CHAPTER 30

Static and dynamic views of visual cortical organization

Vivien A. Casagrande[1,2,3]*, Xiangmin Xu[2] and Gyula Sáry[1]

Departments of [1]Cell Biology, [2]Psychology, and [3]Ophthalmology and Visual Sciences, Vanderbilt University, Nashville, TN 37232-2175, USA

Abstract: Without the aid of modern techniques Cajal speculated that cells in the visual cortex were connected in circuits. From Cajal's time until fairly recently, the flow of information within the cells and circuits of visual cortex has been described as progressing from input to output, from sensation to action. In this chapter we argue that a paradigm shift in our concept of the visual cortical neuron is under way. The most important change in our view concerns the neuron's functional role. Visual cortical neurons do not have static functional signatures but instead function dynamically depending on the ongoing activity of the networks to which they belong. These networks are not merely top-down or bottom-up unidirectional transmission lines, but rather represent machinery that uses recurrent information and is dynamic and highly adaptable. With the advancement of technology for analyzing the conversations of multiple neurons at many levels in the visual system and higher resolution imaging, we predict that the paradigm shift will progress to the point where neurons are no longer viewed as independent processing units but as members of subsets of networks where their role is mapped in space-time coordinates in relationship to the other neuronal members. This view moves us far from Cajal's original views of the neuron. Nevertheless, we believe that understanding the basic morphology and wiring of networks will continue to contribute to our overall understanding of the visual cortex.

Introduction

From the time of Cajal to the present day, the primary visual cortex of mammals has remained one of the most studied areas of the nervous system. Literally thousands of research papers have focused on this area starting well before Cajal began his classical studies. Cajal's elegant drawings of individual Golgi impregnated cells and of the arrangement of layers in the visual cortex describe the architecture of a structure that was already known during the peak of his career to be the recipient of visual signals from the retina. Cajal's genius was to go beyond the details of individual cells, beyond the limitations of the techniques of his day, beyond cytoarchitectural variations and to generalize about cortical structure in a functional context. Without the aid of recording electrodes and modern imaging techniques Cajal speculated that cells in the visual cortex were connected in circuits involving cells with short axons and that vision involved successive steps of processing from the periphery through the thalamus to successive cortical areas. Cajal also was well ahead of his time in suggesting that connections in the adult cortex are not static but instead are dynamic and plastic.

Although it was known at the time of Cajal that the outside world was topographically mapped onto the visual cortex, no knowledge existed about the receptive fields of individual neurons, or how sensory quality might be represented by cortical neurons, or how neurons communicated with one another. The explosion of new technologies within the last 20–30 years has added an enormous wealth of detailed information about the cells, connections, pharmacology and physiology of the visual cortex. The big question is, however, to what degree has

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*Corresponding author: Tel.: (615) 343-4538; Fax: (615) 343-4539; Email: vivien.casagrande@mcmail.vanderbilt.edu

this knowledge changed our view of the structural and functional organization of this brain area or any other brain area. In other words, has current knowledge created a "paradigm shift" in the words of Kuhn (1970) in our thinking about the organization and operation of this area of the brain in the one hundred years since Cajal published his 1899 description of the human visual cortex (see pages 147–187 in DeFelipe and Jones, 1988 for translation)? In this chapter we will try to build a case in favor of the view that we are in the midst of a paradigm shift in the way science views the structure and function of the visual cortex and other brain areas, but with the following caveats. First, a paradigm shift is only recognized retrospectively; we are only proposing that one be in progress. Second, according to Kuhn's view paradigm shifts are abrupt changes in which new scientific theories replace old ones that are "proven wrong". In the strict sense arguing in favor of a paradigm shift would mean arguing that Cajal was wrong in his views. Instead, we would argue that the paradigm shift in progress is more similar to the main example given by Kuhn of the shift from classical mechanics to quantum mechanics. In quantum mechanics, the physicist calculates probabilities for particles following certain paths, rather than calculating the exact paths themselves as in classical mechanics. In other words, at one level quantum mechanics is dynamic while classical mechanics is more static. Although the approaches differ, classical mechanics is still applicable to most situations and is still considered a valid part of any curriculum in physics. In fact, natural science in today's world still rests on a foundation of Newtonian physics that has not changed much in hundreds of years. We will argue here that similarly to classical mechanics Cajal's contributions to brain structure remain and will in the future remain valid while a paradigm shift takes place in our view of functional organization. The rationale for focusing on the visual cortex is that it was studied in detail by Cajal and scientists of his time and remains one of the most studied areas of the brain today.

The remainder of this chapter is divided into four sections. In the first section we examine briefly Cajal's contributions to our knowledge of the anatomy of the visual cortex as well as relevant views of the day on the function of this region and its relation to sensation and perception. In the second section we focus on current views of the structure and function of the visual cortex showing how new technologies have not only added

details, but also provided a different framework for looking at function. In the third section we show how our current knowledge is leading us to view the behavior of neurons within visual cortex as a cooperative and dynamic network and how these views are forcing us to reexamine how information is coded by neurons. Finally, in the last section we return to our original question concerning paradigm shifts and summarize the evidence for and against the view that our perspective is different from Cajal's; we also address what shifting such a perspective predicts about future directions in the field. Throughout the chapter no effort is made to provide an exhaustive survey of the topic, but instead to provide the reader with specific examples to support relevant points.

Cajal's view of the visual cortex

When Cajal initiated his studies of the cerebral cortex he began at a time when there was already intense interest in the structure and function of this brain region. As reviewed in detail by Polyak (1957) and DeFelipe and Jones (1988) technological advances in the area of brain anatomy already had allowed for more detailed examination of the microscopic structure of cortex including advances in the fixation and hardening of tissue, microtome brain sectioning, and the use of carmine and other stains on tissue slices. Different cell types had already been identified in cortex by von Kölliker (1887), and Golgi (1884); and subsequently beginning with Meynert (see Jones, 1984) a significant effort was devoted to the cytoarchitecture of cortex with different laminar schemes proposed. On the functional side major debates concerning localization of mental activity within the brain had already appeared in the literature. Among the many contributions that preceded Cajal's work on visual cortex were discoveries based upon clinical observations of brain damaged patients and lesion and stimulation experiments in animals. By 1824 Wollaston had explained homonymous hemianopia in terms of partial decussation at the chiasm. Flourens (1824) had demonstrated the loss of vision following cortical lesions and provided the first proof that the cortex is involved in vision. Flourens, however, argued against functional localization within specific regions of cortex. Prior to Cajal's major works, Panizza (1861, see Polyak, 1957) had shown that the occipital lobe was essential for vision although Munk (1883, 1890) is generally

credited with this discovery based upon his experimental observations of visual abnormalities after occipital lobe ablation studies in dogs. Munk later formulated the concept of a topographic projection of the retina onto occipital cortex. Contemporaneous with Cajal, major works on cortex such as those of Flechsig (1896 see Polyak, 1957) described the course of the visual radiation from the lateral geniculate nucleus (LGN) to primary visual cortex (striate cortex) providing the anatomical link between the eyes and the cortex. Cajal acknowledged the groundwork that went before him often summarizing the state of knowledge prior to presenting his own data. Cajal also made reference to past and on-going work in his defense of localization of function within the cortex and in his speculations concerning the roles of different regions of cortex in processing sensory information.

Cajal focused his efforts on details of the cellular architecture. His contributions to our understanding of cortical architecture including the visual cortex outlasted those of his contemporaries not only based upon the sheer volunie of his scientific output (although this certainly didn't hurt), but also because he always constructed conceptual schemes in order to interpret his anatomical data in a functional context. Cajal classified cells, axons, connections and the laminar structure of cortex in an effort to define both what was fundaniental about an area (its structural plan) and what differentiated functionally distinct areas. Although the unit of his investigation was the structure of the neuron and its processes, Cajal's goal was always to tie structure to function.

To examine how views have changed since Cajal investigated the visual cortex it is appropriate here to summarize his ideas and main contributions. Cajal believed that comparative anatomy was essential to providing an understanding of the fundamental principles of brain organization. Therefore, he began his cortical studies on small mammals including rats, mice and rabbits and used results in these species to compare with his findings in human cortex. Cajal provides his most extensive description of visual cortex at the peak of his studies of human cortex (1899–1902; see Chapter 14 DeFelipe and Jones, 1988). Cajal's basic tenets on visual cortical organization are presented in the latter chapter, although data are later provided on cat visual cortex and summarized in subsequent years in the context of newer physiological and anatomical data of others.

