PART 2

Sensation and Perception

10

Thalamocortical Relations

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The thalamus is a paired structure joined at the midline and located at the center of the brain (Figure 10.1). Each half is roughly the size of a walnut. The main part of the thalamus is divided into a number of discrete regions, known as relay nuclei. These contain the relay cells that project to the cerebral cortex. (In this chapter, cortex refers to neocortex, which does not include the hippocampal formation or olfactory cortex.) Lateral to this main body of the thalamus is the thalamic reticular nucleus (*TRN* in Figure 10.1), which fits like a shield alongside the body of the main relay nuclei of the thalamus. The thalamic reticular nucleus is comprised entirely of GABAergic neurons that do not innervate cortex but instead innervate thalamic relay cells. In Figure 10.1, all but the front part of the thalamic reticular nucleus has been cut away to reveal the relay nuclei. Strictly speaking, the relay nuclei are the *dorsal thalamus,* while the thalamic reticular nucleus is part of the *ventral thalamus;* here, dorsal and ventral reflect embryonic origin rather than relative location in the adult, meaning that the relay nuclei and thalamic reticular nucleus have different developmental origins. Unless otherwise specified, thalamus refers to the relay nuclei of the dorsal thalamus.

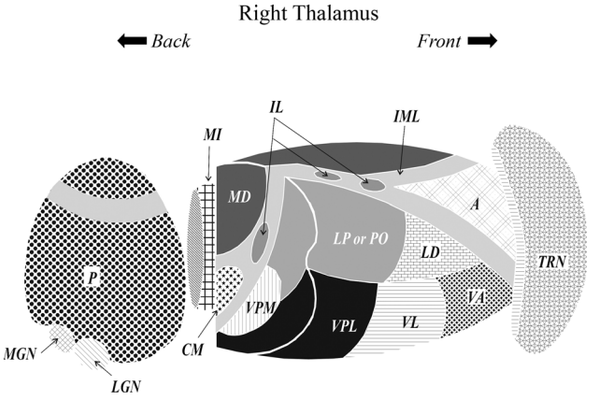

Figure 10.1 Schematic view of the right thalamus of the human. Shown are the main relay nuclei plus the thalamic reticular nucleus (TRN), of which only the anterior portion is visible; the remainder has been removed to reveal the thalamic relay nuclei. Normally, the thalamic reticular nucleus extends the length of thalamus as a thin shield closely apposed to the lateral surface of the relay nuclei. ***Abbreviations:*** *A,* Anterior Nuclei; *CM,* Central Medial Nucleus; *IL,* Intralaminar Nuclei; *LD,* Lateral Dorsal Nucleus; *LGN,* Lateral geniculate Nucleus; *LP* or *PO,* Lateral Posterior or Posterior Nucleus; *MD,* Medial Dorsal Nucleus; *MGN,* Medial Geniculate Nucleus; *MI,* Midline Nuclei; *P,* pulvinar; *TRN,* thalamic reticular nucleus; *VA,* Ventral Anterior Nucleus; *VL,* Ventral Lateral Nucleus; *VPL,* Ventral Posterolateral Nucleus; *VPM,* Ventral Posteromedial Nucleus.

Virtually all information reaching the cortex must pass through and be relayed by the thalamus. Thus anything we are consciously aware of and all of our perceptions of the outside world depend on thalamic relays. This relay is dynamically controlled by behavioral states and processes, including attentional demands. Each of the main relay nuclei shown in Figure 10.1 innervate one or a small number of cortical areas and, as far as we know, every area of cortex receives a thalamic input. The thalamus is there not just to get peripheral information to the cortex, but it continues to play a vital role in the further processing of this information by the cortex.

