35 The Visual Relays in the Thalamus

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The lateral geniculate nucleus[1] is the thalamic relay of retinal input to the visual cortex. It is the best understood of the thalamic relays and, because there is an overall structure shared by all thalamic nuclei, it can serve as a general model for the thalamus. We first consider the lateral geniculate nucleus and then, using this as a prototype, look at other thalamic relays on the visual pathways, the lateral posterior nucleus and the pulvinar. For convenience, both will be referred to jointly as the *pulvinar region*. We look at features that are shared by the lateral geniculate nucleus and the pulvinar region and explore the extent to which the organizational principles that are well defined for the lateral geniculate nucleus can help us to understand aspects of pulvinar organization. The lateral geniculate nucleus will be treated as a first-order relay (Guillery and Sherman, 2002b; Sherman and Guillery, 2001), sending ascending visual messages from the retina to primary receiving cortex and the pulvinar region as a higher-order relay carrying messages from one cortical area through the thalamic relay to another cortical area and thus playing a potentially crucial role in corticocortical communication. First- and higher-order relays are defined more fully below, but it suffices to note here that the former represent the initial relay of a particular sort of information (e.g., visual or auditory) to cortex, while the latter represent further relay of such information via a cortico-thalamo-cortical loop.

The complex cell and circuit properties of thalamic relays have been defined during the past three or four decades, and these are a clear indication that thalamic circuits must be concerned with significant tasks. In spite of this, thalamic relays are often still treated as they were in the nineteenth century, when it was enough to trace a pathway, such as the auditory, visual, or somatosensory pathway, to the thalamus and then conclude that the function of that part of the thalamus had been defined. Glees and Le Gros Clark (1941) described a one-to-one relationship between incoming retinogeniculate axon terminals and geniculate cells in macaque monkeys, which suggested a relatively simple transfer of visual information. We now know that this was an error and that, as we show below, the synaptic relationships are, in fact, very complex, with the vast majority of synapses onto relay cells coming from nonretinal sources (Guillery, 1969; Van Horn et al., 2000; Wilson et al., 1984). In spite of this, when, more recently, the distinctive receptive field properties of cells in the retina and the visual cortex were being defined (reviewed in Hubel and Wiesel, 1977), the lateral geniculate nucleus was treated as a simple, machine-like relay. This reflected the great success of the receptive field approach to vision. Initially, in anesthetized animals, this approach showed that receptive fields become increasingly elaborated along the synaptic hierarchies through retina and cortex, with the one glaring exception being the retinogeniculate synapse: the center/surround receptive fields of geniculate relay cells are essentially the same as those of their retinal afferents. From this arose the misleading conclusion that nothing much of interest was happening in the geniculate relay (Hubel and Wiesel, 1977; Zeki, 1993). Indeed, this raises certain questions: Why have a geniculate relay at all? Why not have retinal axons project directly to visual cortex? Or, more generally, why bother with thalamic relays? One of the main purposes of this chapter is to provide a partial answer to these questions. A second purpose is to indicate that currently we are far from having a complete answer. It is highly probable that much of what the thalamus does still remains to be defined.

As we shall see, even on the evidence available today, there is much of interest happening in the geniculate relay, and in retrospect, the lack of receptive field elaboration seen in the geniculate relay is not evidence of nothing happening there but, rather, evidence that something completely different but important occurs. That is, this is a crucial synapse in the visual pathways doing something other than receptive field elaboration: geniculate circuitry is involved in affecting, in a dynamic fashion, the amount and nature of information relayed to cortex. One reason this was missed in earlier studies is that these functions depend largely on the behavioral state of the animal and are suppressed in anesthetized animals. This dynamic control, dependent on the animal's behavioral state and considered below, can be seen to represent the neuronal substrate for many forms of visual attention.

[1] By *lateral geniculate nucleus* in this chapter, we mean the *dorsal* lateral geniculate nucleus. Like all thalamic nuclei providing a relay to neocortex, the lateral geniculate nucleus is developmentally a part of the dorsal thalamus. The *ventral* lateral geniculate nucleus, which is part of the ventral thalamus, does not send axons to cortex and will not be considered further.

Functional organization of the lateral geniculate nucleus

For those who still consider the lateral geniculate nucleus as a simple relay, the complexity of its organization will no doubt come as a surprise. The nucleus is organized into a number of layers with a detailed topographic map of visual space that cuts across layers, and its circuitry involves several cell types, many distinctive groups of afferents, and complex synaptic relationships.

Maps There is a precise map of the contralateral visual hemifield in the lateral geniculate nucleus of all species so far studied, and in this the visual system is like other sensory systems that are mapped in their thalamic relays. The map in the lateral geniculate nucleus is laid out in fairly simple Cartesian coordinates in all species (see Fig. 35.1, where the visual field and its retinal and geniculate representations are shown as tapered arrows). Each layer maps the contralateral hemifield, either through one or the other eye, and all of these maps are aligned across the various layers that characterize the lateral geniculate nucleus of most species (see below and Fig. 35.1). Thus, a point in visual space is represented by a line, called a *line of projection*, that runs perpendicularly through all the layers. The precise alignment of these maps, which matches inputs from the nasal retina of one eye across layers with inputs from the temporal retina of the other eye, is seen in all species and is somewhat surprising when one thinks about the developmental mechanisms needed to produce such a match, which forms before the eyes open and before the two visual images can be matched. We shall see that there are nonretinal afferent axons that innervate the lateral geniculate nucleus and distribute terminals along the lines of projection. In this way, these afferents can have a well-localized action on just one part of the visual input, even though this comes from different eyes and distributes to distinct sets of layers (see the section "Afferents to the A Layers").

Layering The lateral geniculate nuclei of all mammalian species so far studied show some form of layering, although there is considerable difference among species as to what the layers represent functionally. For all mammals, each layer receives input from only one eye, but the distribution of distinct functional types of retinal afferents to the layers differs greatly from one species to another. Chapters 30 and 31 describe the various classes of retinal ganglion cell that give rise to several parallel retinogeniculate pathways, and these frequently relate to specific geniculate layers. Figure 35.2 shows the layering of the lateral geniculate nucleus in the macaque monkey[2] and the cat, the two best-studied species. The figure illustrates the variation in layering seen across species and introduces the several parallel pathways

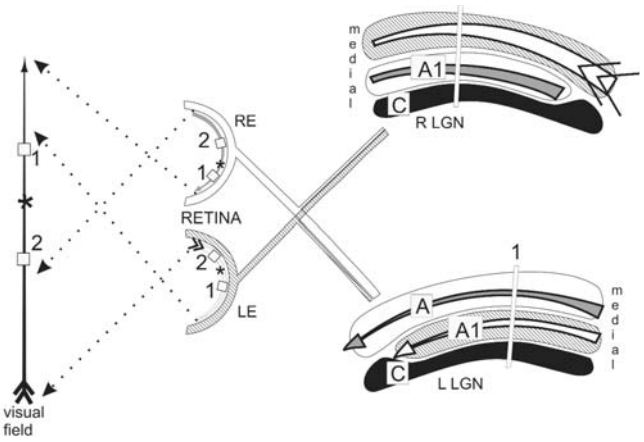

Figure 35.1. Schematic view of the representation of the retina and visual field in the layers of the lateral geniculate nucleus of a cat. The visual field is represented by a straight arrow, and the projection of part of this arrow onto each retina is shown. Small white areas of the visual field and corresponding parts of the retina are labeled "1" and "2." The representation of this part of the visual field in the lateral geniculate nucleus is shown as a corresponding white column going through all of the geniculate layers "like a toothpick through a club sandwich" (Walls, 1953). Each such column is bounded by the lines of projection, which also pass through all of the laminae. *A*, *A1*, and *C*, the major geniculate layers; *L LGN* and *R LGN*, left and right lateral geniculate nuclei; *LE* and *RE*, left eye and right eye; asterisk, central point of fixation.

that are relayed through the lateral geniculate nucleus to the cortex.

Both species have three main retinal ganglion cell classes that project to the lateral geniculate nucleus. For the macaque monkey (Casagrande, 1994; Casagrande and Kaas, 1994; Hendry and Reid, 2000), these are the P (for parvocellular, meaning small-celled), M (for magnocellular; large-celled), and K (for koniocellular; tiny or dust-like cells) cells, comparable respectively to the X, Y, and W cells in the cat (reviewed in Casagrande and Norton, 1991; Lennie, 1980; Sherman, 1985). The terminology for the macaque monkey relates to the geniculate layers to which the cell classes project. P and M cells project to parvocellular and magnocellular layers, respectively. In the macaque monkey, K cells project to the ventral regions of all layers, where very small cells lie scattered, and the projections overlap with those of M and P cells. However, in *Galago*, a prosimian primate, each of the homologous retinal cell types projects to a separate set of layers (not shown)—koniocellular, par-

[2]Unless otherwise specified, we shall refer to this as the *monkey* in what follows, noting, however, that the macaque can be regarded as representative of Old World monkeys and that the lateral geniculate nucleus in New World monkeys has a slightly different structure.

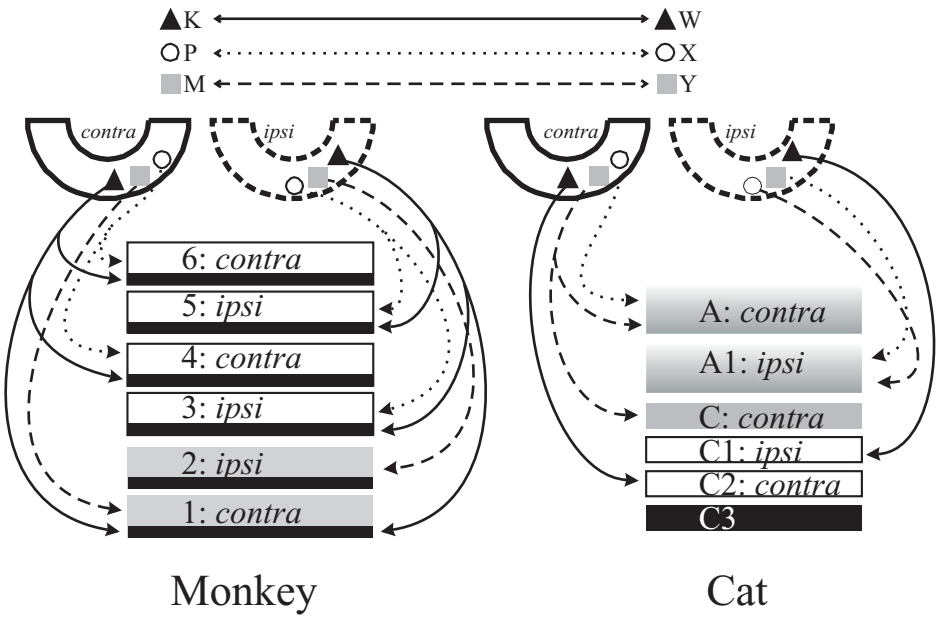

FIGURE 35.2. Comparison of layering in lateral geniculate nucleus of cat and macaque monkey. See text for details. For simplicity, the medial interlaminar nucleus, which is part of the lateral geniculate nucleus medial to the main laminated portion, present in the cat but not in most other species, is not shown.

vocellular, and magnocellular—and it was in this species that the koniocellular pathway was first clearly recognized (Conley et al., 1985; Itoh et al., 1982; Norton et al., 1988). In the cat, X and Y cells have overlapping projections to the A layers, Y cells also project to layer C, and W cells project to layers C1 and C2; there is no retinal input to layer C3, which is therefore shown in black in Figure 35.2 (Hickey and Guillery, 1974). Strictly speaking, layer C3 should perhaps not be included in the lateral geniculate nucleus, which can be defined as the thalamic relay of retinal inputs. What is common to cat and macaque monkey is that each layer is innervated by only one eye. What is different is the partial segregation of parallel pathways through each layer. In the macaque monkey, the P and M pathways use separate layers, the parvocellular for P and the magnocellular for M; the K pathway overlaps with each and is thus represented in all layers. In the cat, the W pathway uses separate layers (C1 and C2), and the Y pathway has exclusive use of layer C, but the X and Y pathways are mingled in the A layers.

Despite the overlap within layers of many of the parallel pathways, there is no functional overlap at the cellular level; within the A layers of the cat, retinal X and Y axons innervate their own classes of relay cell. A similar pattern exists for the macaque monkey, with each of the K, P, and M retinal axons targeting separate classes of geniculate relay cell, whose axons, in turn, have distinct distributions in the visual cortex (see Chapter 31).

New World primates have a slightly different layering arrangement from that shown for the macaque monkey. So far as we know, the human lateral geniculate nucleus is closely comparable to that of the macaque monkey, although there are commonly more than six layers (Hickey and Guillery, 1979), and we have no direct evidence concerning the distribution of distinct functional types to the different layers.

Thus, layering in the lateral geniculate nucleus separates left eye from right eye afferents and also, to a more limited extent, relates to the separation of functionally distinct parallel pathways. The binocular separation is constant across species, but the functional separation into distinct layers is highly variable, so that the number of layers, their sequence from superficial to deep, and their total number show great variability across species. Most of the information we have for cell and circuit properties of the lateral geniculate nucleus specifically and the thalamus more generally comes from the A layers in the cat, and most details presented below are from these layers. However, this focus on the A layers should not obscure two important facts. One is that in terms of the general arrangements of synaptic circuitry, there is a common thalamic plan that applies to the pulvinar region and to most other parts of the thalamus; the other is that structural details vary significantly among different layers and species. That is, there are details of functional organization that remain unknown but almost certainly will ultimately have to be added to our account of the A layers. For some details of geniculate relays beyond the A layers in the cat and in other species, see Jones (1985), Casagrande and Norton (1991), and Casagrande and Kaas (1994).

