19 The Lateral Geniculate Nutleus and Pulvinar

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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 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 are referred to jointly as the pulvinar. We look at features that are shared by the lateral geniculate nucleus and the pulvinar 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 (Sherman & Guillery, 2006, 2011), receiving ascending visual messages from the retina and sending them to primary receiving cortex, and the pulvinar as a "higher order" relay, relaying 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, and the latter represent further relay of such information via a corticothalamocortical loop.

When the distinctive receptive field properties of cells in the retina and the visual cortex were being defined (reviewed in Hubel & 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 & Wiesel, 1977; Zeki, 1993). Indeed, this raises several 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 complete answers. 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 inteFest happening in the geniculate relay and also throughout the thalamus. 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 largely depend on the behavioral state of the animal and are suppressed in anesthetized animals (e.g., attentional mechanisms) (McAlonan, Cavanaugh, & W rtz, 2008; Schneider & Kastner, 2009; see also chapter 32 by Swadlow and Alonso).

FUNCTIONAL ORGANIZATION OF THE LATERAL GENICULATE NUCLEUS

For those who still have in mind 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 whose receptive surfaces 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 figure 19.1, which shows the relationships in a cat and where the visual field and its retinal and geniculate representations are shown as tapered arrows). Each layer maps the contralateral hemifield 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 mammals (see below and figure 19.1). 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 mammals and is surprising when one thinks about the necessary developmental mechanisms needed to produce such a match because the match is formed before the eyes open and before the two visual images can be matched. There are nonretinal afferent axons that innervate the lateral geniculate nucleus and that 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 geniculate layers (see Afferents below).

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, how easy they are to identify, and how the sequence of the layers is arranged. 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. This is described in chapter 16 by Kaplan and chapter 86 by Kaas. Figure 19.2 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 also serves to introduce the several parallel pathways that are relayed through the lateral geniculate nucleus to the cortex.

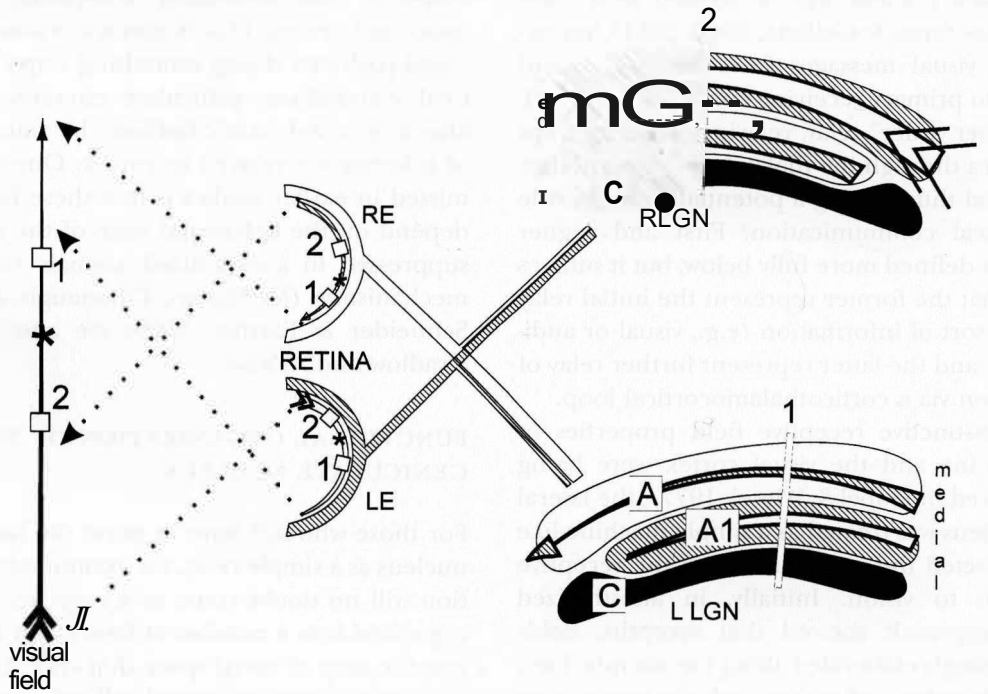

FIGURE 19.1 **Schematic view of the representation of the retina and visual field in the laminae of the lateral geniculate nucleus of a cat. The visual field is represented by a straight arrow, and the projection of a part of this arrow onto each retina is shown. Small white areas of the visual field 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 identify the major geniculate layers; L LGN and R LGN, left and right lateral geniculate nuclei; LE and RE, left eye and right eye; *, central point of fixation.**

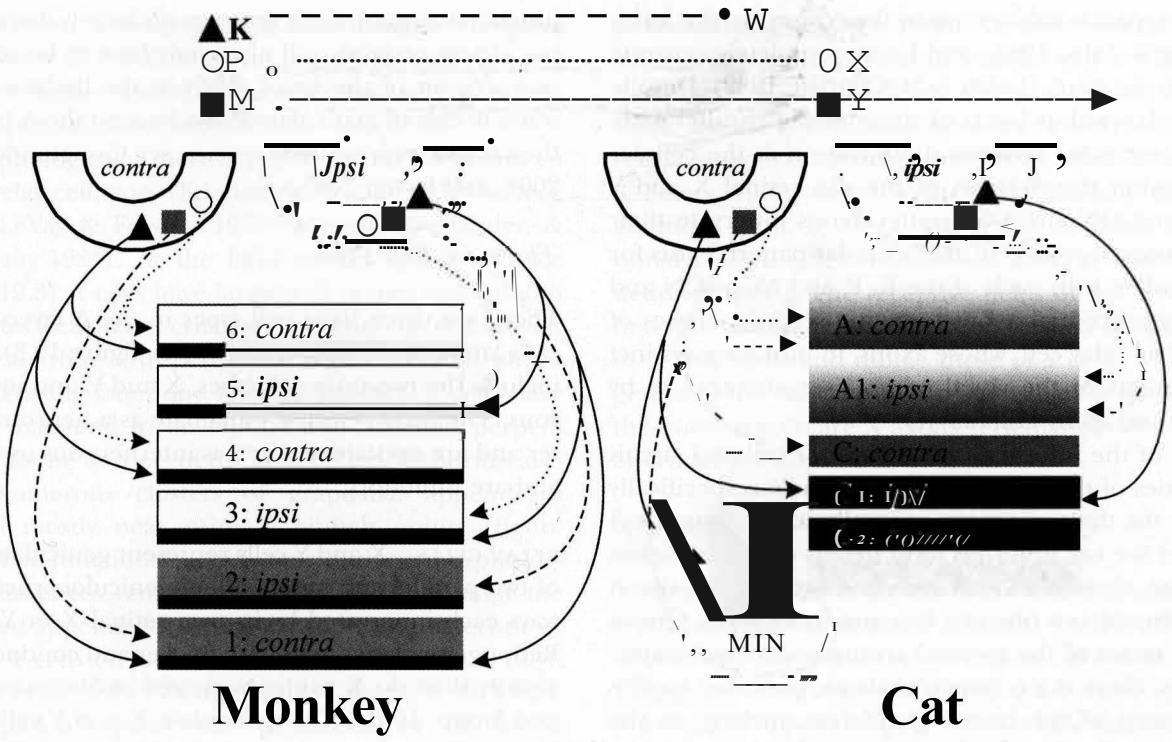

FIGURE 1g.2 Comparison of layering in lateral geniculate nucleus of cat and monkey. See text for details; MIN is the medial interlaminar nucleus.

Both species have three main retinal ganglion cell classes that project to the lateral geniculate nucleus. For the monkey (Casagrande & Xu, 2004), these are the P (for parvocellular, meaning small celled), M (for magnocellular; large celled), and K (for koniocellular; tiny or dust-like cells), and these are comparable respectively to the X, Y, and W cells in the cat (Sherman, 1985; Stone, 1983). The terminology for the monkey relates to the geniculate layers to which they project. P and M cells project to parvocellular and magnocellular layers, respectively. In the monkey the K cells project to the ventral regions of all the 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, parvocellular, and magnocellular, and it was in this species that the koniocellular pathway was first clearly recognized (Casagrande & Xu, 2004; Conley, Birecree, & Casagrande, 1985; Itoh, Conley, & Diamond, 1982). 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 (Sherman, 1985; Stone, 1983); there is no retinal input to layer C3, which is therefore shown in black in figure 19.2 (Hickey & 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. The cat and other carnivores also have a part of the lateral geniculate nucleus known as the medial interlaminar nucleus (see figure 19.2), which also has separate zones innervated by ipsilateral and contralateral inputs from W and Y axons (Sherman, 1985). What is common to cat and 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 monkey the P and M pathways use separate layers, but the K pathway overlaps with each; in the cat the W pathway uses separate layers, and the Y pathway has exclusive use of layer C, but the X and Y pathways are mingled in the A layers.

The separation of the two ocular inputs to one or another set oflayers is constant across species, although in most rodents there is a functional and topographic separation of the inputs from the two eyes but no histologically distinctive identification of the lamination. The separation of different functional types into distinct layers, however, is highly inconsistent, so that the number of layers and their sequence from superficial to deep show great variability across species. For instance, even in closely related carnivores, the cat, ferret, and mink, cells with ON center receptive fields comingle with those with OFF center fields in the A layers of the cat (Sherman, 1985; Stone, 1983) but

occupy separate sublaminae of the A layers in the ferret (Stryker & Zahs, 1983) and lie in completely separate layers in the **mink** (LeVay & McConnell, 1982). Despite the overlap within layers of some of the parallel pathways, there is no functional interaction at the cellular level; within the A layers of the cat, retinal X and Y axons and ON and OFF center axons innervate their own classes of relay cell, and a similar pattern exists for the monkey, with each of the K, P, and M, or ON and OFF center retinal axons targeting separate classes of geniculate relay cell, whose axons, in turn have distinct distributions in the visual cortex (see chapters 16 by Kaplan and 25 by Callaway).

Most of the information we have for cell and circuit properties of the lateral geniculate nucleus specifically and for the thalamus more generally comes from the A layers in the cat, and thus most details described 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 all parts of the lateral geniculate nucleus, to the pulvinar, 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 largely unexplored but almost certainly will ultimately have to be added to our account of the visual relays in the thalamus. (For some details of geniculate relays beyond the A layers in the cat and seen in other species, see Casagrande & Xu, 2004, and Jones, 2007.)

Thalamic Cell Types

There are three basic cell types in the A layers of the cat's lateral geniculate nucleus (see figure 19.3). These include the two relay cell types, X and Y, and interneurons. The relay cells use glutamate as a neurotransmitter and are excitatory, whereas interneurons use GABA and are inhibitory.

