane contains active conductances that could amplify the synaptic signal (Jack et al., 1975; Perkel and Perkel, 1985; Miller et al., 1985; Rall and Segev, 1987; Segev and Rall, 1988). Shepherd et al. (1985) and others (Rall and Segev, 1987; Baer and

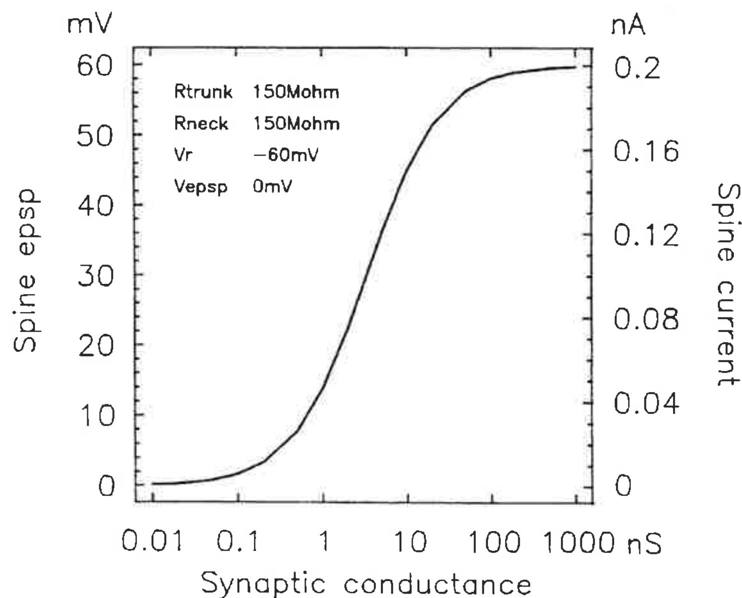

Fig. 12.9. Simulation of steady-state activation of synapse on the spine head. Effect of synaptic conductance on the amplitude of EPSP in the spine head, and the magnitude of the current delivered through the spine neck resistance (R_{neck}) to the trunk dendrite resistance (R_{trunk}) for a simulated spine and dendrite. V_r, resting potential; V_{EPSP}, reversal potential of EPSP.

Rinzel, 1991) have suggested that this amplification could lead to spinous action potentials. The saltatory transmission of these action potentials from spine to spine, conditional on their synaptic input, could form the basis of Boolean algebraic-like processing along the dendrite. Although these notions are attractive, the experimental evidence consistent with spiking spines has been obtained only in cerebellar Purkinje neurons (Denk et al., 1995).

Nonsaturating Spines. If the synapse on the spine is not driven into saturation, but operates instead within the linear range of Fig. 12.9, then the synapse will be particularly susceptible to nonlinear interactions with other spines. Because the resistance of the spine head membrane is much greater than the axial resistance of the neck, the dendritic potential is transferred to the spine head with little attenuation. Consequently, a depolarization of the dendritic trunk will reduce the driving potential of the spine synapse and mediate nonlinear interactions between neighboring spines. These interactions are only possible if the spines operate in their linear range. If the spines operate in saturation, then their synapse will be insensitive to modulations of local driving potential.

Inhibition on Spines. A small proportion (about 10%) of neocortical spines receive input from a type 2 (GABA-ergic) synapse in addition to the type 1 (excitatory) synapse (Jones and Powell, 1969c; Peters and Kaiserman-Abramof, 1970; Sloper and Powell, 1979b; Somogyi et al., 1983; Beaulieu and Colonnier, 1985; Dehay et al., 1991). This arrangement raises the possibility that some excitatory inputs receive selective inhibition. Nonlinear inhibition of excitatory inputs on the same spine can be large and is essentially limited to the affected spine (Koch and Poggio, 1983). The large series resistance of the spine neck masks changes that occur in the head from the trunk dendrite and so may effectively restrict the inhibitory control to the affected spine. This specific effect has attracted much theoretical interest (Koch and Poggio, 1983; Segev and Rall, 1988) because of its computational possibilities, but only a small percentage of the excitatory input onto a single neuron could be gated in this way. It is possible that the spines that are controlled by an inhibitory synapse all receive input from a strategically important class of afferents, such as the thalamocortical inputs for example. However, Dehay et al. (1991) have shown that this selective inhibition does not occur.