Cajal divided the human visual cortex into 7–9 cellular layers (see Fig. 1) based upon a combination of stains, comparisons with the schemes proposed by others and detailed Golgi studies of cell structure. Within this scheme Cajal argued that the cellular composition of the supragranular layers was similar to that found in other cortical regions. What he believed distinguished the striate cortex were: (1) the stria of Gennari made up of fibers of axons of intrinsic and extrinsic origin,
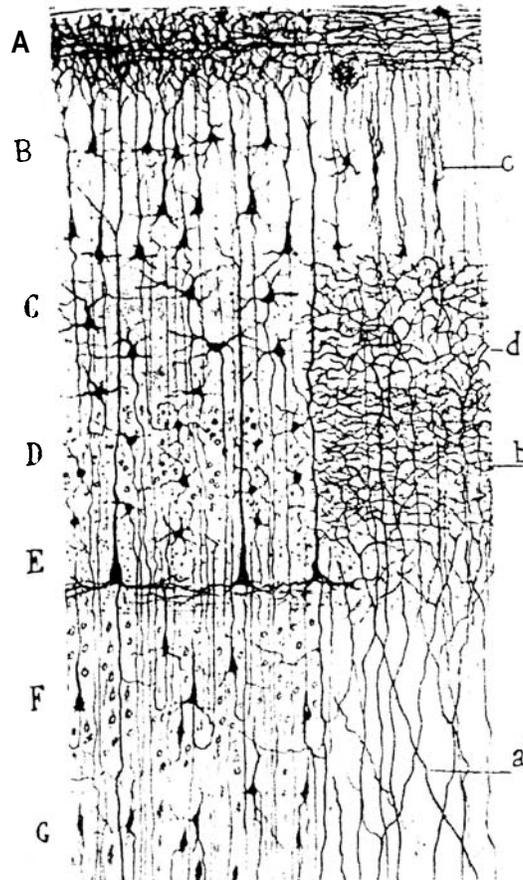

Fig. 1. Scheme of the main cells and layers of the visual cortex of man (calcarine fissure). A, molecular layer; B, layer of the small and medium pyramids; C, layer of the large stellate cells; D, layer of the granule cells or of the minute star-shaped cells; E, layer of the giant cells; F, layer of the pyramids with arciform axon; G, layer of the polymorphic cells; a, b, d, terminal arborizations of the centripetal visual fibers. (From Cajal) Modified from DeFelipe and Jones (1988), figure 57, with permission of the publisher.

(2) a dense granular layer (his layer 5, layer IVC of Brodman, 1909) made up of small stellate cells that received input from the thalamus, and (3) the infragranular layers that contained both smaller pyramidal cells than seen in other regions of cortex, and cells with ascending axons not found in other areas.

Within the layers of visual cortex Cajal was able to describe most of the morphological cell types we recognize today even though he had no way to distinguish them except on the basis of morphology. In the area of morphology Cajal focused heavily on cell body shape and axonal morphology and less on the details of the dendrites themselves. Nevertheless, he believed that the intellectual power of human cortex over that of other species might be related to the elaboration of dendritic processes of pyramidal cells which Cajal referred to as "psychic" cells.

Cajal arranged his descriptions by layer because he believed that the laminar pattern of cortex, not just the cell structure itself, held functional significance. In Cajal's scheme the first layer or plexiform layer, layer I, contained special cells with long processes (today identified as the Cajal-Retzius cells), other cells with short axons, recurrent axons from cells in the lower layers and white matter, and the tufts of pyramidal cells lying in other layers. In Cajal's scheme layer I held special significance. Cajal believed signals from the association areas and from incoming sensations within striate cortex were combined in layer I to initiate action in the larger pyramidal cells of the infragranular layers. In visual cortex the "action" initiated within the pyramidal cells was seen by Cajal as driving special types of movements related to vision including movement of the head and eyes. Cajal's proposal concerning the motor functions of visual cortex made sense in light of the results of Munk (1889; see Polyak 1957) who had elicited head and eye movements following visual cortical stimulation in animals using high currents.

Layers II and III were described as containing mainly small and medium size pyramidal cells as well as several types of stellate and other nonpyramidal cells with short axons. Cajal showed that many of the pyramidal cells in layer III sent axons into the white matter as well as collaterals to other layers. **As** mentioned, Cajal believed that the cellular organization of the supragranular layers was common to all cortical regions reflecting some fundamental functional design. The short axon cells found in these and other layers, Cajal believed, played two roles in visual cortex, namely, they were used to "increase the energy of the optic impulse to create sensation" and to propagate sensory signals to cells in other layers and different locations within a layer. This view has a decidedly modern ring.

Layers IV (the stria of Gennari, layer IVB of Brodmann) and V were identified by Cajal as the site of termination of optic fibers from the thalamus. We now know that such terminations are limited in human visual cortex to Cajal's layer V (layer IVC of Brodmann). Cajal characterized these layers as containing large (layer IV) and small (layer V) stellate cells. For Cajal these layers were the sites of initiation of sensation. He also believed that the axons of these cells transmitted sensory impulses directly to association cortex for memory formation. In addition to these stellate cells Cajal identified several other cell types within layers IV and V including both small pyramidal and nonpyramidal cells.

The infragranular layers VI–IX of visual cortex were described by Cajal as special because they contained some cells unique to visual cortex including pyramidal or ovoid cells that sent axons into the upper layers and giant pyramidal cells (Meynert cells) with descending axons. Cajal also described basket cell axons and other arrangements of axons and dendrites within these layers that he believed were unique elements. For Cajal the significance of the infragranular layers lay in their motor functions related to vision. The giant pyramidal cells (Meynert cells) he believed were part of optic reflex pathways concerned with movements of the eyes, lids, and pupils. In terms of function these ideas were not original with Cajal but reflected the prevailing view of other investigators of the time.

Generally when one thinks about Cajal's contributions to our understanding brain areas such as visual cortex, the emphasis is upon his description of the individual neuron. Yet Cajal's neurons are always placed within a scheme that emphasizes relation to function. Layers of visual cortex were considered functional units or modules, and, even though he fought throughout his career against the "reticularists" view of the nervous system defended by Golgi, Cajal certainly believed that groups of neurons must work together cooperatively as networks. This view is best exemplified in his diagrams not of visual cortex, but of the cerebellum and hippocampus where arrows are provided in his drawings of the proposed direction of flow of information within neural networks.

Advances in our knowledge of visual cortex

In the hundred years since Cajal published his major works describing the architecture and cell morphology of visual cortex there has been a technological revolution in neuroscience. Although the basic descriptions of cell morphology and anatomical architecture provided by Cajal remain valid today, great advances have been made in understanding the visual system and its functional architecture. The concepts of the visual receptive field and response properties of individual neurons did not exist during the peak period of Cajal's career. These concepts, initiated with the studies of Hartline working in the frog retina (1940), are now key to studies designed to understand the organization and function of the visual system at all levels. The visual system is currently viewed as a parallel distributed network designed to provide a description of the location and identification of objects that have survival value to the species. This is not done by transmission of a faithful camera-like representation of the sensory world as suggested at the time of Cajal. Instead, beginning with the construction of center-surround receptive fields in the retina the visual system selects what is needed to accomplish this goal. The retina contributes to this selection process by throwing away information about absolute light intensity, emphasizing local image contours, and compressing the wealth of information provided by receptors into manageable bits to be transmitted to the LGN via ganglion cells. The LGN regulates the flow of visual signals and informs the cortex about signal relevance while maintaining the basic sensory message transmitted from the retina. Primary visual cortex (hereafter referred to as V1) contributes by coding important aspects of local image features including their size, orientation, local direction of movement, and binocular disparity. All of these local descriptions of stimulus quality are critical for the more global and complex identification of objects ("what") and spatial relations ("where") that will take place in multiple extrastriate visual areas. We now know that in order for this to occur, V1 must solve the geometry puzzle of representing all stimulus qualities necessary for the subsequent steps of analyses within the different parts of the visual field map. V1 accomplishes this goal by a division of labor between different layers (as imagined by Cajal) and by different iterated modules within each layer. Below, we outline briefly specific advances in our understanding of V1.