Where thalamocortical relationships are understood (e.g., the projection of the lateral geniculate nucleus to the primary visual cortex), the thalamic input plays a major role in determining the functional properties of the cortical target area. It has been shown that if retinal inputs in the ferret are diverted into the medial geniculate nucleus instead of the normal auditory inputs, the auditory cortex acquires visual responsiveness and organizes orientation-specific domains normally seen only in the visual cortex (Sharma, Angelucci, & Sur, 2000). Since all thalamic nuclei innervate cortex and all cortical areas are thus innervated, this might suggest that the functional properties of any cortical area follow its thalamic input rather than inputs from other cortical areas. This is a rather subversive idea that runs counter to the traditional dogma that cortical processing depends solely on direct cortico-cortical pathways. Cortico-thalamo-cortical pathways play a heretofore neglected and perhaps dominant role in cortical functioning.

To understand the functional relevance of the thalamus, it is necessary to understand some details about cell and circuit properties. Fortunately, these are mostly conserved throughout thalamus, so once we appreciate these for a model nucleus, we can extrapolate these properties for the entire thalamus. This is not to say that there are not important differences found among thalamic relay nuclei, but we concentrate in this chapter on those major properties that are common to the thalamus. The best-known and most thoroughly studied of the thalamic nuclei is the lateral geniculate nucleus, which relays retinal information to the visual cortex. We use this nucleus as our model template for cell and circuit properties.

For details of the thalamus beyond the scope of this chapter, see recent books on this topic by Jones (2007) and Sherman and Guillery (2006).

BASIC CELL TYPES

There are three major cell types involved in thalamic circuitry: relay cells, local interneurons, and thalamic reticular nucleus cells. The relay cells use glutamate as a neurotransmitter, whereas the other cell types are GABAergic.

Relay Cells

Although the evidence for different classes of relay cells is scattered and incomplete outside of the lateral geniculate nucleus (e.g., Li, Bickford, & Guido, 2003; Yen & Jones, 1983), the evidence is firm for several distinct types of geniculate relay cell. For example, the main geniculate relay cell classes in the cat are called X and Y (see Figure 10.2), and the equivalent types in the monkey are called parvocellular and magnocellular based on the geniculate laminae in which they are located (Casagrande & Xu, 2004; Hendry & Reid, 2000; Sherman, 1985). Another cell type, called W in the cat and K in the monkey, has also been described, but it is unclear if this is one or several distinct classes, and these cells are relatively poorly understood; further details can be found in Casagrande and Xu (2004; Hendry and Reid (2000); and Sherman (1985). These X and Y cell types in the cat's lateral geniculate nucleus are innervated by equivalent, distinctive retinal cell types and thus represent an independent, parallel, retino-geniculo-cortical neuronal ~~stream~~ of information. X cells have smaller cell bodies and dendritic arbors that are largely bipolar and oriented perpendicular to the laminar borders of the lateral geniculate nucleus (Friedlander, Lin, Stanford, & Sherman, 1981; Stanford, Friedlander, & Sherman, 1983); Y cells have larger cell bodies and thicker dendritic ~~oriented~~ more or less in a spherical volume (Friedlander et al., 1981; Stanford et al., 1983). For both cells, retinal inputs innervate relatively proximal dendrites, within about 100 µm from the cell body (Wilson, Friedlander, & Sherman, 1984). On Y cells, these retinal synapses are formed fairly simply onto dendritic shafts, but in X cells, these tend to contact curious grape-like appendages found near proximal dendritic branch points.