Cell Types within the A Layers There are three basic cell types in the A layers of the cat's lateral geniculate nucleus (see Fig. 35.3). These include the two relay cell types, X and Y, and interneurons. The relay cells use glutamate as a neurotransmitter, whereas interneurons use GABA.

Relay cells. X and Y cells represent geniculate relays of two parallel and independent geniculocortical pathways, each innervated by its own retinal X or Y axons, which are excitatory. Retinal Y axons are thicker and conduct more rapidly than do X axons (reviewed in Sherman, 1985). Also, within the A layers, the terminal arbors of retinal Y axons are much larger than those of X axons and give rise to many more synaptic terminals (Bowling and Michael, 1984; Sur et al., 1987). As a result of this and because the postsynaptic relay cell types do not differ much in the number of synapses that they receive from the retina, each retinal Y axon innervates many more relay cells than does an X axon. It has been estimated that the X:Y ratio, which is roughly 10:1 in the retina (Leventhal, 1982; Wässle et al., 1975; Wässle et al., 1981), becomes 1:1 or 2:1 for geniculate relay cells (Sherman, 1985).

These geniculate relay cells differ from one another with respect to their functional and morphological properties. Both cell types have the center/surround organization for their receptive fields typical of retinal and geniculate cells generally. However, Y cells have larger receptive fields and respond better to higher temporal and lower spatial frequencies, whereas X cells have smaller receptive fields and respond better to lower temporal and higher spatial frequencies. Further, Y cells exhibit subtly more nonlinear summation (for further details, see Hochstein and Shapley, 1976a, 1976b; Sherman, 1985). All these receptive field differences are already present in the retinal afferents, and for this reason they will not be considered further.

Morphologically, there are some differences between these relay cell types (Friedlander et al., 1981; Guillery, 1966; LeVay and Ferster, 1977; Wilson et al., 1984). At the light microscopic level (see Fig. 35.3), Y cells have larger cell bodies and smooth dendrites that have cruciate branches in a relatively spherical arbor, with peripheral segments of dendrites often crossing from one layer to another. X cells have arbors that tend to be bipolar and oriented perpendicular to the layers' borders. Their dendrites also have numerous clusters of grape-like appendages located mostly near primary branch points (Fig. 35.3). The functional significance of these morphological differences remains to be defined, although the clustered appendages of the X cells represent the postsynaptic site of retinal inputs, where complex synaptic relationships are formed that are characteristic of X but not of Y cells (the *triadic* arrangements described below). These and other differences in the microcircuitry of these cells types are described below.

Interneurons. Interneurons have the smallest cell bodies in the A layers and long, sinuous dendrites, and the dendritic arbors are always oriented perpendicular to the layers, often spanning an entire layer (see Fig. 35.3). The dendrites have the appearance of terminal axonal arbors and for that reason have been described as axoniform in appearance (Guillery, 1966). Terminals of these dendritic arbors are presynaptic to local dendrites, containing synaptic vesicles and thus resembling axon terminals, and they are also postsynaptic to other axons, generally those coming from either the retina or the brainstem (see also below and Erişir et al., 1997; Famiglietti and Peters, 1972; Hamos et al., 1985; Ralston, 1971). In addition, most, if not all, interneurons have conventional axons that terminate in the general vicinity of the dendritic arbor. The receptive fields of the few identified interneurons that have been studied are like those of X relay cells and unlike those of Y cells, which suggests that the retinal inputs responsible for their firing are X rather than Y axons (Friedlander et al., 1981; Sherman and Friedlander, 1988).

Afferents to the A Layers The major sources of inputs to the A layers, besides the retina, include the thalamic reticular nucleus, layer 6 of cortex, and the parabrachial region[3] of the midbrain. These are summarized in Figure 35.4. Other afferent sources not shown in Figure 35.4 include the nucleus of the optic tract (midbrain), the dorsal raphé nucleus (midbrain and pons), and the tuberomamillary nucleus (hypothalamus) (reviewed in Sherman and Guillery, 1996, 2001).

Retinal afferents. Retinal afferents to the A layers are glutamatergic (see Fig. 35.4). They are relatively thick axons and have a distinct terminal structure involving richly branched, dense terminal arbors with boutons densely distributed mostly in flowery terminal clusters (not illustrated; see Guillery, 1966). In contrast, most nonretinal inputs described below are thinner, and have an equally distinct structure with smaller terminals *en passant* or on short side branches (see Fig. 35.5, *right*). The retinal axons innervate both relay cells and interneurons in the A layers. Each retinal axon has an arbor strictly limited to one of the A layers, although Y axons and occasional

[3] Another term frequently used for this area is *pedunculopontine tegmental nucleus*. We prefer *parabrachial region*, because the scattered cells that innervate the thalamus from this area do not have a clear nuclear boundary, and they are found scattered around the brachium cojunctivum.

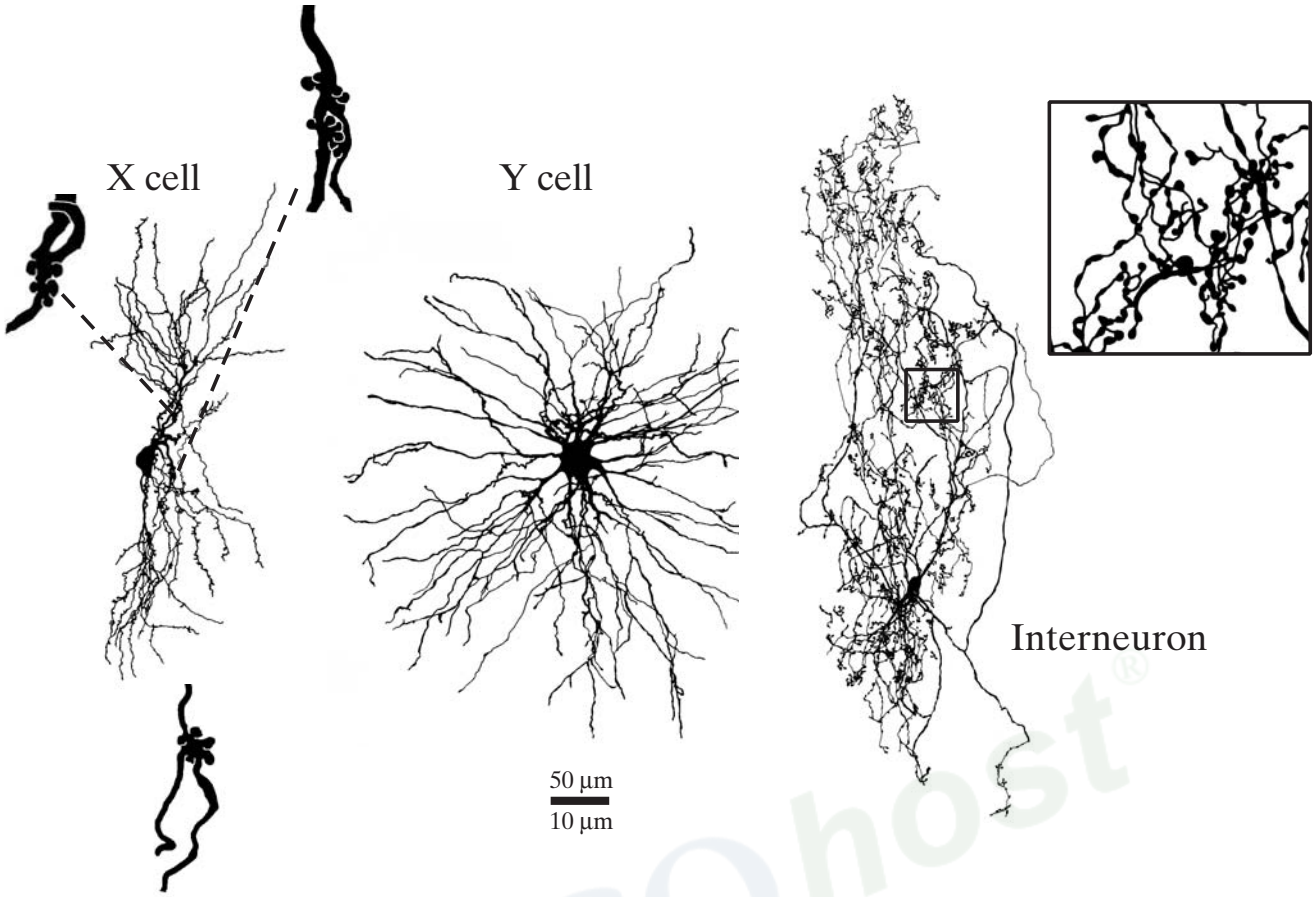

FIGURE 35.3. Reconstruction of an X cell, Y cell, and interneuron from A layers of the cat's lateral geniculate nucleus. The larger scales are for the insets for the X cell and interneuron.

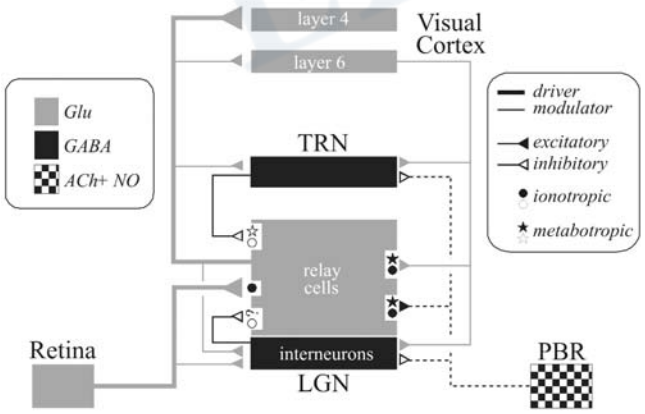

FIGURE 35.4. Neuronal circuitry related to A layers of the cat's lateral geniculate nucleus. Shown are the various inputs, the neurotransmitters associated with them, and the type of receptor, ionotropic or metabotropic, that each activates. Driver versus modulator inputs are also shown (see text for details).

X axons branch to innervate the C layers and/or the medial interlaminar nucleus[4] as well. As would be expected from the earlier description of the lines of projection, the terminal arbors of the retinogeniculate axons are also organized so that they occupy relatively narrow columns that are bounded by lines of projection, either within a single layer or across more than one layer. Y arbors are larger and contain more boutons than do X arbors. A more subtle difference between them is that the boutons in Y arbors are fairly evenly distributed, while those in X arbors tend to be found in clusters with gaps between them (Bowling and Michael, 1984; Sur et al., 1987). All retinal X and Y axons innervating the lateral geniculate nucleus branch to innervate the midbrain as well (a point that is discussed further below; see also Guillery and Sherman, 2002a,b), but they do not innervate the thalamic reticular nucleus.

[4]The medial interlaminar nucleus is a part of the lateral geniculate nucleus found in carnivores.

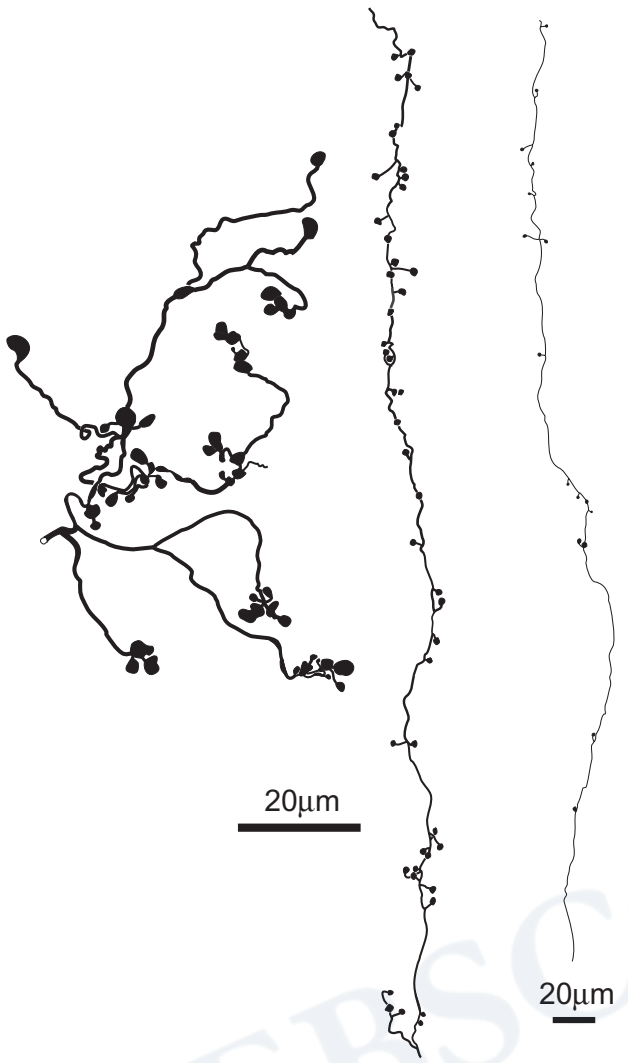

FIGURE 35.5. Tracings of partial terminal arbors of three corticothalamic axons in the pulvinar region labeled by biotinylated dextran amine. The axon on the left exhibits driver morphology from cortical layer 5, and the two axons on the right exhibit modulator morphology from layer 6. (From Sherman and Guillery, 2001.)