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. Retinogeniculate Y axons are thicker and conduct more rapidly than do X axons (reviewed in Sherman, 1985, and Stone, 1983). The geniculate X and Y cells differ from one another with respect to their functional and morphological properties. Their receptive field differences are already present in the retinal afferents:

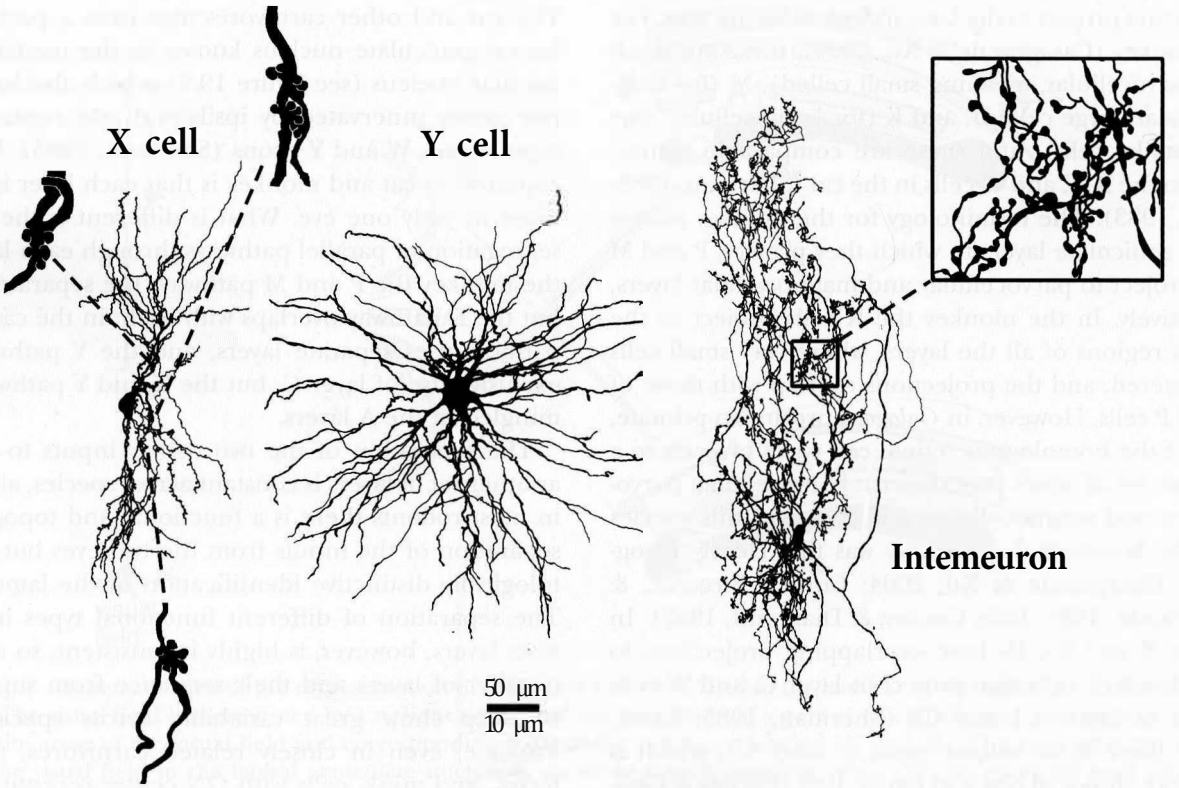

FIGURE 19.3 Reconstruction of X cell, Y cell, and interneuron from A layers of the cat's lateral geniculate nucleus. The larger scales are for the insets for the X cell and interneuron.

compared to Y cells, X cells have smaller receptive fields, more linear summation properties, and respond better to higher spatial frequencies but more poorly to higher temporal frequencies.

Morphologically, there are some differences between these relay cell types (Friedlander et al., 1981; Guillery, 1966; LeVay & Ferster, 1977; Wilson, Friedlander, & Sherman, 1984). At the light microscopic level (see figure 19.3), 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 borders of the layers. Their dendrites also have numerous clusters of grape-like appendages located mostly near primary branch points (figure 19.3). The functional significance of these morphological differences remains to be defined, although the clustered appendages, which are more characteristic of X than Y cells (Wilson, Friedlander, & Sherman, 1984; Harnos et al., 1987; Datskovskaia, Carden, & Bickford, 2001) and are particularly prominent in the lateral geniculate nucleus of the cat, represent the postsynaptic site of retinal inputs, where complex synaptic relationships known as triads (see below) are formed.

INTERNEURONS Interneurons have the smallest cell bodies in the A layers and long, sinuous dendrites whose arbors are oriented perpendicular to the layers, often spanning an entire layer (see figure 19.3). The dendrites have the appearance of terminal axonal arbors and for that reason have been described as axoniform (Guillery, 1966). Terminals of these dendritic arbors contain synaptic vesicles and are both presynaptic to local dendrites and also postsynaptic to other axons, generally those coming from either the retina or from brainstem (Eri ir et al., 1997; Famiglietti & Peters, 1972; Harnos 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 the firing of the interneurons are X axons (Friedlander et al., 1981; Sherman & Friedlander, 1988).

Afferents

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 19.4. Other afferent sources not shown in figure 19.4 include the nucleus of the optic tract (midbrain), the dorsal raphe nucleus (midbrain and pons), and the tuberomamillary nucleus of the hypothalamus (reviewed in Sherman & Guillery, 1996, 2006).

RETINAL AFFERENTS Retinal afferents to the A layers are glutamatergic (see figure 19.4). 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

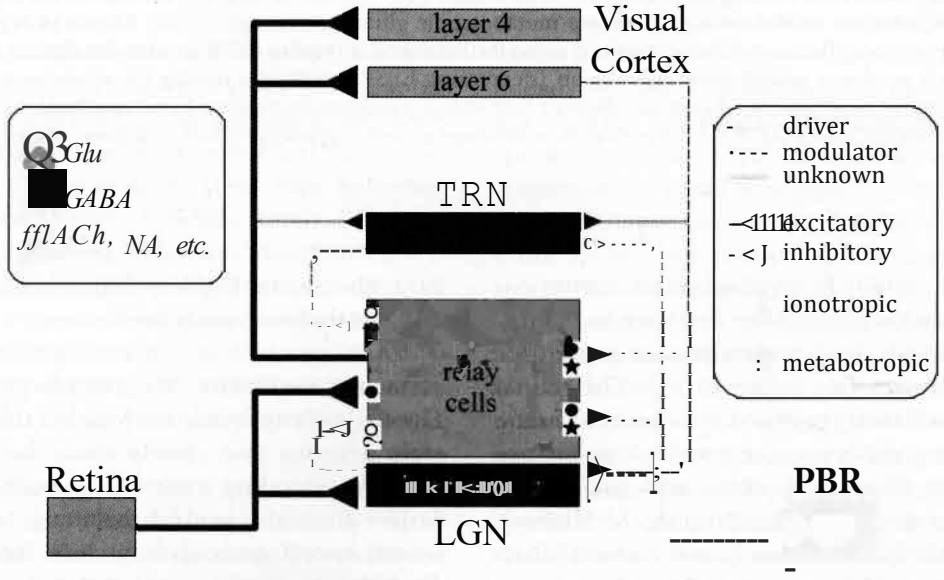

FIGURE 19.4 Neuronal circuitry related to A layers of the cat's lateral geniculate nucleus. Shown are the various inputs, the neurotransmitters associated with them, and the type of receptor, ionotropic or metabotropic, each activates. Also, driver versus modulator inputs are shown (see text for details).

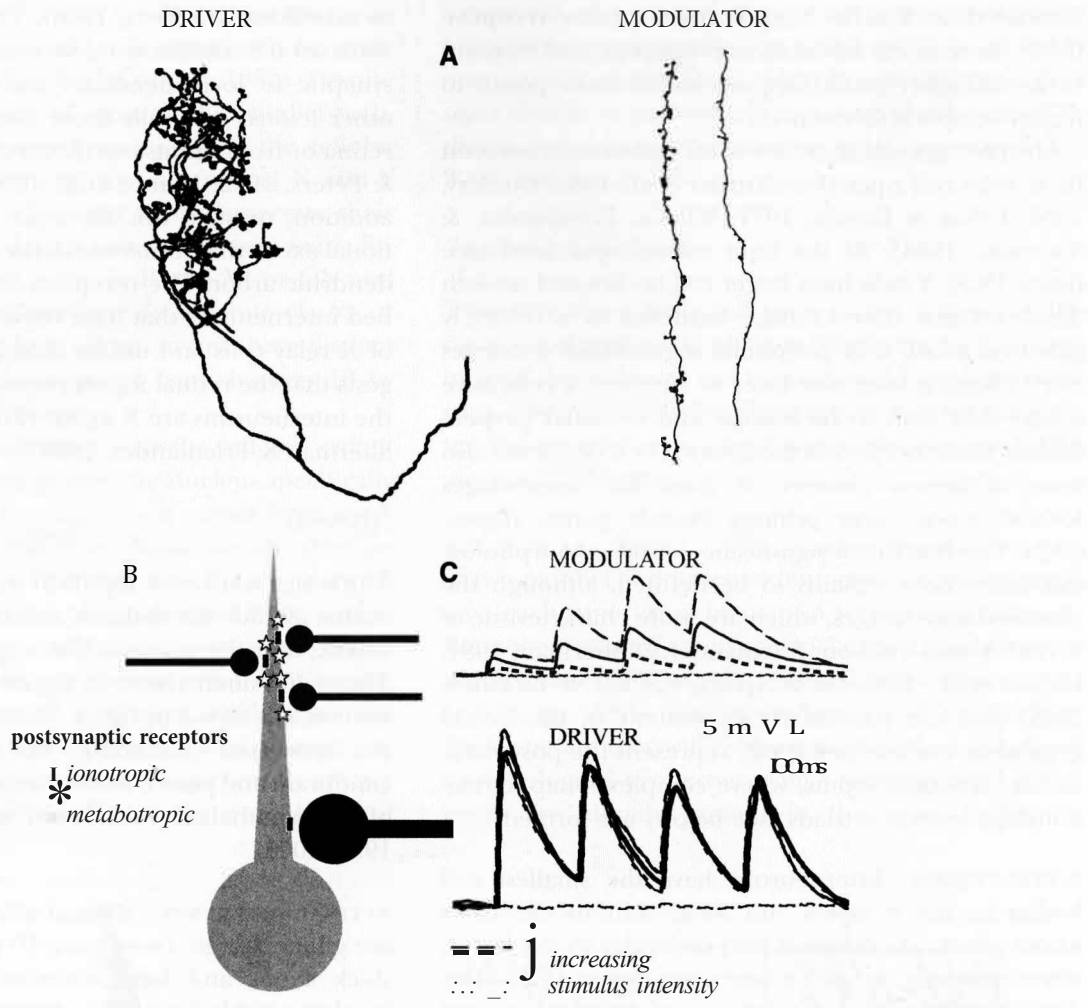

FIGURE 19.5 Distinguishing glutamatergic driver from modulator inputs to thalamus. (A) Light microscopic tracings of a driver afferent (a retinogeniculate axon from the cat) and a modulator afferent (a corticogeniculate axon from layer 6 of the cat). (B) Modulators (gray) shown contacting more peripheral dendrites than do drivers (black). Also, drivers activate only ionotropic glutamate receptors, whereas modulators also activate metabotropic glutamate receptors. (C) Effects of repetitive stimulation on EPSP amplitude: for modulators it produces paired pulse facilitation (increasing EPSP amplitudes during the stimulus train), whereas for drivers it produces paired pulse depression (decreasing EPSP amplitudes during the stimulus train). Also, increasing stimulus intensity for modulators (shown as different line styles) produces increasing EPSP amplitudes overall, whereas for drivers it does not; this indicates more convergence of modulator inputs compared to driver inputs. (Redrawn from Sherman & Guillery, 2011.)

clusters (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 figure 19.5A). The retinal axons innervate both relay cells and interneurons in 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 & 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 & Sherman, 2002a,b, 2011; Sherman & Guillery, 2006), but they do not innervate the thalamic reticular nucleus.