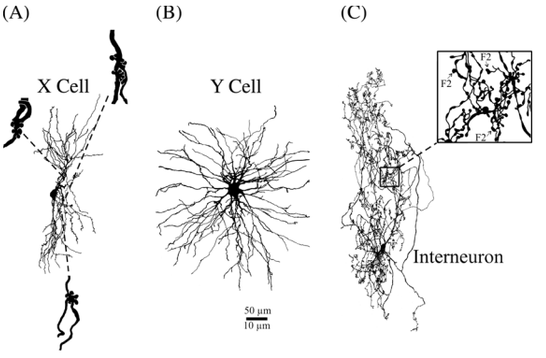

Figure 10.2 Examples of thalamic cell types from lateral geniculate nucleus of the cat. These tracings were made from intracellular labeling ~~of~~ during *in vivo* recording (Friedlander et al., 1981; Hamos et al., 1985). **A:** X relay cell. Note the grape-like appendages near primary branch points. Three examples are shown at higher magnification. **B:** Y relay cell. **C:** Interneuron. The dendrites have the appearance of an axonal terminal arbor, and the many boutons seen among the dendrites are indeed synaptic boutons known as F2. ~~Three examples~~ are shown in the higher magnification. **Scale:** The scale bar is 50 µm for the cell drawings and 10 µm for the insets of **A** and **C.**

Interneurons

Interneurons are particularly interesting cells because, in addition to conventional axonal outputs, they also produce presynaptic terminals from their dendrites, and these dendritic outputs are more numerous than are the axonal (Friedlander et al., 1981; Hamos et al., 1985; Wilson et al., 1984). Figure 10.2C shows an example of an interneuron from the lateral geniculate nucleus of the cat. The dendrites look so much like an axonal terminal arbor that they have been called *axoniform* (Guillery, 1966). The axonal arbor distributes within the dendritic arbor, and they look so much alike that, with light microscopy, it is often impossible to distinguish the axon. However, because the axon is myelinated and the dendrites are not, they can readily be distinguished with an electron microscope.

Also, much work at the electron microscopic level (Famiglietti & Peters, 1972; Guillery, 1969; Hamos et al., 1985; Ralston, 1971) has made it possible to distinguish the axonal terminals (called F1) from the dendritic terminals (called F2; see Figure 10.2C). One important distinction is that the axonal (F1) terminals are strictly presynaptic

(to relay cells and other interneurons), whereas the dendritic (F2) terminals are both presynaptic (mostly to the grape-like clustered appendages of X cells; see Figure 10.2A and Wilson et al., 1984) and postsynaptic (mostly to retinal terminals). The F2 terminals are the only postsynaptic terminals so far described in the thalamus. The circuits entered into by these F2 terminals and the functional properties of interneurons are discussed further later in the chapter.

Thalamic Reticular Nucleus Cells

The final major cell type in the thalamus is the reticular cell, found in the thalamic reticular nucleus. These tend to have elongated dendritic arbors oriented parallel to the borders of the thalamic reticular nucleus (Figure 10.3; Uhlrich, Cucchiaro, Humphrey, & Sherman, 1991). Their axons project into the main relay nuclei of the thalamus and selectively target relay cells (Cucchiaro, Uhlrich, & Sherman, 1991), and local collaterals provide for contacts between reticular cells (Lam, Nelson, & Sherman, 2006; Sanchez-Vives, Bal, & McCormick, 1997). These cells are also functionally connected via gap junctions (Lam et al., 2006; Landisman et al., 2002).