V1 inputs

The revolution in anatomical techniques, particularly those that have allowed for tracing of connections using active transport mechanisms and a host of distinguishable labels, has allowed us to identify the majority (perhaps all) of the inputs to V1. Anatomical studies, often combined with physiological recording and immunocytochemical identification of transmitter/neuromodulator content, also have provided a detailed description of the structure and functional contribution of many of the V1 inputs. It was known at the time of Cajal that LGN cells sent axons to V1 but the system was viewed as serial in the sense that sensations arriving from the retina were processed in V1 and were sent to other cortical areas for "association" with other inputs and for memory storage; ultimately action was taken by motor cortex or projections to motor related subcortical structures. We now view information processing to and from V1 in terms of parallel inputs and outputs, complex feedback loops and interposed steps of integration. As shown in Fig. 2 on the input side at least 3 classes of LGN cells, the koniocellular (K), magnocellular (M) and parvocellular (P) cells send separate signals to V1 that terminate within different layers (see Casagrande, 1994; Hendry and Reid, 2000). Studies done in anaesthetized monkeys have shown that activation of V1 neurons depends completely on these inputs since chemical inactivation of the LGN blocks all visually evoked potentials (Malpeli et al., 1981). Additionally, we know based upon a variety of techniques including the down regulation of immediate early genes that input arriving from the left and right eye remains segregated in the form of ocular dominance columns in V1 of both humans and other primates, although the degree of segregation varies greatly between primate species (Florence and Casagrande, 1986; Florence and Kaas, 1992). Cajal was aware, from studies done by others, that binocular input reached V1. Only following the development of modern recording, labeling and optical imaging techniques, however, have the details of ocular dominance maps come to be appreciated. Figure 3 shows the complete pattern of ocular dominance columns on a flattened reconstruction through layer IV of V1 in a macaque monkey. In this case the pattern of eye input was revealed using a histochemical stain following loss of input from one eye. Such a loss results in local down regulation of cytochrome oxidase (CO) mitochondrial enzyme activity.
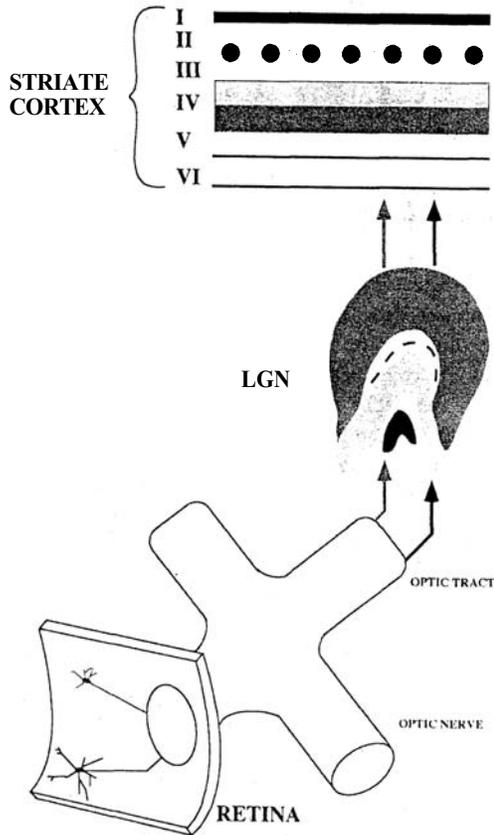
Fig. 2. In primates there are 3 parallel pathways from the retina through the lateral geniculate nucleus (LGN) to the striate cortex (V1): the parvocellular (P) pathway shown in medium grey, the magnocellular (M) pathway shown with light grey and the koniocellular (K) pathway shown with dark grey. Each pathway passes through separate LGN layers and terminates in different layers of cortex indicated by roman numerals. P and M LGN cells mainly terminate in lower and upper tiers of layer IV. These pathways also have other connections not shown. K LGN cells terminate within the cytochrome oxidase blobs in layer III and in layer I (see text for details).

CO staining is normally quite dark in all layers of V1 that receive input from the LGN; therefore loss of one eye results in lighter staining in zones connected to that eye. The result is shown in Fig. 3 in tangential sections through layer IV of V1 following flattening of the tissue. Black regions depict CO dense areas in cortex connected to the normal eye.

Besides the LGN, it is now known that V1 receives a variety of modulatory inputs both from subcortical and
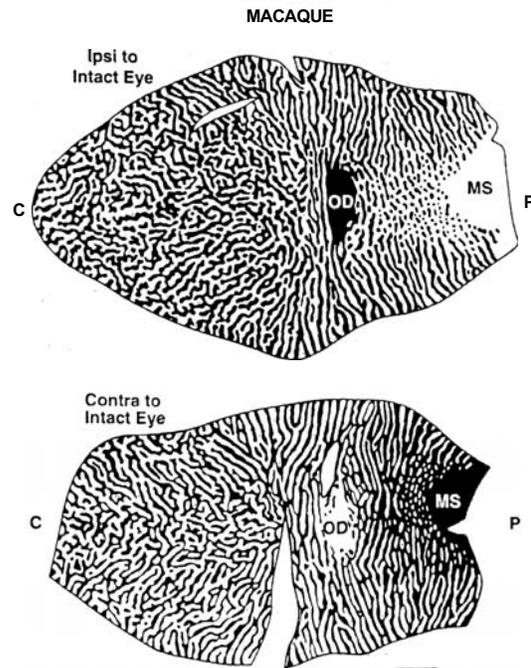

Fig. 3. Distributions of ocular dominance columns in a macaque monkey ipsilateral and contralateral to the intact eye. These drawings were made from photographic montages. Black regions depict CO-dense reactivity related to the intact eye. The ocular dominance patterns in the two hemispheres are highly similar, although not identical. Splits that occurred during the flattening process are shown. The visual field is represented from central (C) to the peripheral (P) as indicated. The representation of the optic disc (OD) of the nasal retina is centered 17 deg from the fovea. The unbanded segments to the right correspond to the monocular temporal segment (MS) of the visual field. Scale bar = 5 μm. Reproduced from Florence and Kaas (1992), with permission of the publisher.

cortical areas. Although Cajal had speculated that the axons he identified in cortical layer I of V1 were from other cortical areas the technology did not exist that would allow him to directly identify the sources of incoming axons to V1. We now know that these extrageniculate inputs include serotonergic, noradrenergic, and cholinergic inputs from the brainstem and basal forebrain nuclei, respectively (Morrison et al., 1998), and that the latter inputs show differences in density within the V1 layers. Other input sources identified using modern tract tracing tools include the intralaminar nuclei of the thalamus and pulvinar, both of which send broad projections most heavily to layer I of V1. Additionally, there are

retinotopically more specific sources of input to V1, many of which also receive projections from V1 including the claustrum, visual areas 2, 3, **4** (DL), and **5** (MT) (Casagrande and Kaas, 1994; Lyon and Kaas, 2001). Many higher order visual areas in the temporal and parietal lobes that do not receive direct projections from V1 nevertheless send axons to V1. These connectional details and the functional knowledge of various extrastriate visual areas are but a few of the many discoveries that have occurred since the time of Cajal.

The development of other technologies also has allowed us to ask questions concerning the functional significance of extrageniculate inputs to V1 in humans. An example of the impact that these nonLGN connections to V1 can have has been demonstrated using functional magnetic resonance imaging (fMRI) methods. Using these imaging methods it has been shown that topographic regions of V1 can be activated simply by asking normal subjects to imagine (with eyes closed) visual objects within particular areas of the visual field (i.e., in the *absence* of any direct stimulus to the retina, Chen et al., 1998). These findings argue that nonLGN inputs from extrastriate visual areas actually can have a strong impact on activity in V1. The noninvasive functional mapping methods of fMRI, positron emission tomography (PET) and other imaging methods have opened new doors for the investigation of brain function in humans. Prior to the development of these imaging technologies studies of brain function in humans were, as in Cajal's day, limited to clinical observations following brain damage or pathology.

V1 outputs

Cajal was aware that axons leaving V1 exited both from the superficial and deeper layers and that deep layer cells sent some axons subcortically. **As** with the inputs to V1, current knowledge of the outputs of V1 and their cellular origins and targets have allowed us to construct much more detailed anatomical wiring diagrams. These wiring diagrams combined with our knowledge of the cell properties and connections of output targets of V1 have fostered models of the flow of visual signals within the visual system. The important way that these details have changed our thinking concerns the function of the targets of V1 efferents. We now know that the lower layers, V and VI, send axons back to the thalamus and to the midbrain and pons. Layer VI is unique in that cells in this layer send both direct and indirect (via the thalamic reticular nucleus) feedback to the LGN and provide major pathways for V1 to regulate its own input. Cells in layer VI also send axons to the visual sectors of the claustrum, which appears also to modulate the responses of V1 neurons via feedback. Cells in layer V provide the major driving input to many cells in the pulvinar nucleus of the thalamus in monkeys; the pulvinar, in turn, provides input to a number of extrastriate areas that also feed signals back to V1. In addition, cells in layer V send a major projection to the superficial layers of the superior colliculus and other midbrain areas such as the pretectum, as well as nuclei in the pons that are concerned with eye movements. Thus, V1 is in a position to inform these structures of its activities and be informed by them indirectly through connections with the LGN or through feedback from extrastriate areas (see Casagrande and Kaas 1994 for overview).