AFFERENTS FROM THE THALAMIC RETICULAR NUCLEUS

The thalamic reticular nucleus is a thin shell of GABAergic neurons that closely abuts the entire thalamus laterally, extending somewhat dorsally and ventrally. It derives from the ventral thalamus, together with the ventral lateral geniculate nucleus (see note 1) and is divided into sectors, each related to thalamic relay nuclei concerned with a particular modality or function (e.g., visual, auditory, somatosensory, and motor), each

mapped in a distinct sector of the nucleus (Crabtree, 1992a, 1992b, 1996; Crabtree & Killackey, 1989; Guillery, Feig, & Lozsadi, 1998; Montero, Guillery, & Woolsey, 1977). There are strong reciprocal connections between relay cells and reticular cells linking corresponding parts of the reticular and the geniculate maps (Gentet & Ulrich, 2003; Pinault, Bourassa, & Deschenes, 1995; Pinault & Deschenes, 1998; Uhlrich et al., 1991), and the cortical afferents from layer 6 (next section) are mapped along the same coordinates (Murphy & Sillito, 1996). Thus, the portion of the thalamic reticular nucleus innervating the lateral geniculate nucleus[4] is mapped in retinotopic coordinates.

In addition to this, the visual sector of the reticular nucleus is also reciprocally linked to the pulvinar of the bush baby (Conley & Diamond, 1990) and rat (Pinault, Bourassa, & Deschenes, 1995) with the pulvinar representation external to the geniculate representation. These cells of the thalamic reticular nucleus in the cat, which lie just external 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 mainly geniculate relay cells with only a very sparse innervation to interneurons (Cucchiaro, Uhlrich, & Sherman, 1991; Wang et al., 2001). Thus, the thalamic reticular nucleus provides a potent inhibitory GABAergic input to relay cells (see figure 19.4). Their receptive fields tend to be larger than those of relay cells and are often binocular (So & Shapley, 1981; Uhlrich et al., 1991).

AFFERENTS FROM LAYER 6 OF THE CORTEX Cortical afferents from layer 6 of visual cortex (see also chapter 22 by Briggs and Usrey), which are glutamatergic, have thin axons in the lateral geniculate nucleus with most boutons located at the ends of short side branches (figure 19.5A) (see Murphy & Sillito, 1996). They are topographically organized, with each axon having terminal arbors passing roughly along lines of projection and 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, and this corticoreticular 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 & Singer, 1987). Most of these axons are cholinergic, but some are noradrenergic. Light microscopically, they resemble the cortical afferents more than the retinal afferents, but their terminal arbors are more widespread, and most appear to terminate in a nontopographic 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 19.4 have been described, but they are small in number, not well documented, and are mentioned only briefly here (for further details, see Sherman & Guillery, 1996, 2006). There is a limited serotonergic input from the dorsal raphe nucleus in the midbrain and pons. GABAergic cells of the nucleus of the optic tract in the midbrain also provide a limited input. The projection from the superior colliculus to the lateral geniculate nucleus targets the C layers nearly exclusively. Finally, the tuberomamillary nucleus of the hypothalamus provides a small histaminergic input.

POSTSYNAPTIC RECEPTORS In addition to showing the inputs and their transmitters onto relay cells, figure 19.4 also 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 Conn & Pin, 1997; Mott & Lewis, 1994; Nicoll, Malenka, & Kauer, 1990; Pin & Duvoisin, 1995; Recasens & Vignes, 1995).

Ionotropic receptors (iGluRs) include AMPA and NMDA receptors for glutamate, $GABA_A$ for GABA, and nicotinic receptors for acetylcholine. These receptors 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 ion channel, leading to transmembrane flow of ions and a change in the postsynaptic potential. Ionotropic responses are rapid and brief, typically with a latency for postsynaptic potentials of <1 ms and a duration of 1 ms up to a few tens of milliseconds. Metabotropic receptors include various glutamate receptors (mGluRs), $GABA_B$, and various muscarinic receptors for acetylcholine. These are not directly linked to ion channels but instead involve a series of complex biochemical reactions after transmitter contact, and these reactions ultimately lead 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 IPSP as K^+ flows out of the cell and, when closed, produces an EPSP as leakage of K^+ is reduced. However, these postsynaptic responses are slow and prolonged, with a latency of > 10 ms and a duration of hundreds of

milliseconds to several seconds. Also, in general, metabotropic receptors require higher firing rates from inputs to be activated; this is thought to be related to the observation in electron micrographs that these receptors are located perisynaptically, slightly further from the synaptic site than are ionotropic receptors, so that more transmitter must be released to reach them (Lujan et al., 1996).

As shown in figure 19.4, retinal inputs activate only ionotropic receptors, whereas all nonretinal inputs activate metabotropic receptors, and some of these also activate ionotropic receptors (reviewed in Sherman & Guillery, 1996, 2006).

The prolonged metabotropic responses have a number of important effects. Because retinal inputs activate only ionotropic receptors, their EPSPs are relatively fast and brief. This has the virtue that the rate of 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. The prolonged metabotropic responses act as a low-pass temporal filter, and thus higher temporal frequencies are not faithfully transmitted. So the fact that retinal inputs activate only ionotropic receptors serves to produce a more faithful transfer of higher temporal frequencies. However, it is not clear whether any individual nonretinal axon can activate both ionotropic receptors and metabotropic ones. Nonetheless, the activation of metabotropic receptors means that these inputs can create sustained changes in the baseline membrane potential, which, among other things, means that these inputs can have sustained effects on 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 & Guillery, 1996, 2006): (1) RL (round vesicle, large profile) terminals, which are the retinal terminals, are the largest terminals in the A layers. They form asymmetric[5] contacts consistent with their identity as excitatory inputs and each terminal forms many contacts. (2) RS terminals (round vesicle, small profile) are smaller than RL terminals but also form asymmetric contacts, rarely more than one. The vast majority of these come from either layer 6 of cortex or from the parabrachial region. **(3) Fl** terminals (flattened vesicles) form symmetric contacts consistent with their origin from the GABAergic axons of reticular cells or interneurons. (4) F2 terminals represent the dendritic outputs of interneurons, and they also have flattened vesicles and form symmetric contacts. Unlike all of the other terminals that are strictly

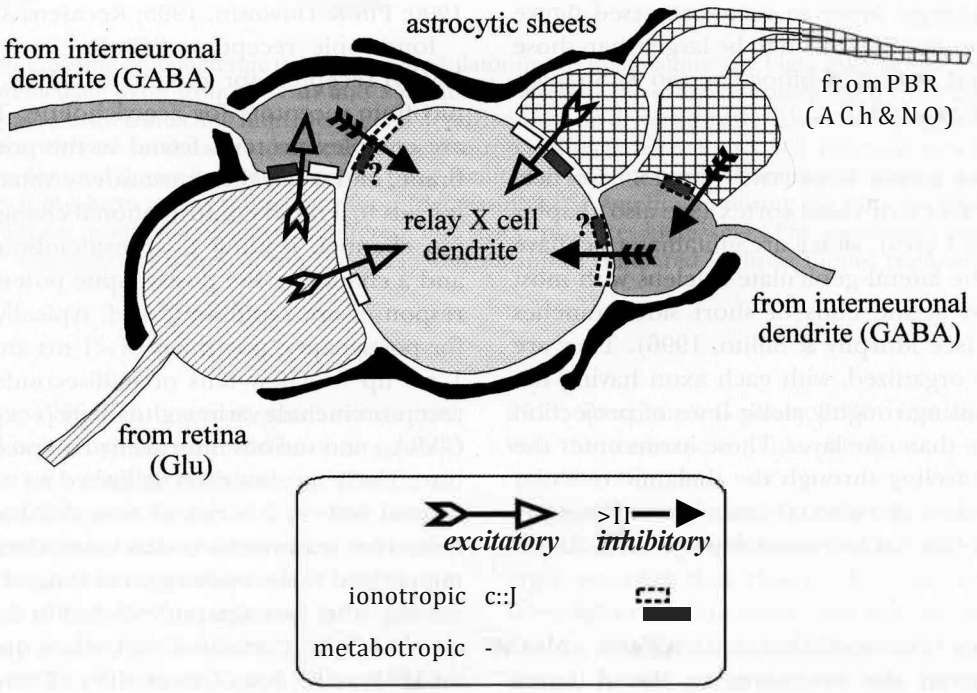

FIGURE 1g.6 Schematic view of triadic circuits in a glomerulus of the lateral geniculate nucleus in the cat. The arrows indicate presynaptic-to-postsynaptic directions. The question marks postsynaptic to the dendritic terminals of interneurons indicate that it is not clear whether or not metabotropic ($GABA_B$) receptors exist there.

presynaptic, these are both presynaptic and postsynaptic, with inputs either from retinal or parabrachial terminals.

Triadic synaptic arrangements involving F2 terminals are common in the A layers (see figure 19.6). In most 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 a preterminal branch of the same axon contacting a relay cell dendrite, again with the F2 terminal contacting the same relay cell dendrite (see figure 19.6). 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. Triads are typically found in complex synaptic zones that lack astrocytic processes but that are surrounded by sheets of astrocytic cytoplasm; these are called *glomeruli.* It is not at all clear how the triads function, but several suggestions have recently been offered (Guillery & Sherman, 2002b; Sherman, 2004). The arrangement of the synaptic inputs for the drivers that transmit the message to cortex for other modalities are essentially the same as those described here for the retinal inputs. We treat these as characteristic for all thalamus, including pulvinar, of inputs that carry messages for transfer to cortex.

DISTRIBUTION OF INPUTS TO RELAY CELLS The dendritic arbors of relay cells can be divided into two distinctsectors with little or no overlap (Wilson, Friedlander, & Sherman, 1984; Eriir et al., 1997): a proximal region (up to about 100 μm from the cell body or generally close to the firsch point) and a distal region (further than about 1 μm from the cell body). Retinal terminals contact t 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.

