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Neurobiology of Neocortex
eds. P. Rakic and W. Singer, pp. 219–240
John Wiley & Sons Limited

Group Report
Neuronal and Synaptic Organization in the Cortex

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THE CELLULAR CONSTITUENTS AND INTRINSIC CIRCUITRY OF CORTEX

Though different cortical regions serve radically different functions, there is a body of evidence suggesting that all cortical areas may operate on a common algorithm. The cell types found in different areas, for example, are similar. Moreover, the cell content is remarkably similar in different regions of cortex. Within a column of arbitrary width, the total number of neurons is the same (approximately 130 in a 35 μm 147m wide column) in all but one cortical area in all species. This suggests that the cytoarchitectural differences seen in different areas are a matter of taking the same basis set of neurons and altering their size and laminar distribution. Area V1 of primates represents the sole exception, having twice the density of neurons seen in any other area. An extension of this work has been done for the GABAergic neurons. In 10 different areas of monkey cortex the GABAergic neurons represent a constant 25% of the total. Once again V1 represents an exception, with the proportion falling to 18%, probably due to the increase in number of spiny cellate cells in layer 4C. One caveat to this line of reasoning is that it does not take into account the size of functionally defined columns within any particular area. Also, the subcategories of GABAergic cells, as defined by their content of peptide transmitters, may vary in proportion from one area to the next.

Classification of Cell Type

There are two principal varieties of cortical neuron: spiny and spine-free. The spiny cells are probably excitatory, and include both pyramidal and spiny stellate cells. Pyramidal cells are characterized by their eccentric dendrite extending towards the pia (though not necessarily reaching the pial surface) and a skirt of shorter dendrites clustering around the base of the soma. This distribution pattern allows the apical dendrite to sample a different set of inputs from the basal dendrite, though there is currently insufficient information on the partitioning of inputs onto different dendrites of a given cell.

Pyramidal cells can be subclassified according to their efferent targets (which often correlate with the layer in which the cell resides) and the layer in which the apical dendrite arborizes (which often correlates with the laminar distribution of the cell's recurrent axon). It has been shown that there can be a relationship between the morphology and intrinsic projections of a pyramidal cell class and its efferent target. For example, V1 pyramidal cells of layer 5 may project either to the lateral geniculate nucleus or to the claustrum. The corticoclaustral cells have a different apical dendritic shape, with arbor within layer 5 and then extending to the pia, than that of the corticogeniculate cells, which have an extensive arbor ramifying in layer 4.

This operational definition of a cell class characterized by unique inputs and outputs may eventually be extended to include other criteria, such as transmitter type, receptive field type, and other biophysical properties that determine discharge patterns.

The inputs to the pyramidal cells include excitatory synapses predominantly with the dendritic spines and inhibitory synapses which contact somata, axon initial segments, and dendritic shafts. Inhibitory terminals can also contact spines. Each of these inputs appears likely to be served by different populations of inhibitory interneurons.

The axons of pyramidal and spiny stellate cells themselves form an extensive excitatory plexus within each cortical area. This excitation may be mediated by the excitatory amino acid transmitters. The postsynaptic cells in this circuit are mainly other excitatory neurons, indicative of a facilitatory function. Each pathway, however, tends to have two parallel components: one a direct excitatory connection and the other a disynaptic connection through an inhibitory interneuron. This is true for both thalamic and intrinsic cortical connections.

The transmitters used by pyramidal cells have not been definitively characterized, but there are several lines of evidence implicating the acidic amino acids (aspartate and glutamate) in excitatory pyramidal cell transmission. Glutamate release has been shown in the LGN, striatrum,

superior colliculus and spinal cord. The localization of glutamate does not necessarily imply a role in neurotransmission because of its presence in general metabolic pathways. Specific, high affinity uptake and retrograde transport of glutamate and/or aspartate have been used as evidence in support of the association of various pyramidal cell populations with excitatory amino acid transmission. Immunoreactivity to glutamate, which may be relatively nonspecific in cell bodies, may be more meaningful when localized in nerve cell terminals. The best evidence for this has been shown in the cerebellum. Though the actual identity of the excitatory transmitter may not be established (some have suggested acidic amino acid-containing peptides, such as NAAG [N-acetyl aspartyl glutamate], as potential candidates), there are clearly several classes of receptors involved in this transmitter system.

The collateral branches of the axons of pyramidal cells are extremely widespread, often travelling 6 mm within a single cortical area. The terminal ramifications of the axon collaterals can be grouped into distinct clusters, which are given off at discrete intervals. The trajectory of these collaterals suggests a possible relationship with the dendrites of other pyramidal cells. Though much of our knowledge of the morphology of pyramidal cells had already been acquired at the time of Cajal, the full extent of the horizontal plexus of pyramidal cell axons was revealed less than ten years ago. The connections formed by pyramidal cell axons are quite specific, so despite their widespread distribution, they should not be thought of as being diffuse. These axons probably represent a major route for lateral excitatory interactions. They are common to all cortical areas, and therefore represent another example of the existence of processing mechanisms common to all cortical areas. Pyramidal cells also participate in feedforward and feedback cortico-cortical connections. There is very little information on the functional role of feedback circuits in the cortex. Perhaps as we learn more about the physiological contextual effects and phenomena dependent on attention and behavioral state, it will be possible to discover properties under the control of recurrent projections.

The axon terminals of pyramidal cells form asymmetric synapses (which are presumably excitatory), and they contact the spines of other pyramidal cells. In the cat, it has been shown that 85% of the synapses are axospinous. The remainder are with shafts or somata, but few of the postsynaptic profiles show immunoreactivity for GABA (less than 5%).