As mentioned, Cajal was also aware that the superficial cortical layers of V1 provide output connections to some other cortical areas. Beginning with the seminal work of Ungerleider and Mishkin (1982) and Livingstone and Hubel (1988), working in macaque monkeys, we now know that V1 projects to a number of extrastriate cortical areas that are arranged within hierarchical-parallel systems designed to determine either object identification (the ventral stream) or location or visual action (the dorsal stream) (see Fig. 4). These connections emerge from different V1 layers or modules within layers suggesting that they carry different messages; a suggestion borne out by comparison of the response properties of cells within the different V1 layers in primates. In macaque monkeys the largest output connection is to visual area 2 (V2). Connections to V2 emerge from three populations of cells. Cells within the CO rich blobs of layer IIIA and IIIB send a major input to thin CO rich bands in V2, while the cells between the CO blobs (the interblobs) send projections to CO pale bands of cells (the interbands) in V2. Finally cells in layer IVB (also called the stria of Gennari) send axons to the thick CO bands in V2. In addition to these connections there are direct connections from layer IIIB to the dorsal medial visual area (DM, also called V3a) and patches of cells that lie below the CO blobs in layer IVB that project directly to extrastriate area MT (Boyd and Casagrande, 1999). Other output connections of layer III of V1 include projections to areas V3 and V4 (for review see Casagrande and Kaas, 1994).
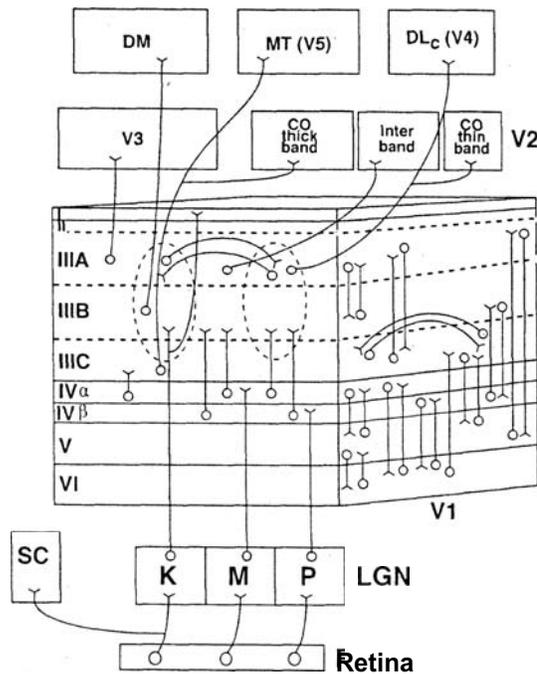
Fig. 4. A schematic diagram indicating the main intrinsic and extrinsic connections of V1 in primates as described in the text. No effort is made to define the strength of connections, or to indicate true axon collaterals or species-unique features. Feedback connections to V1 and the LGN as well as connections between extrastriate areas are not shown. The major input to V1 is from the lateral geniculate nucleus (LGN) which arrives via three pathways, the koniocellular (K), magnocellular (M) and parvocellular (P) pathways. The retina also projects to other targets, including the superior colliculus (SC) which also can in turn project to the LGN (connections not shown). Within V1, cell layers are heavily interconnected, not only by some of the axonal pathways shown but also via dendritic arbors (not shown). The main ipsilateral connections to extrastriate cortex exit from layer III. In layer IIIA, the cells within cytochrome oxidase (CO)-rich blobs, indicated by dotted ovals, and CO-poor interblobs send information to different target cells within bands in V2. In layer IIIB, cells within the CO blobs send projections to DM. Cells that lie under the CO blobs in layer IIIC send information to MT (V5). While the connection between V1 and V3 has been documented, it is not known from which layer or module this connection arises. Abbreviations of the visual areas are as follows: DL, (V4), dorsolateral caudal; DM, dorsomedial; MT (V5), middle temporal. Modified from Casagrande and Kaas (1994) with permission of the publisher.

In Cajal's day information processing was seen as serial from sensation through association to action. The notion of parallel inputs and outputs was restricted to the parallel processing of separate sensory modalities.

The prevailing views concern links between parallel input and output pathways *within* modalities. In vision it has been popular until recently to suggest that there is a direct link between the parallel input and output pathways of V1, namely that M LGN cells support motion perception (dorsal stream hierarchy) and P cells support color and form perception (ventral stream hierarchy). The best evidence for such a direct link comes from studies in which input from the macaque M and P pathways and associated K cells were briefly blocked with micro-injections of GABA (Nealey and Maunsell, 1994). This study clearly demonstrated that the majority of input to the middle temporal visual area (MT) comes from M cells or M and neighboring K cells since the two could not be inactivated separately in these studies. In spite of this, some MT cells could still be driven by the remaining P and/or K cells within the LGN. The importance of M input to area MT is not surprising given that cells in MT can detect rapid motion to which M cells are selectively sensitive. A fairly direct pathway for signals from M LGN cells to area MT has also been demonstrated anatomically; tract tracing studies have shown that cells in layer IVCα, the target layer for LGN M cells, send axons directly to cells in layer IVB which, in turn, can send signals to area MT. Nevertheless, cells in layer IVB that project to MT do not reflect the receptive field properties of M cells; instead most are complex direction selective cells whose receptive fields are constructed through circuits within the cortex (Movshon and Newsome, 1996). Even more opportunity for integration between pathways seems to exist before signals enter the ventral stream ("what" pathway). Blockade of the P layers and surrounding K layers does not silence cells within output layers IIIA and IIIB both of which respond well with either M or P layers blocked (Allison et al., 2000; see also below). Moreover, anatomically much of the output to the ventral stream leaves from layer IIIA which gets no direct input from layer IVC, but receives signals only after they have passed to other layers. Thus, both the wiring and physiology suggest that considerable integration of signals takes place in V1 before they are transmitted into the ventral stream for further analysis of object identity. Finally, the fact that lesions of either M or P layers in the LGN (together with associated K layers) do not eliminate either form or motion vision reinforces the view that it is inappropriate to equate complex visual behavior with the threshold properties of retinal and LGN cells (Schiller et al.1990; Merigan and Maunsell, 1990).

Cell types and receptive field properties

As mentioned earlier, one of the major advances in our knowledge of visual cortex since Cajal's day concerns the physiological characterization of properties of individual neurons. In the late 50s and early 60s Hubel and Wiesel (1962, 1968) began to characterize the properties of V1 receptive fields in cats and monkeys using a variety of patterns including line segments and spots of light displayed at discrete locations on a screen. In these seminal studies they showed that V1 cells could be subdivided based upon their responses to light. Hubel and Wiesel (1977) proposed that the cell types in V1 were arranged in serial order of complexity beginning with those that receive input directly from the LGN, which they termed simple cells. Hubel and Wiesel described these cells as orientation selective. Although there is still enormous debate over whether the property of orientation selectivity in V1 arises strictly from the arrangement of LGN cell inputs or is shaped by inhibitory connections within V1 (Bonds, 1989), there is no debate concerning the universal existence of this property in V1 of all primates. Hubel and Wiesel originally proposed that the receptive fields of each V1 cell class (namely simple, coniplex, and end-stopped cells) built upon the properties of their predecessors in serial order. We know now that the connections are more complex, that complex cells can receive input directly from the LGN and that end-stopped cells can either be simple or complex cells.

Hubel and Wiesel (1977) also introduced the idea that V1 must be made up of repeating colunmar units. They described both the repeating cycles of orientation columns and ocular dominance columns. This concept of the vertical modular organization of individual cortical areas has had a tremendous impact on current thinking about the organization and function of cortex. Cajal never envisioned the visual cortex as modular. Hubel and Wiesel (1977) were cognizant of the problem that local stimulus attributes would need to be represented again and again at each locale. What they noticed early on in their studies was that orientation preference in cat and monkey V1 changes regularly as one moves an electrode tangentially within any layer (see Fig. 5). An advance of 1–2 mm was usually found to be sufficient to rotate twice through 180 degrees of orientation preference. This distance was also found to be sufficient to include at least one left and right eye ocular dominance column. From this information Hubel and Wiesel constructed a model in which they proposed that
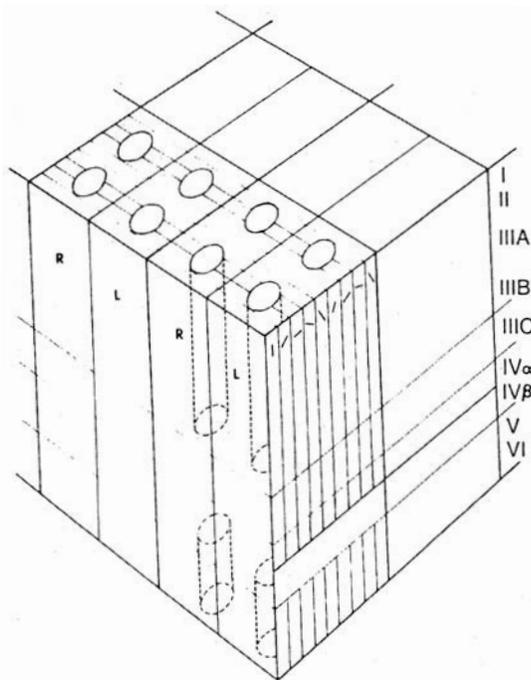

Fig. **5**. Schematic diagram of the modular organization of V1. Each module (or hypercolumn; see text for details) consists of two ocular dominance columns (representing right and left eyes), a series of orientation columns (representing 180 degrees of rotation) and cytochrome oxidase blobs (representing color information). Reproduced from Livingstone and Hubel (1984) with permission of the publisher.

the cortex is composed of repeating modules called *hypercoluinns*. They argued that each hypercolunm, whose exact boundaries were not fixed, should contain all of the machinery necessary to analyze one portion of visual space. More recently, Livingstone and Hubel (1984) argued that CO blobs should be added to this modular organization as zones uniquely equipped to transmit color signals to the next level. Although there is considerable debate as to whether CO blobs are actually uniquely designed for color processing since they appear to exist in all primates, even nocturnal species with only a single cone type (Casagrande, 1994), the fact that these modules are the targets of LGN input from a separate class of cells, the K cells, suggests that CO blobs do something special. Moreover, there appear to be enough CO blobs so that whatever is processed within these modules can clearly be represented across all topographic areas. Since CO blobs are positioned in the centers of ocular dominance columns

398

in macaque monkeys they were added as another dimension to be included within a V1 hypercolumn (Fig. 5). The geometric problem is not so difficult for the cortex to solve when only three stimulus properties, orientation, ocular dominance, and color, must be constrained by topography, but when more properties known to be represented in V1 such as spatial frequency, direction selectivity, and binocular disparity are added, the task becomes more challenging.