Afferents from the thalamic reticular nucleus. The thalamic reticular nucleus is a thin shell of GABAergic neurons that surrounds the entire thalamus laterally, extending somewhat dorsally and ventrally. It derives from the ventral thalamus, together with the ventral lateral geniculate nucleus (see footnote 1), and is divided into sectors, each related to thalamic relay nuclei concerned with a particular modality or function (e.g., auditory, somatosensory, and motor), and as in the main part of the thalamus, sensory surfaces are mapped in the sectors (Crabtree, 1992, 1996, 1998; Crabtree and Killackey, 1989; Montero et al., 1977; reviewed in Guillery et al., 1998). There are strong reciprocal connections between relay cells and reticular cells linking corresponding parts of the reticular and geniculate maps (Pinault and Deschênes, 1998; Pinault et al., 1995a, 1995b; Uhlrich et al., 1991), and the cortical afferents from layer 6 (next section) are mapped along the same coordinates (Murphy and Sillito, 1996). That is, the portion of the thalamic reticular nucleus innervating the lateral geniculate nucleus[5] is mapped in retinotopic coordinates. In addition, the visual sector of the reticular nucleus is linked reciprocally to the pulvinar region (Conley and Diamond, 1990; Pinault et al., 1995a). There is some evidence that the visual sector of the reticular nucleus can be split into two parts, an inner part linked to the lateral geniculate nucleus and an outer part linked to the pulvinar region. The retinotopic mapping in the pulvinar sector of the reticular nucleus is less accurate than that for the geniculate sector, and there may be no map at all in the former.

The cells of the thalamic reticular nucleus, which lie just dorsal to layer A, have moderate to large cell bodies and dendrites oriented mostly parallel to layer A (Uhlrich et al., 1991). Their axons descend into the A layers, generally along the lines of projection, with terminal arbors that are moderately branched and contain numerous boutons, mostly *en passant*. These terminals innervate geniculate relay cells, but they provide only a very sparse innervation to interneurons (Cucchiaro et al., 1991; Wang et al., 2001). Thus, the thalamic reticular nucleus provides a potent inhibitory GABAergic input to relay cells (Fig. 34.4). Their receptive fields tend to be larger than those of relay cells and are often binocular (So and Shapley, 1981).

Afferents from layer 6 of the cortex. Cortical afferents from layer 6, which are glutamatergic, have thin axons with most boutons located at the end of short side branches (Fig. 34.5; see Murphy and Sillito, 1996). They are topographically organized, with each axon having terminal arbors bounded by lines of projection and passing across more than one layer. These axons enter the A layers after traveling through the thalamic reticular nucleus, where they also give off branches to innervate cells there; this projection, too, is topographic.

Afferents from the parabrachial region. Most of the input from the brainstem to the A layers derives from the parabrachial region (Bickford et al., 1993; de Lima and Singer, 1987). These axons are cholinergic but also appear to colocalize nitric oxide (Bickford et al., 1993; Erişir et al., 1997). Light microscopically, they resemble the cortical afferents more than the retinal afferents, but their terminal arbors are rather diffuse and most appear to terminate in a nontopographic

[5] In the cat, the major portion of the thalamic reticular nucleus innervating the lateral geniculate nucleus is the *perigeniculate nucleus*.

fashion. These axons contact both relay cells and interneurons in the A layers and also branch to innervate cells in the thalamic reticular nucleus.

Other afferents. Some other afferents to the A layers not shown in Figure 35.4 have been described, but they are small in number, not well documented, and will be mentioned only briefly here (for further details, see Sherman and Guillery, 1996, 2001). Lying among the cholinergic cells of the parabrachial region, there are also some noradrenergic cells that innervate the A layers. There is limited serotonergic input from the dorsal raphé nucleus in the midbrain and pons. GABAergic cells of the nucleus of the optic tract in the midbrain also provide limited input. Finally, the tuberomamillary nucleus of the hypothalamus provides a small histaminergic input (Uhlrich et al., 1993).

Postsynaptic receptors. In addition to showing the inputs and their transmitters onto relay cells, Figure 35.4 shows the associated postsynaptic receptors. Note that both ionotropic and metabotropic receptors are postsynaptic in relay cells. There are a number of differences between these two receptor types, but only a few concern us here (for details, see Brown et al., 1997; Conn and Pin, 1997; Mott and Lewis, 1994; Nicoll et al., 1990; Pin and Duvoisin, 1995; Recasens and Vignes, 1995).

Ionotropic receptors include AMPA receptors for glutamate, $GABA_A$, and nicotinic receptors for acetylcholine. These are complex proteins found in the postsynaptic membrane, and when the transmitter contacts the receptor, it leads to a rapid conformational change that opens an ionic channel, leading to transmembrane flow of ions and a postsynaptic potential. Activation of ionotropic receptors leads to fast responses, typically with a latency for postsynaptic potentials of less than 1 msec and a duration of a few tens of milliseconds. Metabotropic receptors include various glutamate receptors, $GABA_B$, and various muscarinic receptors for acetylcholine. These are not directly linked to ion channels. Instead, when the transmitter contacts the receptor protein in the membrane, a series of complex biochemical reactions takes place that ultimately leads to the opening or closing of an ion channel, among other postsynaptic events. For thalamic cells, this is primarily a K^+ channel that, when opened, produces an inhibitory postsynaptic potential (IPSP) as K^+ flows out of the cell and, when closed, produces an excitatory postsynaptic potential (EPSP) as leakage of K^+ is reduced. However, these postsynaptic responses are slow: there is usually a latency of 10 msec or longer and a duration of hundreds of milliseconds or more. Also, in general, metabotropic receptors require higher firing rates from inputs to be activated. This is thought to be related to the observation that electron micrographs show these receptors to be located slightly farther from the synaptic site than are ionotropic receptors, so that more transmitter must be released to reach them.

The more sustained responses associated with metabotropic receptors have a number of important implications. One has to do with the fact that retinal inputs activate only ionotropic receptors in relay cells. This means that retinal EPSPs are relatively fast and brief. This has the virtue that firing in the retinal afferents can reach relatively high levels before temporal summation of the EPSPs occurs, and thus each retinal action potential has a unique postsynaptic response associated with it. If, instead, metabotropic glutamate receptors were activated, the sustained EPSPs would mean that relatively low rates of firing in the afferent would produce temporal summation postsynaptically. This, in turn, means that higher-frequency information would be lost in retinogeniculate transmission or, more formally, that the retinogeniculate synapse would operate like a low-pass temporal device, filtering out higher frequencies. Thus, the fact that retinal inputs activate only ionotropic receptors serves to maximize the transfer of higher temporal frequencies. Note that the population of nonretinal inputs as a whole activates both metabotropic and ionotropic receptors (reviewed in Sherman and Guillery, 1996, 2001). However, it is not clear whether any individual nonretinal axon can activate both ionotropic and metabotropic receptors. Nonetheless, the activation of metabotropic receptors means that these inputs can create sustained changes in baseline membrane potential, which, among other things, means that these inputs can have sustained effects on the overall responsiveness of relay cells. Other consequences of these sustained postsynaptic responses are considered below.

Synaptic structures. Over 95% of all synaptic terminals in the A layers can be placed into one of four categories (reviewed in Sherman and Guillery, 1996, 2001): (1) *RL* (*R*ound vesicle, *L*arge profile) terminals, which are the retinal terminals, are the largest terminals in the A layers. They form asymmetric[6] contacts consistent with their identity as excitatory inputs. (2) *RS* terminals (*R*ound vesicle, *S*mall profile) are smaller than RL terminals but also form asymmetric contacts. The vast majority of these come from either layer 6 of cortex or the parabrachial region. (3) *F1* terminals (*F*lattened

[6] One ultrastructural characteristic of synaptic contacts is a thickening of the postsynaptic membrane, which includes the postsynaptic receptors (Sheng, 2001). When the thickening is especially prominent, the postsynaptic membranes are much thicker than the presynaptic ones, and this characterizes an *asymmetric* synapse. When the thickening is less prominent, there is a less pronounced difference in thickness between presynaptic and postsynaptic membranes, and this characterizes a *symmetric* synapse. Typically, asymmetric synapses are excitatory, and symmetric ones are inhibitory.

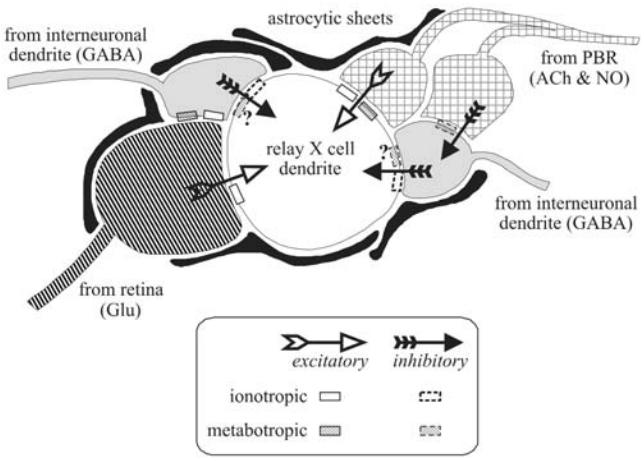

FIGURE 35.6. Schematic view of triadic circuits in a glomerulus of the lateral geniculate nucleus in the cat. The arrows indicate presynaptic to postsynaptic directions. The question marks postsynaptic to the dendritic terminals of interneurons indicate that it is not clear whether or not metabotropic ($GABA_B$) receptors exist there.

vesicles) form symmetric contacts consistent with their origin from axons of reticular cells or interneurons. (4) *F2* terminals represent the dendritic outputs of interneurons; they also have flattened vesicles and form symmetric contacts. Unlike all of the other terminals, which are strictly presynaptic, these are both presynaptic and postsynaptic, with inputs from either retinal or parabrachial terminals.

Triadic synaptic arrangements involving F2 terminals are common in the A layers (Fig. 35.6). In some triads, an RL terminal contacts both an F2 terminal and the dendrite of a relay cell, and the F2 terminal contacts the same relay cell dendrite. A slightly different kind of triad can be formed by a parabrachial terminal contacting an F2 terminal and a different parabrachial terminal from the same axon contacting a relay cell dendrite, again with the F2 terminal contacting the same relay cell dendrite (Fig. 35.6). Nearly all F2 terminals are involved in one or the other form of triad. Curiously, these triads are quite common for relay X cells and rare for Y cells, the latter thus receiving very few inputs from F2 terminals.[7] Triads are typically found in complex synaptic zones that lack astrocytic processes but are surrounded by sheets of astrocytic cytoplasm; these are called *glomeruli*. It is not at all clear how the triads function.

Distribution of inputs to relay cells. The dendritic arbors of relay cells can be divided into two distinct sectors with little or no overlap (Erişir et al., 1997; Wilson et al., 1984): a proximal region (up to about 100 μm from the cell body or generally close to the first branch point) and a distal region (farther than about 100 μm from the cell body). Retinal terminals contact the former region, whereas cortical terminals contact the latter. F2 and parabrachial terminals also contact relay cells in the proximal zone. Axonal inputs from interneurons mostly contact the proximal zone, whereas those from reticular axons mostly contact the distal zone.

A small minority of synaptic inputs onto geniculate relay cells derive from retina. In the A layers of the cat's lateral geniculate nucleus, for instance, only about 5–10% of the synaptic input to relay cells comes from the retinal axons: roughly 30% comes from local GABAergic cells (interneurons plus reticular cells), 30% from the cortical input, and 30% from the parabrachial region (Van Horn et al., 2000). In the parvocellular C layers, even fewer synapses—2% to 4%—onto relay cells derive from the retina (Raczkowski et al., 1988). If one had only the anatomical data, and for many other thalamic relays that is all we have, one might well conclude that the lateral geniculate nucleus relays parabrachial input to cortex and that the retinal input plays only a minor, undetermined role For the lateral geniculate nucleus we know that it is the retinal input that is relayed to cortex, so we accept that the small number of retinal afferents serve as the crucial drivers of geniculate function. However, for thalamic nuclei that we do not understand as well as the lateral geniculate nucleus, the point is important, as we will see when we discuss corticocortical communication.

Drivers and modulators. It follows that not all inputs to the thalamus are equal in their action on the relay cells. We have distinguished two different types of input (Sherman and Guillery, 1998, 2001): *drivers* and *modulators*. The drivers are the information-bearing input that is to be relayed to cortex, and this is the retinal input for the lateral geniculate nucleus. All other inputs are modulators. Examples of modulation are provided below, and details of how drivers might generally be distinguished from modulators is provided elsewhere (Sherman and Guillery, 1998, 2001). One difference is seen in Figure 35.4: the driver (retinal) input activates only ionotropic receptors, whereas the modulators activate metabotropic and often ionotropic receptors. Note that, of the main extrinsic inputs to the lateral geniculate nucleus, the retinal input is a driver, but the layer 6 cortical and parabrachial inputs are both modulators. The corticothalamic input must be seen as modulatory because, among other

[7] Recent descriptions of triads that relate to Y cell terminals suggest more similarities between the X and the Y pathways than reported in the earlier studies (e.g., Wilson et al., 1984; Sherman and Friedlander, 1988). Datskovskaia et al. (2001) offer evidence that many retinal Y axons in the A layers terminate on dendritic presynaptic F2 terminals and thus are likely to contribute significantly to triads. Also a recent account of triads related to Y cell axons in the geniculate C layers (Dankowski and Bickford, 2003) adds new information on the subject, and the issue of the extent of triadic circuitry in the Y pathway remains to be resolved.

reasons, its elimination (by cooling, ablation, etc.) has only subtle effects on the receptive fields of geniculate relay cells, not altering their basic center/surround organization (Cudeiro and Sillito, 1996; Geisert et al., 1981; Jones and Sillito, 1991; Kalil and Chase, 1970; McClurkin and Marrocco, 1984; McClurkin et al., 1994). This is in contrast to corticothalamic afferents from layer 5, which go to higher-order thalamic relays but not to the lateral geniculate nucleus, and which must be regarded as drivers because their elimination essentially abolishes the characteristic receptive fields in such target thalamic relays as the posterior medial nucleus or pulvinar region (Bender, 1983; Chalupa, 1991; Diamond et al., 1992; see also the section "The Pulvinar Region as a Visual Relay").