Pyramidal cells are not the only spiny cells in the cortex. The spiny stellate cell appears in all cortical areas, though its shape and density vary. In V1, where the thalamic input is found in a relatively narrow layer, the cell's dendritic fields tend to be spherical. In parietal cortex, where the thalamic input is distributed in a broader layer (parallel to the distribution of the

corticocortical input), the cell's dendrites are drawn out more vertically. This suggests that the spiny cell type is specialized as a thalamic recipient cell. Even so, at most 20% of the excitatory input to these cells is thalamic in origin, the remainder coming principally from other layer 4 spiny cells (and a small proportion from layer 6 and the claustrum). Though it is difficult to determine the relative importance of a given input merely from its proportion (for example, inputs proximal to the soma are likely to have greater effect than inputs on distal dendrites), one can nevertheless conclude that the spiny cell is the major target of thalamic input.

In considering the functional role of any given cell type, it is important to know its coverage across the cortical sheet. In the visual cortex, for example, this provides a measure of the density of sampling within the visual field for a given functional parameter. Though this kind of analysis has not been applied in the cortex as it has in the retina, it is interesting to compare the extent of dendritic fields in cats and monkeys. On an admittedly biased sample of pyramidal cells in V1, the lateral spread of the basal dendrite in cats is larger (on the whole) than in the monkey. The hypercolumn (defined as an area of cortex including a full complement of columns in any one submodality, such as orientation or ocular dominance) in the monkey is only slightly narrower than in the cat, which suggests that monkey cells may be more sharply tuned for given parameters than cells in the cat.

After the spiny cells in cortex, the second principal class is that of the smooth and sparsely spiny cell. As mentioned earlier, these represent approximately 25% of cortical neurons (20% in the cat). They are considered to be inhibitory since most are GABAergic. Within the general category of smooth stellates there are several subclasses, each of which tends to have a specific postsynaptic target. Two that certainly do are the chandelier cell, which contacts the axon initial segments of spiny cells, and the basket cell, which contacts cell bodies and proximal dendrites and spines. Various other types (including neurogliaform and bitufted), do not form synapses with somata; rather, most of their synapses appear to be more distally placed on the dendrites of their target cells.

In contrast to the axons of pyramidal cells, the axons of most smooth stellate cells are more local, tending to ramify close to their dendritic fields and vertically between layers, thus relating more to the column in which the cell bodies reside. The axons of the most laterally extended stellates, the basket cells, do not extend much more than 1 mm (though in motor cortex they can be much longer, possibly reflecting differences in cell sizes, related in turn to packing density).

The target specifity of chandelier cell is the best example of the specificity of connections by smooth stellate cells. The basket cell, in contrast, forms only 0.5% of its contacts with axon initial segments. Basket cells vary in

the degree to which they synapse preferentially with cell somata. In some basket cells of the cat only 25–30% of synapses are formed with cell somata, 50% are with dendritic shafts, and 20% with spines. This contrasts with basket cells of the monkey motor cortex, whose axons more clearly contact somata, and proximal dendrites.

There are at least two remaining cell types having axons known to contact spiny dendrites. One is the neurogliaform cell, with a large axon density within the area covered by its dendritic fields. The other is the bitufted cell, often having a sparsely spiny dendrite, an axon with a lower density of collaterals within the dendritic field and large varicosities. The latter tends to be sparsely spiny. The postsynaptic targets of these cells tend to be similar, with 20% of their contacts with spines and 80% with small dendritic shafts. All of the major categories of smooth stellate cell area seen throughout the cortical depth (though their proportions and densities vary from layer to layer), and they form a tight inhibitory control on the excitatory throughput pathways.

The most established inhibitory transmitter is GABA, and it seems possible to associate many smooth stellate cell types with GABAergic transmission. Other substances, such as taurine and glycine, have been proposed as inhibitory transmitters, but it is unlikely that they mediate inhibition in the cortex. Their release, for example, is not calcium-dependent. Some peptides may also be inhibitory, but they are usually found colocalized with GABA. It is suggested that the inhibitory inputs to a given cell tend to be paired with the excitatory inputs, forming a potential switch for local excitation. This inhibitory control can be particularly effective for NMDA receptors, because of the voltage dependency of the current they induce when activated.

The tangential distribution of the GABAergic cells is a matter of some debate. In one region, lateral frontal cortex, they have a periodic distribution. In ten others it is uniform. This difference may reflect the relative activity of different GABA cell populations, since the immunoreactivity can be influenced by activity levels even if the absolute number of GABAergic cells stays the same. In visual cortex the GABA levels can be influenced by enucleation, injection of TTX, lid suture, and even the use of a lens implant causing a slight myopia. However, variations have not been seen in visual cortex of normal animals. The variations seen in frontal cortex might reflect a difference in the plasticity of different areas to experience.

The input to the cortex from thalamus appears to be specific for the class of postsynaptic cell. The X and Y pathways in the cat contact primarily spiny neurons, but they also contact inhibitory neurons such as the local layer 4 basket cell, as well as the basket cell in layer 3. Both basket cells receive some of their thalamic input on the soma. In addition, of course, the inhibitory neurons receive inhibitory inputs. Within the axonal field of

a thalamic afferent, around 7 to 10 GABA-containing cells are contacting (on their somata) and they probably correspond to basket cells. Other GABAergic cells are likely to receive thalamic input only on their dendrites. Interestingly, X-axons contact a population of GABA cells with smaller soma size than do Y-axons.

The coverage factor of each afferent type is quite large in cat V1. For X-type LGN axons it is around 300 to 900. That is, at any one point in layer 4 the axonal fields of at least 300 X-cells are superimposed. In many instances only a single contact is made between a given afferent and a given spiny stellate cell, suggesting a substantial amount of convergence between them. At first sight, this seems to conflict with the results of cross-correlation analysis, which shows that a single thalamic afferent contributes in the order of 10% of the firing of a simple cell. However, this discrepancy may only be due to the difficulty in finding the postsynaptic cells (which would be few in number) with the greatest number of inputs from a particular afferent. The anatomical data do show, however, a relatively low probability that a spiny stellate cell will receive input from any given thalamic afferent that overlaps with its dendritic field. In the monkey, coverage factors in V1 are about two orders of magnitude smaller, which is indicative of the striking species differences seen even in primary sensory areas.