Only a small minority of synaptic inputs onto geniculate relay cells derive from the retina. In the A layers of the cat's lateral geniculate nucleus, for instance, 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 (Eriir, Van Horn, & Sherman, 1997; Van Horn, Eriir, & Sherman, 2000; Wilson, Friedlander, & Sherman, 1984). If one had only the anatomical data, and for many other thalamic relays that is all we have, one might well conclude that the numerically small retinal input plays only a minor role in geniculate functioning. Because we have functional data, mainly in the form of receptive field comparisons, we know that it is the retinal input that provides the main information relayed to cortex, so we accept that the small number of retinal afferents serve as the inputs carrying the message that is relayed to cortex, and we refer to these inputs as the *drivers* (see Drivers and Modulators below).

Intrinsic Properties of Thalamic Cells in the A Layers

There are three factors that largely control 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 effects of retinal EPSPs at the cell body or the region of action potential generation. Second is the geniculate circuitry that, by affecting many of the intrinsic membrane properties, also controls how retinal EPSPs lead to 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 below.

Generally, all thalamic cells show a wide range of intrinsic membrane properties that are found generally in neurons of the brain (reviewed in Sherman & Guillery, 1996, 2006). 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 resting membrane potential, various voltage- and Ca^{2+}-gated K^+ currents (I_A, $I_{K[ca2+]}$, etc.) and a voltage-gated cation current (I_h). Because these are properties found widely in the brain, they are not considered further here. (Additional details of these as they apply to thalamic neurons can be found in Sherman & Guillery, 1996, 2006.)

One feature that is of particular interest is the presence in all thalamic relay cells of a voltage-gated Ca^{2+} conductance based on T-type (for transient) Ca^{2+} channels that, when activated, leads to a current (h) large enough to produce an all-or-none Ca^{2+} spike (reviewed in Sherman & Guillery, 1996, 2006; see also chapter 32 by Swadlow and Alonso). This spike is large enough to induce a high-frequency burst of 2-10 action potentials riding its crest, and when this occurs, the cell is said to respond in *burst mode;* when h is inactivated, the cell responds with single action potentials, and this is known

as *tonic mode*. The voltage and time requirements of the two modes are as follows (see figure 19.7). I_T becomes inactivated after the cell has been depolarized above about -65 mV for roughly 100 ms,6 and the cell then responds to a suprathreshold depolarizing input (e.g., an EPSP) with action potentials that appear throughout the period of depolarization (figure 19.7A). If, however, the cell is suitably hyperpolarized for 100 ms or so, I_T is deinactivated and primed to fire a Ca^{2+} spike, so the next sufficient depolarization evokes the Ca^{2+} spike, leading to a brief burst of action potentials (figure 19.7B). Note that the same depolarizing pulse in figure 19.7A, B leads to very different patterns of response. It is also important to emphasize the point that only the conventional action potentials are transmitted to cortex: the Ca^{2+} spike propagates along the membranes of the dendritic tree and soma, but not up the axon, because the requisite T-type Ca^{2+} channels are available in the dendritic membranes but not in those of the axons. Thus, the means by which the Ca^{2+} spike affects thalamocortical transmission is through its activation of conventional action potentials.[7]

There are at least three clear consequences of these firing modes for thalamic relays. The first, as shown in figure 19.7C, is that the tonic mode is much more linear, meaning that the postsynaptic response rises monotonically with the size of the input (Zhan et al., 1999). This occurs because the greater the input depolarization or EPSP, the more action potentials are produced. However, with burst firing, the action potentials are not evoked directly from the input EPSP but rather from the Ca^{2+} spike, and because this spike is all-or-none, once the EPSP is large enough to reach threshold for this spike, larger EPSPs do not evoke a larger Ca^{2+} spike, and so the input-output relationship is more like a step function than a linear relationship (figure 19.7C). Second, because burst firing occurs after a period of hyperpolarization, the burst of action potentials occurs against a background of low spontaneous firing

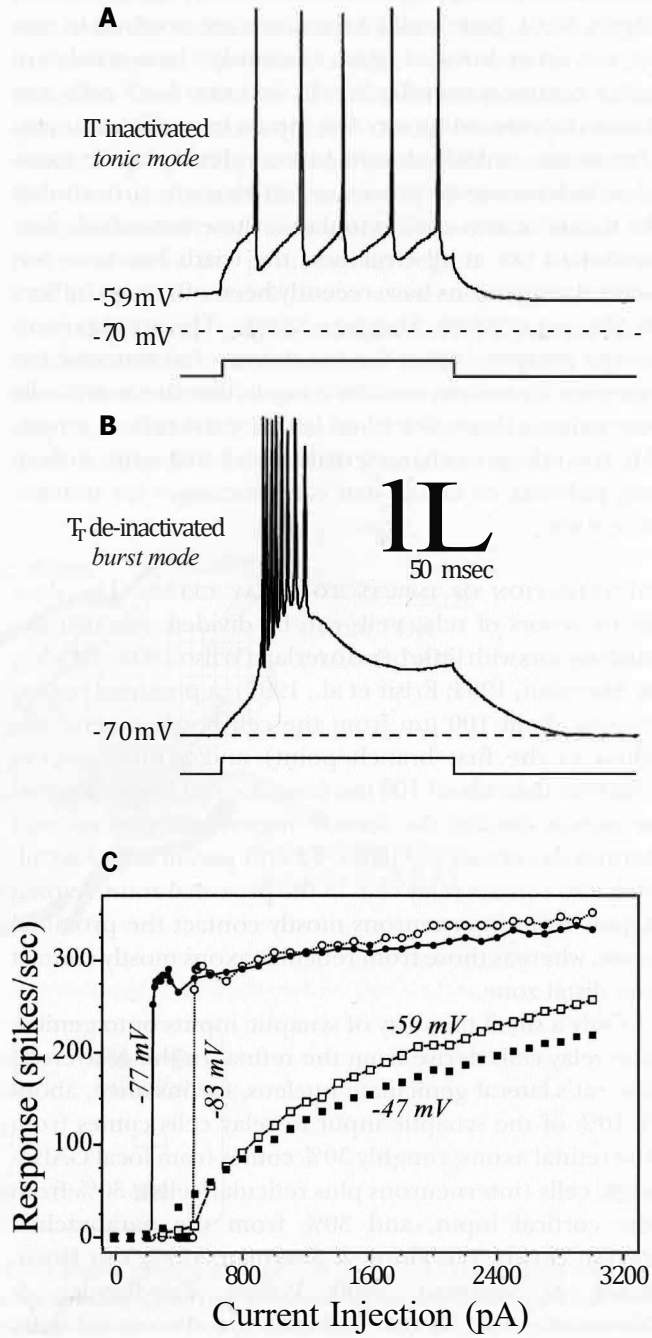

FIGURE 19.7 Properties of burst and tonic firing. (A, B) Voltage dependency of the low-threshold Ca^{2+} spike for a geniculate relay cell recorded intracellularly in vitro. Responses are shown to the same depolarizing current pulse administered intracellularly but from two different initial holding potentials. With relative depolarization (A), I_T is inactivated, and the response is a barrage of unitary action potentials lasting for the duration of the suprathreshold stimulus. This is the *tonic mode* of firing. With relative hyperpolarization (B), I_T is deinactivated, and the response is a low-threshold spike with eight action potentials riding its crest. This is the *burst mode* of firing. (C) Input-output relationship for another geniculate relay cell recorded intracellularly in vitro. The input variable is the amplitude of the depolarizing current pulse, and the output is the evoked firing frequency determined by the first six action potentials of the response, because 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, whereas -77 mV and -83 mV reflect burst mode. (Redrawn from Sherman & Guillery, 2002.)

compared to tonic mode. Spontaneous firing can be regarded as noise, and as such the signal-to-noise ratio of burst firing is considerably greater than that of tonic firing, so that the thalamic response and thus the signal that is passed to cortex, is more detectable (Sherman, 1996). Third, because a burst can occur only after I_T has been deinactivated, and this requires a 100-ms or so period of sustained hyperpolarization, it follows that the cell cannot have fired action potentials in the period before a burst.

Geniculocortical synapses show the property of paired-pulse depression (explained more fully below in Drivers and Modulators), meaning that an action potential produces a smaller EPSP if it follows another within about 100 ms or so. During tonic firing, when rates usually exceed 10 action potentials/s, the geniculocortical synapse will usually be depressed; however, a burst of action potentials would arrive at the thalamocortical synapse when it has been relieved of depression, and thus the postsynaptic response evoked would be greater. This, in turn, predicts that the first action potentials in a burst should evoke a greater response in cortex than a typical tonic action potential, and this indeed occurs (Swadlow & Gusev, 2001; Swadlow, Gusev, & Bezdudnaya, 2002; see also chapter 32 by Swadlow and Alonso).

Overall, these differences suggest that burst firing produces a larger signal that is more readily detected in cortex compared to tonic firing. However, the more linear responses of tonic firing suggest that this represents a more faithful relay mode for information transfer. Together, these differences have led to the hypothesis that burst firing can provide a "wake-up call" to cortex to strongly signal that a novel stimulus has occurred after a quiescent period; once this signal has been detected, circuitry can then be brought to bear to depolarize the relay cell to switch to tonic mode so that further presence of the novel stimulus can be faithfully relayed (Sherman, 1996).

CLASSIFICATION OF GLUTAMATERGIC INPUTS

In the section on Afferents above, we described basic features of afferent input to the lateral geniculate nucleus, but here we wish to continue this discussion with a different emphasis, namely to consider the properties of these various inputs and the classification these properties lead to. It follows from a consideration of geniculate circuitry that not all thalamic afferents are equal in their action. Inputs to geniculate relay cells include various transmitters, such as GABA, ACh, NA, and 5-HT, which are commonly considered as modulatory, but as regards a classification of inputs, that involving an identification of transmitters involved is only a first step to a useful classification.