Intrinsic Properties of Thalamic Cells in the A Layers

The relay nature of the lateral geniculate nucleus depends on the mechanisms by which retinal inputs evoke firing in geniculate relay cells, and these mechanisms are also present in thalamic relays more generally. There are three factors that largely control this retinogeniculate transmission, and they are considered below. First are the intrinsic membrane properties of relay cells, including their passive and active membrane properties, because these determine the effect of retinal EPSPs at the cell body or region of action potential generation. Second is the geniculate circuitry that, by affecting many of the intrinsic membrane properties, also controls the effect of retinal EPSPs on relay cell firing. Third, the nature of the postsynaptic receptors largely determines the postsynaptic response of relay (and other) cells to their active inputs; this feature is considered in the section "Control of Response Mode."

Generally, all thalamic cells show a wide range of intrinsic membrane properties that are found generally in neurons of the brain (reviewed in Sherman and Guillery, 1996, 2001). These include passive cable properties, voltage-sensitive and -insensitive conductances, and conductances sensitive to other factors, such as Ca^{2+} concentration. The conductances underlie transmembrane currents, including a leak K^+ current ($I_{K[leak]}$) that helps control the resting membrane potential, various voltage- and Ca^{2+}-gated K^+ currents (I_A, $I_{K[Ca^{2+}]}$, etc.), and a voltage-gated cation current (I_h). Since these are properties found widely in the brain, they will not be considered further here, but additional details of these as they apply to thalamic neurons can be found in Sherman and Guillery (1996, 2001) Two features that are of particular interest in thalamic neurons are considered below. One is the apparent cable properties of interneurons, which suggests that synaptic inputs onto their dendritic terminals affect them locally but have little effect on the cell body and axonal output, permitting these cells to provide numerous input/output routes independently and simultaneously (see below). The other is the presence in all cells of a voltage-gated Ca^{2+} conductance based on T-type (for transient) Ca^{2+} channels that, when activated, leads to a current (I_T) large enough to produce an all-or-none Ca^{2+} spike (reviewed in Sherman and Guillery, 1996, 2001). This spike alters the response properties of the thalamic cells in a functionally highly significant manner.

Passive membrane or cable properties. Determining how current spreads through cells with complex geometries of their dendritic trees poses a formidable computational problem. Modeling the cell and its membranes as a cable provides a useful means of approximating current flow. Details of cable modeling for thalamic neurons can be found in Bloomfield et al. (1987) and Bloomfield and Sherman (1989) and will be briefly summarized here. Relay cells and cells of the thalamic reticular nucleus have relatively thick dendrites that branch in a way that suggests efficient current flow through the dendrites. The result of cable modeling for these cells indicates that they are electrotonically compact, meaning that EPSPs and IPSPs generated even on peripheral dendrites will produce significant voltage changes at the cell body and axon hillock (Bloomfield et al., 1987; Bloomfield and Sherman, 1989). Thus, all synaptic inputs to these cells can be considered influential in affecting the cell's firing. Since the dendrites of relay cells are purely postsynaptic structures, the only synaptic output of these cells is via their axons, so that any synaptic input to the distal dendrites that could not produce a voltage change at the spike-initiating region would be ineffective for spike initiation.

In contrast to relay cells, interneurons are built differently in two ways. First, as noted above, in addition to having a conventional axonal output, these cells have presynaptic terminals on peripheral dendrites, which provide these cells with numerous dendritic outputs. Second, these presynaptic terminals are attached to the stem dendrites by long, thin stalks; overall, the thin dendrites and the nature of the dendritic branching suggest poor current flow through the dendritic trees. Cable modeling suggests that EPSPs and IPSPs generated on the peripheral dendrites, where the retinal and brain stem axons provide significant input to the dendritic presynaptic boutons, will have little influence on the cell body and axon hillock (Bloomfield and Sherman, 1989). Thus, the interneuron appears capable of multiplexing: the axonal output is controlled by synapses located on proximal dendrites, whereas the several separate dendritic outputs are controlled locally and independently of each other by local synaptic inputs. However, this concept of the functioning of the interneuron remains a hypothesis that requires more direct evidence than currently exists (Cox and Sherman, 2000).

Properties of I_T in relay cells. The voltage-dependent low-threshold Ca^{2+} spikes that are based on T channels are

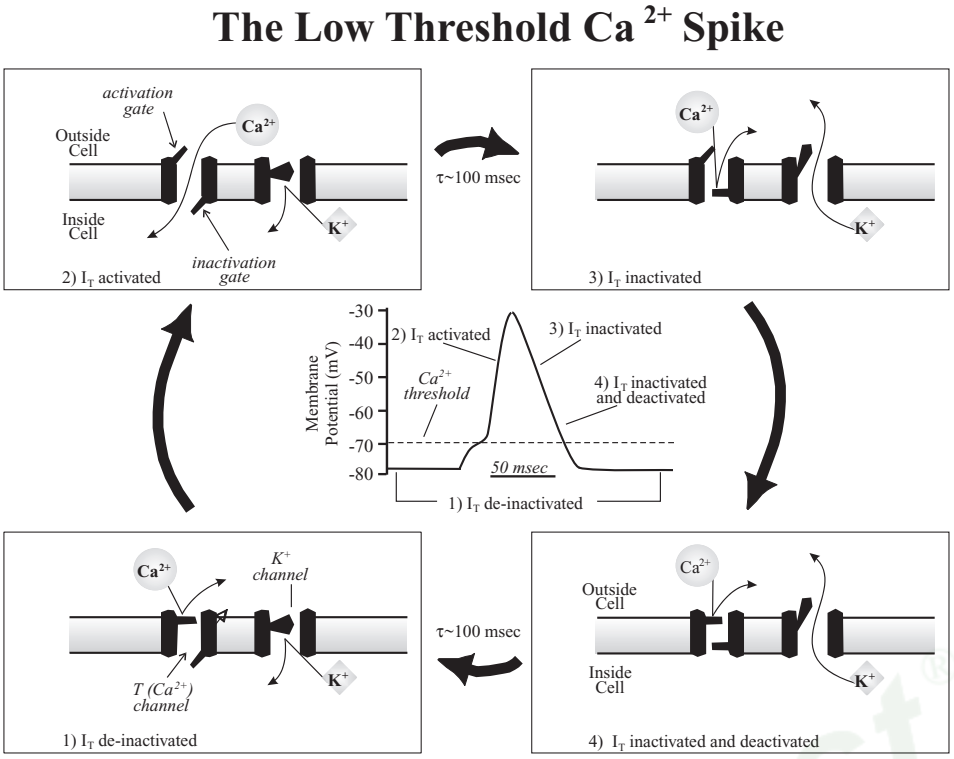

FIGURE 35.7. Highly schematized view of the actions of voltage-dependent T (Ca^{2+}) and K^+ channels underlying a low-threshold Ca^{2+} spike. The four numbered panels show the sequence of channel events, and the central graph shows the effects on membrane potential. The T channel has two voltage-dependent gates: an *activation* gate that closes at hyperpolarized levels and opens with depolarization, and an *inactivation* gate that shows the opposite voltage dependency. The K^+ channel shown is really a conglomeration of several such channels that have only a single gate that opens during depolarization; thus, these channels do not inactivate. *1*, At a relatively hyperpolarized resting membrane potential (~70 mV), the activation gate of the T channel is closed but the inactivation gate is open, so the T channel is deinactivated. The single gate for the K^+ channel is closed. *2*, With sufficient depolarization to reach its threshold, the activation gate of the T channel opens, allowing Ca^{2+} to flow into the cell. This depolarizes the cell, providing the upswing of the low-threshold spike. *3*, The inactivation gate of the T channel closes after roughly 100 msec ("roughly," because closing of the channel is a complex function of time and voltage), and the K^+ channel also opens. These combined actions lead to the repolarization of the cell. While the inactivation gate of the T channel is closed, the channel is said to be inactivated. There are probably several different kinds of K^+ channels involved with different time constants, but in general, they open more slowly than does the activation gate of the T channel. Also, not shown, K^+ channels dependent on Ca^{2+} entry are probably involved. *4*, Even though the initial resting potential is reached, the T channel remains inactivated, because it takes roughly 100 msec ("roughly" having the same meaning as above) of hyperpolarization to deinactivate it; it also takes a bit of time for the various K^+ channels to close. Note that the behavior of the T channel is qualitatively exactly like that of the Na^+ channel involved with the action potential, but with several quantitative differences: the T channel is slower to inactivate and deinactivate, and it operates in a more hyperpolarized regime.

ubiquitous to thalamic relay cells: they have been found in every relay cell of every thalamic nucleus of every mammalian species so far studied (reviewed in Sherman and Guillery, 1996). Figure 35.7 shows the voltage dependence of the T channels and that of K^+ channels also involved in the generation of the low-threshold spikes. The T channels have two voltage-sensitive gates, an activation gate and an inactivation gate, and both must be open for Ca^{2+} to flow into the cell and thus depolarize it. At the normally hyperpolarized resting membrane potentials (Fig. 35.7*(1)*), the activation gate is closed but the inactivation gate is open, so the channel is deinactivated. The single gate of the K^+ channel is closed at this membrane potential. If the cell is now sufficiently depolarized (e.g., by an EPSP), the activation gate pops open, and Ca^{2+} flows into the cell, providing the uspwing of the low-threshold spike (Fig. 35.7*(2)*). However, depolarization causes the inactivation gate to close (Fig. 35.7*(3)*), but this takes time, on the order of 100 msec or so.[8] The single gate of the K^+ channel, because of its

[8] Actually the opening or closing of the inactivation gate is a complex function of voltage and time (Jahnsen and Llinás, 1984), so that the more depolarized (or hyperpolarized) the more quickly the gate closes (or opens), but the important point is that under normal conditions, roughly 100 msec is required for these actions.

voltage dependency, also opens, and the combined inactivation of the T channel and activation of the K^+ channel serve to repolarize the cell (Fig. 35.7(*4*)). Although not shown, in addition to voltage-dependent K^+ channels, Ca^{2+}-dependent ones are also activated by the Ca^{2+} entry and assist the repolarization process. While the membrane is repolarized to its initial potential, the T channel remains inactivated, because it takes roughly 100 msec of this hyperpolarization to deinactivate these channels, after which time the initial conditions are reestablished (Fig. 35.7(*1*)). To reiterate: when the cell is sufficiently hyperpolarized for more than about 100 msec, the T channel is deinactivated; if deinactivated, a suitable depolarization can then activate the channel, but continued depolarization for more than about 100 msec will inactivate it; the inactivation can then be removed by suitable hyperpolarization for more than about 100 msec.

This voltage dependency of the T channels provides the relay cell with two different firing modes: if the cell is relatively depolarized, the T channels are inactivated and do not participate in the cell's responses; here the cell is said to be in *tonic firing mode*. If the cell is relatively hyperpolarized, the T channels are deinactivated and thus primed for action. They can become activated and, on the basis of mechanisms considered below, can affect how the cell fires; here the cell is said to be in *burst firing mode*.

The voltage-dependent properties of the T channels are qualitatively identical to those of the Na^+ channels underlying the action potential, but there are several important quantitative differences: (1) Opening or closing of the inactivation gate is roughly two orders of magnitude faster for the Na^+ channel. (2) The T channels are found in the cell body and membranes, but not in the axon; thus, the low-threshold spike can be propagated through the dendrites and cell body but not along the axon to cortex. That is, the T channels can affect the signal reaching cortex by the effect of the low-threshold spike on the generation of action potentials (see below). (3) The T channels operate in a somewhat more hyperpolarized regime, and their activation at more hyperpolarized levels is the reason the resultant Ca^{2+} spike is called *low threshold*. (4) The T channels operate in a slightly more hyperpolarized regime than the Na^+ channels.

Figure 35.8 shows recordings from relay cells of the cat's lateral geniculate nucleus, illustrating some of the functional consequences of I_T. When the membrane is more depolarized than roughly −60 to −65 mV for more than ~100 msec, I_T becomes inactivated (Fig. 35.8*A*), and activation by a depolarizing pulse evokes a steady stream of action potentials lasting for the duration of the stimulus: this is tonic firing. When the membrane is more hyperpolarized than about −65 to −70 mV for more than ~100 msec (Fig. 35.8*B*), I_T becomes deinactivated. Now the very same depolarizing pulse activates I_T, leading to a low-threshold spike, which, in turn, leads to a burst of a few action potentials: this is burst firing. Note that the same excitatory stimulus produces two very different signals relayed to cortex, and the difference depends on the initial membrane potential of the relay cell, because this determines the inactivation state of I_T. The stimulus in this example is a current pulse, but the same would apply to a sufficiently large EPSP.

The size of the activated low-threshold spike depends on the extent to which the cell is hyperpolarized before being activated, because the more the cell is hyperpolarized, the more T channels are deinactivated and thus available to contribute to the low-threshold spike (Fig. 35.8*C*). As would be expected, the larger the low-threshold spike, the larger the number of action potentials evoked in the associated burst (Fig. 35.8*C*). However, in addition, the low-threshold spike is activated in an all-or-none manner, because at any one initial membrane potential, suprathreshold activating inputs activate low-threshold spikes of essentially the same amplitude, regardless of how far above threshold the activating input is (Fig. 35.8*D*). One implication of this for the difference in input/output relationships between burst and tonic firing is shown in Figure 35.9. This relationship is fairly linear for tonic firing, because there is a direct link between the input depolarization and activation of action potentials, leading to the monotonic relationship as shown. However, the relationship is indirect for burst firing, since it is the low-threshold spike that controls firing, and, as Figure 35.8*D* shows, larger activating inputs do not produce larger low-threshold spikes.