Computational Capacities of the Single Cell

In considering the processing mechanisms of cortical cells, we should not restict ourselves to the pattern of connections converging onto a cell. Considerable computational capacity is also obtainable by use of the myriad variety of ion channels and receptor types. Transmitters can work in several ways that are different from the simplistic idea of short-term excitation and inhibition. A transmitter may change the gain of the response at a different synapse, it may change the temporal pattern of spike output, it can redistribute the activity over the neuronal array (for example by recurrent inhibition), and it can initiate long term changes in the responsiveness of a cell. Each voltage-dependent current has its own kinetic range—the range of voltage over which it can be seen—which represents a characteristic fingerprint for that channel. *In vitro* studies of cortical hippocampal cells largely derived from rodents at least 12 voltage-dependent ion channels and an even larger number of receptor types, some of which may be extrajunctional, have been described. In contrast to earlier views, most transmitter activated channels have some voltage-sensitive component. Voltage-dependent channels can also be modulated by transmitters. For example, the M current channel opens as the cell depolarizes and cholinergic agonists close the channel. Some receptors may not contribute directly to conductance changes that depolarize or hyperpolarize the cell, but rather

may activate second messenger systems that affect other cell processes. A number of receptors, such as the $GABA_B$, M1, 5HT1, α, and β, have been shown to be coupled to channel phosphorylation through activation of second messengers. Some transmitter actions cannot be strictly classified as excitatory or inhibitory; rather they change the pattern of spiking in the postsynaptic cell.

The spiking behavior of dendrites varies in different cell types. Cerebellar Purkinje cell dendrites contain no Na channels but have a high density of Ca channels, wheras Ca and Na-mediated spikes occur in hippocampal pyramidal cell dendrites. These appear to provide a booster potential for EPSPs. Thalamocortical cells have prominent low thresholds: probably somatic Ca channels allowing them to switch from a regular firing pattern to firing in bursts, as well as presumed high threshold calcium channels on dendrites. Little is known about the electrical properties of cortical pyramidal cell dendrites.

Receptors can control membrane conductances determined by the channel to which they are coupled. A given neurotransmitter may activate more than one receptor on a particular subclass of neuron. Also, one receptor subtype can be coupled to different ionophores in different cells. The classification of the receptor type is based in its pharmacology. For example, activation of type 2 muscarinic receptors (M2) on GABAergic cortical cells produces depolarization due to a cation conductance, whereas nucleus reticularis M2 receptors are coupled to an increase in K conductance, which produces a hyperpolarization—quite a different action.

Is there any evidence that one can alter receptor subtypes or the behavior of a given receptor within a structure? The available information is limited. In one example, somatostatin reportedly changes the ratio of M1 and M2 receptors. One recent report suggests that repetitive circuit activation may induce or strengthen the coupling of NMDA receptors on dentate granule cells to ionophores. A major concern is the presence of species differences in the complement of receptors in a given structure. For example, in relay cells of the LGN of the cat, ACh produces a nicotinic excitation followed by a slow muscarinic excitation. In the guinea pig LGN the response is characterized by an initial muscarinic hyperpolarization followed by the slow depolarization.

Cells can often be differentiated according to their membrane properties. Neocortical GABAergic cells have a relatively linear relationship between spike frequency and degree of depolarization, with very little accommodation of frequency, and also tend to have spikes of short duration. These features may be related to the absence of calcium activated K conductances and faster spike repolarization due to qualitative and quantitative variations in voltage dependent K channels. These and other properties of GABAergic cells including a high input resistance, tend to produce a steep relationship

between depolarization and spike frequency, allowing EPSPs to evoke repetitive firing. Pyramidal cells have more nonlinear membrane properties. They also tend to show spike frequency accommodation due to a Ca activated K current and to other voltage-dependent K currents. Their membrane properties make them effective integrators. One functional variety of pyramidal neuron located in layer 4/upper 5 of sensorimotor cortex possesses intrinsic burst generating properties.

Certain issues concerning the mechanisms for generating specific receptive field properties have led to hypotheses about specific synaptic mechanisms. It has been suggested that orientation selectivity, as well as a number of other properties, may involve inhibition of inputs without observed changes in membrane potential (shunting inhibition). However, one problem with shunting inhibition is that it requires stringent synchronization of the EPSP and IPSP. The bursty firing pattern of certain GABAergic cells, however, may relax this requirement by producing much longer lasting IPSPs in the postsynaptic cell. In fact, evoked IPSPs in cortex have a much longer time course than the EPSPs and may last hundreds of milliseconds, while the duration of spontaneous IPSP may be 10–30 ms. Activation of the $GABA_B$ receptor produces much longer hyperpolarizations. Cross-correlations have shown evidence for the long lasting inhibition when one uses electrical or visual stimulation. With spike trigger averaging techniques the IPSPs are somewhat shorter, lasting for 10 ms. The stimulation may therefore produce repetitive firing of the GABAergic cells. In cortex, there is evidence for a constant barrage of IPSPs at rest with cells subject to a tonic inhibitory drive, which could act as a substrate for disinhibitory events.

Another issue related to the activation of GABA receptors is the presence of depolarizing as well as hyperpolarizing responses to applied GABA. In the hippocampal pyramidal cell GABA has been shown to hyperpolarize the soma and to depolarize the dendrite. The depolarization, however, is still inhibitory since it involves an increase in conductance and reverses below threshold. The mechanism for depolarizing dendritic inhibition is not known; however, a reversed chloride gradient in dendrites has been suggested. It has been further suggested that the dendritic inhibition allows one to silence locally the dendritic depolarization without hyperpolarizing the cell body.