Drivers and Modulators

We normally regard glutamatergic inputs as the main carrier of information, but it is clear that the two main glutamatergic inputs to geniculate relay cells, from retina and layer 6 of cortex, are not functionally equivalent. A consideration of the receptive field properties of geniculate relay cells helps to clarify this point: their receptive fields, and thus the information they relay to cortex, closely match those of their retinal inputs and not, for instance, those of cortical layer 6, inputs. The layer 6 feedback evokes weak responses (Granseth & Lindstrom, 2003) that serve to modulate retinogeniculate transmission without major ***qualitative*** changes in receptive field properties (Sherman, 2007; Sherman & Guillery, 2006). Removal of the layer 6 input causes only minor effects on geniculate receptive fields (e.g., Baker & Malpeli, 1977; Geisert, Langsetmo, & Spear, 1981; Kalil & Chase, 1970; McClurkin & Marrocco, 1984), effects that can be recognized as modulation (see below). We have thus distinguished two different glutamatergic types of thalamic input (Sherman & Guillery, 1998, 2006): ***drivers*** and ***modulato;s.***[8] The drivers are the information-bearing input that is to be relayed to cortex, and in the lateral geniculate nucleus this is the retinal input. All other inputs, including the cortical layer 6 input, are modulators. Details of how drivers are distinguished from modulators for glutamatergic inputs are provided in detail elsewhere (Sherman & Guillery, 1998, 2006) and summarized briefly here (see figure 19.5 and table 19.1).[9]

- Drivers activate only ionotropic receptors, mainly AMPA but some NMDA, whereas modulators in addition activate metabotropic receptors.
- Drivers produce larger initial EPSPs that show paired-pulse depression, indicating a high probability of transmitter release, whereas modulators produce smaller initial EPSPs that show paired-pulse facilitation, indicating a low probability of transmitter release (Dobrunz & Stevens, 1997).
- The available counts of afferent synapses from anatomical studies combined with a comparison of the all-or-none activation of driver inputs with the graded activation of modulators indicate that, although the driver synapses form a minority of the inputs to the target neurons, they dominate the action of the target neurons. For instance, corticogeniculate modulator inputs produce 5-10 times as many synapses as do retinal driver inputs to geniculate relay cells, and yet

TABLE 19.1

Differences between drivers and modulators for glutamatergic inputs

Driver (e.g., retinal)	Modulator (e.g., layer 6)
Large EPSPs	Small EPSPs
Synapses show paired-pulse depression	Synapses show paired-pulse facilitation
Less convergence onto target	More convergence onto target
Dense tefminal arbors (type 2)	Sparse terminal arbors (type 1)
Thick axons	Thin axons
Large terminals	Small terminals
Contacts target cell proximally	Contacts target cell peripherally
Activates only iGluRs	Activates iGluRs & mGluRs

driver inputs are functionally dominant (reviewed in Sherman & Guillery, 2006). Thus, assessing the relative strength of inputs based solely on anatomical numbers can be very misleading.

• Drivers have thicker axons with larger terminals that contact proximal dendrites and are distributed in denser, more tightly localized terminal arbors, and their terminals in thalamus have a characteristic light and electron microscopic appearance and synaptic relationships often involving triadic relationships in glomeruli (see above).

Some Effects of Modulation

The function of the driver input to thalamic relay cells seems obvious and straightforward; its role is to provide the main information to be relayed, that is, to carry a message about events in the brain, the body, or the world for relay to cortex. Modulatory functions are more varied and complex. That for traditional modulatory inputs, such as GABA and ACh, is often related to overall effects on excitability via inhibitory or excitatory actions, but by activating metabotropic receptors, these effects can be prolonged. The same thus applies to glutamatergic modulatory inputs via the activation of metabotropic glutamate receptors.

Because activation of metabotropic receptors produces membrane potential changes that typically last >100 ms (see above), such activation provides the necessary time and voltage shift needed to control various voltage- and time-gated ion channels. These have been described above, and the properties of the T-type Ca^{2+} channels that underlie the burst/tonic r sponse modes help to show the importance of thf\,pfoio gechhariges characteristic of the metabotrripic recepfors. To inactivate the channel requires a sustained (>100 ms) depolarization. Activation of ionotropic receptors such as AMPA (glutamate) or nicotinic (ACh) receptors produces brief EPSPs with little effect on the inactivation state of this channel. However, activation of appropriate muscarinic (ACh) or metabotropic glutamate receptors produces a sufficiently long EPSP to inactivate the channel. Likewise, activation of the $GABA_A$ receptor (ionotropic) produces a brief IPSP that will not lead to much deinactivation of the channel, but activation of the $GABA_B$ receptor (metabotropic) produces a sustained IPSP that will do so.

There is evidence from cortex that activation of metabotropic glutamate receptors also affects the size of evoked EPSPs from driver inputs (Mateo & Porter, 2007; DePasquale & Sherman, 2013). Data from the la:teral geniculate nucleus suggest that this may is the case for the retinogeniculate synapse (Govindaiah, et al., 2012; Lam & Sherman, 2013). Here activation of metabotropic glutamate receptors located on the retinal terminals, via glutamate released either from the retinal terminals themselves or from the layer 6 modulator feedback input (Lam & Sherman, 2013), reduces the retinogeniculate EPSP amplitude.

THE FUNCTIONAL ORGANIZATION OF THE PULVINAR

The Pulvinar as a Visual Relay

MAPS IN THE PULVINAR The pulvinar, like the lateral geniculate nucleus, receives topographically organized representations of the contralateral visual hemifield, with the region receiving from area 17 forming a mirror reversal of the geniculate map and also receiving inputs from other visual areas, including areas 18 and.19 in the cat (Berson & Graybiel, 1978; Guillery, Feig, & Van Lieshout, 2001). Lines of projection are identifiable, as in the lateral geniculate nucleus of the cat, on the basis of the driver inputs and of the thalamocortical connections, and it appears that each line of projection receives from more than one cortical area suggesting that in the pulvinar these lines represent the arrangement of distinct cortical functions, and these all relate to the same small area in visual space, but their functions are not identified at present.

PULVINAR CIRCUITRY Although much less is known about the pulvinar than about the lateral geniculate nucleus, it provides an important pathway to many, possibly to all, higher visual cortical areas. Many or all of the cells in this complex have visual receptive fields (Bender, 1982; Casanova & Savard, 1996; C_halupa,

1991; Hutchins & Updyke, 1989), and their links with extrastriate visual cortical areas have long been recognized (Jones, 2007), 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 afferents have been described above, and it was shown that they are clearly distinguishable in terms of their properties (see table 19.1) and their functions as driver or modulator.

Experiments using retrograde tracers have shown that the pulvinar receives afferents from layers 5 and 6 of visual cortex (Abramson & Chalupa, 1985), whereas the lateral geniculate nucleus receives afferents only from layer 6 of cortex but not from layer 5 (Gilbert & Kelly, 1975). The question of whether any part of the pulvinar receives direct retinal input is unclear.[10] Injections of anterograde tracers that labeled axons of individual cells in layer 6 of area fl 7 show that the terminals of these axons in the pulvinar have the structural characteristics of the modulatory corticogeniculate afferents described above for the lateral geniculate nucleus (see figure 19.5). Limited data from slice preparations of rodents indicate that the synaptic properties of the layer 6 input to the pulvinar are the same as those to the lateral geniculate nucleus: In the rat evoked synaptic properties from activating corticothalamic axons include the property of paired-pulse facilitation (see table 19.1), although the layer of origin for this input could not be determined (Li, Guido, & Bickford, 2003); in the mouse, layer 6 input to the posterior medial nucleus, which can be considered as the somatosensory thalamic equivalent of the pulvinar, shows the properties of a modulator (Reichova & Sherman, 2004).

In contrast to the layer 6 cells, which relate to pulvinar much as they do to the lateral geniculate nucleus, individual layer 5 cells in area 17 have been shown to send no labeled axons to the lateral geniculate nucleus (Bourassa & Deschenes, 1995; Rockland, 1996) but do send axons that terminate in the pulvinar, where they have the characteristics of the retinogeniculate driver afferents described above, both in terms of their light microscopical appearance (Bourassa & Deschenes, 1995; Ojima, Murakami, & Kishi, 1996) and synaptic arrangements seen with the electron microscope (Mathers, 1972; Robson & Hall, 1977b; Ogren & Hendrickson, 1979; Feig & Harting, 1998). Evidence from slice preparations of rodents indicates that the synaptic properties of these layer 5 corticothalamic afferents are very much like those of retinogeniculate inputs (Li, Guido, & Bickford, 2003; Reichova & Sherman, 2004; Theyel et al!, 20i,-0). We thus regard them as the drivers of the pulvin3lcells, and it is because these drivers come' f((mr areas of cortex classifiable as "visual" that we· see_ visual••n?ceptive fields in the pulvinar. Further 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 that the receptive field properties of many pulvinar cells are not unlike the receptive field properties of cells in cortical layer 5 (Chalupa, 1991).

Besides the distinction between layer 5 and 6 inputs to pulvinar as driver or modulator there is a difference in their patterns of termination in the thalamus. The layer 6 projection is organized as a feedback, innervating the same regions of pulvinar from which it receives its thalamic input, whereas the layer 5 projection is organized in a feedforward pattern (Van Horn & Sherman, 2004). Also, whereas the layer 6 afferents send a rich innervation to the thalamic reticular nucleus, the layer 5 afferents do not but instead send branches to lower extrathalamic centers.

The Pulvinar as a Higher Order Thalamic Relay

The fact that the pulvinar 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 at least once. For this reason the pulvinar 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 and for the first time to cortex (Guillery, 1995; Sherman & Guillery, 1996, 2002, 2006). We define a first order thalamic relay as one that receives its driver input from a subcortical source (e.g., retina) with no driver inputs from cortex and a higher order one as receiving a si$_{g\,n}$ificant part of its driver input from layer 5 of cort(,x. This distinction between first and higher order relays is found not only for the visual pathways but for other relays to cortex as well (reviewed in Sherman & Guillery, 2006, 2011). 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 thalam\Is and also a much greater area of cortex than does the first order visual relay in the thalamus. That is, the pulvinar is far larger than is the lateral geniculate nucleus, and the areas of cortex in receipt of inputs from the pulvinar are, in total, far greater than area 17.

We have described the pulvinar 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 pointed out in note 10, we regard this as a part of the lateral geniculate nucleus. The input from the superior colliculus and pretectum to a part of the pulvinar raises another issue. Are these driving or modulatory inputs?

There were strong arguments in the past (Diamond, 1973; Schneider, 1969; Sprague, 1966, 1972; Sprague, Berlucchi, & Di l!erardino, 1970) for the view that there are two parallel visual pathways going to the cortex, one from retina through the lateral geniculate nucleus to cortex and the other from retina via the superior colliculus to the pulvinar and then to cortex. This was based on behavioral studies primarily in cat, hamster, and tree shrew and on anterograde tract-tracing studies that demonstrated axonal pathways from the region of the colliculus to the pulvinar (Altman & Carpenter, 1961). One logical flaw with this notion is that the superior colliculus in mammals receives massive input from both retina and visual cortex, and the latter seems to provide an input, perhaps driver, that is required for normal collicular responses to visual stimuli (Wickelgren & Sterling, 1969), and so this raises doubts about independent pathways from retina through the superior colliculus to cortex. Further, the collicular receptive fields in a normal cat resemble those of cortical cells and not of retinal cells, but after cortical silencing they resemble those of retinal cells (Wickelgren & Sterling, 1969), suggesting that if the colliculus does send information to the pulvinar for relay to cortex, it is information about cortex rather than about colliculus.