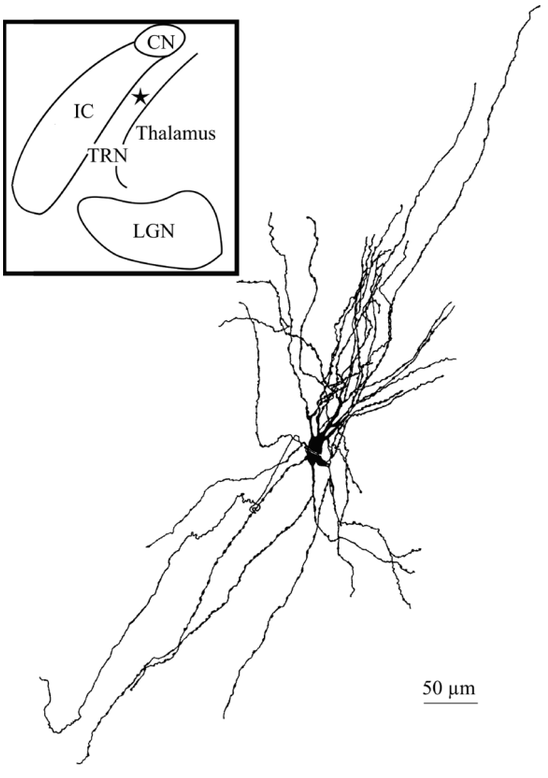

Figure 10.3 Example of cell in the thalamic reticular nucleus of *Galago* filled with neurobiotin. The star in the inset shows the location of the cell body. Redrawn from Figure II-12 of (Sherman and Guillery, 2006) from data supplied by P Smith, K Manning and D Uhlrich. ***Abbreviations:*** As in Figure 10.1, plus *IC,* internal capsule.

CELL PROPERTIES OF THALAMIC RELAY NEURONS

Thalamic relay cells, like cells throughout the central nervous system, have numerous voltage- and time-gated ionic channels in their membranes. The best known of these are the Na^+ and K^+ channels underlying the conventional action potential (see Figure 10.4). There are many others, including channels for other cations. One that is especially important to thalamic relay cells involves T-type Ca^{2+} channels. (For details of T channel properties, see Huguenard & McCormick, 1994; Jahnsen & Llinás, 1984a, 1984b; and for other voltage gated channels in thalamic neurons, see Huguenard & McCormick, 1994; Sherman & Guillery, 2006.) The properties of these T channels are qualitatively the same as those of Na^+ channels involved with the action potential. Figure 10.4 summarizes these properties, emphasizing the similarities with the T channels shown in Figure 10.5.

Basic Properties of the T Channel

Figure 10.4 is a review of the main properties of the Na^+ (and K^+) channels underlying the action potential. When the Na^+ channel is open, Na^+ flows into the cell, producing a depolarizing current known as I_{Na}. However, the Na^+ channel has two voltage sensitive gates—an *activation gate* and an *inactivation gate*—and both must be open for Na^+ to flow into the cell. At a normal resting membrane potential (e.g., −65 mV), the inactivation gate is open, but the activation gate is closed, and thus there is no inward flow of Na^+ (Figure 10.4A). Here I_{Na} is deactivated because the activation gate is closed, but it is also relieved of inactivation (or is de-inactivated) because the inactivation gate is open. When the membrane is depolarized to a certain level, the ~~inactivation~~ threshold for I_{Na} (Figure 10.4B), the activation gate pops open and so I_{Na} is both activated and de-inactivated; the result is that Na^+ flows into the cell, producing the depolarizing upswing of the action potential. This depolarization, after a suitable period of 1 msec or so, leads to closing of the inactivation gate, and so while the Na^+ channel remains activated, it is also ~~de-inactivated~~ (Figure 10.4C). This plus the opening of various slower K^+ channels (channels that do not inactivate because they have only an activation gate), which produces a hyperpolarizing outward flow of K^+, repolarizes the membrane to near its starting position (Figure 10.1D). However, despite being repolarized, I_{Na}