Inhibition may be responsible for controlling the excitatory synaptic coupling between cells. An example of this is seen in the hippocampus. Ordinarily, the excitatory interaction between pyramidal cells in CA3 is relatively rare, with about 5% of the population interacting under normal conditions. If one applies a GABA blocker to produce small decreases in IPSPs, one recruits many more cells into excitatory interaction, although the pathway over which they interact may be polysynaptic. The inhibitory input to a cell is itself under inhibitory control, presumably due to the

extensive inhibitory synaptic input that different classes of smooth stellate cells have on their somata. By adjusting the rate of stimulation of inputs the inhibitory system is recruited to varying degrees. When the size of the complex IPSP is reduced, additional neurons may be recruited by one cell, and the aggregate input to a cell is greatly enlarged. Application of bicuculline will result in evoked field potentials that move across the cortex, presumably mediated by the long range horizontal polysynaptic excitatory connections. If inhibitory proceses are sufficiently depressed, epileptogenesis results.

There are several mechanisms for modulating the effect of synapses. As noted above, in the dentate gyrus it has been shown that NMDA receptors are normally uncoupled from the ionophore, and under certain stimulus conditions (in this case, repetitive activation in an experimental kindling paradigm) they can be coupled. Activation of cholinergic input to a cortical pyramidal cell has been shown to affect the neuronal response decreasing Ca-activated and voltage dependent K^+ conductances. The former effect reduces the duration of the afterhyperpolarization, and the latter reduces the M current. ACh also causes a depolarization of inhibitory interneurons. The net effect is to increase the activity of inhibitory cells and to increase the response of pyramidal cells to stimuli. The laminar distribution of the cholinergic input provides a potential for selectively switching the output of selected channels. The change in level of cholinergic activity in the sleeping versus waking state has been shown to be associated with changes in the responsiveness and specifity or cortical neurons. The application of ACh to cortical cells produces changes in visual cortical cell response properties which are qualitatively similar to those observed in cats moving from sleeping to waking state.

Another set of transmitter systems to be considered are the peptides. Peptides have generally been associated with fast synaptic effects (though CCK produces excitation with a similar time course to glutamate in hippocampal granule cells). Because of the coexistance of peptides and GABA in many cells, the supposition is that the peptides can modulate the action of GABA. However, no evidence for this has been presented. Many cells have two or more peptides coexisting (for example, somatostatin, neuropeptide Y, and substance P have been found in single cells). It is tempting to speculate that the neuron can regulate the stoichiometry of release of its compliment of peptides (perhaps depending on the rate of discharge of the cell), significantly altering the functional role of the cell at different times. The effects of the peptides range from excitation to inhibition, but are usually small in amplitude. The more intriguing possibility is that of longer term effects than the immediate changes in membrane potential, possibly mediated by second messengers.

Regional variation in transmitter systems represents one currently identified

difference between cortical areas. Though every transmitter is probably present in every area, there is significant variation in amount. For example, dopamine is found mainly in frontal, cingulate, and entorhinal cortex, and is found at much lower levels in more posterior cortical regions. It is not clear to what extent these differences covary with other differences, such as in cortical lamination. It is apparent that there are greater regional differences in the catecholamines than in the intrinsic transmitter systems. In addition to their spatial distribution, many transmitter systems change level and cellular distribution during development and aging.

For completeness we should also consider interactions other than those mediated by chemical transmitters. Electrical ephaptic interactions have been proposed; however they are most likely to have functional significance in pathological states such as epileptic discharges. Changes in the extracellular milieu, such as K^+ concentration (which can change from 3 to 12 mM during large scale discharges), affect the firing of cells in the area. Electrical transmission through gap junctions is a possibility, but these have very rarely been observed in the adult brain. They may play a greater role in the developing brain, however. The cortex is relatively conservative in terms of the type of synaptic interactions it exhibits. For example, there are no dendrodendritic or axoaxonic synapses and, as mentioned above, gap junctions are rare.

The relative positioning of different inputs on a cell's dendritic field may be an important factor in understanding the importance of the various receptors and ion channels, and in understanding a cell's processing strategies. For example, distal inhibition may serve to eliminate voltage-dependent components of NMDA-receptor mediated EPSPs, and shunt voltage-dependent Ca-mediated events on dendrites. Also, it has been shown that inhibitory inputs placed proximally to excitatory inputs on dendrites are more effective than distal inhibition; although proximal inhibition is more effective on larger numbers of excitatory inputs, distal inhibition has the advantage of being more selective. At present relatively little is known concerning the partitioning and positioning of inputs on the dendritic field.

In the future it will be necessary to determine mechanisms of regulation of the receptors and channels. These mechanisms include changes in intracellular second messengers and developmental programs. The longer term changes may be related to memory and learning.

HOW RESPONSE PROPERTIES ARE GENERATED

There are many receptive field properties attributable to cortical processing. The mechanisms underlying these properties have been studied in most detail in primary visual cortex. It must be emphasized that these represent

a fraction of the properties observed even in V1. In this report we shall focus on directionality, ocular dominance, orientation and end-inhibition.

Directionality

This refers to the preference by many cells for stimulus movement in one direction over movement in the opposite direction. It has long been presumed that this property requires some spatial asymmetries in the connections between cells. One could generate directionally either by a cascade of inhibitory connections, as suggested by Barlow, or by a cascade of excitatory connections. The results of intracellular recording and bicuculline application indicate that the mechanism involves inhibitory processes.

The amount of movement within the receptive field required to show directionality can be quite small, ranging from 10 to 20″ of arc. Using stroboscopic illumination one can examine the optimal temporal delays and spatial displacements to elicit the effect. In V1 of the cat the maximum displacement ranges from 0.5 to 3.0°. Interestingly, the initial position can be outside the excitatory portion of the cell's receptive field. Directionality is velocity-dependent and can disappear with very slow stimulus movement. The displacement required for optimum directionality can also be expressed in terms of the "spatial wavelength" of the cell. The strongest directionality is elicited by displacements equivalent to a 90° phase shift.

The basket cell is a candidate for the source of directionality. Since it receives thalamic input, it can generate the feed-forward inhibition, and its axosomatic synapses are appropriate for "divisive inhibition." This form of inhibition is characterized by cutting the activation of a cell by a constant fraction at any of a wide range of levels of activation.