Less selective locations of inhibitory synapses may also permit strong nonlinear effects. For example, inhibitory synapses on the trunk dendrite would reduce interspine communication and could control saltatory conduction between spines (Shepherd and Brayton, 1987). This raises the possibility of enabling or disabling selected branches of dendrites. However, logical computations in spines do not necessitate inhibitory inputs. Triggering an action potential could also be conditioned by activation of the spine-head synapse (e.g., the NMDA receptor is voltage-dependent only if gated by neurotransmitter). If saltatory conduction were conditional on excitatory input, then this arrangement would provide an elegant means of signal gating that depends on the coincidence of excitatory inputs, rather than the interaction of excitatory and inhibitory inputs.

BIOCHEMICAL COMPARTMENTS

The strong role of calcium in synaptic plasticity and the need to localize plasticity to the activated synapse have led to the suggestion that the spines provide the necessary isolated biochemical compartment (Gamble and Koch, 1987; Zador et al., 1990). The notion is that the spine neck limits the diffusion of calcium between the head and the dendrite. It is proposed that restriction in calcium movement through the neck arises from the calcium sink created by the calcium pumps in the neck membrane. Their activity has the effect of shortening the calcium space constant in the neck, leading to significant calcium attenuation across the neck.

Calcium could enter the head through NMDA channels, voltage-dependent calcium channels, and second-messenger channels. Studies in hippocampal neurons have provided evidence that calcium levels in the spine head are to some extent uncoupled from those in the parent dendrite (Guthrie et al., 1991; Muller and Connor, 1991; Yuste and Denk, 1995). Similar experiments in neocortical neurons are awaited.

FUNCTIONAL OPERATIONS

SINGLE NEURONS OR NEURAL NETWORKS

The history of ideas of cortical function makes a fascinating account of the interplay of hypothesis and experiment (Martin, 1988). In particular, the experimental results from microelectrode recordings from single cortical units (neurons) have had a deep influence on our ideas of cortical function. Much of the motivation for studying the functional properties of single units in the cortex in such detail arises from the fact that the activities of cortical neurons are thought to describe the world and so to reflect our subjective experiences. However, the nature of the encoding used by the neurons to represent the world is still a matter of intense and interesting debate.

The encoding problem is important because it determines to a large extent the success with which the nervous system can interact with the world. It is clear that the attributes of the world must be encoded in the variables of the nervous system. If the neural encoding is suitable, then the nervous system will be able to represent the world well, and the efficiency interactions with the physical world will be enhanced. For example, in artificial neural networks, learning and generalization improve with the quality of data representation.

One central question is whether the nervous system uses a data representation in which the encoding of objects is distributed across many neurons, or whether the representation is localized. This debate is usually couched in the domain of perception. There the question is whether the discharge of a combination of neurons, or the discharge of just one neuron, reflects the experience of a percept. These opposing views of the operation of cortex have a long and distinguished history. Sherrington (1941), for example, contrasted the notion of "one ultimate pontifical nerve-cell . . . [as] the climax of the whole system of integration [with the concept of mind as] a million-fold democracy, whose each unit is a cell."

The case for localized encoding has been formalized in the *neuron doctrine* proposed by Barlow (1972). He proposed five dogmas that encapsulate the powerful idea that percepts are the product of the activity of certain individual cortical neurons, rather

than by some more complex (and obscure) properties of the combinatorial rules of the usage of nerve cells. The force of Barlow's thesis in molding our ideas is evident in most textbooks of psychology and neurobiology, which are well stocked with illustrations showing how the specificity of neurons arises from a hierarchical sequence of processing through the cortical circuits.

Recently, the pendulum has begun to swing back. The antithetical proposition that perceptual processing occurs through the collective properties of parallel cortical networks rather than through the activity of single units has been receiving close attention from theoreticians working on *neural networks* or *connectionist* models of cortical function. Results obtained from computer simulations of these hypothetical nerve circuits have led to a model of cortical function that is quite different from that proposed in the neuron doctrine.