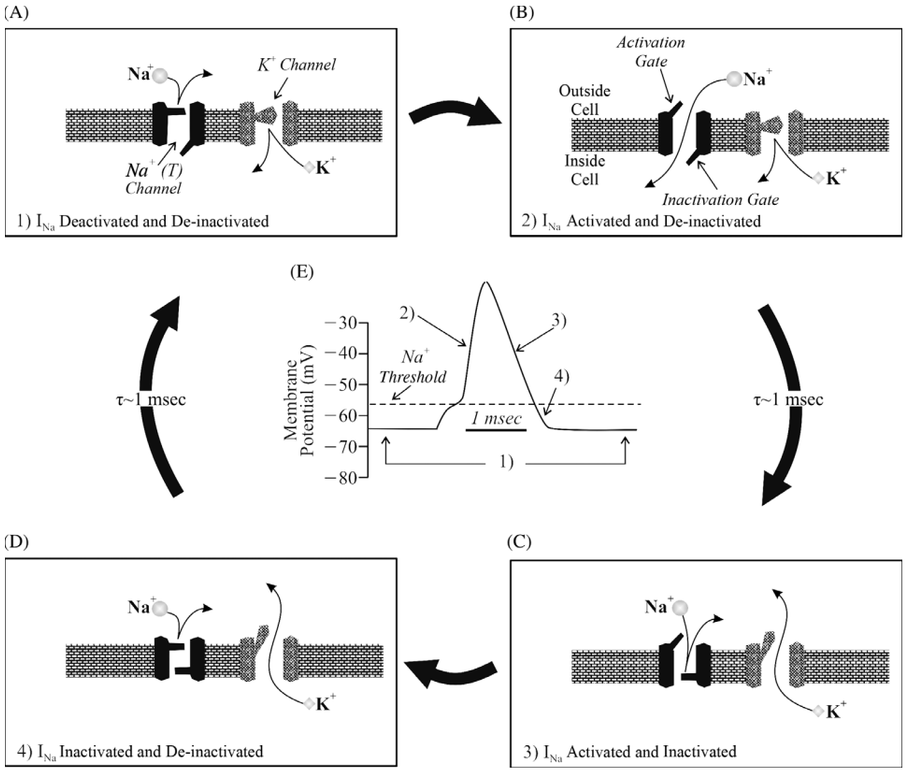

Figure 10.4 Schematic representation of voltage dependent Na^+ and K^+ channels underlying the conventional action potential. **A-D** show the channel events and **E** shows the effects on membrane potential. The Na^+ channel has two voltage dependent gates: an *activation gate* that opens at depolarized levels and closes at hyperpolarized levels, and an *inactivation gate* with the opposite voltage dependency. Both must be open for the inward, depolarizing Na^+ current (I_{Na}) to flow. The K^+ channel (actually an imaginary combination of several different K^+ channels) has a single activation gate, and when it opens at depolarized levels, an outward, hyperpolarizing K^+ current is activated. **A:** At a resting membrane potential (roughly −60 to −65 mV), the activation gate of the Na^+ channel is closed, and so it is deactivated, but the inactivation gate is open, and so it is de-inactivated. The single gate for the K^+ channel is closed, and so the K^+ channel is also deactivated. **B:** With sufficient depolarization to reach its threshold, the activation gate of the Na^+ channel opens, allowing Na^+ to flow into the cell. This depolarizes the cell, leading to the upswing of the action potential. **C:** The inactivation gate of the Na^+ channel closes after the depolarization is sustained for roughly 1 msec ("roughly," because inactivation is a complex function of time and voltage), and the slower K^+ channel also opens. These combined channel actions lead to the repolarization of the cell. While the inactivation gate of the Na^+ channel is closed, the channel is said to be inactivated. **D:** Even though the initial resting potential is reached, the Na^+ channel remains inactivated, because it takes roughly 1 msec ("roughly" having the same meaning as above) of hyperpolarization for de-inactivation. **E:** Membrane voltage changes showing action potential corresponding to the events in **A** to **D.** Redrawn from Figure IV-4 of (Sherman and Guillery, 2006).

remains inactivated because it takes roughly 1 msec of this hyperpolarization to open the inactivation gate, restoring the initial conditions of Figure 10.1A. Thus the two gates of the Na^+ channel have opposite voltage dependencies and both respond relatively quickly to voltage changes. Finally, note that the roughly 1 msec of hyperpolarization needed to de-inactivate the Na^+ channel provides a refractory period limiting firing rates for the action potential to ≤1000 Hz.

While Figure 10.4 shows the basic voltage gated properties of the Na^+ channel, one other feature is essential to propagating an all-or-none action potential. That is, the density of Na^+ channels must be sufficiently high that, once threshold is reached, the further depolarization caused by the initial channels to open causes a self-regenerating, explosive opening of other channels, and this propagates as an action potential. If the Na^+ channel density were too low, the initial channels to open would lead only to a local depolarization that would decay exponentially.