More recently, a pathway in the monkey from the superior colliculus through the pulvinar to the MT (medial temporal) area of cortex was defined (Berman & Wurtz, 2010). Two problems need to be resolved with such studies. One is the question as to whether this input to pulvinar is actually a driver or modulator. The other is technical: when stimulating the tectothalamic pathway or labeling it for anatomical study from the superior colliculus, it may be that, instead of activating or labeling these axons, the layer 5 axons that branch to innervate both the superior colliculus and pulvinar are activated or labeled (Bourassa & Deschenes, 1995).

The available evidence as to whether the tectothalamic pathway is driver or modulator (or other) is incomplete. Recordings from cells in the pulvinar of cats and monkeys have shown that the receptive field properties of cells there are dependent on cortical inputs, not on collicular inputs (Bendr,r,.1983; Chalupa, 1991; Chalupa, Anchel, & Lindsltj!r 191"; --suggesting that the collicular inputs are not--qrive .imrervating a pulvinar first order relay (see also Smith & Spear, 1979). The morphological evidence on the structure of the tectopulvinar connections is conflicting (Mathers, 1971; Partlow, Colonnier, & Szabo, 1977; Robson & Hall, 1977a,b), 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 (Kelly et al., 2003; Mathers, 1971; Partlow, Colonnier, & Szabo, 1977; Robson & Hall, 1977a).11 This issue needs to be resolved. Because there are several distinct subdivisions of the pulvinar that are not easily compared across species, it is possible that there are some tectal drivers innervating 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, Gross, & Albright, 1989, 1990), but at present the nature of any information transmitted from colliculus to cortex through the pulvinar remains undefined.

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 different issue regarding the possible integration in thalamus of different driver inputs. Do they interact on single relay cells, or do they, like X cells and Y cells in the A layers of the cat's lateral genic_ulate nucleus, or ,ON and OFF center cells, form two essentially independent parallel pathways?

Driver Afferents to Pulvinar Are Branching Axons

Most or all driver inputs to both first and higher order thalamic relays, including the lateral geniculate nucleus and pulvinar, arrive via branching axons, with one or more extrathalamic branches that innervate brainstem or spinal motor centers (reviewed in Sherman & Guillery, 2006, 2011). Thus, most or all retinal axons that innervate the lateral geniculate nucleus branch to innervate midbrain regions involved in head and eye movements; accommodation, pupillary control, and so on. Details of experimental evidence for these retinofugal branching patterns can be found elsewhere (Guillery, 2003; Guillery & Sherman, 2002b, 2011). Furthermore, layer 5 corticothalamic axons from visual cortex to pulvinar also branch to innervate many of the same brainstem motor regions (Bourassa & Deschenes, 1995; Bourassa, Pinault, & Deschenes, 1995; Guillery, Feig, & Van Lieshout, 2001).

This branching pattern has suggested a novel and unexpected function for driver afferents to thalamus (Guillery & Sherman, 2011): the extrathalamic branches

carry messages to motor centers, and the thalamic branches necessarily carry the same message.[12] This means that driver inputs to thalamus carry a copy of motor instructions currently on their way to subcortical centers. In this regard driver inputs to thalamus serve as efference copies[13] in the sense used by others (Sommer & Wurtz, 2004; Sperry, 1950; von Holst & Mittelstaedt, 1950) and provide information about forthcoming movements. An intriguing observation that appears to be related involves the "forward receptive fields" described for several cortical areas (Duhamel, Colby, & Goldberg, 1992; Sommer & Wurtz, 2006; Umeno & Goldberg, 1997), because these represent an anticipation of a movement, and such receptive fields may well depend on driver inputs to the appropriate thalamic relays carrying information in the form of efference copies. Further details of this hypothesis and its ramifications can be found in Guillery and Sherman (2011).

The Pulvinar Region as a K_{ey} Relay in Corticocortical Visual Communication

The distinction between first and higher order relays outlined above is based on the pathways from layer 5 cells, which provide the pulvinar with visual inputs from the cortex, and it is based on the evidence, summarized above, that these cortical inputs are drivers of pulvinar cells. That is, the pulvinar serves as a relay from one visual cortical area to other cortical areas, providing information about outputs to lower centers that are currently being sent by the first cortical area. 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 different perspective introduced by these corticothalamic drivers is highlighted by figure 19.8, which contrasts the conventional view (figure 19.8A) with the alternative view offered here (figure 19.8B). In the conventional view, information enters striate cortex from the lateral geniculate nucleus and is then processed entirely within cortex, from primary sensory cortex through sensorimotor areas until finally reaching motor cortex, where needed motor commands are initiated. Analyses of perceptual and motor control mechanisms are commonly presented as going from the thalamus through a hierarchy of cortical areas for perceptual processing before they are passed to motor areas of cortex (e.g., Andreas et al., 2001; Galletti et al., 2001). The prevailing interpretation strictly involves direct corticocortical connections among many discrete areas (over 30 in the monkey and probably fewer in the cat) organized into several (five or six in the monkey) hierarchical levels, with feedback as well as feedforward connections. Higher order thalamic relays such as the pulvinar are generally ignored in this conventional view except for a suggestion, without direct supporting evidence, that the pulvinar provides a modulatory influence on visual cortex in the service of attentional requirements (Olshausen, Anderson, & Van Essen, 1993; Van Essen, Anderson, & Felleman, 1992). As noted above (Driver Afferents to Pulvinar Are Branching Axons), the axons that go from cortical layer 5 represent one of several striking features that play no role in the current, conventional approaches schematized in figure 19.8A. One is that driver connections are seen in the transthalamic pathway from the primary visual cortex to the higher order thalamic relay (i.e., the pulvinar) and the target cortical areas in occipital, parietal, and temporal lobes. That is, the transthalamic pathway offers a novel route for the transmission of information from one cortical area to another (see also Theyel, Llano, & Sherman, 2010), and this must be seen as one essential part of the function of 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 any one visual cortical area to another through a higher order thalamic relay is also a copy of descending messages that will act rapidly on motor pathways without the prior complex route through a hierarchical scheme of corticocortical connections to areas of motor cortex (Guillery & Sherman, 2011).

The important point for understanding corticocortical communication among visual cortical areas is that there are potentially important but largely unstudied and unrecognized transthalamic pathways that go from layer 5 in one cortical area through a pulvinar relay to another cortical area in the occipital, parietal, or temporal lobe. These transthalamic pathways, shown in figure 19.8B, are likely to differ in their functional properties from the more widely cited direct corticocortical routes (Van Essen, Anderson, & Felleman, 1992). Specifically, the thalamic relay has, as we have seen, properties that can modify or block transmission in accord with different functional needs, and because the direct corticocortical pathways lack such a thalamic relay, these properties are unavailable to the direct pathways.

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

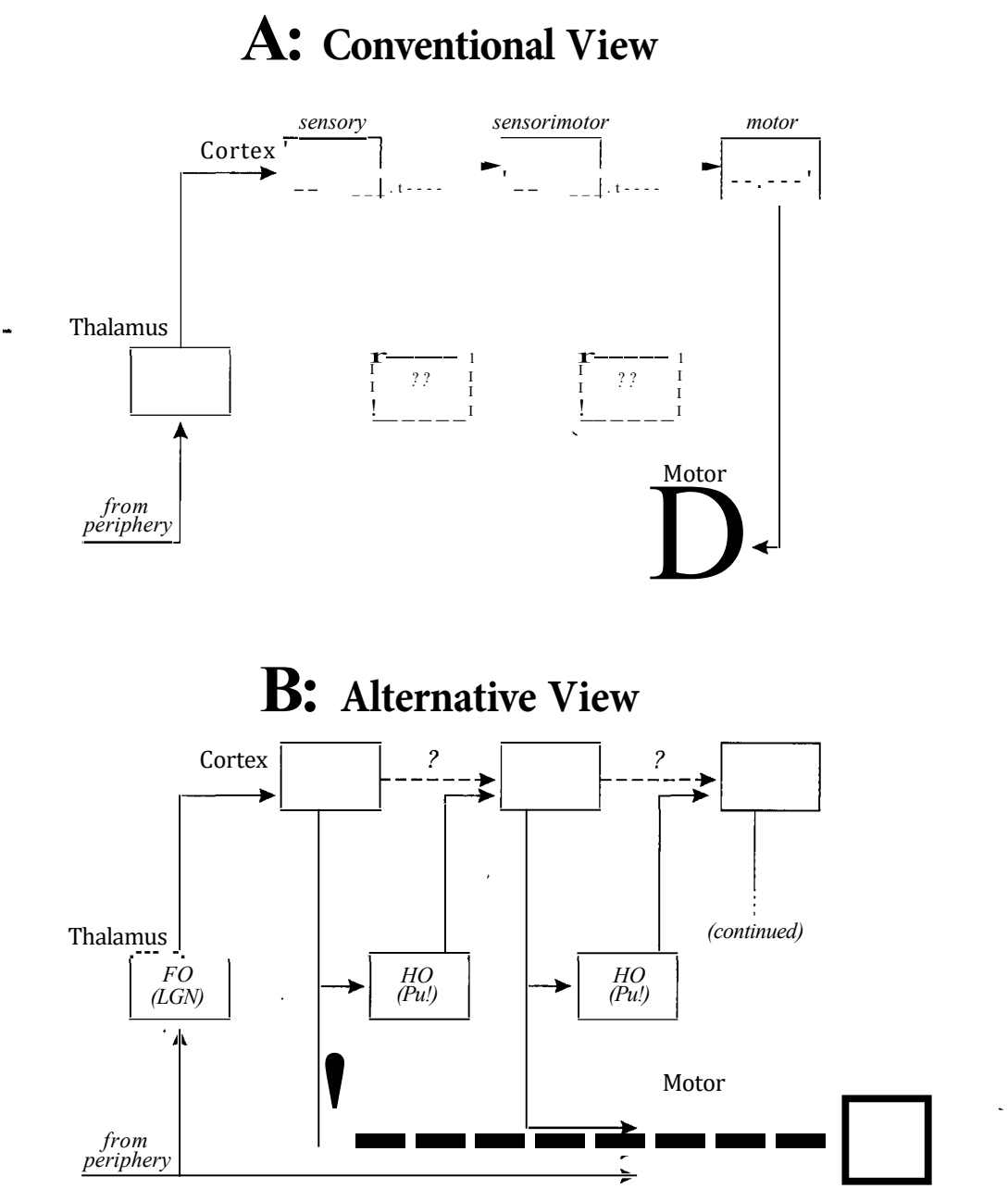

FIGURE 19.8 Comparison of conventional view (A) with the alternative view proposed here (B). FO, first order; HO, higher order; LGN, lateral geniculate nucleus; Pul, pulvinar. (Redrawn from Sherman, 2005.)