The dialectic of the one versus many neurons is best considered in the context of the visual system, where the physiology and anatomy are known in greatest detail, and where the behavioral performance is well established.

SINGLE NEURONS OR NEURAL NETWORKS?

It is evident that visual perception is a complex task. We need only to only not determine the form, movement, and position in space of the objects we encounter, but also to recognize them as being particular objects. Solving this key problem was central to Barlow's development of the neuron doctrine. He proposed that the primary visual cortex dealt only with the elemental building blocks of perception, the detection of orientated line segments, or the local motion of these segments, for example. In order to build these responses into neurons that were selective for, e.g., a cat, chair, or grandmother, he proposed a hierarchical sequence of processing within single cortical areas and through the many visual areas. Thus, the *grandmother cell* scheme is essentially a classification network in which the input is classified according to which output neuron is activated. In nervous systems, the classification occurs in a hierarchical network. The neurons at each stage of the hierarchy become progressively more selective to the attributes of the stimulus, so that while the neurons in the primary visual cortex would respond to many objects, neurons at the highest level of the hierarchy would respond only to particular objects. Barlow (1972) suggested that the activity of about 1000 of these high-level *cardinal* neurons would be sufficient to represent a single visual scene. Because the number of possible percepts is very large, however, the total number of cardinal cells would have to be a substantial fraction of the 10^{10} cells of the human neocortex (Barlow, 1972).

The single neuron representation faces two major difficulties: poor generalization, and limited encoding capacity. If individual objects are very specifically encoded by single neurons, then it is difficult for the neurons to generalize their classification to novel intermediate cases. For example, given only a "red apple" neuron and a "green apple" neuron, how does the nervous system respond to a yellow apple? Either it must quickly recruit a new neuron with very similar connections and assign it to yellow apples, or else the yellow apple percept must arise from some combination of the activity of the red and green neurons, in which case the single-cell encoding hypothesis is weakened. Moreover, if new neurons must be recruited for each new feature (such as yellow) that is added to the classification scheme, then the number of neurons required

to encode selectively the various combinations of features increases explosively and soon exceeds the number of neurons available.

Despite these difficulties, selective encoding representation has remained a popular implicit hypothesis in experimental neuroscience. Since 1972 many of the visual areas beyond area 17 have been explored in some detail. Efforts to discover whether cardinal cells reside in these visual areas have met with mixed success. In most areas, the stimulus requirements for activating neurons are not very different in quality from those for area 17. If anything, the requirements are less restrictive, in that only a single property of the stimulus might be important, such as its direction of motion, or color, or depth in visual space. Only in the primate inferotemporal region of cortex have neurons with higher-order properties been found (Gross et al., 1972). These neurons respond preferentially to parts of the body, especially faces, although they respond to other visual stimuli as well (Gross et al., 1972; Bruce et al., 1981; Richmond et al., 1983; Young and Yamane, 1992). Other cells in the inferotemporal region have large receptive fields that respond quite specifically to complex shapes, but close neighbors tend to respond to similar features (Tanaka et al., 1991; Fujita et al., 1992; Miyashita, 1988; Miyashita and Chang 1988). Neurons in these areas appear to "learn" specific complex stimuli.

Direct examination of neuronal responses involved in the perceptual foundation of a decision process (Salzman and Newsome, 1994; Shadlen and Newsome, 1996) have also brought some support for the cardinal cell view. It appears that in the motion discrimination task, the reliability of the animal's decision is not much better than that of a single observed neuron, which argues against the view that the animal bases its decision on an average across many neurons.

Nevertheless, the general conclusion from the many studies that have examined encoding is that individual neurons do not respond completely selectively to single *trigger features*. Instead, each neuron is sensitive to a number of different stimulus characteristics, such as contrast, dimension, depth, and orientation. Single cortical neurons appear unable to signal unambiguously the presence of a particular stimulus, and therefore cannot act as cardinal cells. An important reason why such cardinal cells are not found may lie in the basic organization of the cortical circuitry, which expresses much stronger lateral and recurrent interactions between neurons than is expected of a feedforward classification network.