As shown in Figure 10.5, the voltage behavior of the T channel is qualitatively the same as that of the Na^+ channel, with the same two types of voltage gate. At the starting position of Figure 10.5A, the activation gate is closed, but sufficient depolarization opens it (Figure 10.5B), allowing the inward I_T that further depolarizes the cell. This depolarization eventually inactivates I_T (Figure 10.5C) which, along with the activation of K^+ channels, repolarizes the cell (Figure 10.5D). This repolarization eventually leads to de-inactivation of I_T (Figure 10.5A).

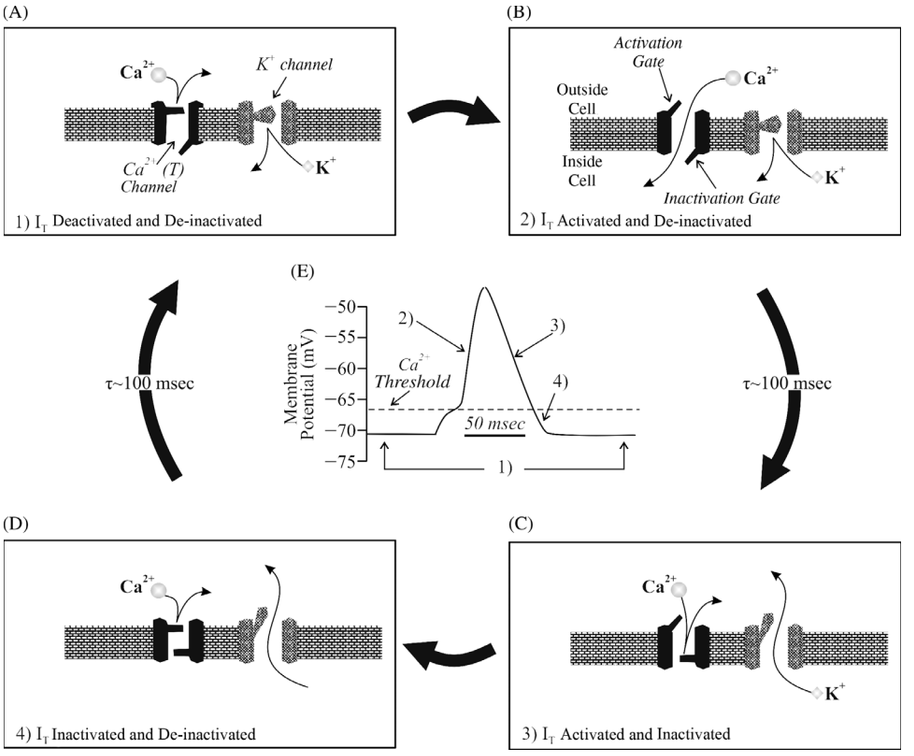

Figure 10.5 Schematic representation of actions of voltage dependent T (Ca^{2+}) and K^+ channels underlying low threshold Ca^{2+} spike; conventions as in Figure 10.4. Note the strong qualitative similarity between the behavior of the T channel here and the Na^+ channel shown in Figure 10.4, including the presence of both activation and inactivation gates with similar relative voltage dependencies. **A-D** show the channel events and **E** shows the effects on membrane potential. **A:** At a relatively hyperpolarized resting membrane potential (roughly −70 mV), the activation gate of the T channel is closed, but the inactivation gate is open, and so the T channel is deactivated and de-inactivated. The K^+ channel is also deactivated. **B:** With sufficient depolarization to reach its threshold, the activation gate of the T channel opens, allowing Ca^{2+} to flow into the cell. This depolarizes the cell, providing the upswing of the low threshold spike. **C:** The inactivation gate of the T channel closes after roughly 100 msec ("roughly", because, as for the Na^+ channel in Figure 10.4, closing of the channel is a complex function of time and voltage), inactivating the T channel, and the K^+ channel also opens. These combined actions repolarize the cell. **D:** Even though the initial resting potential is reached, the T channel remains inactivated, because it takes roughly 100 msec of hyperpolarization for de-inactivation. **E:** Membrane voltage changes showing low threshold spike corresponding to the events in **A** to **D.** Redrawn from Figure IV-5 of (Sherman and Guillery, 2006).