In the cat, directional selectivity is seen in all layers; in the monkey, there is a much greater prevalence of directionally selective cells in layers 4B and 6. This is quite appropriate in view of the projection targets of cells in these layers, including the motion area. However, one cannot presuppose that area MT inherits its directional properties directly and only from V1. In MT the fields are much larger and the cells show directional responses to much larger stimulus displacements than seen in V1. thus, under certain stimulus conditions cells in V1 are nondirectional; but cells in MT are quite directional, suggesting that similar mechanisms may have to be repeated at successive stages in the visual pathway. A columnar distribution of directional cells has been observed in V1 of the cat and in MT. In the latter, cells with opposite directional preference are located side by side in adjacent columns.

Ocular Dominance

The morphological substrate of ocular dominance is much clearer than that for directionality or orientation preference. It is related to the distribution

of inputs from right and left eye geniculate afferents in layer 4 and the subsequent mixing of projections in the supra- and infragranular layers. However, the property of ocular dominance may not be the salient property for which the mixing of inputs from the two eyes is dedicated. If one considers stereopsis to be the purpose of superimposing the visual field representations from the two eyes, then disparity sensitivity would be more to the point.

Disparity sensitivity comes in several forms: cells tuned for stimulus placement on the plane of fixation ("tuned excitatory" cells), and cells tuned for stimulus placement in front of and behind the plane of fixation ("near" and "far" cells). Some studies have also presented evidence for a fourth class, the "tuned inhibitory" cells. There is a relationship between the ocular dominance of a cell and the type of disparity tuning found, so that one can presume an organized distribution of the various types.

The mechanism of disparity sensitivity for at least some of these classes may be related to the presence of inhibitory regions flanking the receptive field of cells along the movement axis (originally referred to as "inhibitory side-bands"). The extent of these inhibitory regions is roughly equivalent in diameter to the excitatory core of the receptive field.

Orientation Selectivity

Though the phenomenon of orientation selectivity was first described almost 30 years ago, to this day the mechanism underlying it is hotly debated. The original postulate by Hubel and Wiesel, that orientation selectivity arises from convergence of excitation from the LGN along a line in the visual field, was questioned on the basis of the shape of the receptive fields. That is, could orientation tuning be as sharp as one observes in a field that is nearly as wide as it is long? Though the actual shape of the receptive field is still debated, a series of pharmacological experiments provided strong evidence for an alternate mechanism. When one applies bicuculline, a GABA antagonist, to cortical cells, there is loss of orientation tuning in approximately 50% of the cells. In contrast to the data on orientation selectivity, directionality appears to require a lower dose of bicuculline for elimination. The relationship between orientation selectivity and GABA transmission seemed to be in agreement with data pointing toward the existence of "cross orientation inhibition", where a cell's firing can be reduced by stimulating it with a line orthogonal to its optimum orientation. An independent line of experiments questioned the idea of cross-orientation inhibition. When one records intracellularly, both the EPSPs and IPSPs are tuned to the orientation of a cell (as measured by its spiking behavior).

This result may have arisen if the cross-orientation inhibition was a shunting inhibition on a remote dendrite, and thus not observable at the level of the cell soma.

To a degree, these conflicts are resolvable if one considers an alternative form of inhibition. One problem with cross-orientation inhibition is the issue of bootstrapping. One cannot have vertical cells inhibiting horizontal cells, and vice versa, without some means of setting up their orientation selectivity in the first place. It has been suggested that the initial orientation tuning could be provided by orientation selectivity of the geniculate cells, but there is disagreement as to the degree of orientation selectivity found in the LGN. The alternative model for inhibition was suggested by Heggelund, who proposed that inhibition between cells having circularly symmetric receptive fields that were slightly offset could produce orientation selectivity. A problem with this model is that, at least in the cat, there are no cells with unoriented fields in the cortex (this is not a problem in the monkey, which has a large population of unoriented cells in layer 4C). Thus there would be no unoriented cells to provide the inhibition. However, one can get around this in the following way: having two mutually inhibitory cells in the cortex which are oriented, but with the same orientation preference. They each receive input from LGN, but from cells with slightly offset receptive field positions. Thus one would achieve orientation selectivity by *same* orientation inhibition, which would be more consistent with the data from intracellular recording. The existence of both excitatory and inhibitory interactions between cells of the same orientation have been observed with cross-correlation techniques.

One need not resolve this dispute in favor of any one of the alternative mechanisms, since all, to varying degrees, may apply. What remains to be found out is the relative contribution of each mechanism. Convergence of excitatory inputs along a line is an important component (for at least some cells), and the amount of such a contribution will be determined by accumulating data on the shape of the receptive field. In the future, it may be possible to determine the distribution of cells that are presynaptic to a given cell, and this information will contribute toward determining the role of excitatory convergence. The second mechanism, involving inhibition between geniculate afferents with offset receptive fields, will be manifest as inhibition between columns of the same orientation selectivity. A third mechanism, involving an overlay of input from cells of all orientations, may provide a general threshold mechanism that can restrict the width of tuning for any of a number of receptive field properties. One advantage of having multiple mechanisms for a single receptive field parameter is that it loosens the requirements for invoking any one of them. For example, if one were to generate a narrow orientation tuning curve exclusively by excitatory

convergence, the precision of alignment of the geniculate receptive fields could require a specificity in connections that would be difficult to achieve. A second advantage of the multiple mechanisms is that each could contribute to several parameters. A like-orientation inhibition between cells with slightly offset receptive fields could contribute to selectivity for orientation, direction, spatial frequency, and stereopsis. Finally, when using more complex stimuli or longer bar stimuli one may invoke the longer-range facilitatory interactions that can reinforce responses at the optimum orientation.