NEW DESIGNS FOR THE VISUAL CIRCUITS

When Barlow proposed his neuron doctrine in 1972, the modern study of cortical microcircuitry was in its infancy. Anatomical studies had emphasized the vertical, columnar structure of cortex. This view was reinforced by many electrophysiological studies, which showed vertical functional columns. Technical advances since the late 1970s have resulted in a wealth of new information about the cortical microcircuitry. The technique of intracellular labeling of neurons (e.g., Figs 12.3 and 12.4) has revealed an extensive system of horizontal connections within the cortex. Certain markers, such as horseradish peroxidase or biocytin, fill the entire axonal arborization, including the boutons, and so estimates of the number and spatial distribution of the synapses made by a single neuron are now available for the first time. The horizontal spread of connections means that each point in cortex is covered by axons of a very large number

of neurons. For example, estimates for the number of geniculate X cells (see Chap. 8) that provide input to any point in cat area 17 range from 400 to 800 (Freund et al., 1985), whereas the figure for Y cells may be even higher. The geniculate axons form less than 10% of the excitatory synapses on spiny stellate neurons in layer 4 (Ahmed et al., 1994; see Synaptic Connections, above), so the number of cortical neurons providing the input to a single point must be considerably higher. Because one cortical neuron supplies only a few synapses to any other cortical neuron, each neuron can potentially be activated by hundreds of other neurons. It is this highly divergent and convergent connectivity that is the feature of neocortex, and that differs considerably from that of the lateral geniculate nucleus (Chap. 8), where there is a much tighter coupling between neurons.

The widespread and rich connections of the thalamic afferents ensure that even the smallest detectable disturbance of the retinal receptor layer—for example, that induced by a dim flash of light—alters the probability of firing of thousands of cortical neurons in the primary visual cortex. The signal is then amplified by the divergent axonal arbors of the cortical neurons, which ensure that many thousands more neurons are activated both within area 17 and in the other cortical areas to which these neurons project. Thus, although there certainly is the convergence of many inputs that is required to create the cardinal cells, the considerable divergence of the connections of each neuron ensures the simultaneous activation of many neurons. In such a context it is difficult to see that the activity of any single neuron can be completely isolated from that of its companions in order to signal a unique percept. Instead, the combined activity of large numbers of cortical neurons seems more likely to be the basis of our perceptual experience. However, distributed representations have problems of their own, such as the ambiguity of interpretation when a particular neuron is permitted to respond in more than a single context. For example, many neurons may implement the distributed encoding of apples, and some common fraction of these will be activated by particular red, yellow, and green apples. If this common fraction is activated in a number of different contexts, what is the unique neural object that defines a particular apple? Von der Malsburg (1981) has proposed that the population of neurons activated by the stimuli of a particular physical object is bound together transiently by a common physiological process. One possibility is that the 40 Hz oscillation of discharge observed in cortical neurons reflects such a binding process (Gray and Singer, 1989; Crick and Koch, 1992; Singer, 1994).

PARALLEL PROCESSING IN NEURAL NETWORKS

It is evident from the above discussion that normal vision involves the activity of very large numbers of cortical neurons. These large numbers do not simply reflect redundancy, which an efficient coding must avoid, but are a necessary part of perception. This is evident in the example of color vision, where both behavioral and theoretical studies show that the relative stability of the perceived color of objects in the face of changing illumination (e.g., moving from indoors to outdoors) requires the comparison of the reflected wavelengths over a large region of the visual field (Jameson and Hurvich, 1959; Land, 1959a,b, 1983). This phenomenon of color constancy necessarily involves the coordinated activity of large numbers of cortical neurons. Similar considerations apply in the case of binocular vision, where two slightly different views of