Properties of I_T in interneurons and reticular cells. I_T is present in both interneurons and reticular cells, but its action is subtly different in these cells. Its activation in interneurons is a matter of some controversy. Several studies suggest that I_T is rarely activated in these cells, because it is masked by I_A (Pape et al., 1994). I_A is a K^+ conductance with a voltage dependence similar to that of I_T: it is inactivated at depolarized levels and deinactivated at hyperpolarized levels, from which it can be activated (for details, see McCormick, 1991). However, unlike I_T, I_A creates hyperpolarization, since the current is composed of K^+ ions leaving the cell. Some evidence suggests that, in interneurons, the relative voltage dependency of these two currents is such that I_A is typically activated before I_T, thereby preventing activation of I_T (Pape et al., 1994). In relay cells, the relative voltage dependency is different, so that I_T is activated first (Pape et al., 1994). However, other evidence suggests that if the input resistance of the interneuron is high enough, low-threshold spiking is readily produced (Zhu et al., 1999). At present, it is difficult to reconcile these views. Nonetheless, it should be appreciated that tonic firing and burst firing in the interneuron, to the extent that

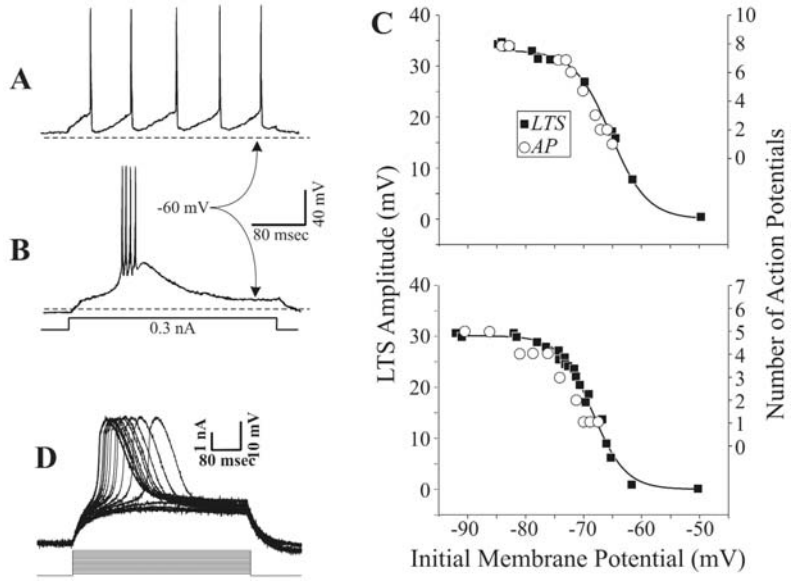

FIGURE 35.8. Properties of I_T and the low-threshold spike; examples from intracellular in vitro recordings of geniculate relay cells of the cat. *A*, *B*, Voltage dependency of the low-threshold spike. Responses are shown to the same depolarizing current pulse delivered intracellularly but from two different initial holding potentials. With relative depolarization of the cell (*A*), I_T inactivates, and the cell response is a stream of unitary action potentials lasting for the duration of a suprathreshold stimulus. This is the *tonic mode* of firing. With relative hyperpolarization of the cell (*B*), I_T deinactivates, and the current pulse activates a low-threshold spike with four action potentials riding its crest. This is the *burst mode* of firing. *C*, Voltage dependency of low-threshold spike amplitude and associated burst response. Examples for two cells are shown. The number of action potentials were recorded first in the experiment, and then the procedure was repeated after tetrodotoxin (TTX) application to eliminate action potentials and isolate the low-threshold spike for measurement. The more hyperpolarized the cell before activation (*Initial Membrane Potential*), the more action potentials (*AP*) in the burst (open circles) and the larger the low-threshold spike (filled squares and curve). *D*, All-or-none nature of low-threshold spikes in another geniculate cell, measured in the presence of TTX. After initial hyperpolarization of the cell, current pulses were injected in 10 pA incremental steps. Smaller (subthreshold) pulses produced resistive-capacitative responses, but all larger (suprathreshold) pulses evoked low-threshold spikes that are all of the same amplitude, regardless of how far the depolarizing pulse exceeded activation threshold. (*C* redrawn from Sherman, 2001; Zhan et al., 2000; *D* redrawn from Zhan et al., 1999.)

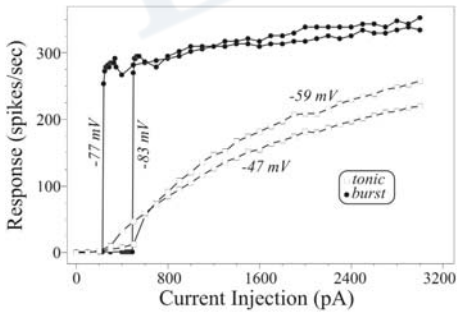

FIGURE 35.9. Input output relationship for a geniculate relay cell recorded intracellularly in vitro. The input variable is the amplitude of the depolarizing current pulse, and the output is the firing frequency of the cell. To compare burst and tonic firing, the firing frequency was determined by the first six action potentials of the response, since this cell usually exhibited six action potentials per burst in this experiment. The initial holding potentials are shown; −47 mV and −59 mV reflect tonic mode (open squares and curves), whereas −77 mV and −83 mV reflect burst mode (filled curves). (Redrawn from Zhan et al., 1999.)

they exist, describe axonal outputs of interneurons, and their dendritic outputs may follow quite different and independent patterns.

Cells of the thalamic reticular nucleus also have burst firing based on voltage-dependent T channels, but the temporal properties are slightly different from those in relay cells, leading to longer low-threshold spikes and more prolonged bursts in reticular cells (for details, see Destexhe et al., 1996).

SIGNIFICANCE OF BURST AND TONIC FIRING The first studies of thalamic bursting in vivo emphasized the presence of rhythmic bursting in thalamic relay cells during slow-wave sleep and certain pathological conditions, such as epilepsy, in which this bursting is synchronized across large cell populations. In these conditions, such bursting also interferes with normal relay functions, and it was thus considered not to be a relay mode of firing (Fanselow et al., 2001; Steriade and Llinás, 1988; Steriade and McCarley, 1990; Steriade et al., 1990, 1993).

Because such rhythmic bursting was not seen during waking behavior, this led to the notion that bursting occurs

only during sleep or pathological state and that tonic firing is the normal relay mode during waking behavior. However, it is now clear that bursting also occurs during normal waking behavior (Edeline et al., 2000; Fanselow et al., 2001; Lenz et al., 1998; Magnin et al., 2000; Ramcharan et al., 2000; Swadlow and Gusev, 2001), but because the bursting then is not rhythmic it is harder to detect, and this perhaps explains why it was not emphasized in earlier studies. It may also be that the rhythmic bursting seen during slow-wave sleep provides a positive signal to cortex that nothing is being relayed despite the possible presence of sensory stimuli, and this is less ambiguous than no activity, which could mean either no relay or no stimulus. In contrast, when the bursting is arrhythmic, this arrhythmicity can represent responses evoked by sensory stimuli.

Most relay cells during waking behavior fire more often in tonic mode, and the amount of bursting seems to go down to small values as the animal becomes more alert (Ramcharan et al., 2000; Swadlow and Gusev, 2001). Nonetheless, both modes effectively relay retinal information to cortex (Ramcharan et al., 2000; Reinagel et al., 1999; Sherman, 2001), and thus the presence in an awake animal of both modes, tonic and nonrhythmic bursting, raises the obvious question: what is the significance of these two modes? They represent very different ways in which the relay cell responds to the same input, indicating that the same message is relayed to cortex in one of two different ways. Thus, when messages arrive at the relay cell, the level of its membrane potential, which determines the inactivation state of I_T, can strongly influence the nature of the information that is transmitted to cortex. Receptive field analysis from relay cells of the cat's lateral geniculate nucleus indicates that both response modes convey comparable levels of information in the relay to cortex (Reinagel et al., 1999), although it is also clear that the nature of that information differs between modes (Sherman, 1996, 2001). There may be many differences related to these two modes, but two that have received considerable attention are linearity of the relay process and detectability of the message that is relayed to cortex.

Linearity. From the cellular properties described above (e.g., Fig. 35.9), it is clear that tonic firing represents a more linear relay mode. This is also seen in the responses of geniculate relay cells to visual stimuli. A clear example is shown in Figure 35.10, which shows the responses to a drifting sinusoidal grating of a relay cell recorded in vivo in an anesthetized cat. When the cell is in tonic mode, the response to the grating has a sinusoidal profile (Fig. 35.10*A*, *lower*). This means that the response level closely matches the changes in contrast, indicating a very linear relay of this input to cortex. However, when the same stimulus is applied to the same cell, but now in burst mode, the response no longer seems sinusoidal (Fig. 35.10*B*, *lower*), indicating considerable nonlinear distortion in the relay. Thus, tonic mode is better at preserving linearity in the relay of information to cortex (Sherman, 1996, 2001).

Detectability. The upper histograms of Figure 35.10 show further that spontaneous activity is lower during tonic than burst firing. Higher spontaneous activity is actually useful for maintaining linearity of response, because it helps prevent rectification of the response to inhibitory phases of visual stimulation, and rectification is a nonlinearity. Perhaps more interesting is the notion that spontaneous activity represents firing without a visual stimulus and can thus be considered a noisy background against which the signal—the response to the visual stimulus—must be detected. In this regard, the signal-to-noise ratio appears to be higher during burst firing, and indeed, the use of a method from signal detection theory involving the calculation of *receiver operating characteristic* curves (Green and Swets, 1966; Macmillan and Creelman, 1991) shows that stimulus detectability is improved during burst firing compared to tonic firing (Sherman, 1996, 2001).

Bursting as a "wake-up call." The above differences in firing modes as regards linearity and detectability suggest the following hypothesis (Sherman, 1996, 2001). Tonic firing is better for faithful, detailed reconstruction of the stimulus,

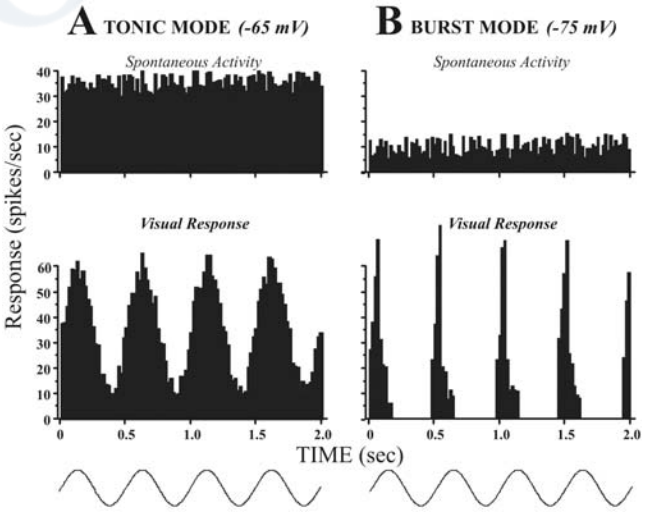

FIGURE 35.10. Tonic and burst responses of relay cells from the cat's lateral geniculate nucleus to visual stimulation. *A*, *B*, Average response histograms of responses of one cell to four cycles of drifting sinusoidal grating (*lower*) and during spontaneous activity (*upper*). The contrast changes resulting from the drifting grating are shown below the histograms. The cell was recorded intracellularly in vivo, and current injected through the recording electrode was used to bias membrane potential to more depolarized (−65 mV), producing tonic firing (*A*), or more hyperpolarized (−75 mV), producing burst firing (*B*).

because the nonlinear distortions created during burst firing would limit the extent to which cortex receives an accurate copy of the messages that are being passed through the thalamus. However, burst firing would be better for initial stimulus detectability. For instance, when an animal is drowsy, it might be advantageous to have geniculate relay cells in burst mode to maximize detection of a new visual stimulus; after detection, the relay can be switched to tonic firing for more faithful stimulus analysis (for details of this hypothesis, see Sherman, 1996, 2001). Indeed, there is evidence from the somatosensory system of awake, behaving rabbits that thalamic relay cells in burst mode are much more likely to evoke an action potential in their cortical target cells than when these relay cells are firing in tonic mode (Swadlow and Gusev, 2001). This finding that bursts punch through the thalamocortical synapse much more effectively than tonic firing is consistent with, but of course falls short of proving, the notion that bursts serve as a wake-up call.

Control of response mode. For this hypothesis to be plausible, there must be ways in which thalamic circuitry can be employed to control the firing mode. In fact, the functional circuitry shown schematically in Figure 35.4 provides this requirement. As noted above, to switch the inactivation state of I_T requires a change in membrane voltage that must be sustained for roughly ≥100 msec. Sustained depolarization is needed to inactivate I_T and sustained hyperpolarization for deinactivation. Activation of ionotropic receptors with their fast postsynaptic potentials seems poorly suited to this task, because without extensive temporal summation, the changes in membrane polarization would be too transient to affect the inactivation state of I_T significantly. Metabotropic receptors are much better suited for this task, since their activation would produce sufficiently sustained postsynaptic potentials. Thus, activation of metabotropic glutamate receptors from cortex or muscarinic receptors from the parabrachial region produces a sufficiently long EPSP to inactivate I_T and switch the firing mode from burst to tonic. In contrast, activation of $GABA_B$ receptors, mainly from activation of reticular inputs but also possibly from interneuronal inputs, produces a sufficiently long IPSP to deinactivate I_T and switch the firing mode from tonic to burst. Indeed, evidence for such switching from activation of these inputs exists from both in vivo and in vitro studies (reviewed in Sherman and Guillery, 1996, 2001).