The character of the mechanism underlying orientation selectivity raises the issue of where (i.e., in which layer) the property is generated and if it is generated at more than one place within V1. In experiments in which the activity of layer 4 was blocked by pharmacological inactivation of the A laminae of the LGN, superficial layer cells were left still active and having oriented receptive fields. This suggests that whatever the mechanism, orientation selectivity can be generated independently in different layers. In other instances, there is conflicting evidence concerning the independence of different layers. Lesioning or blocking the activity of cells in the superficial layers has been reported to affect directional selectivity among layer 6 cells, but other experiments fail to show this effect.

End-inhibition

Many cortical cells respond well to a line that fills the receptive field, but their response is suppressed once the line is extended beyond the excitatory core of the receptive field. This property allows cells to be sensitive not only to the length of a line, but also for local curvature. Recent experiments in the cat have suggested an association between a specific component of the cortical circuit and this property. Pyramidal cells in layer 6 project to layer 4. Many of the layer 6 cells have receptive fields much longer than the fields of cells in layer 4. However, the layer 4 cells have long inhibitory flanks along their orientation axis, equivalent in extent to the fields of the layer 6 cells. By contacting an inhibitory interneuron in layer 4, the layer 6 cells can generate these end zones which have previously been shown to have the same orientation preference. Ultrastructural evidence provides the morphological substrate for this circuit. If one blocks the activity of layer 6 cells by local injection of GABA, the cells in layer 4 above the site of inactivation lose the property of end-inhibition during the blockade of layer 6.

Though the direct projection from layer 6 to layer 4 represents a likely pathway through which the property is generated, there are other pathways in which layer 6 cells play a role. These cells can influence layer 4 cells via the claustrum and the lateral geniculate nucleus. In fact, there is evidence

for the participation of both these pathways in end-inhibition. Lesions of claustrum cause a partial reduction in the degree of end-inhibition found in the cortex. Cells in the LGN can show end-inhibition, and ablation of areas 17 and 18 cause a partial reduction in the end-inhibition, of LGN cell receptive fields. Presumably, the remaining end-inhibition comes from the surround inhibition inherited directly from retinal ganglion cells and from the feed-forward inhibition in the retino-geniculate pathway. However, the limited inactivation of layer 6 cells eliminating end-inhibition in layer 4 does not affect the end-inhibition of geniculate cells. There are therefore several stages through which this property can be generated, though the effect differs in degree and in the convergence required to influence it. Inactivation of a small (600 μ diameter) portion of layer 6 can eliminate end-inhibition via the pathway to layer 4, but a much larger scale blockade (ablation of more than one cortical area) is required for reducing end-inhibition in the LGN.

In considering the specific mechanisms responsible for generating receptive field properties such as directionality, orientation, disparity sensitivity, and length tuning, some common patterns emerge. Within a modality, and in fact within a single cortical area, one can generate several receptive field properties through several mechanisms. The lateral inhibition between cells with offset receptive fields can mediate orientation selectivity, directionality, and disparity sensitivity. Thus it may not be necessarily to evolve distinct mechanisms for each parameter; instead, the same mechanisms can be applied to very different functions. In this way the same mechanisms used for the analysis of visual information serve other sensory modalities. The auditory cortex may generate sensitivity to localization of sound sources in space by binaural interactions similar to the binocular interactions seen in stereopsis. The "EE" and "EI" cells (referring to interaural summation and inhibition responses, respectively) are analogous to the tuned excitatory and near/far cells of binocular interaction in the visual cortex. One can imagine how these cell classes in the different sensory modalities are generated by similar mechanisms. In the somatosensory cortex, cells are found with directional sensitivities similar to those found in the visual cortex. In the end, one can imagine that the cortex repeats the same algorithm, via a stereotyped set of inhibitory and excitatory connections, to generate different functional properties. Thus it may not be so surprising if, within a single cortical area, the same properties might be generated *de novo* in different layers, such that when one layer is inactivated the property is retained in the layers that remain.

Long-range Effects

The above properties are observed when one uses a simple visual stumulus, such as a single bar of light. There are other properties, sometimes referred

to as the "nonclassical" receptive field properties, which can be observed only when using more complex stimuli consisting of multiple contours or textures or colored fields. These properties endow cells with a sensitivity to context in the visual environment. Contextual effects have been observed in several different submodalities. Cells in area V4 have the property of color constancy, giving them a sensitivity to the color of an object independent of the conditions of illumination. Contextual effects in the motion domain have been observed in pigeon tectum, cat suprasylvian gyrus, and monkey area MT, where the cells firing can be potentiated by opposing background movement outside the classical receptive field. The presence of oriented lines outside the receptive field can affect the orientation tuning of a line inside the receptive field.

The long-range interactions have been observed at as early a stage as the retina, and have been observed at every subsequent stage in the visual pathway where they have been studied. In V1, cells can be suppressed by a textured background moving at the same speed as a bar in the center. A similar effect is seen in the LGN. In some V1 cells, the directional specificity of a cell can be altered by background movement. These effects are specific for the axis of movement, indicating facilitory interactions between cells of the same orientation preference. Support for these long-range interactions has been provided by both anatomical and cross-correlation studies. The exact relationship between the horizontal connections and the columnar structure is an issue currently under debate.

The long-range effects may be manifested differently at different stages of development. In the cortex of the kitten, 10–15% of the cells have one or two ectopic fields. These are activating areas rather than the modulatory influences seen in the adult. The area of visual space covered by these fields is of the same order of magnitude as that predicted by the long range horizontal connections seen at these stages.

Dynamic Receptive Field Properties

Another "classical" view of receptive field structure is that it is relatively fixed in visual field position and specificity. There has been some suggestion, based on results in behaving animals in extrastriate cortex and on theoretical considerations in striate cortex, that under appropriate conditions one may be able to dynamically shape the response parameters of a cell. In area V4, for example, it is possible to change the relative sensitivity of a cell to stimulus placement in different parts of the receptive field by the use of conditioning stimuli. This sharpening of specifity has been observed not only in the spatial domain but also with respect to color and orientation.