the same complex scene must be fused to produce a single vision and stereopsis. Attempts to replicate this performance have shown that it is a difficult task (Marr and Poggio, 1979; Mahowald, 1994). Yet we fuse the image and extract the exact three-dimensional information effortlessly and far more rapidly than any computer yet can. One reason for this difference is that the strict hierarchy of serial processing used by computers with von Neumann architecture is slow. In the cerebral cortex, by contrast, the higher degree of divergence in the connections makes it likely that much of the processing occurs simultaneously through parallel pathways. Of course, computers have transistors that can generate digital impulses at very high rates and transmit them at light speeds to perform their computations. By comparison, neurons generate impulses at very low rates and transmit them at meters/second. However, the neocortex makes many connections to and from each neuron, whereas the limitations of size and thickness mean that silicon components have limited connectivity. Thus advantages of speed are offset against limited connectivity.

The increase in speed offered by parallel processing has been exploited in a number of models of visual processing based on feedforward artificial neural networks. The most common form of feedforward network is composed of three layers of highly abstract neurons whose activity typically varies between 0 and 1. A first layer, or *input layer*, connects extensively to units of a second, *hidden layer*, which in turn sends its output to the third, *output layer*. The sensory input is applied via the input layer. The responses of units in the hidden and output layers are determined by summing activities of all the units in the previous layer. The effect of each of the inputs is governed by a synaptic *weight*, which may be positive (excitatory) or negative (inhibitory). The values of these weights determine what functions of the input the network can compute, and so what overall task the network performs. These weights may be specified directly, but more often they are organized by a learning algorithm, for example, *back-propagation* (Rumelhart and McClelland, 1986; Hertz et al., 1991; Anderson, 1995). Such networks turn out to be powerful and are capable of solving some of the perceptual problems of depth, form, and motion perception (Lehky and Sejnowski, 1988; Zipser and Andersen, 1988).

ARE NEURAL NETWORKS LIKE CORTICAL CIRCUITS?

The neural network models, besides being functionally successful, have a strong appeal because of their superficial resemblance to the structure of the cortex: they are layered and have highly interconnected units. However, this superficial resemblance should be examined more critically in the light of our knowledge of the structure of area 17. The basic circuit of Fig. 12.10 illustrates some of the main neuronal components and their connections within area 17. Comparing this figure with the feedforward neural network of Fig. 12.11 shows a number of similarities. The first layer in the neural network corresponds to the map of the geniculate terminals, the second layer units, to the neurons in layer 4 that project to the superficial layers, and the third, to the pyramidal neurons projecting from cortical layers 2 and 3. In respect of this laminar organization, the pattern of the model corresponds to that of cortex in that very few neurons of layer 4 provide an output to other cortical areas, whereas a large proportion (70%) of the pyramidal neurons in layers 2 and 3 do project to other areas. However, it is evident at a glance that the organization of cortex shown

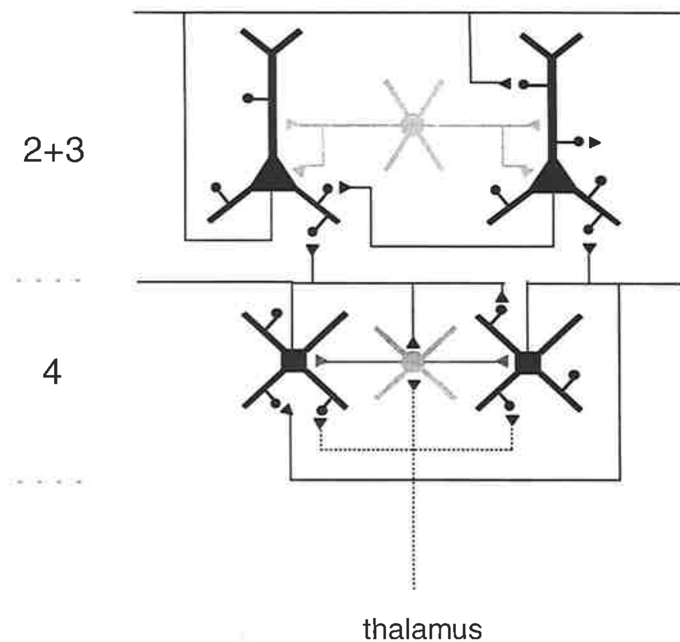

Fig. 12.10. Possible recurrent connections in neocortex. This figure is an elaboration of Figs. 12.8 and 12.6. The feedforward thalamic inputs synapse with spiny stellate neurons and a small basket cell in layer 4. Some of the spiny stellate connections are recurrent to other spiny stellates. They also synapse onto superficial pyramidal cells that in turn have recurrent connections with one another.

in Fig. 12.10 is in many important respects different from the neural network circuit of Fig. 12.11.