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 numbers 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 5-10% of the synapses in the lateral geniculate nucleus (Van Horn, Erilir, & Sherman, 2000), and the geniculocortical afferents in area 17 also represent only about 5-10% of the synapses in cortical layer 4 (Ahmed et al., 1994; Latawiec, Martin, & Meskenaite, 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 the 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 (e.g., reflected in 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 a major information-bearing driver input to higher cortical areas will come from the thalamus, as it does for all first order cortical areas.

Another important and practical reason why the transthalamic corticocortical pathways have received much less attention than have the direct corticocortical pathways 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. 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 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, Schwartz, & Jessen, 2000; Van Essen, Anderson, & Felleman, 1992) or outputs to memory storage represent a false view about the nature of the cortical processes that relate to visual perception and its relation to movement control.

Not only, as indicated, do all cortical areas receive thalamic inputs, but most, probably all, have descending outputs from layer 5. Some of these layer 5 outputs have branches to thalamus, and some lack such branches, but those that innervate thalamus all have long descending extrathalamic branches (reviewed in Guillery & Sherman, 2011; Sherman & Guillery, 2006). Although the final destination of these descending branches is often undefined, many innervate regions with clear motor functions. The significance of knowing the functions of the descending branches for understanding the relevant transthalamic pathway is explored in the next section. Here it is important to look at these multiple pathways from many cortical areas as a good reason for seeing cortical processing as being continually in touch with lower motor centers (figure 19.8B).

For example, area 17 sends axons to the superior colliculus, which is concerned with the control of head and eye movements (e.g., Tehovnik, Slocum, & Schiller, 2003), and there are comparable outputs from many other visual cortical areas that have connections with the pulvinar. The fact that area 17, like other primary sensory areas, sends a layer 5 output to motor centers starts to blur the distinction between sensory and motor cortex.

The Transpulvinar Corticocortical Pathway 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 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 with branches to lower centers. This pattern of connectivity may seem surprising because it seems to turn the thalamic relay into a monitor of motor commands 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. It can be seen in most or all 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 & Sherman, 2011; Sherman & Guillery, 2006). 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, particularly in relation to eye movements, pupillary control, or accommodation.

Connectional and Cellular Properties in the Pulvinar Region

There is a basic similarity in the cell types seen in the pulvinar 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 & Harting, 1998; Mathers, 1972; Ogren & Hendrickson, 1979; Rockland, 1996, 1998). The afferents, too, are readily comparable to the afferents that innervate the lateral geniculate nucleus provided one recognizes that the drivers come from different sources: retina for the lateral geniculate nucleus and from layer 5 (and/or superior colliculus) [14] for the pulvinar. Both cell groups, in addition to their driving afferents, receive modulatory afferents from cortical layer 6, from the thalamic reticular nucleus, and from the brainstem.

There are some subtle differences, however, between the lateral geniculate nucleus and pulvinar as regards cell and circuit properties. Many of these differences are seen generally as common to first versus higher order relays:

- Electron microscopic studies indi ate that the relative percentage of driver synapses is lower in pulvinar, being only 2% compared to about 7% for the lateral geniculate nucleus (Van Horn, Eril]ir, & Sherman, 2000; Van Horn & Sherman, 2007; Wang, Eisenback, & Bickford, 2002).
- Certain inputs relatively selectively target higher order relays, including the pulvinar. This includes a GABAergic input from the zona incerta (Lavallee et al., 2005; Power, Kolmac, & Mitrofanis, 1999) and a dopaminergic input from as yet unspecified sources (Garcia-Cabezas et al., 2007; Sanchez-Gonzalez et al., 2005).
- Modulatory serotonergic and cholinergic inputs i:hat depolarize all first order relay cells, including those of the lateral geniculate nucleus, h_{yp}erpolarize a significant minority (about one-fifth) of higher order relay cells, including those of the pulvinar (Varela & Sherman, 2007, 2008).
- Higher order, including pulvinar, relay cells have a greater tendency to burst firing (Ramcharan, Gnadt, & Sherman, 2005), and this might be related to the· above point that modulatory inputs h_{yp}erpolarize many higher order relay cells, which is a prerequisite to burst firing or to the recent observation that pulvinar relay cells have a higher density of T-type Ca^{2+} channels (Wei et al., 2011).

Properties of Pulvinar Connections to Cortex

A vital piece of information needed for understanding the function of the pulvinar is the pattern of projections from the relay cells to the various cortical areas that receive afferents from the pulvinal. This is: nt> t merely a question of enumerating the cortit:jil ar s' that receive afferents from the pulvinar, although this information is, of course, essential but, unfortunately, very difficult to summarize from the literature at present. Studies of retrograde cell degeneration in the thalamus, of retrograde cell labeling, or of anterogradely labeled axonal pathways (Hackett, Stepniewska, & Kaas, 1998; Rockland et al., 1999; Walker, 1938; Wong et al., 2009; Wong-Riley, 1977) all indicate that there are widespread axonal projections from the pulvinar to the cortex. To some extent these studies indicate pathways from particular subdivisions of the pulvinar, but, in general, the information that allows one to relate each pulvinar subdivision to particular groups of cortical areas is not available, nor, where we have such information, do we know which are drivers and which are modulators.

We generally assume that pulvinar projections to cortex, like thalamocortical projections more generally, are feedforward and driver in nature. Indirect evidence from slices of mouse brain, in which analogous somatosensory and auditory higher order thalamic inputs to cortex were functionally tested, revealed these to be driver pathways (Lee & Sherman, 2008; Theyel, Llano, & Sherman, 2010. This suggests, by extrapolation, that this will prove true for pulvinar inputs to higher areas of visual cortex. However, this property of pulvinar projections to extrastriate cortical areas has yet to be explicitly tested in any species, and this remains a key unanswered question. It may be relevant in this context to note that, in the mouse, the projection from the posterior medial nucleus, a higher order somatosensory thalamic relay organized much like the pulvinar is for vision, has a pr.:ojection to primary somatosensory cortex that is entirely modulatory, unlike its driver inputs to the second somatosensory area (Viaene, Petrof, & Sherman, 2011a). Recent evidence in monkeys indicates a modulatory function for the pulvinar projection to striate cortex (Purushothaman et al., 2012), suggesting the possibility to be tested that higher order thalamic relays such as pulvinar provide a driving input in feedforward co·nnections but are modulatory in feedback.

Role of Pulvinar in Corticocortical Communication

Until recently, ideas of corticocortical communication among visual areas have been dominated by the notion that, once information reaches striate cortex from the lateral geniculate nucleus, it remains in cortex, being processed strictly via direct corticocortical pathways (Bond, 2004; Hilgetag & Kaiser, 2004; Lamme, 2003; Moore & Armstrong, 2003; Salin & Bullier, 1995; Van Essen, Anderson, & Felleman, 1992; Wise et al., 1997; Womelsdorf et al., 2006) with no role for subcortical

structures such as the pulvinar. We now propose a very specific role for the pulvinar as a thalamic link in indirect corticothalamocortical circuits critical for corti'cal functioning. We have generally suggested such a role for all higher order thalamic relays, such as the pulvinar, and examples for the somatosensory and auditory systems are the dorsal medial geniculate nucleus and posterior medial nucleus, respectively (Sherman & Guillery, 2011).

Another important feature of the transthalamic cortical pathways in general is that often, perhaps always, a direct connection between two cortical areas is paralleled by an indirect one through thalamus. This suggests, ,for instance, that the direct pathway between striate cortex and the medial temporal cortex (known as MT) is paralleled by one relayed through pulvinar. This raises a series of qu_estions related to differences between the direct and transthalamic cortical pathways, considered below, for which we have only partial answers.

Differences between Direct and Transpulvinar Visual Cortical Pathways

The basic question, from which others spring, is: Why is some information transmitted from one cortical area to another sent directly and other information sent through a thalamic relay?

WHAT IS DIFFERENT ABOUT THE SYNAPTIC PROPERTIES OF THE DIRECT VERSUS TRANSPULVINAR CIRCUITS? It is remarkable that so much thinking about cortical functioning is based on ideas about direct corticocortical interconnections when, as noted above, we know rather little about the actions of these connections. That is, schemes such as that of Van Essen and colleagues (Felleman & Van Essen, 1991; Van Essen, Anderson, & Felleman, 1992), which dominate thinking about corticocortical interactions, are based virtually entirely on neuroanatomical studies of connectivity. Only recently has there been any synaptic study of such direct corticocortical connections, based on recordings from slices of mouse brain, and this shows, for connections between areas of both visual and auditory cortices, that both driver and modulator connections exist with complex laminar relationships (Covic & Sherman, 2011; DePasquale & Sherman, 2011).

Several interesting and surprising conclusions can be drawn from these mouse data. Both presumed feedforward (primary visual or auditory cortex to secondary cortex) and feedback (secondary visual or auditory cortex to primary cortex) directions were studied, and whereas one prediction would be for a -i:elative dominance of d f e s in the feedforward direction compared to .th dback, this was not seen. Indeed, no clear,..different', s were seen between directions in the laminar-patteHl"bf driver and modulator inputs in the corticocortical pathways, which markedly differs from the pattern suggested for the monkey (Felleman & Van Essen, 1991).

Although clearly more examples are needed from other mammalian species, it seems reasonable to conclude at least that direct corticocortical connections, including those between visual areas, contain drivers among the inputs to the target area. If so, then both the direct and transthalamic pathways include driver components and thus routes of information transfer. Nonetheless, _important details about these circuits remain to be determined.

One telling difference in the circuits, besides the obvious one of whether or not a thalamic relay is present, is the relationship of the circuits to subcortical processes. As noted above, the layer 5 axons that innervate pulvinar are the first link in the transthalamic pathway branch, with the extrathalamic branch targeting various brainstem sites. The direct pathways, with rare exceptions,[15] are comprised of axons with no subcortically directed branches (Petrof, Viaene, & Sherman, 2012). Thus, the messages sent via the transthalamic pathways relate to various subcortical centers, whereas the direct pathways carry messages that are strictly cortical.

WHAT IS DIFFERENT IN THE INFORMATION CONTENT OF THE DIRECT VERSUS TRANSPULVINAR CIRCUITS? As noted above, the transthalamic route involves branching axons from layer 5 that also target subcortical sites, so the message in the transthalamic 13athway may be regarded as a copy of an upcoming motor command, that is, an efference copy of the command sent to the lower motor centers via the branching axon. If so, this means that the nature of the transthalamic information is at least in part to inform higher cortical areas about motor commands sent out from lower areas. On this basis we suggest that the most parsimonious explanation for the direct connections is that they may be involved primarily in basic information processing about the environment.