Recently, optical imaging of intrinsic signals has been used in an attempt to determine the relationship between maps of different stimulus properties in single animals. Using this relatively high-resolution technique it has been found that changes in Orientation selectivity are represented mainly in pinwheel formation with some regions also showing more gradual linear or abrupt fractures in the orientation map. The structure of orientation maps in different primates and in other species shows a great deal of similarity suggesting that orientation selective cells are organized the same way in humans. Maps of different stimulus qualities also suggest that, although not organized exactly as originally envisioned in the hypercolumn

model of Hubel and Wiesel (1977), maps of stimulus attributes are nevertheless iterated in such a manner that there are no "holes" in the map across space (see Fig. 6).

V1 cells and circuits

More than a hundred years ago Cajal described the morphology of most of the cells in V1 and postulated the direction of information flow. As mentioned earlier, Cajal's descriptions of V1 cells were always presented within a functional context. In spite of the fact that the functional roles of cells, layers and connections could only be guessed at, Cajal's guesses surprisingly often were correct (see above). Today, virtually all anatomical studies of cells and circuits in V1 are presented in a functional context. The numbers of cell classes and complexity of connections of V1 that have been identified and the controversies over the functional significance of the many circuits identified in V1 are beyond the scope of this short chapter (for recent review see Callaway, 1998).
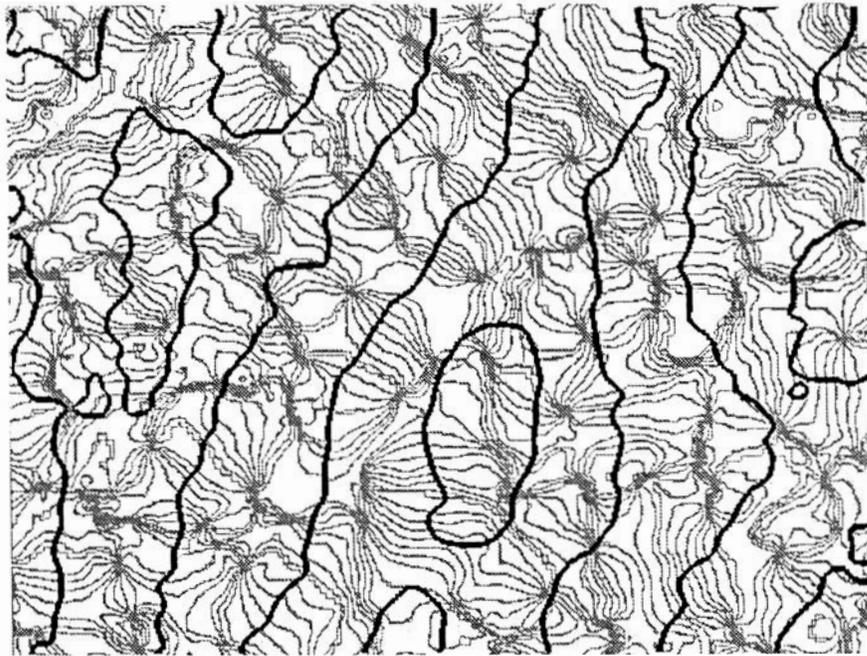

Fig. *6.* Example of a contour plot of orientation preferences in overlay with the borders of ocular dominance bands imaged from macaque monkey V1. Iso-orientation lines (*gray*) are drawn in intervals of 11.25 degrees. **Black** *lines* indicate the border of ocular dominance bands. Reproduced from Obermayer and Blasdel (1993) with permission of the publisher.

Our aim here is to examine how the field has advanced over Cajal's contributions. The focus in current research at the level of cells and circuits in V1 is to compile sufficient detail on the morphology, neurochemistry and connections of individual cells in V1 that computer models of individual neurons and small and large groups of neurons can be generated.

Within these models V1 cells are divided into two main classes: pyramidal and nonpyramidal spiny cells containing glutamate (80% of V1 cells) and non-pyramidal, aspiny cells containing GABA (–20% of V1 cells). The former would fall into Cajal's long axon class while most of the latter would fall into varieties of Cajal's short axon class. Many subclasses of GABAergic interneurons have been identified based upon morphology, the presence of different calcium binding proteins such as calbindin and parvalbuniin, or various peptides. The proportion of glutamate/GABA cells remains fairly constant across layers at least in macaque monkeys (Morrison et al., 1998).

We now know that connections between layers can be made by both excitatory and inhibitory neurons (for review see Lund, 1988; Callaway, 1998). Efforts to trace the general flow of information using pharmacological manipulations have suggested that layer IV becomes active first and after this the upper layers followed by the lower layers (Bolz et al, 1989). Circuits that connect layers III and V are especially robust as are circuits that connect layers IV and VI (at least from VI to IV, see Callaway, 1998). At the level of microcircuitry one concern to modellers has been the degree of precision in these circuits. If the local connectivity is based upon probability not on precision then efforts to document details of morphological differences between individual cells and their connections may not be meaningful. Recent studies, however, using dual recording, stimulation and calcium imaging techniques in slices of mouse visual cortex have suggested that cortical circuits of identified cells are surprisingly precise (Kozloski et al., 2001).

Most of the connections between V1 cells are local either within a layer or within a vertically defined column of cortex approximately 350–500 microns wide. There are, however, longer connections of up to 3 mm in macaque monkeys that occur typically between cells with similar properties (e.g., selectivity for the same orientation or ocular preference). These long tangential connections are found most commonly in layers I, 1ll and V (Rockland and Lund, 1982). Cajal's drawings suggested that he had identified both types of connections although without the functional frame of reference we have today. The impact of these longer connections has been noted in the responses of V1 cells when areas beyond the classical receptive field are stimulated. Studies have shown that although V1 cells generally do not respond directly to stimuli presented outside of their receptive fields, if these cells are actively responding to a preferred stimulus within their classical receptive field this response can be modulated by stimuli presented simultaneously at other locations in the field (Levitt and Lund, 1997). Such interactions, which are considered in more detail below, suggest a means whereby responses to local features might begin to be put together to represent the global features of objects (Gilbert et al., 2000).

A dynamic view of visual cortex

The biggest change in our view of individual neurons within the visual system from Cajal's day until the present concerns their functional role. Although Cajal was well ahead of his time in suggesting that connections in adult cortex are not static but instead are dynamic and plastic, the tools were not available for him to eavesdrop on cells and sample their millisecond by millisecond conversations. We can now listen to the conversations of not one but many neurons while manipulating sensory inputs and pharmacology. We can sample neuronal activity at all levels from detailed neuronal interactions in slice preparations to fMRI imaging in awake humans. From all of these technological advances has emerged the idea that neurons do not have static functional signatures but instead change their messages depending upon the activity of the network at that instant in time. When speaking about neural networks one tends to think of a top-down or bottom-up flow of information. While these terms help us to dissect the network they fail to emphasize the recurrent nature of information flow in the nervous system. In other words the top-down or bottom-up view of information flow is, in fact, a bi-directional, continuous exchange of information between neurons and brain areas. In this section we consider the dynamic nature of V1 neurons beginning with "bottom-up" regulation of signals reaching V1 neurons and how these change the nature of their responses. Next, we examine how the concept of the receptive field of

V1 cells is changing based upon new information about network interactions. Finally, we review examples of "top-down" influences of V1 cell behavior and consider, in particular, the impact of arousal level, attention, and memory.