Ultimately, it is the cortical and parabrachial inputs that control firing mode via their direct inputs to relay cells, which promote tonic firing, and their indirect inputs, via reticular (and possibly interneuron) inputs, which promote burst firing. At the cellular level, both inputs seem to have the same effect. However, the corticogeniculate pathway is highly topographic and purely visual, so that this pathway would presumably control firing mode for groups of geniculate cells based on specific visual parameters such as different locations within the visual field. The diffuse nature of the parabrachial input suggests that its effects are more widespread in the lateral geniculate nucleus and might relate more globally to overall levels of attention (e.g., more bursting exists during states of drowsiness; see Ramcharan et al., 2000; Swadlow and Gusev, 2001) or to which sensory system is being used.

This is not to say that the only purpose of cortical and brainstem inputs is to control firing mode. For example, the corticogeniculate input seems quite heterogeneous, and several other functions have been proposed for it (e.g., McClurkin and Marrocco, 1984; McClurkin et al., 1994; Schmielau and Singer, 1977; Sillito et al., 1993, 1994). The point here is that these multiple functions are not mutually exclusive.

The functional organization of the pulvinar region

The Pulvinar Region as a Visual Relay Although much less is known about the pulvinar region than about the lateral geniculate nucleus, it provides an important pathway to many, possibly all, higher visual cortical areas. The cells in this complex have visual receptive fields (Bender, 1982; Chalupa, 1991; Hutchins and Updyke, 1989), and their links with extrastriate visual cortical areas have long been recognized (Jones, 1985), but the functional nature of this link has become clear only more recently. In order to appreciate the nature of this link, it is important to recall that the lateral geniculate nucleus receives modulatory afferents from layer 6 of cortex and driving afferents, providing the visual inputs, from the retina. These two types of afferent were described above, and it was shown that they are clearly distinguishable in terms of their light and electron microscopic appearance, in terms of the patterns of synaptic connections that they establish, and in terms of their driving or modulatory functions: silencing the retinal inputs abolishes the receptive field properties of lateral geniculate cells, whereas silencing the cortical inputs changes the receptive field properties of geniculate cells only slightly (Baker and Malpeli, 1977; Geisert et al., 1981; Kalil and Chase, 1970; McClurkin and Marrocco, 1984; McClurkin et al., 1994; Schmielau and Singer, 1977). Further, the receptive field properties of lateral geniculate cells are very similar to those of retinal cells but are not like those of layer 6 cortical cells.

We know from injections of retrograde tracers into the lateral geniculate nucleus that this nucleus receives afferents from cortical layer 6 but not from cortical layer 5 (Gilbert and Kelly, 1975). Further, injections of anterograde tracers into cells in layer 6 of area 17 label the axons having the characteristics of the modulatory afferents described above (Fig. 35.5, *right*), whereas injections of layer 5 cells produce no labeled axons in the lateral geniculate nucleus (Bourassa

and Deschênes, 1995; Rockland, 1996). The pulvinar region is different. Experiments using retrograde and anterograde tracers have shown that it receives afferents from layers 5 and 6 of visual cortex (Abramson and Chalupa, 1985), and apart from a very small region (the geniculate wing, which we regard as part of the lateral geniculate nucleus rather than the pulvinar; see Guillery et al., 1980), it receives no retinal afferents. The afferents from layer 6 seem quite similar to the layer 6 afferents that go to the lateral geniculate nucleus. They have the same characteristic light microscopic appearance (Bourassa and Deschênes, 1995; Ojima et al., 1996), and corticothalamic terminals with the same electron microscopic appearance, and the same distribution of synaptic contacts, have been described in the pulvinar region (Feig and Harting, 1998; Mathers, 1972a; Ogren and Hendrickson, 1979; Rouiller and Welker, 2000). We regard them as modulators, almost certainly functioning very much like the layer 6 modulators to the lateral geniculate nucleus, although currently there is little experimental evidence about their functional roles. The afferents from layer 5 of visual cortex look remarkably like the retinal afferents in the lateral geniculate nucleus in terms of their light microscopic (Bourassa and Deschênes, 1995; Ojima et al., 1996) and electron microscopic appearance (Feig and Harting, 1998; Mathers, 1972a; Ogren and Hendrickson, 1979; Rouiller and Welker, 2000). Further, they establish the same pattern of synaptic contacts. We regard them as the drivers of the pulvinar cells, and it is because these drivers come from areas of cortex classifiable as visual that we see visual receptive fields in the pulvinar region. Evidence that these layer 5 afferents function as drivers is provided by the fact that silencing the cortical areas that send layer 5 afferents to the pulvinar relay abolishes (Bender, 1983) or greatly diminishes (Chalupa, 1991) the visual responses of the pulvinar cells and by the fact that the receptive field properties of pulvinar cells are not unlike those of cells in cortical layer 5 (Chalupa, 1991).

So far, we have not specified which visual areas give rise to which afferents. In the cat, the lateral geniculate nucleus receives layer 6 afferents not just from areas 17, but also from areas 18 and 19 (Gilbert and Kelly, 1975; Murphy et al., 2000; Updyke, 1977) and from other visual cortical areas farther afield (Abramson and Chalupa, 1985; Gilbert and Kelly, 1975; Updyke, 1981). The pulvinar region receives afferents from areas 17, 18, and 19 (in the cat) and from other visual cortical areas such as posteromedial lateral suprasylvian sulcus (PMLS) and posterolateral lateral suprasylvian sulcus (PLLS) (Updyke, 1977, 1981), and many of these are characteristic layer 6 afferents (Guillery et al., 2001). Other inputs to the cat's pulvinar region, however, come from cortical layer 5 and have the characteristics of layer 5 afferents, and these also come from areas 17, 18, and 19 (Fig. 35.5, *left*; see also Abramson and Chalupa, 1985; Guillery et al., 2001). We look at some of the details of these connections more closely for the cat in the section "The Pulvinar as a Monitor of Motor Outputs." For now, it is sufficient to recognize that the pulvinar region receives two types of cortical afferent and that the layer 6 afferents can be regarded as modulators, whereas all the layer 5 afferents are reasonably regarded as drivers, although currently only some have been tested from this point of view. Closely related to the distinct functional roles of these two cortical afferents to the pulvinar region is the fact that whereas the layer 6 afferents send a rich innervation to the modulatory cells of the thalamic reticular nucleus, the layer 5 afferents do not.

First-Order and Higher-Order Thalamic Relays The fact that the pulvinar region receives driving afferents from layer 5 of visual cortex shows that the pulvinar serves as a relay in the visual pathways for messages that have already been through cortical processing once. For this reason, the pulvinar region has been called a *higher-order visual relay*, in contrast to the *first-order relay* in the lateral geniculate nucleus, which transfers ascending messages directly to cortex (Guillery, 1995; Guillery and Sherman, 2002b; Sherman and Guillery, 1996, 2001). This distinction between first- and higher-order relays is found not only for the visual pathways but for other relays to cortex as well. However, only the visual relays concern us here. One important point about the higher-order visual relays is that they involve a much greater volume of thalamus, and a much greater area of cortex, than does the first-order visual relay in the thalamus. That is, the pulvinar region is far larger than the lateral geniculate nucleus, and the areas of cortex in receipt of inputs from the pulvinar region are, in total, far greater than area 17.

We have described the pulvinar region as providing higher-order relays to extrastriate cortical areas. However, the possibility that there may also be first-order pulvinar relays of ascending afferents has not been excluded. The small direct input to the pulvinar from the retina was mentioned earlier but, as noted above, we regard this as part of the lateral geniculate nucleus. It clearly represents a first-order relay. The input from the superior colliculus and pretectum to a part of the pulvinar raises another problem. Are these driving or modulatory inputs?

There were strong arguments in the past (Diamond, 1973; Schneider, 1969; Sprague, 1966, 1972; Sprague et al., 1970) for the view that there are two parallel visual pathways going to the cortex. This conclusion was based on behavioral studies primarily in the cat, hamster, and tree shrew and on anterograde tract tracing studies that demonstrated axonal pathways from the region of the tectum to the pulvinar (Altman and Carpenter, 1961). One of these parallel pathways from the retina goes through the lateral geniculate nucleus to striate cortex, and the other relays through the

tectum and then the pulvinar to the extrastriate cortex. However, recordings from cells in the pulvinar region of cats and monkeys have shown that the receptive field properties of cells there are dependent on cortical inputs, not tectal inputs (Bender, 1983; Chalupa, 1991; Chalupa et al., 1972), suggesting that the tectal inputs are not drivers innervating a pulvinar first-order relay (see also Smith and Spear, 1979, on the effects of tectal lesions on responses in higher cortical areas of cats).

The morphological evidence on the structure of the tectopulvinar connections is conflicting (Mathers, 1971; Partlow et al., 1977; Robson and Hall, 1977), with some reports showing terminals like those of the layer 6 modulators and others showing terminals like those of the layer 5 drivers and the retinal terminals. This issue needs to be resolved. Since there are several distinct subdivisions of the pulvinar, which are not easily compared across species, it is possible that there are some tectal drivers innnervating some first-order relays in some regions of the pulvinar, with other tectal inputs acting as modulators. It is possible that there are significant species differences in the extent to which such tectopulvinar driver afferents may or may not play a significant role in the transfer of visual information to higher cortical areas (Rodman et al., 1989, 1990). Further, since cells in layer 5 of visual cortex send terminals to the pulvinar region and to the superior colliculus (Guillery et al., 2001), it is possible that lesions or injections in the colliculus will produce changes in the pulvinar region that do not represent a tectopulvinar pathway. The possibility that parts of the pulvinar may be in receipt of drivers from the tectum and also from layer 5 of cortex raises a question addressed in the section "Parallel Pathways through the Pulvinar Region," that arises wherever one finds two driving inputs innervating the same part of the thalamus. Do they interact on single relay cells or do they, like X cells and Y cells in the A layers of the lateral geniculate nucleus, form two essentially independent parallel pathways?

THE PULVINAR REGION AS A KEY RELAY IN CORTICOCORTICAL COMMUNICATION The distinction between first- and higher-order relays outlined above shows the pathways over which the pulvinar region receives its visual inputs from the visual cortex and provides grounds for thinking of these as the drivers of pulvinar cells. Recognizing the pulvinar as a higher-order relay provides a clear functional role for the cells of the pulvinar, at least in the sense that the functional roles of visual, auditory, and somatosensory thalamic relays were assigned in the nineteenth century when the ascending afferent pathways to these relays were defined. That is, the pulvinar serves as a relay from one visual cortical area to other cortical areas. Further, the functional parallel between retinal inputs to the lateral geniculate nucleus and cortical layer 5 inputs to the pulvinar provides a useful key for comparing these two visual relays, which we explore in subsequent sections. Before looking at these comparisons more closely, however, it is important to stress that the pulvinar as a higher-order relay takes on a vitally important role as a key participant in corticocortical communication.

The pathway that goes from layer 5 in one cortical area, through a pulvinar relay, to another cortical area provides a potentially important, but largely unstudied and often unrecognized, transthalamic route for corticocortical communication. This transthalamic pathway is likely to differ in its functional properties from the more widely studied direct corticocortical route (Van Essen et al., 1992; and see Fig. 35.11). Specifically, the thalamic relay has, as we have seen, properties that can modify transmission in accord with attentional needs, and so far as we know, these properties are not characteristic of the direct corticocortical pathways. Further, the thalamic relay is, as we show below, transmitting information that goes from cortex by a branched axon to thalamus and to lower, motor or premotor centers (Guillery et al., 2001; Guillery and Sherman, 2002a), so that the transthala-

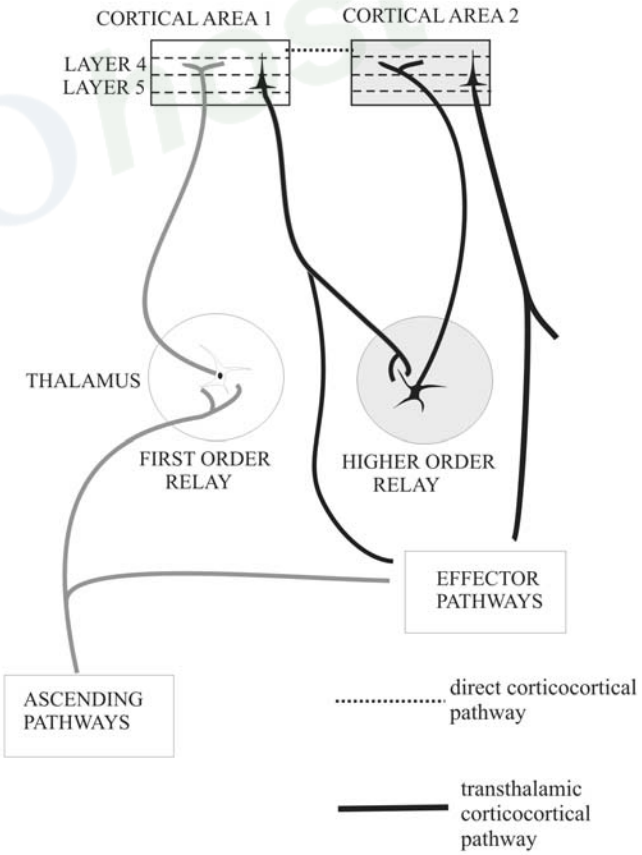

FIGURE 35.11. Schema showing first-order and higher-order thalamic relays and the relationship of each to effector pathways passing through the brainstem. Note the distinction between direct corticocortical pathways and transthalamic corticocortical pathways.

mic pathway can be seen as sending a copy of a motor instruction from one cortical area to another.