Unlike the neural network, the primate visual cortex receives at least two physiologically and anatomically distinct inputs from the thalamus, which are laminar specific. The cortex has twice as many or more layers, particularly if the subdivisions of the six basic layers are taken into account. This may be a requirement of the cortex to divide its output destinations ("addresses") into laminar-specific zones. However, the internal connectivity and physiology differ in different layers, indicating that there may be important differences in the processing within layers. In contrast to the units within a single layer of the neural network, there are extensive lateral connections within a single lamina or sublamina of cortex. Thus, the local connectivity of cortical neurons resembles that of the recurrent neural networks (Hopfield, 1982, 1984). However, unlike typical recurrent artificial neural networks, the cortical ones are not fully connected. Instead, they are quite sparsely connected. Similarly, the interconnections between cortical laminae are highly specific and do not simply connect adjacent layers as in the units of the neural network. Both the vertical and the lateral connections in the cortex are clustered, focusing on discrete zones. This columnar structure is a feature of cortical organization, but it is the exception rather than the rule to incorporate such horizontal organization within network models.

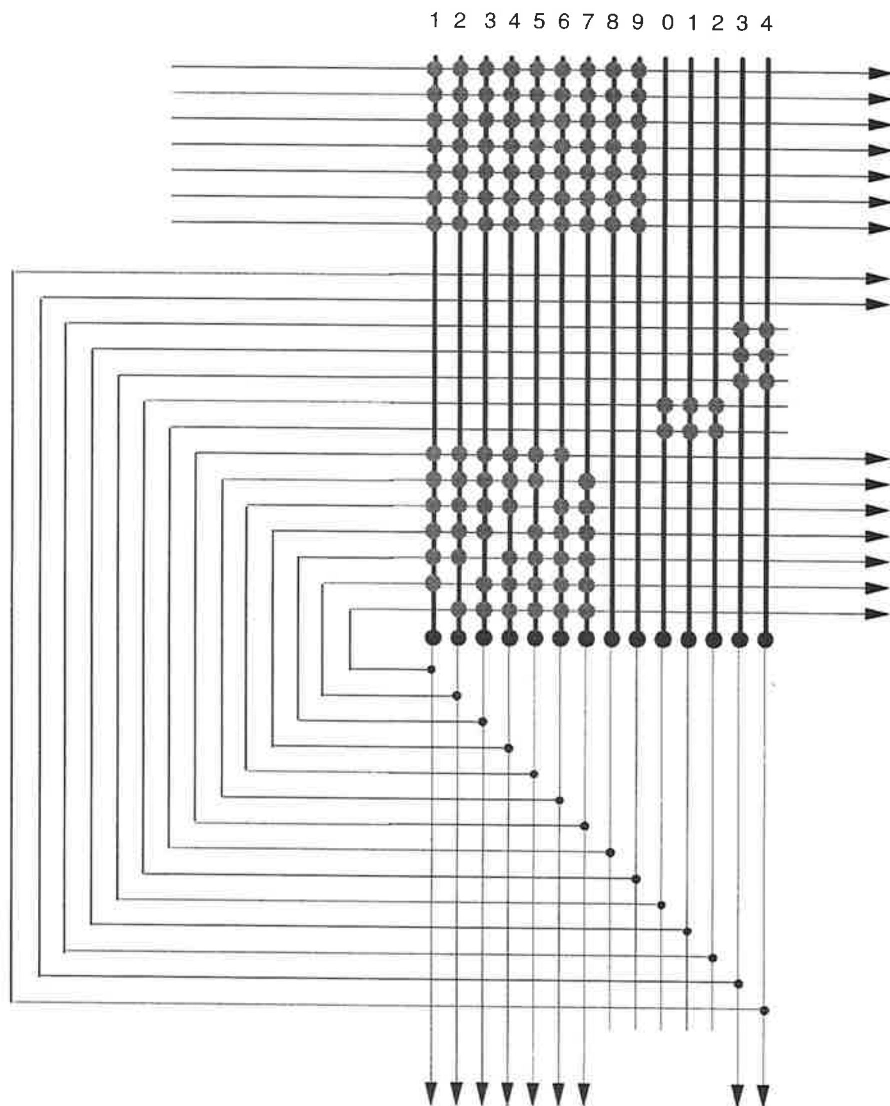

Fig. 12.11. A hypothetical cortical neuronal network composed of two subnetworks; one feedforward, and the other feedback. Neurons of the network (black) receive input synapses (gray circles) onto their dendrites (thick black vertical lines). The effects of these neurons are integrated into the neuronal somata (black circles) and their outputs are transmitted along their axons (thin black lines). Branch points of the axons are indicated as small black dots on the axons. The neurons are numbered from 1 to 14. Feedforward inputs enter via the 7 horizontal axons above. **Feedforward network:** The feedforward inputs synapse with the first layer of cortical neurons (8 and 9), which project to the second layer (10, 11, and 12), and from there to the final layer (13 and 14), whose outputs project out of this region of cortex. The intermediate computations of this entirely feedforward network are unaffected by connections between cells in the same layer, or by backward projections from later layers. **Feedback network:** The feedforward inputs synapse with the distal dendrites of the recurrently connected population of neurons (1 through 7). Their axons synapse with all other members of their population (but not with