Bottom-lip regulation

The concept of parallel input channels discussed earlier led to the idea that there might be labeled lines of communication between input and output pathways in V1. Evidence now shows that the majority of V1 cells integrate information from incoming pathways. Their response output appears to be dynamically regulated by the content of the stimulus. For example, it was shown recently that cells in all layers of V1 outside of layer IV show evidence of combined input from both the LGN M and P pathways (Allison et al., 2000). In other words these two pathways do not independently drive V1 cells. Evidence for this view was provided by selectively

blocking either the P or M pathways via **GABA** pressure injections into the appropriate LGN layers in the prosimian primate, bush baby (Allison et al., 2000). Prior to this blockade, the optimal orientation and spatial and temporal frequency of a drifting sine wave grating stimulus necessary to drive the cell was established. Contrast responses in V1 neurons were measured after blocking M or P layers in the LGN since M and P LGN cells are known to differ in contrast sensitivity. As can be seen in Fig. 7, V1 cells reflect different LGN inputs depending upon the contrast of the stimulus, At low contrast the V1 cells were entirely dependent upon the M pathway while at higher contrasts their responses reflected a combination of M and P inputs. Thus, whether a V1 cell is driven by one parallel input pathway or another is a reflection of stimulus content and its physical features.

Another example of dynamic "bottom-up" regulation of V1 inputs in relation to the LGN concerns the recent evidence that task relevance and other information can be
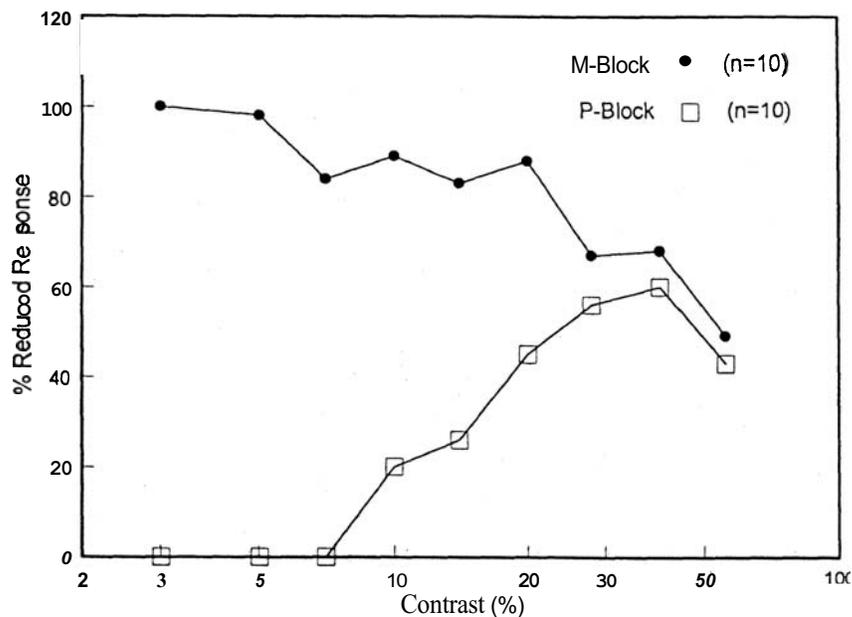

Fig. 7. The average percent reduction in response to each stimulus contrast following inactivation of either the LGN M layer 1 (filled circles) or P layer 6 (open squares) pathway. For the cells recorded during M layer 1 inactivation, the amount of response reduction decreased when stimulus contrast was increased, especially above 20% contrast. Conversely, the magnitude of response reduction during inactivation of P layer 6 increased when stimulus contrast was increased, especially above 10% contrast. The contributions of each pathway to the contrast-dependent response of V1 cells are clearly distinguishable. Reproduced from Allison et al. (2000) with permission of the publisher.

communicated directly to V1 cells along with sensory signals. In a recent study Sáry et al. (2001) were able to demonstrate in an awake monkey paradigm that LGN cell activity can either be enhanced or suppressed in relationship to a cue informing the monkey about task requirements. This enhancement or suppression of activity occurred while the monkey maintained fixation prior to any sensory stimulation of the receptive field of the LGN cell itself; the receptive fields of these cells were located an average of 10 degrees from the fixation point. An example of the enhancement in LGN activity under these conditions is shown in Fig. 8. This surprising result suggests that individual LGN cells carry multiple messages to their V1 targets. In addition, in the same study Sáry et al. (2001) were able to demonstrate that in a number of LGN cells response magnitude to the identical stimulus depends upon task requirements; some cells fire more vigorously to the stimulus if the monkey is required to make a saccade to the stimulus than when the monkey is required to keep its eyes

on the fixation point. Sáry et al (2001) have argued that modulation of LGN neurons (and thus V1 neurons as well) and increased response levels might achieve a better signal to noise ratio and ultimately lead to better localization of the target and better performance in a task where the target has behavioral relevance.

Dynamic regulation of V1 receptive field properties

The prevailing view since Hubel and Wiesel's (1962, 1965) seminal studies has been that each neuron in V1 is activated by stimuli over a limited range of visual space, which is called its receptive field. Recently, it has become clear that receptive fields of V1 cells are dynamically regulated. Classically, receptive fields were delimited based on the use of a single stimulus such as a light bar or an edge with a minimum discharge field defining the edges of the field (Hubel and Wiesel, 1962; Barlow et al., 1967). More recently, the size of each V1 cell's excitatory receptive field has been defined by use of patches of drifting sinusoidal gratings presented at the optimal orientation and spatial and temporal frequency (DeAngelis et al., 1992; 1994; Levitt and Lund, 1997). The length and width of these grating patches are varied independently; receptive-field length and width then are determined from the dimensions of the smallest grating patch required to elicit a maximal response (DeAngelis et al., 1992). This classical view of V1 receptive fields has been extended, because it was found that the responses of cells could be strongly modulated by stimuli or textural patterns placed far from the outer borders of their classically defined receptive fields (DeAngelis et al., 1992; Knierim and van Essen, 1992; Kapadia et al., 1995; Zipser et al., 1996; Levitt and Lund, 1997). The existence of facilitatory, inhibitory or disinhibitory surround effects has led to a broader definition of receptive field encompassing both the 'classical receptive field' and the 'nonclassical receptive field'. The key difference between the two definitions is that appropriate visual stimuli evoke responses from V1 cells within the 'classical receptive field'. In contrast, the impact of the nonclassical receptive field is only evident when both regions are stimulated simultaneously in which case the nonclassical receptive field can exert robust suppressive or facilitatory effects on the overall response of
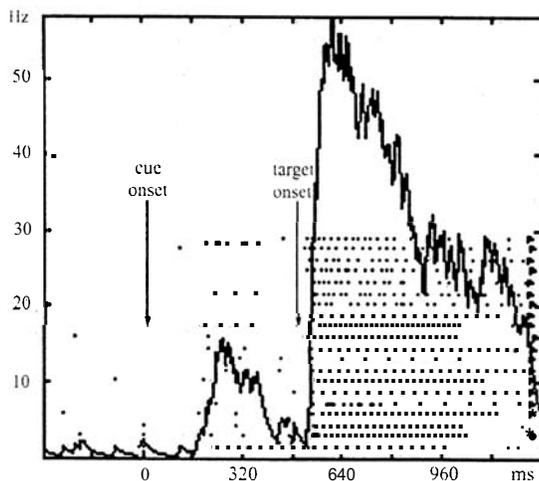

Fig. 8. Presentation of a behavioral cue influences LGN activity prior to target onset. Dots in the peristimulus time histogram represent individual neuronal spikes during the trials, the curve represents the average of 20 trials. Small triangles at the end of each raster line show reward for successful trials. The arrows point to the cue onset (time 0) and target onset, respectively. The first peak in the histogram shows the pretarget modulation with an onset latency of about 240 ms before presenting the visual stimulus. The second, larger peak shows the response of the LGN cell to the target presented in the receptive field. See also Sary et al. (2001).

the cell (see Gilbert, 1992; 1998 and Fitzpatrick, 2000 for reviews). This distinction has important implications for the function of V1 neurons and suggests that these neurons may be performing more complex forms of analysis than previously thought. For instance, facilitatory surround effects may explain contour integration and illusory contours (Kapadia et al., 1995; Field et al., 1993), and suppressive effects could relate to perceptual 'pop-out' and curvature detection (Dobbins et al., 1987; Knierim and van Essen, 1992; Lamme, 1995).