There are a number of reasons why the thalamic input to higher cortical areas has received much less attention than has the direct corticocortical input. One is that for many years it was simply not recognized as a possibility, because the layer 5 and layer 6 afferents could not be distinguished from each other, and there was no reason to consider the layer 5 input to thalamus as a driver. A second reason concerns the number of axons involved. The thalamocortical afferents represent a relatively small group of afferents to cortex, and thus attention was directed at the apparently much more massive, direct corticocortical connections. However, this consideration has to be viewed in relation to what we know about the first-order visual relay, where the afferents from retina represent only about 5% to 10% of the synapses in the lateral geniculate nucleus (Van Horn et al., 2000), and the geniculocortical afferents in area 17 also represent only about 5% to 10% of the synapses in cortical layer 4 (Ahmed et al., 1994; Latawiec et al., 2000). The modulators, in fact, far outnumber the drivers in these pathways, and, as noted above, a strategy that considered only the size of an input would not lead one to see the retinal input as a major source of drivers to the lateral geniculate nucleus. The large number of synapses arising from modulators probably reflects the delicate adjustments that the modulators are capable of, and may also indicate that there are modulatory functions that still remain to be explored; the numbers cannot be taken as a good indication of which pathway carries the information that the pathway is processing (the receptive fields in the visual pathways). Insofar as it is reasonable to expect some common organizational pattern to characterize all thalamocortical pathways, one should expect that the main information bearing driver input to higher cortical areas will come from the thalamus, as it does for all first-order cortical areas. That is, the driver visual inputs to area 17 come from the thalamus, not from other cortical areas, which instead are modulators there.

Another important and practical reason why the transthalamic corticocortical pathways have received much less attention than has the direct corticocortical pathway is that it is generally easier to explore the cortical surface than the depths of the thalamus, particularly when it comes to tracing the pathways. We stress in later sections ("Parallel Pathways through the Pulvinar Region" and "Projections from the Pulvinar Region to the Cortex") some of the difficult problems that need to be overcome before we can expect to understand the functional organization of the pathways that are relayed in the pulvinar region. However, looking for evidence about the nature of corticocortical processing by studying the direct corticocortical pathways, which are readily accessible on the surface, and ignoring the deeper transthalamic pathways, which are likely to prove more difficult, can at best be justified by arguments such as those used by the proverbial drunk, searching for lost keys under the lamppost, where it was light.

So far as we know, all cortical areas receive thalamic afferents, and for almost all higher cortical areas, the functional contribution made by the thalamic afferents remains essentially unexplored. This evidence in itself suggests that schemes tracing connections to primary cortical receiving areas, and from these through corticocortical pathways progressively to higher and higher cortical areas, for perceptual processing and eventually for motor outputs (e.g., Kandel et al., 2000; Van Essen et al., 1992) represent a false view about the connections that underlie the cortical relationships of sensory inputs, perception, and movement control.

Not only do all cortical areas probably receive thalamic inputs, but most, possibly all, have descending outputs from layer 5. The axonal pathways of these layer 5 outputs have been studied for several cortical areas recently by tracing individual axons, and it has been found that where corticofugal axons provide a characteristic driver innervation for a higher-order thalamic relay, they very commonly also send a branch through the thalamus more caudally to the midbrain or pons (reviewed in Guillery and Sherman, 2002a). Although the final destination of these more caudal branches is not always defined, we have to think of the corticothalamic drivers as representing branches of an axon that also has descending, motor connections. This issue is explored in the next section. Here it is important to look at these multiple output pathways from many cortical areas as an important reason for seeing cortical processing as being continually in touch with lower motor centers (Fig. 35.12). Messages may be processed through several stages in many functionally distinct cortical areas on their way to motor cortical areas, but at almost any stage there is direct output to motor or premotor centers. Area 17 sends axons to the superior colliculus, which is concerned with the control of head and eye movements, and there are comparable outputs from many other visual cortical areas that have connections with the pulvinar.

In summary, there is an important difference between conventional views of corticocortical processing for vision and the one that recognizes the importance of transthalamic corticocortical pathways. In the conventional views, information enters striate cortex from the lateral geniculate nucleus and is then processed entirely within cortex. The processing strictly involves direct corticocortical connections among many discrete areas (more than 30 in the monkey and probably fewer in the cat) organized into several (5–6 in the monkey) hierarchical levels, with feedback as well as feedforward connections and, occasionally, with the recognition that there may be some modulatory influences from the thalamus (Olshausen et al., 1993; Van Essen et al., 1992).

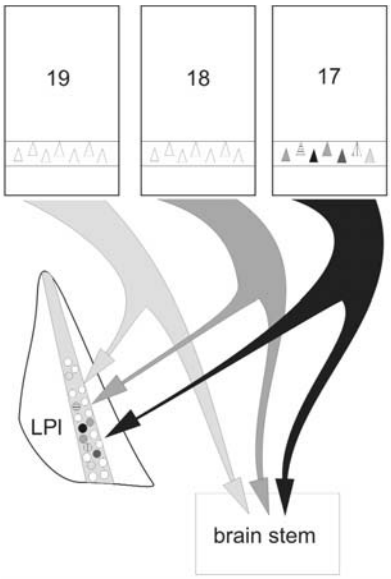

FIGURE 35.12. Three cortical areas, 17, 18, and 19, are shown, with layer 5 projections going to a single (gray) isocortical column in the lateral part of the lateral posterior thalamic nucleus (*LPl*). Layer 5 cells in area 17 are shaded differently to indicate (potentially) distinct functional types. The axon terminals from these cells in LP1 (*small circles*) are shaded correspondingly and go to different levels of the isocortical column. Each corticothalamic axon is a branch of an axon that continues to the brainstem, where it can act, directly or indirectly, on motor pathways. Details are presented in text. (Based on Guillery et al., 2001.)

Analyses of perceptual and motor control mechanisms commonly go from the thalamus through a hierarchy of cortical areas for perceptual processing before they are passed to motor areas of cortex (Andreas et al., 2001; Galletti et al., 2001). The axons that go from cortical layer 5, sending one branch to the thalamus and one branch to lower centers, demonstrate several striking points that play no role in the current conventional approaches. One is that essentially all cortical areas have descending outputs that are likely to act, directly or indirectly, on motor systems. Another is that there are good potential lines of communication for driver inputs on the transthalamic route. The extent to which the direct corticocortical pathways may then be modulators rather than drivers is open to serious question. Another key point is that recognizing the importance of the transthalamic route provides a significant functional role for the pulvinar, which represents a far larger part of the thalamus than does the lateral geniculate nucleus. A further point is that the information that is passed from one visual cortical area to another through a higher-order thalamic relay is a copy of descending messages that have the opportunity to act on motor pathways without the complex traverse of a hierarchical scheme of corticocortical connections. One final point can be made concerning the hypothesis that the transthalamic route involving higher-order thalamic relays is an important and perhaps the sole route for corticocortical communication: this would mean that all information reaching a cortical area, whether from the periphery via a first-order thalamic relay or from another cortical area via a higher-order relay, benefits from thalamic processing.

THE PULVINAR AS A MONITOR OF MOTOR OUTPUTS We have seen that the messages received by higher-order thalamic relay cells from layer 5 of cortex are also being sent to other centers where, directly or indirectly, they will have motor actions. That is, the relay cells of the pulvinar region can be regarded as sending to cortex copies of motor instructions that are being sent out by visual cortex, not only by area 17, but also by many other visual areas that send layer 5 axons to the thalamus and to more caudal centers. This pattern of connectivity may seem surprising, because it seems to turn the thalamic relay into a part of motor systems instead of just a sensory relay on the way to the cortex, which is how it has long been seen. The relationship is not special to the pulvinar region. It can be seen in most thalamic relays, first-order and higher-order. That is, a detailed survey shows that most thalamic relays receive either afferents that are branches of axons that innervate motor centers or afferents that come from cells innervated by axons that have such branches (for a fuller account, see Guillery and Sherman, 2002a). For the visual system, these connectivity patterns raise an important issue about the way in which activity in thalamocortical pathways is interpreted. Where one records activity that seems to have a close relationship to perceptual processing, one is likely, at the same time, also to be looking at activity that relates equally closely to motor control patterns.

CONNECTIONAL AND CELLULAR PROPERTIES IN THE PULVINAR REGION There is a basic similarity in the cell types seen in the pulvinar region and the lateral geniculate nucleus. Relay cells and interneurons are distinguishable on the basis of the same criteria, and the general appearance of the synaptic zones is closely comparable (Feig and Harting, 1998; Mathers, 1972b; Ogren and Hendrickson, 1979; Rockland, 1996, 1998). The afferents, too, are readily comparable to the afferents that innervate the lateral geniculate nucleus, provided that one recognizes that the drivers come from different sources: from retina for the lateral geniculate nucleus and layer 5 (and/or tectum) for the pulvinar region. That is, both cell groups, in addition to their driving afferents, receive afferents from cortical layer 6, from the thalamic reticular nucleus, and from the brainstem.

The quantitative data noted above for the percentage of synapses onto relay cells in the cat's lateral geniculate nucleus now can be extended to the pulvinar. Wang et al. (2002) report that only about 2% of inputs to relay cells

there derive from terminals with driver (i.e., RL) morphology. Overall, estimates suggest that driver input in pulvinar and the lateral geniculate nucleus range between roughly 2% and 7%.

We have very little information about the membrane properties of cells in the pulvinar (but see Jahnsen and Llinás, 1984), but on the basis of the structural similarities and on the basis of the ubiquitous distribution throughout thalamus of the critical conductances described in the section "Properties of I_T in Relay Cells," it is reasonable to conclude that generally the same ground rules for transmission to cortex apply. This is an area where detailed studies may reveal functional differences that are currently undefined. We shall assume that the pulvinar region functions much like the lateral geniculate relay in terms of how modulators act, how the burst and tonic modes are controlled, and how information is transmitted from the drivers to cortex.

Layers and Maps The pulvinar region can be divided into a number of distinct zones. Some of these zones are defined on the basis of differential staining properties, some are defined on the basis of their connections, and others are defined by mapping the visual field and identifying a new area wherever a new visual field map can be demonstrated (Adams et al., 2000; Graybiel and Berson, 1980a; Gutierrez et al., 2000; Shipp, 2001; Updyke, 1981). This last is basically the same argument that was originally and successfully used for defining cortical areas. Each functionally distinct cortical area was defined as a single map, which may have a particular distortion of the visual field and may even not include the whole visual field, but any one map contains no duplications (Lane et al., 1971; Tusa et al., 1979; Zeki, 1969). At present the differential stains, the connections, and the maps do not produce precisely matching subdivisions, and especially for the monkey, there are some problems still to be resolved before one can clearly identify the separate zones of the pulvinar region.

In the cat, Updyke's studies of receptive fields and of corticothalamic axonal projections have produced a relatively clear picture (Updyke, 1981) that allows one to distinguish a number of major subdivisions, each with its own map and each receiving distinctive patterns of afferents from several visual cortical areas or from the superior colliculus. In each subdivision, it is possible to define lines that correspond roughly to the lines of projection in the lateral geniculate nucleus. That is, the lines correspond roughly to a single point in visual space, although the accuracy of the relation is less than it is in the lateral geniculate nucleus. These lines also correspond, roughly, to single points in the cortical area from which these subdivisions receive their cortical afferents, and thalamic cells grouped around such a line have been called *isocortical columns* (Guillery et al., 2001).

Given that there are maps and lines of projection, the next question is, are there layers? If one is looking for architectonically distinguishable layers such as the A layers of the cat or the parvocellular layers of the monkey, then the answer is "no," there are no such layers identifiable in the pulvinar region of any species. If, however, one asks whether there are identifiable functional and morphological differences as one moves from one end of an isocortical column to the other, then there is evidence that it may be possible to separate functionally distinct "layers." In this the pulvinar region may be more like the lateral geniculate nucleus of the rabbit (Holcombe and Guillery, 1984) or the "C" regions of the cat (Hickey and Guillery, 1974), where distinct cell groupings are separated from each other along the lines of projection, but with no overt separation of layers.

The best example of this is the lateral part of the lateral posterior nucleus in the cat, where the isocortical columns run from rostrodorsal to caudoventral. Several connectional differences can be recorded along this axis. The layer 5 afferents change their appearance, becoming more compact caudoventrally (Guillery et al., 2001), the cortical afferents come from different sources (cortical areas 5 and 7 most rostrally, areas PMLS and PLLS most caudally) (Heath and Jones, 1971; Kawamura et al., 1974; Robertson and Cunningham, 1981; Updyke, 1981) and whereas areas 17, 18, and 19 all send layer 5 corticothalamic afferents to the middle and ventral parts of the columns, area 19 also sends cortical afferents to the more rostral parts, but these are primarily or entirely from layer 6 (Guillery et al., 2001; Updyke, 1977). The functional implications of these connectional differences have not yet been explored for this part of the pulvinar region, but one should expect to find that, as in the lateral geniculate nucleus, the functional properties of the relay cells change as one moves from one end of an isocortical column to the other.