A suggestion for dynamic processes within V1 was proposed as a solution to the problems posed by variability in fixation. Although the alignment of

the two eyes drifts over a range of 1/4° to 1/2°, the world appears very stable in depth and the visual image remains coherent. To compensate for these eye movements, it has been proposed that there could be an active change in the mapping from layer 4 to the superficial layers. This may be related to the fact that there are 50–60 times as many cells in layer 4 as fibers in the optic radiation. This could be accomplished by stacks of neurons with slightly diverging connections and an inhibitory control to shunt the inappropriate connections. Physiologically, this would appear as a constant shifting in the position of the receptive field of any given cell. Evidence for such changes, on the order of an ocular dominance period, have already been observed in behaving monkeys.

INTRA- AND INTERAREAL DIVERSITY

Even within V1, there are many more receptive field properties than discussed thus far. These include color, selectivity for width or spatial frequency, and velocity selectivity. Much less is known about the range of functional properties in the various areas of extrastriate cortex. At present count there are on the order of 24 areas in the Macaque monkey serving the visual modality, 6 serving somesthesis. None of these areas appear to polysensory, though that has not yet been systematically explored. Within these areas one can consider two categories of stimulus sensitivities. One is the response of cells to classical stimuli (bars and gratings), which has been explored in about six of the visual areas. No striking new properties are observed as one goes up in the cortical hierarchy, nor does one see a dramatic sharpening in the selectivity for the known parameters. (There is some question as to whether color may be an exception). One does see differences in the proportion of cells having a given property, such as direction selectivity in V5 (MT) and color selectivity in V4.

A second kind of sensitivity, which does appear to be area-specific, is the response of cells to complex stimuli. In V2 cells have been shown to respond to subjective contours. These are seen in optical illusions, where an observer perceives a nonexisting line or boundary crossing between two existing boundaries. In V4 cells have the property of color constancy mentioned above, and in V5 (MT) cells are sensitive to the movement of patterns and not to the component contours making up the patterns.

Is there any way to predict systematically what would be the appropriate stimulus to use in studying these areas? One fruitful approach has been to use psychophysics as a guide. Another approach is to develop computational algorithms that suggest unique solutions to visual problems. We may also try to obtain clues from the patterns of connections observed within a particular area and their relationship to the functional properties of cells

participating in these connections. Finally, it has been useful to obtain cues from the behavior of the animal. For example, the bat auditory cortex is specialized for echolocation, and the properties of cells in MT are better understood as a result of considerations of the environment in which the animal lives.

In studies of the cortical areas serving different sensory modalities, there is the notion of a hierarchical order between them. Evidence in support of the idea that one area is "higher" than another comes from the finding of more complex interactions in the receptive fields of cells. As one ascends the hierarchy, the fields get progressively larger and lose selectivities for certain parameters. An alternate view is that the different areas are simply specialized to analyze certain parameters, with no sense of one being higher than another. Still, there are anatomical asymmetries in the pattern of projections between areas. Following the anatomical rules, one can follow a sequence of projection leading to area 7 in the parietal cortex, and a second pathway leading to the hippocampus and entorhinal cortex. Except for V1, in any one area there may be only a few parameters or processes that are analyzed. The best evidence for the functional specificity of individual areas comes from clinical evidence showing specific deficits related to restricted lesions of visual cortex and from experimental studies involving small chemically induced lesions in MT.

SERIAL AND PARALLEL MECHANISMS

On an anatomical basis alone there is clear evidence for segregated pathways within any sensory modality. Thus both serial and parallel processing mechanisms coexist. There are several lines of evidence indicating that the parallel streams may feed into each other at different points along the pathways.

Support for serial processing mechanisms comes from cross-correlation and electrical stimulation studies. Input from the lateral geniculate nucleus is segregated onto different classes of postsynaptic cell. In the cat the X input contacts simple cells, with the ON and OFF center LGN cells contributing to the subfields of simple cells of the same sign. In addition, some simple cells receive a single line of input from geniculate cells. These cells are referred to as E-On and E-Off cells. They may not be different from simple cells with multiple subfields, but their flanking subfields may require conditioning stimuli to be demonstrated. Y-afferents contact special complex cells, and it has been shown that they contact simple cells as well, since they ramify in one of the principal zones where simple cells are found. Some complex cells receive direct input from the LGN (mostly Y), but layer 2 complex cells do not receive direct thalamic input.

Serial inhibition has also been observed: the E-On and E-Off cells provide inhibition for simple cells, potentially providing antagonism between subfields and receptive field properties such as orientation selectivity. The cross-correlation results have only shown antagonism between simple and complex cells, though the existence of simple spiny stellate cells projecting up to the superficial layers suggests that there must be an excitatory connection as well. Serial excitation within the cortex has been seen between complex cells, both locally and at long-range horizontal separations.

When one inactivates the On-cell pathway with APB application to the retina, orientation selectivity is preserved, though the "leading edge" response to light bar stimuli is lost or reduced. This suggests that the excitatory drive from On-center LGN afferents drops out, but that the inhibition from E-off cells can provide whatever inhibition-dependent orientation sensitivity is necessary.

Despite this clear-cut evidence for an excitatory throughput from layer 4 to the superficial layers, many cells appear to be capable of functioning when one removes one of the several thalamic sources of input to the cortex. Malpeli has shown that cells in the superficial layers appear to have normal response properties (including orientation, direction, and length tuning) under conditions where a major source of their input is inactivated. Thus it appears at least superficially that cells can operate on input from alternative sources. This is quite curious, since the properties of the cells in the different input pathways are very distinct. It would suggest that the unique properties contributed by any one input may not be fully characterized. One could imagine that the X-pathway may be important for properties such as binocular interaction, or that it endows cells with sensitivies over a different contrast range than the Y-input. In other instances one can demonstrate a clear deficit when one of two alternative pathways is destroyed. For example, in the APB experiments, where the On but not the Off cells are silenced, there is a selective loss of response to light but not dark moving edges.