Other evidence that the receptive fields of individual V1 cells are dynamic comes from work showing that the size of the classical receptive field in alert monkeys is not fixed but varies with stimulus contrast and the relationship between foreground and background (Kapadia et al., 1999). On average in these experiments, the length of the excitatory receptive field was 4-fold greater for a low-contrast stimulus than for a stimulus of high contrast (See Fig. 9). In addition, embedding a high-contrast stimulus in a textured background suppressed neuronal responses and produced an enlargement in receptive field
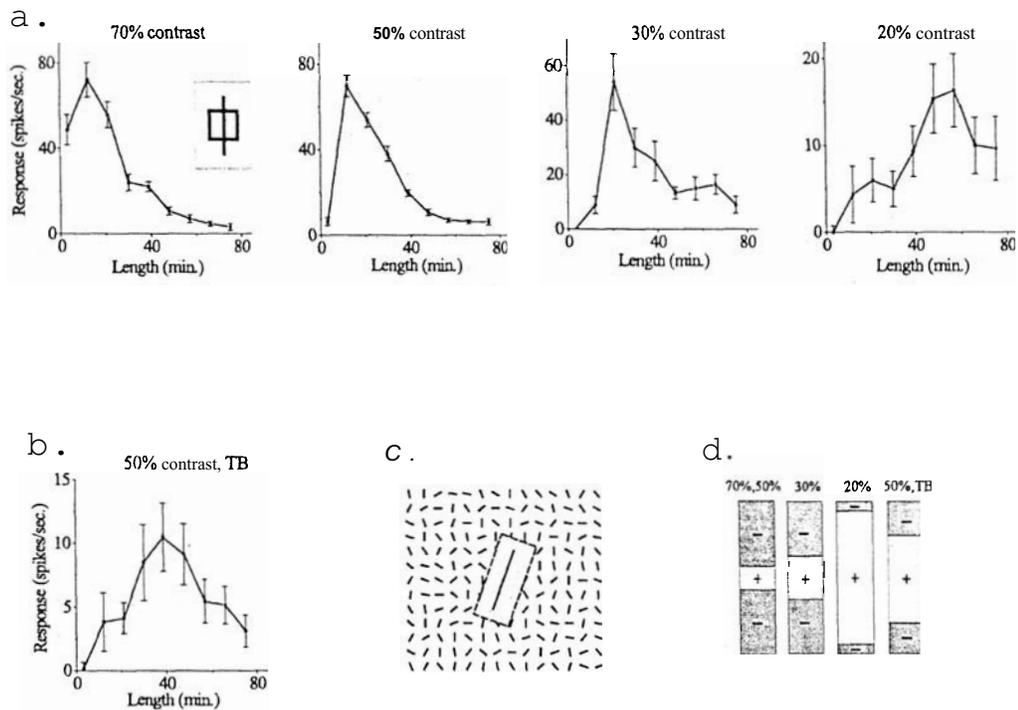

Fig. 9. The dimensions of V1 receptive fields are stimulus-dependent. **(a)** Length-tuning measurements in these four panels show the neuron's responses to optimally oriented bars of different lengths and **3'** wide, presented at the central region of receptive field at four different contrasts. The extent of the excitatory receptive field is defined as the stimulus length that produces the maximal response at each contrast. The neuron shows spatial summation over a region 5-fold larger at low contrasts than at high contrasts. **(b)** Length-tuning measurements in a textured background. The stimulus is described in **c.** The background stimulus causes a suppression in the response to the bar stimulus and enhances spatial summation, even though the local contrast of the bar is still *50%* (compare with 50% contrast condition in **a).** Response to background stimulus alone is 0.8 ± 1.2 spikes/sec. **(c)** Schematic of the textured background stimulus used in **b** and **d. A** 5° **x** 5° array of randomly oriented lines surrounds the receptive field (each bar measures 15' **x** 3' and the receptive field is depicted as an open square), whereas an optimally oriented bar is presented at different lengths at the central region of the receptive field. **(d)** Schematic summary of the changes in size of excitatory and inhibitory receptive field subregions under different stimulus conditions. Plus symbols **(+)** represent excitatory subregions and minus symbols **(–)** represent inhibitory subregions. **As** stimulus contrast is decreased, the excitatory region becomes larger and the inhibitory flanks become smaller. Embedding a high-contrast stimulus in a textured background produces changes similar to those produced by lowering its contrast. Modified with permission from Kapadia et al. (1999).

size similar to that produced by decreasing the contrast of an isolated stimulus. Kapadia and co-workers (1999) showed that receptive field dimensions are regulated in a dynamic manner that depends both on local stimulus characteristics, such as contrast, and on global relationships between the stimulus and its surroundings. The work of Sceniak et al. (1999) confirmed that the size of the receptive field (the extent of spatial summation) of macaque V1 cells depends on contrast, and was on average 2.3 fold greater at lower contrast. In the latter study, they measured cell response as a function of stimulus area to determine the spatial extent of the classical receptive field of V1 cells at various contrasts. The receptive field extent showed a strong stimulus dependence, and the extent of spatial summation shrank at high stimulus contrast. A similar dynamic dependence on stimulus contrast also has been reported in studies using multiple stimuli in the surround. The type of effect induced by presentation of a collinear stimulus outside the receptive field can often be switched from facilitation to suppression by increasing the contrast of the stimulus within the classical receptive field (e.g., Toth et al., 1996; Polat et al., 1998). If the size of the receptive field of V1 cells is not fixed but can vary with contrast and context, this means that the same region of visual space can exert no effect, a facilitatory effect, or a suppressive effect on a cell's response, depending on the stimulus Characteristics.

In the above examples one could argue that the dynamic regulation of receptive field size does not actually alter other key properties such as direction selectivity or orientation selectivity. Recent studies show, however, that these key emergent properties also are not fixed but can be dynamically regulated (Bonds, 1989, 1991; Chapman et al., 1996; Ringach et al., 1997; Sharma et al., 2000; Dragoi et al., 2001). For example, Ringach et al. (1997) demonstrated that the development of orientation selectivity is time-dependent. Using the method of reverse correlation in the orientation domain over time they found that orientation tuning develops after a delay of 30–45 ms and persists for 40–85 ms. Neurons in layers 4Cα or 4Cβ of V1, which receive direct input from the LGN, show a single orientation preference which remains unchanged throughout the response period. In contrast, the preferred orientations of output layer neurons (in layers 2, 3 4B, 5 or 6) can change with time. In many cases the orientation tuning preferences can shift with time. These dynamic changes in response to different orientations is accompanied by a change in the sharpness of orientation tuning; cells in the input layers are more broadly tuned than cells in the output layers. The results of the latter study and others indicate that orientation selectivity is dynamically regulated within the V1 intracortical machinery, suggesting that V1 cells are more than a bank of static oriented filters (Ringach et al., 1997; See Vidyasagar et al., 1996; Ferster and Miller, 2000 for reviews).

Additional evidence that orientation selectivity of V1 cells can be dynamically regulated comes from a study in which input from the lower cortical layers was inactivated with GABA while responses of individual V1 cells were measured in the more superficial layers (Allison et al., 1995). Depending upon the location of the blocking electrode relative to the recording electrode, upper layer V1 cells exhibited a change in their orientation preference, a reduction in their orientation tuning, and/or an increase in their response amplitude. The effects on the orientation tuning of V1 cells were restricted in all cases to within ±30 degrees of the preferred stimulus Orientation. This means that layer blocking affects cells with preferred stimulus orientations similar to those of the recorded neurons. Only cells located within 500 microns tangential to the vertical axis of the injection site exhibited these effects. These results suggest that cells within layers 5 and 6 provide organized, orientation-tuned inhibition that regulates or dynamically sharpens the orientation tuning of cells in the upper cortical layers within the same, or closely neighboring, cell columns.

Adaptation effects on V1 cells

Other examples of the dynamic regulation of V1 responses are studies that show a reduction or shift in response depending upon the history of the cell. In an interesting recent demonstration of this effect on orientation, Dragoi et al. (2000) employed single-unit recording and intrinsic signal imaging (optical imaging) techniques to demonstrate systematic shifts in orientation preference away from the orientation used to adapt a V1 cell for 10 s to 10 min. In contrast to the common view of adaptation as a passive process that suppresses responses around the adapting orientation, this study showed that changes in orientation tuning occur due to response increases at orientations away from the adapting orientation. This suggests that adaptation-induced

orientation plasticity is an active time-dependent process that involves network interactions and includes both response depression and enhancement (Dragoi et al., 2000).

More classical examples of such adaptation effects have been shown for both primate and cat V1 cells in contrast adaptation. Contrast sensitivity and gain of V1 cells are reduced after short exposure to high-contrast stimuli (Bonds, 1991; Allison et al., 1996). The temporal changes related to contrast adaptation were examined in detail by Bonds (1991). He explored these effects by stimulating cortical cells with drifting gratings in which contrast sequentially incremented and decremented in a stepwise fashion over time. All responses showed a clear hysteresis, in which contrast gain dropped on average 0.36 log units and then returned to baseline values within 60 s (Bonds, 1991).