For other subdivisions of the pulvinar region in cat and in monkey, visual field maps or maps of isocortical columns have also been described (Adams et al., 2000; Graybiel and Berson, 1980b; Gutierrez et al., 2000; Shipp, 2001; Updyke, 1981), but there are no observations about the extent to which connectivity patterns change along the direction of any one column or line of projection. Receptive field properties have been described, and they generally resemble the receptive fields of layer 5 cortical cells. However, the extent to which they may vary from one subdivision of the pulvinar region to another or from one part of a column to another has not been explored.

Cortical Afferents to the Pulvinar Region Much of the earlier evidence about the cortical inputs to the pulvinar region comes from experiments using methods such as autoradiographic labeling, horseradish peroxidase labeling,

or axonal degeneration, which label the afferents from layers 5 and 6 together and do not allow the discrimination of one from the other. These have been useful for helping to define the maps in the relay (see above), and have helped to show the several cortical areas that send axons to this region. Only fairly recently have methods become available for labeling just a few cortical cells and their axons, and allowing identification of the cortical layer giving rise to the axons or the morphological characteristics of the axons. As indicated above, cortex sends two types of axon to the pulvinar region: layer 5 cells send axons with large, flowery terminals, and layer 6 sends finer axons with small terminals that are mostly on short, stubby side branches distributed irregularly along the length of the axons. They are readily distinguished from each other (Fig. 35.5).

Cortical areas 17, 18, and 19 in the cat all send layer 5 afferents to the lateral part of the lateral posterior nucleus (Guillery et al., 2001). Small, well-localized injections into any one of these cortical areas label a small number of corticothalamic axons, each having a single small terminal zone 100–200 μm across. These terminal zones from a single small injection site are irregularly scattered around, but not accurately along, the ventral and caudal two-thirds of the isocortical columns (Fig. 35.12). The overall terminal distributions of all layer 5 axons from areas 17, 18, and 19 overlap entirely in this region, and as indicated above, the shapes of the terminal arbors are more compact caudoventrally than rostrodorsally (not shown in the figure). This part of the nucleus receives few or no layer 6 afferents from areas 17 and 18 (Abramson and Chalupa, 1985; Guillery et al., 2001), but it does receive a rich layer 6 innervation from area 19. These layer 6 axons have a far more widespread distribution in the nucleus around the areas occupied by the layer 5 terminals and also in the most rostral and dorsal part that receives no layer 5 afferents from area 19 but presumably receives layer 5 drivers from other parts of cortex. Where the cortical injections into area 19 are small, there is a striking local sparsity of layer 6 afferents in the region where layer 5 axons from the same injection site have their termination (Fig. 35.13). Of course, there is no corresponding reciprocity for the axons from areas 17 and 18, since the layer 6 terminals do not go to the same nuclear subdivision as the layer 5 terminals.

These observations on just one subdivision of the pulvinar region show that any one part of a single isocortical column can receive driver afferents from more than one functionally distinct cortical area, and that each cortical area distributes its driver terminals quite broadly along any one isocortical column. Further, the distribution of the modulators from layer 6 suggests that there is no simple rule that relates the distribution of the corticothalamic drivers to the distribution of the modulators for any one cortical region, although the relationships we have described suggest that the layer 6 input serves to modulate layer 5 inputs that do not come from the same small column of cortex or even from the same cortical area.

Parallel Pathways through the Pulvinar Region We have seen that a single small cortical injection site labels axons that have terminals widely distributed along the length of a single isocortical column. If there are functional differences along the length of a column, as the connections and the structural features of the terminals suggest there may be, then there is an interesting parallel to be drawn between the parallel pathways of the retinogeniculate connection and the corticopulvinar connection. That is, for the retinogeniculate pathway, a single small area of retina contains several functionally distinct ganglion cell types. Their axons distribute to different parts of the same line of projection in the lateral geniculate nucleus, and their differential distribution along a line of projection is a signal of their functional differences. To some extent this differential distribution of the terminals in the nucleus relates to the geniculate layers, and to some extent it relates to functional differences that are not expressed by layer separations. It is worthwhile to look at the possibility that closely comparable relationships for parallel processing obtain for the corticopulvinar projection where several functionally distinct cortical layer 5 cells can be expected in any one small cortical area or column. These cortical cells then send axons to the pulvinar region that are segregated along the isocortical columns in accordance with their functional characteristics (Fig 35.13). This is admittedly speculative, but it provides a guide to studying the distribution of functions that is currently not available for studies of the pulvinar region.

The previous paragraph introduced the idea of parallel processing in the corticopulvinar pathways that is comparable to the parallel processing of the retinogeniculate pathways. However, we have seen that there is another, more obvious type of parallel processing that may also have to be recognized in the pulvinar. This is represented by the fact that any one isocortical column receives driving afferents from several distinct cortical areas. Each of these pathways can be seen as a separate input to the pulvinar region, so that corticopulvinar axons from separate cortical areas may also provide parallel pathways through the pulvinar. The issue of whether these represent parallel pathways like the X and Y pathways going through the A layers of the lateral geniculate nucleus with essentially no interaction, or whether there are integrative interactions between the pathways, remains to be resolved.

Although these observations of the distributions of layer 5 and layer 6 axons from cortical areas 17, 18, and 19 to one small part of the pulvinar region can show how it may be possible to analyze cortical afferents in relation to the isocortical columns, it has to be stressed that even for this one

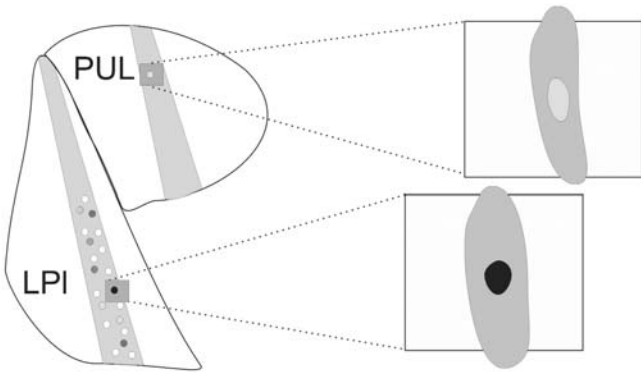

FIGURE 35.13. The lateral part of the lateral posterior nucleus (*LPI*) and the pulvinar (*PUL*) of a cat are shown on the left. The afferents from layer 5 of cortical areas 17, 18, and 19 to LP1 are shown as for Figure 35.12. In addition, the terminals of two layer 5 afferents from area 19 are shown shaded in the small squares in LP1 and in PUL. The area of these small squares is shown enlarged on the right, where the layer 5 terminals are shown in black for LP1 and pale gray for PUL, and the layer 6 terminals from the same cortical column are shown in intermediate gray. There are virtually no layer 6 terminals in the colored zone occupied by the (colored) layer 5 terminals. The layer 6 terminals extend beyond the layer 5 terminals, especially along the direction of the isocortical columns. Note that we do not know whether the terminals in LP1 and PUL can arise from the same layer 5 cortical cell or always come from different layer 5 cells. They are shown in different shades here, suggesting that they come from different cells. (Based on Guillery et al., 2001.)

part of the complex (the lateral part of the lateral posterior nucleus) our information is incomplete, and for other parts of the complex the information is either entirely unknown or only very sketchy.

Projections from the Pulvinar Region to the Cortex

A vital piece of information needed to understand the function of the pulvinar region is the pattern of projections from the relay cells to the various cortical areas that receive afferents from the pulvinar. This is not merely a question of enumerating the cortical areas that receive afferents from the pulvinar region, although this information is, of course, essential. Studies of retrograde cell degeneration in the thalamus, of retrograde cell labeling, or of anterogradely labeled axonal pathways (Rockland et al., 1999; Walker, 1938; Wong-Riley, 1977) all indicate that there are widespread axonal projections from the pulvinar region to the cortex. To some extent these studies indicate pathways from particular subdivisions of the pulvinar region, but, in general, the information that would allow one to relate each pulvinar subdivision to particular groups of cortical areas is not available.

A more serious consideration arises when one looks at the comparison we have drawn between the pulvinar region and the lateral geniculate nucleus and focuses on differences that can be seen along the lines of projection in the lateral geniculate nucleus or along the isocortical columns in the pulvinar region. We have focused on the cat's A layers of the lateral geniculate nucleus, which send their axons predominantly to area 17. However, there are also projections to area 18 from the A layers, and these come from the largest cells, which represent the Y cells (Ferster, 1990a, 1990b; Garey and Powell, 1967; Geisert, 1980; Humphrey et al., 1985; Mitzdorf and Singer, 1978; Stone and Dreher, 1973). The C layers in the cat project predominantly to area 19 and to the lateral suprasylvian cortex (Holländer and Vanegas, 1977; Laemle, 1975; Maciewicz, 1975; Raczkowski and Rosenquist, 1980). In the monkey there is also a projection to extrastriate cortical areas, and some of these axons probably arise from the koniocellular elements (Fries, 1981; Yoshida and Benevento, 1981; Yukie and Iwai, 1981). That is, there are two features that make the pattern of cortical projections difficult to analyze. One is that in any one small region along a line of projection there are neighboring cells that are functionally distinct and that also have distinguishable cortical projections. The second is that cells that lie in different sectors of a line of projection are likely to have different cortical projections. Once we have a system of parallel processing passing through a thalamic nucleus, the problem of tracing the separate but intermingled pathways through the thalamic relay becomes particularly difficult, and this applies to both the pulvinar region and the lateral geniculate nucleus. We know almost nothing about the functional significance of thalamic afferents to extrastriate cortex, regardless of whether these are first-order afferents coming through the lateral geniculate nucleus or higher-order afferents coming through the pulvinar. This will, before long, prove to be an important issue for understanding the nature of cortical processing in extrastriate visual cortical areas.

Conclusions

Clearly, the thalamus can no longer be viewed as a passive, machine-like relay of information to cortex. We have outlined a number of important functional properties of a dynamic nature that occur during thalamic relays and that relate to behavioral states such as attention and alertness. This is probably the tip of the iceberg, with many additional functions likely to emerge as our understanding of thalamic properties expands.

It is important to note in this context that the thalamus offers a last "bottleneck" for general behavioral states to have an effect on information processing. Thalamic relays represent a relatively small number of neurons and synapses compared to their target cortical areas. Thus, if the object were to increase or decrease the salience of a particular bit of information, say a visual stimulus at the expense of an auditory one, it would require orders of magnitude less synaptic

processing to modulate at the thalamic level than at the cortical level. For visual processing in mammals, there is no opportunity for the rest of the brain to affect processing in retina. The lateral geniculate nucleus is not only a convenient last bottleneck of information flow, it is the most peripheral site at which such processing can be modulated. In other sensory systems, it is possible to modulate processing more peripherally than at the thalamus, but for all pathways going to cortex, the thalamic level remains the last convenient stage at which modulation can efficiently affect information flow before it is passed to cortex.

When one looks at the visual relays in the thalamus, it is necessary to recognize that there is a quite well-studied *first-order* relay in the lateral geniculate nucleus and a series of more elusive *higher-order* relays in the pulvinar region. The lateral geniculate nucleus relays several functionally distinct, largely independent, topographically organized, parallel visual pathways from the retina to the cortex. It serves, among other possible but currently undefined functions, to modify transmission to visual cortex in accord with attentional needs, acting either in *tonic mode*, where accurate linear transfer of information from the periphery to the cortex is required, or in *burst mode*, where the need is for identification of novel signals that merit attention. Messages from the retina are carried to the lateral geniculate nucleus by the retinogeniculate *drivers*. These represent less than 10% of the afferent synapses to the lateral geniculate nucleus and have characteristic structural features, synaptic connectivity patterns, and functional relationships in terms of transmitters and receptors. The rest of the afferent synapses are formed by *modulators*, which can serve to switch transmission from burst to tonic or from tonic to burst mode. These come from several distinct sources. Some, specifically those from the neocortex and the thalamic reticular nucleus, relate closely to the topographic representation of the retina in the lateral geniculate nucleus and can thus have a local action, whereas others, particularly those from the brainstem, show no topography and appear to have a global action.

The higher-order relays in the pulvinar region serve to transmit information from one cortical area to others. The *drivers* come from pyramidal cells in layer 5 of cortex and represent branches of axons that are going to lower (motor) centers. That is, the pulvinar serves to send copies of motor outputs from one cortical area to another. We stress the likely importance of these transthalamic pathways in corticocortical communication, a role that has not been recognized in the past. Corticopulvinar driver afferents can be analyzed on the basis of comparisons with the lateral geniculate relay. They show a topographical organization between cortex and thalamus. There are multiple parallel corticopulvinar pathways coming from several cortical areas that are relayed through any one small local region of the pulvinar. In addition, it is probable that the afferent drivers coming from any one of these cortical areas also represent several functionally distinct pathways. An important key to understanding the functional significance of this higher-order thalamic relay will depend on understanding how the several distinct corticopulvinar driver afferents relate to the pathways that go from the pulvinar region to multiple different cortical areas. We know almost nothing about this either in terms of the specific patterns of connectivity that are established or in terms of possible interactions within the thalamic relay. The parallel afferents may prove to show little or no interaction, comparable to the situation in the first-order geniculate relay, or there may be interaction among the several corticopulvinar afferent drivers, and this could strongly influence views of pulvinar functions.

The organization of the modulatory afferents to the pulvinar also merits closer study than it has received to date. We propose that in general terms, the functions of these afferents are comparable to the functions of the modulators in the lateral geniculate nucleus. That is, they serve to switch the relay between the burst and tonic modes. They can do this on a global basis from the brainstem and other sources, or in terms of local parts of the mapped projections from layer 6 of many distinct cortical areas cortex, or from the thalamic reticular nucleus.

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