In the monkey there is a tripartite segregation of pathways. This segregation was discovered with the aid of a histochemical stain for the enzyme cytochrome oxidase, which in the superficial cortical layers has a patchy or "blob"–like distribution. The magnocellular pathway carries information of high contrast sensitivity, direction selectivity, and transient response duration. The "blobs" carry chromatic and low spatial frequency information. The "interblobs" carry information on form, with a high proportion of orientation selective neurons but also a significant incidence of wavelength selectivity.

These pathways are not entirely segregated. There is a significant projection from layer 4B (which is considered part of the magnocellular

system) to layers 2 and 3. There are also inhibitory interactions, with projection by smooth stellate cells in layer 4A to layer 3B and 4B (putatively parvocellular and magnocellular layers, respectively). Selective inactivation of the parvocellular or magnocellular layers of the LGN shows a range of input mixtures, with many cells receiving input from both systems. The receptive field properties of some neurons also indicate a mixing, for example with the color-specific oriented cells.

To date we have treated the modular structure in a given area as a series of stereotyped elements repeated uniformly across the area. To what extent is this a valid assumption? Certainly one knows of variations in functional properties with position in the cortical map. There is little anatomical evidence for changes in the basic circuitry from one part of a cortical area to another, though there are subtle differences in intercolumnar spacing and in cortical thickness. The overriding influence on the change in functional properties with visual field position, however, is most likely to be the distribution of the input axons. It is worth noting that changes in the proportion of a given cell type of functional property with eccentricity in the visual field may provide a useful tool for determining the behavioral significance of that property.

To what extent does the functional architecture of an area reflect the computational strategy of that area? At one level, it seems likely that the functional properties distributed in a columnar fashion may represent the important filtering properties of that area. At another level, one can think that the interaction between the intrinsic local connectivity and the columnar structure allows the cortex to generate specific properties such as orientation or disparity selectivity, or more elaborate functions such as bringing parts of the visual field in the views provided by the two eyes into correspondence.

Continuing with the theme of parallel pathways, it is now clear that in V2 there is an analogous segregation to that seen in V1. Each of the three compartments in V2 receives a specific projection from one of the compartments of V1. There is some evidence indicating that the V2 compartments are interconnected. There is clearly some intermixing at higher levels, but the degree to which these streams remain segregated has yet to be fully worked out. Another source of input to these systems is the thalamus, and it is not known whether, in higher cortical areas, the different processing streams receive input from the same or different thalamic sources.

On a larger scale one can see parallel pathways from widely separated brain regions into the frontal cortex. These input systems have similar structures, with reciprocal projections between frontal and parietal, inferotemporal, cingulate, and parahippocampal cortex. Examples of two parallel systems are arcuate (frontal eye fields) connected with 7ip (parietal), superior temporal sulcus (inferotemporal), cingulate, and parahippocameal; and principal sulcus (frontal) connected with 7a (parietal), and different areas

in the inferotemporal, cingulate, and parahippocampal gyri. There may be many such systems of parallel circuits. In the examples given they have distinct functions, with the circuits including frontal eye fields regulating eye movement. Common to both systems is their role in spatial information processing. In a delayed response behavioral paradigm, a cell in the frontal eye fields will fire after a spot to which the animal is to move its eyes disappears, and continues to fire until the movement is made to the remembered target position. Thus it seems that the cell holds the location of the spot in memory for a short period of time. The receptive fields of these cells appear to be limited in extent, and there is evidence for a visuotopic order within the area. Lesions in the frontal areas prevent an animal from performing manual or oculomotor tasks dependent on spatial memory, as compared with lesions in parietal cortex, which produce spatial neglect.

Where these streams may join is not clear. However, it is possible that the pathways mediating place and object information may merge in the projections from temporal to parietal cortex. The dorsal component of the superior temporal sulcus (including MT and MST, representing the magno or movement pathway), as well as the ventral component (including V4 and inferotemporal cortex, representing the object recognition pathway), project to parietal cortex.

In considering the transformation of receptive field properties as one proceeds from the primary sensory areas to frontal, hippocampals and entorhinal cortex, one wonders what happens to the specificities present at the earliest stages. Do they have access to the behavioral output? The frontal cortex directly accesses many areas along the visual pathway, but the input declines as one goes back to more primary areas. V1 has no direct projection to frontal cortex. On the other hand, even some of the spiny stellate cells in layer 4 of area V1 project out of the area, allowing dissemination of some of the most precise position and orientation information before it is processed in V1. This is a not entirely satisfactory answer to the question. One may speculate that other mechanisms such as feedback circuits, or behavioral shaping of receptive field properties in higher areas, may be used to preserve the most sharply tuned properties. A separate question is whether all cells manifesting a given selectivity are used for that function behaviorally. There is evidence that different cell populations are recruited for a particular task as stimulus conditions are varied. Strobe reared cats showing a sharp reduction in the proportion of directionally selective cells show no deficit in their directional sensitivity behaviorally at high contrast levels, but show a marked reduction in discrimination of direction of movement at lower contrast levels.

Lesion of cat area 17 has no effect on the precision of orientation discrimination when tested with wide high contrast bars. However, the

deficit appears when narrow, low contrast bars are used. In summary, while a substantial body of evidence exists for the cellular constituents, connectivity, and functional properties of cells in primary sensory cortical areas, there are hints that we have only touched the surface in understanding the range of cortical processing mechanisms. In the future, we can anticipate learning more about the role of receptors and channels in integration at the cellular level, about the complexities in response properties introduced as one goes from simple stimuli to the natural sensory environment, about the dynamic changes in functional properties associated with changes in behavioral state, and about the role of "top-down" processes in control of properties of cells at antecedent levels. We may be aided in this effort by insights from psychophysics, ethological and behavioral neuroscience, and from computational models. In any event, there is still a substantial need for accumulating the hard data on cortical structure and function in order to create more informed and realistic models of the cortex.