It is somewhat surprising, given the activity in this area, that the rules of connectivity for neocortex have still to be discovered. At this stage, we know that the different types of neurons connect with some degree of specificity to particular regions of other neurons, e.g., dendritic shafts or spines, but whether single neuron to single neuron connections are specified is still quite unclear. At this stage it seems likely that neurons do not connect on a point-to-point basis, but on a point-to-zone basis, targeting particular subsets of neurons within a zone.

The point is readily made that these and other differences show that the artificial neural networks are different in important respects from the cerebral cortex. Finally, artificial *neural* networks are not really very neural. They are just networks operating according to a specific algorithm, and it would be rash to press their analogy to cortical circuits too far. Nevertheless, the potential usefulness of network models that are biologically based cannot be overestimated. The major problem lies in trying to bridge the gap between experimental data and theory. Our knowledge of the structure of the cortical microcircuitry outstrips our understanding of the function of these circuits. This disparity, together with the sheer complexity of the cortical circuits, is a significant barrier to moving from networks that are simply *neurally inspired* to those that actually incorporate basic features of the biology. To achieve this step, the cortical connections shown in Fig. 12.8, and their associated physiology, have to be simplified. Given the outline of the preceding sections, one such simplification can now be suggested (Fig. 12.12). The form of this "canonical" circuit was arrived at from an analysis of the structure and function of local circuits in the visual cortex (Douglas et al., 1989, 1995; Douglas and Martin, 1991). However, an analysis of the circuits of other cortical structures such as the olfactory cortex (paleocortex) and hippocampus (archicortex) reveals that they, too, bear many resemblances to the circuits of the neocortex (Shepherd, 1988a,b; see Chap. 1). Thus, it is tempting to suppose that there may be some common basic principles that underly the organization and operation of all cortical circuits.

A CANONICAL CORTICAL CIRCUIT

From the anatomy, several components and connections seem to dominate in most cortical areas (Fig. 12.12). Any realistic model must separate inhibitory (GABAergic) and excitatory neurons into distinct populations. The excitatory group (80% of the cortical neurons) can be subdivided into two major pools, one being found in the granular and supragranular layers (layers 2–4), and the other in the deep layers (layers 5 and 6). Although these groups are extensively interconnected, this division is made because their outputs are distinct, and because inhibition appears to be stronger in the deep layers (Douglas et al., 1989). The different types of GABAergic smooth neurons cannot yet be distinguished on functional grounds; they are therefore represented in the diagram of Fig. 12.12 by a single population.