Arousal level

V1 cells are also dynamically regulated based upon global changes in arousal. Recording from awake cats Livingstone and Hubel (1981) originally showed that visual signals are enhanced and spontaneous firing reduced on arousal compared to sleep. Many V1 cells also reduce the irregular burst-like firing and produce a more regular firing pattern when an animal awakes. These changes result in an increase in the signal-to-noise ratio and thus may lead to better transmission of visual signals during wakefulness. **As** discussed earlier these changes likely originate in the LGN. Neurons in the LGN appear to have two functional states: a bursting mode and a single spike mode. These modes determine the fidelity of response to sensory signals (McCormick and Feeser, 1990). During burst mode the LGN neurons are not capable of faithfully representing the incoming signal, while in the single spike mode, responses are tied more directly to the stimulus features themselves. In this way LGN cells can regulate the amount of sensory information that reaches V1 cells. Interestingly, Ranicharan and colleagues (2000) reported that the two modes of firing were also evident in the awake animal. Sherman (2001) has hypothesized that the two modes of activity of LGN neurons in awake animals serve two different purposes. V1 neurons receive a more linear representation of LGN input in the tonic mode. Tonic mode more faithfully describes stimulus features but with poorer detectability,

while in burst mode, V1 neurons receive more accurate information about stimulus change.

Attention

Other examples of dynamic regulation of responses of V1 cells concern the issue of attention. Although many studies suggest that V1 cells are not regulated by attentional shifts, a number of studies support such effects. Haenny and Schiller (1988) provided evidence that activity in V1 neurons can shift depending on attentional state. In the latter study the monkeys were required to perform a sequential matching task and had to detect the repetition of a particular pattern in a series of visual stimuli. This demanded that a decision be made which kept the attention level of the animal constant. Activity of V1 (and of V4) neurons was enhanced by as much as 20% during the presentation of a stimulus that the animal knew would be rewarded. It has been hypothesized that these attentional effects are produced by feedback to V1 cells from extrastriate areas.

To be effective, the feedback signals to V1 that relate to attention should be flexible and capable of rapidly "updating" the different regions of V1. What happens if the stimulus is not stationary, but moves relative to the receptive field while the animal performs a task? Or, the stimulus is stationary and the eyes perform a slow tracing movement along an elongated stimulus or contour line? In an experiment performed by Roelfsema and co-workers (1998) the monkey was involved in a curve-tracing task (using its eyes to trace the curve) while activity of V1 neurons was recorded. Whenever the receptive field of V1 neurons was located on the curve to be traced, neuronal activity was modulated by as much as 30%. Based on the latency differences between the modulation and the visual response proper (about 200 ms), the authors propose that the modulation observed in V1 is object-based. These results are particularly interesting since they suggest that V1 neurons are modified by higher order attentional shifts that can "lock" onto a target of interest.

There also is evidence that levels of attention can dramatically alter responses of V1 in humans. In an fMRI study, human subjects performed a speed discrimination task with sinusoidal gratings moving concentrically inward or outward, or had to view the grating stimuli passively. Performing the task actively resulted in a

significant activation of V1 (Huk and Heeger, 2000). Performing the identical task passively resulted in no fMRI activation of V1. In a similar experiment Gandhi and colleagues (1999) presented a stimulus either in the right or left visual hemifield and measured changes in activity in V1 using fMRI. There was an increase in V1 activity, which shifted from hemisphere to hemisphere. The latter results raise two important points: V1 neurons can increase activity during a visual discrimination task on a population level, and this increase is spatially selective (follows the stimulus shift between the visual hemifields) and thus is likely to be the result of spatial attention.

In the examples given above, attention was shown to modify V1 neurons globally, but local effects have also been demonstrated (Ito and Gilbert, 1999). Earlier in this section we considered the impact of surround effects on the responses to V1 neurons to stimuli presented in the 'classical' receptive field. Ito and Gilbert (1999) also found that these surround effects were dependent upon attention. They found that if monkeys were trained in a brightness discrimination task containing flanking stimuli, and were required to focus their attention on a particular location of the stimulus screen or use it in a distributed way (not knowing where the change to be detected would show up), attention had a significant effect on the contextual facilitation seen in V1 neurons.

Working memory in V1

In the previous subsection we considered the impact of attention on the responses of V1 neurons. In this final subsection we provide evidence that V1 neuronal responses also are dynamically regulated based upon visual memory. Interestingly, Cajal would probably not have been surprised by such a finding because he proposed that centripetal fibers to V1 originated in association areas concerned with visual memory. Evidence for the impact of memory on V1 neuronal responses comes from a study by Super and colleagues (2001), who trained monkeys to perform a delayed-response figure-ground discrimination during which the animal had to remember the spatial location of a motion-defined target stimulus after it had been removed from the screen. After a variable period of time the monkeys had to make a saccade to the location of the remembered target. Neuronal responses in V1 were recorded during

the trials when either the target stimulus or the background fell on the receptive field. While initially V1 cells responded the same way to the target and the background, the authors observed a late modulation of the neuronal activity. This altered response persisted during the delay period even after removal of the stimulus. This modulation continued in trials when the stimulus was a target, whereas it decreased when the same stimulus was used as the background. The authors argue that the V1 cell memory related modulation is an active process and is related to the storage of information needed to successfully finish the task. The authors go on to propose that the altered activity they observe in V1 neurons may serve as a substrate for working memory.

Conclusions and future directions

We have now concluded our short tour highlighting the changes that have taken place in views of the visual cortical neuron since the time of Cajal. Most of the detailed descriptions of individual neurons and their relationships to each other and laminar cytoarchitecture made by Cajal still hold today. Cajal's concept of the neuron as the fundamental independent unit of the nervous system, of course, also still stands. Many of Cajal's speculations concerning the general flow of visual information and the circuits necessary to boost signals in V1 have been supported by modern experiments. There also have been enormous advances in our knowledge about V1 neurons and their connections and relationships to circuits, modules, layers and pathways. Although speculations by Cajal anticipated the simple to complex arrangement of neuronal receptive fields described by Hubel and Wiesel, this familiar concept of visual receptive fields did not exist at the time of Cajal. Moreover, Cajal diagramed circuits as excitatory; Cajal never anticipated that many of the circuits he drew involved inhibitory interneurons. Although Cajal speculated about chemical specificity in a developmental context, he never envisioned the complex intracellular signaling pathways that have been revealed by modern molecular neurobiology. Whether Cajal did or did not anticipate current views of neurons within V1 or any other region of the nervous system, however, does not address the main question we posed in the beginning of the chapter. The key question we posed earlier was whether the current approaches (as reviewed above,) constitute a "paradigm shift" in the words of

Kuhn (1970) in our thinking about the organization and operation of visual cortex over what was espoused by Cajal. What is the evidence for and against the occurrence of a paradigm shift?

The dynamic nature of processing in V1 neurons reviewed earlier provides the strongest evidence for a paradigm shift. Technology is now allowing the scientific community to address long standing conflicts between the psychology of perception and neurophysiology. Theories of perceptual processing have not attempted, until very recently, to bridge the divide between the views of neurophysiology and the subjective quality of a unified visual world. The reason for this is that these properties are inconsistent with classical neurophysiology. Classical neurophysiology is based upon Cajal's neuron doctrine where the input/output function of dendrites and axons, together with transmission across the synapse, suggests that neurons operate as quasi-independent processors in a sequential or hierarchical architecture that processes information in well defined pathways. Our subjective experience is, however, not like an assembly of abstract features but a stable unified whole. There is no accounting in the neuron doctrine for this constructive or generative aspect of perceptual processing. In fact, the apparent continuity of perception (known now as the "binding" problem) was one of the major arguments made against Cajal's neuron doctrine. Not only is perception unified but it is an active process where the acquisition of new sensory information is based upon the goal directed behavior of the organism. Because of these conflicts between classical neurophysiology and psychophysics, we would argue that there is currently an evolving paradigm shift in views of visual system processing. As reviewed under, "a dynamic view of visual cortex", models of V1 must take into account the continuous updating of information that takes place via both top-down and bottom-up signals. Individual V1 neurons are not static filters but instead clearly respond in a context dependent manner. Their responses depend both on their local connections and individual properties and on the global interactions of the networks to which they are connected — networks that carry!information about sensory quality, behavioral relevance and context. These properties lead to the conclusion that the visual cortex is a node in an intricate distributed network, and that it can cooperatively extract high-order information from the visual scene. In this sense the contributions of the individual neuron are never independent of the network. As

the technology for analyzing the conversations of multiple neurons at many levels in the visual system improves and is combined with higher resolution imaging, we predict that the paradigm shift will progress to the point where neurons are no longer viewed as independent processing units but as members of subsets of networks where their role is mapped in space–ime coordinates in relationship to the other neuronal members.

Does this mean that Cajal's contributions will disappear into obscurity? We hardly think so. Recent studies described earlier by Kozloski and co-workers (2001) clearly argue against the view that the morphology of neurons and their cortical circuits are random. Their studies provided evidence for very similar circuits for cells belonging to the same morphological class. Their message was that nature reproduces connections precisely. It is also the case that in tightly topographic systems such as the visual system, adequate coverage requires redundancy of circuits so that an understanding of the basic morphology and wiring of iterated modules will continue to contribute to our overall understanding of visual cortex.

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