The following example ,IJ!ay help to cl rify this distinction. The layer 5 projection from a visual area, say V1, involves one or more branches that innervate subcortical motor areas, such as the superior colliculus, with a message to create some form of movement, perhaps an eye movement (Tehovnik, Slocum, & Schiller, 2003), and this same message is sent through another branch to the pulvinar where it is relayed to a

higher cortical area. This provides information to each visual cortical area about prospective motor commands initiated by cortical areas lower in the hierarchy, and this is precisely what is needed to disambiguate the sensory consequences of eye and head movements from movements in the outside world. It may well be that the direct connections are primarily concerned with an analysis of the visual scene, whereas the transthalamic connections play their major role in relation to the movements, although the connectivity patterns suggest that the two functions are never fully separated.

WHY IS THE TRANSTHALAMIC PATHWAY TRANSTHALAMIC? If the object is to send an efference copy from one cortical area to another via a branching axon, a thalamic relay for this is not an absolute requirement. :rhat is, the same layer 5 cells that innervate pulvinar and send a branch to other subcortical centers, instead of innervating pmlvinar, could project that branch directly to th target cortical area. The Meynert cell may be a rare example of this (see note 15). However, such a connection would lack the modulatory and gating effects that characterize the thalamic relay.

As noted above, certain inputs specifically target higher order relays such as the pulvinar. An interesting one is the GABAergic input from zona incerta of the rat (Lavallee et al., 2005; Power, Kolmac, & Motrofanis, 1999). Although there is no direct evidence to illustrate what effect this .input may have on the pulvinar, evidence from the analogous higher order thalamic relay for the somatosensory system, the posterior medial nucleus, suggests what significance this might have for vision. Under most conditions during which a rat is not alert or actively whisking, the zona incerta is active, and its GABAergic input to the posterior medial nucleus serves to shut down relay cells there, effectively closing the thalamic gate (Bartha, Freund, & Acsady, 2002; Bokor et al., 2005; Lavallee et al., 2005; Masri et al., 2006; Trageser & Keller, 2004; Trageser et al., 2006). Two processes bring about inhibition of zona incerta cells, thus disinhibiting relay cells of the posterior medial nucleus and opening the thalamic gate. One is the level of arousal, because greater activity in parabrachial cholinergic inputs inhibits zona incerta cells (Trageser et al., 2006). The other, which is more interesting, occurs when a rat moves from passive to active whisking (i.e., to an exploratory mode); the now-active motor cortex inhibits zona incerta cells, the silencing of the zona incerta then opens the gate of the posterior medial nucleus (Urbain & Deschenes, 2007), a d this then allows the transthalamic mess ge from primary sensory cortex (Sl) to be passed to lfi$_g$h er-c9rtica]-a reas (S2). In other words, during activer'hiskiag, which is associated with high levels of activity in motor cortex, messages that are processed in somatosensory cortex lead to motor output signals from layer 5, and copies of these are successfully relayed through the posterior medial nucleus up the cortical hierarchy.

One can imagine a similar process applying to gating of pulvinar by the zona incerta. During active vision, messages sent by lower visual cortical areas about motor commands are transmitted through the thalamic relay to affect the higher, target cortical area. During periods when vision is not active, as happens, for instance, during drowsiness or when another sensory system captures attentional mechanisms, these messages are blocked by closing the pulvinar gate.

This sort of process for whisking or vision makes se se if the presumed motor messages sent out by cortical areas do not always result in motor actions, and a consideration of the likely evolutionary history of thalamus and cortex provides a reasonable scenario for this. As thalamocortical circuits evolved, there was no parallel evolution of separate subcortical motor· circuits, although ¡existing ones did continue to evolve, and so cortex ends up sharing these earlier evolved brainstem and spinal motor circuits to affect behavior.

If an animal is actively guiding behavior through visual stimuli, and the auditory system is passive (e.g., taking in stimuli but not guiding behavior), then messages from layer 5 c lls, including copies of messages to move the eyes, would be passed up the cortical hierarchy, and the higher order gates through pulvinar would be held open. Those in the auditory system, however, would be gated shut because any messages created in an auditory cortical area and leading to firing of the layer 5 output cells are unlikely to significantly affect behavior, and these messages then would not get through the thalamic links in the transthalamic auditory pathways.

Another consequence of a traqsthalamic route involves the abil ty to modulate the message in ways not available to the direct route because, as described above, thalamic circuitry offers a number of way to modulate messages in transfer to cortex. We consider one example of this involving the switching of relay cells between tonic and burst firing mode. The details of this, which depend on the inactivation state of T-type Ca^{2+} channels, have been described more fully above (Intrinsic Properties of Thalamic Cells in the A Layers). We have suggested that tonic mode is used for normal processing of information, whereas burst mode is used as a "wake-up call" to cortex that information is once again being relayed after a period of no relay.

This scenario can also be applied to the pulvinar and its Zona incerta input as follows. When the zona incerta

is active, it not only shuts down the pulvinar relay, but it also hyperpolarizes the relay cells, switching them to burst mode by deinactivating the T-type Ca^{2+} channels. Silencing of these zona incerta inputs, presumably when vision becomes active, would then lead to layer 5 inputs evoking bursts in pulvinar relay cells, which in tum would strongly signal the target cortical area that a significant change has occurred.

Consider again the scenario just suggested for the zona incerta input to the pulvinar. During passive vision the zona incerta powerfully inhibits pulvinar relay cells, placing them in burst mode, and activity in layer 5 corticothalamic cells from layer 5 of a visual cortical area is not relayed to higher areas. With a switch to active vision, new outputs from layer 5 of visual cortex inhibit zona incerta cells, removing their inhibition of cells in the pulvinar, and the next output from cortical layer 5 evokes a burst in these relay cells. That burst strongly activates circuits in target visual cortical areas. Persistent activity in layer 5 inputs, in the absence of further inhibition from zona incerta, continues to depolarize pulvinar relay cells and thereby switches their firing to tonic mode, ensuring a more faithful relay of the transthalamic signal.

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 relay functions 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 there is a need to increase or decrease the saliency of a particular message, say, a visual stimulus at the expense of an auditory one, it requires 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 the retina except for possible autonomic effects on accommodation and pupillary control. 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 the thalamus; but for all pathways going to cortex, the thalamic level contains 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 both a relatively well-studied first order relay in the lateral geniculate nucleus and a series of more elusive higher order relays in the pulvinar. 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 only about 5-10% of the afferent synapses to geniculate relay cells 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 and come from several sources, including the glutamatergic feedback from layer 6 of visual cortex.

The higher order relays in the pulvinar serve to transmit information from one cortical area to other cortical areas through the thalamus. 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, and thus efference copies, 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.

Finally, whereas it is now clear that direct and transthalamic corticocortical circuits exist, often or perhaps always organized in parallel, it is not entirely clear what purpose this remarkable neuronal organization serves. Part of the answer may relate to the suggestion that part of the message sent to higher cortical areas is an efference copy, and this is the message that is transthalamic, although it also carries information about the environment (Guillery & Sherman, 2011). In this regard 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 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 the tonic modes. Special GABAergic inputs to the pulvinar, chiefly from the zona incerta and pretectum, may provide an additional function to gate the pulvinar relay, and we have speculated that this may occur to prevent relays through pulvinar of efference copies that are not likely to be related to eventual motor actions when vision is not active.

These ideas provide entirely novel functional possibilities for the pulvinar relay. Clearly, much more work is needed to clarify the validity of this challenging proposal.

NOTES

1. By "lateral geniculate nucleus" throughout 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 is not considered further.
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.
3. Another term frequently used for this area is "pedunculopontine tegmental nucleus." We prefer "parabrachial region," because the scattered cells that innervate thalamus from this area do not have a clear nuclear boundary, and they are found scattered around the brachium conjunctivum.
4. In the cat the major portion of the thalamic reticular nucleus innervating the lateral geniculate nucleus is called the "perigeniculate nucleus."
5. 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 seen as 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 (Gray, 1959). Typically, asymmetric synapses are associated with excitatory synapses, and symmetric, with inhibitory ones.
6. The voltage and time dependencies vary somewhat among cells and also are interdependent because a greater depolarization requires less time to inactivate, and, likewise, greater hyperpolarization is associated with faster deinactivation (Sherman & Guillery, 1996, 2006).
7. Sometimes, "spike" is used to refer to a conventional action potential, but here we use it to refer to an all-or-none Ca^{2+} event. To avoid confusion, when we mean a Na^+/K^+ action potential, we use "action potential" and not "spike."
8. It is worth noting that glutamatergic inputs, even in cortical circuitry, including thalamocortical and corticocortical inputs, show the same two basic types, described here as "drivers" and "modulators." However, a new terminology has been applied-"class 1" for "driver" and "class 2" for "modulator"-for the cortical circuitry because the terms "driver" and "modulator" have implications that seem clear for thalamus but not yet for cortex (Covic & Sherman, 2011; DePasquale & Sherman, 2011; Viaene, Petrof, & Sherman, 2011a, 2011b, 2011c). Nonetheless, we stick with these original terms in this chapter because we feel that the "driver/modulator" terminology does indeed capture the presumed function of each of these inputs.
9. It should be noted that, although these bullet points were written specifically for thalamic circuitry, they apply as well to cortical circuitry (Covic & Sherman, 2011; DePasquale & Sherman, 2011, 2012; Lee & Sherman, 2008, 2009; Viaene, Petrof, & Sherman, 2011a, 2011b, 2011c).
10. A retinal projection to the pulvinar has been described in several species, but this is generally in a region close to or adjoining the lateral geniculate nucleus. One definition of the lateral geniculate nucleus is that it is the collection of neurons that receive a retinal input and whose relay cells project to cortex. If so, then any retinal projection to thalamus can be regarded as innervating a part of the lateral geniculate nucleus, and in this context, in the cat, a thalamic region innervated by retina that so!]le refer to as the "retinorecipient zone of the pulvinar" has instead been called a part of the "geniculate wing" (Guillery et al., 1980). Thus, the issue of whether the pulvinar receives a retinal input is a matter of semantics, but in any case the issue of whether this region, pulvinar or lateral geniculate nucleus, receives other driver inputs from cortex or midbrain and how these might interact has yet to be explored.
11. The variety of tectopulvinar terminals seen suggests that both driver and modulator types of input may be represented in this pathway.
12. The message carried by any axon is coded by the pattern of action potentials that travel down it. Under normal conditions, every action potential traveling down the parent branch will lead to one and only one action potential in each of the daughter branches, thus ensuring that the same message is carried by the parent axon and each branch. Failure to generate an action potential across a branch may sometimes occur in the nonphysiological, antidromic direction, but exceedingly rarely under normal, orthodromic conduction.
13. "Corollary discharge" is often used instead of "efference copy" to describe this feature. We use the latter to stress that it is a copy of a motor output, not of a sensory input.
14. See note 10 for an explanation as to why we do not consider retinal inputs here.
15. The one known exception is the Meynert cell, which in monkeys projects via collaterals from area 17 to both MT and the superior colliculus, but a collateral to thalamus from these cells has not yet been described (Fries, Keizer, & Kuypers, 1985; Rockland & Knutson, 2001).

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