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themselves). In this case, the evolving response of each neuron comes to influence the computations of its fellows. The overall computation is iterative in quality, and converges on a solution which is, in some sense, a consensus amongst the cooperating neurons. The state of the population is transmitted out of this region of cortex.

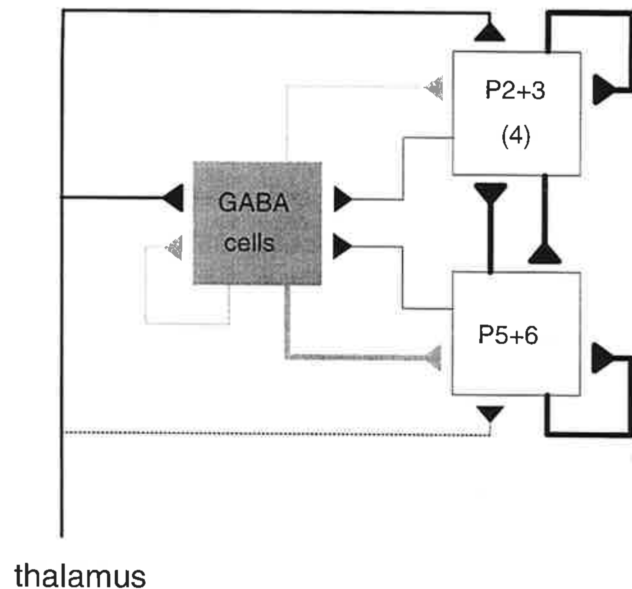

Fig. 12.12. The canonical microcircuit for striate cortex. Three populations of neurons interact with one another: One population is inhibitory (GABAergic cells, gray synapses), and two are excitatory (solid synapses) representing superficial (P2 + 3) and deep (P5 + 6) pyramidal neurons. The properties of layer 4 stellates (4), which contribute 10% of neurons in granular cortex, less elsewhere, are similar to those of the superficial pyramids. The thickness of the connecting lines indicates the functional strength of the input. Note that the dominant connection is between excitatory neurons, so that a relatively weak thalamic input can be greatly amplified by the recurrent excitation of the spiny neurons.

Neurons within each division form connections with other members of that division. The dominant interlaminar connections are between the superficial and deep layer groups of spiny neurons, whereas the inhibitory neurons connect across the laminae to both groups of spiny neurons. All three groups receive direct activation from the thalamic afferents, but because the thalamic input provides only about 10% of the excitatory input, 90% of the excitation is provided here by intracortical connections between pyramidal neurons. This recurrent excitation may provide selective amplification of geniculate input (Douglas et al., 1989, 1995). Such intracortical amplification provides the basis for a number of recent models of cortical computation (Mahowald, 1994; Ben-Yishai et al., 1995; Douglas et al., 1995; Somers et al., 1995; Suarez et al., 1995). Inhibition acts by modulating the recurrent excitation, and so is effective even though it may be relatively weak (Douglas et al., 1995).

The excitatory neurotransmitters act on two major receptor types, the NMDA and non-NMDA receptors. The inhibitory neurotransmitter GABA acts via the $GABA_A$ and the $GABA_B$ receptors. These distinctions are made because the receptor types have distinctly different kinetics. The biophysical characteristics of the cortical neurons, as outlined in the previous sections, also need to be incorporated to give the appropriate response characteristics.

This recurrent excitation model provides the minimum specifications that seem necessary for basic cortical circuits, based on our present level of knowledge. The form of this simplified model is sufficiently general that it can be applied equally well to visual cortex as to motor cortex, and as such, has the properties of a canonical circuit. This circuit forms only a basic building block. Obviously, each cortical area has individual features that need to be incorporated. However, simplicity encourages the convergence of theory and biology through common models, and such convergence is imperative if we are to understand how the synaptic organization of the neocortex produces the complexity of cortical function.