As in the case of Na^+ channels, if a sufficiently high density of T channels exists, the threshold opening of the initial T channels leads to an explosive all-or-none spike. This is the case for thalamic relay cells, and the result is a spike-like depolarization of roughly 25 to 50 mV that propagates throughout the dendrites and soma. T channels are quite common in neurons throughout the central nervous system, but only in rare cells is the density high enough to support all-or-none Ca^{2+} spikes. Thus, this property of all-or-none Ca^{2+} spiking based on T channels is fairly unique to the thalamus. Every relay cell of every nucleus in every mammalian species so far tested shows this property (Sherman & Guillery, 2006).

However, a further inspection of Figures 10.4 and 10.5 reveals certain important quantitative differences between the behavior of the Na^+ and Ca^{2+} channels. Perhaps most important are the temporal properties of the inactivation gates. While the activation gates for both channels respond quickly to voltage changes, as does the inactivation gate of the Na^+ channel, the inactivation gate of the T channel is much slower, requiring roughly 100 msec of a sustained polarization change to open or close. Actually, as is the case for the Na^+ channel, the inactivation gate of the T channel has a complex voltage- and time-dependency, so that the greater the sustained polarization change, the more rapidly the gate opens or closes (Zhan, Cox, Rinzel, & Sherman, 1999). This temporal property for the T channel is important and will be considered further. Another quantitative difference is the functional voltage range: the T channel operates in a more hyperpolarized regime. In fact, because the T channel activates at a more hyperpolarized level, the resulting depolarization, which in thalamic relay cells is an all-or-none Ca^{2+} spike, is also known as the "low threshold spike."

One other important difference not shown in Figures 10.4 and 10.5 is the distribution of these channels: T channels are effectively limited to the soma and dendrites, whereas Na^+ channels, often found there as well, are notable for their distribution along the axon. This allows action potentials to travel from the soma to a target far away, and in the case of thalamic relay cells, this Na^+ channel distribution permits action potentials to be delivered to cortical targets. While T channels underlie Ca^{2+} spikes propagated in the dendrites and soma, these spikes do not propagate to the cortex. Thus the significance of these Ca^{2+} spikes ultimately rests with their effect on conventional action potentials as described in the following section. This effect is dramatic and important.

Burst and Tonic Firing Modes

The primary functional significance of T channels for thalamic relay cells is that they are responsible for which of two very different response modes, called *burst* and *tonic,* characterize these cells' responses (Jahnsen & Llinás, 1984a; Zhan et al., 1999). Figure 10.6 summarizes some of the features of these response modes. If the cell has been initially depolarized by just a few mV (≥5 mV) from rest, the T channels are inactivated and play no role in the response. This leads to tonic firing (Figure 10.6A) where a depolarizing current injection elicits a stream of unitary action potentials that lasts as long as the stimulus is suprathreshold. If, however, the cell has been hyperpolarized initially by ≥5 mV or so from rest, the T channels are de-inactivated and primed to respond to the next suitable depolarization, and the result is burst firing. This is shown in Figure 10.6B where the same depolarizing stimulus as in Figure 10.6A now evokes an all-or-none low threshold Ca^{2+} spike with a burst of high frequency action potentials riding its crest. The exact same stimulus (think of this as the same excitatory postsynaptic potential or EPSP evoked from the same retinal input to a geniculate relay cell) creates a very different pattern of action potentials depending on the recent voltage history of the relay cell, and this pattern of firing is the only signal that reaches cortex.

To summarize: The recent voltage history of a relay cells determines the inactivation state of its T channels, and this, in turn, determines whether the relay cell responds to its next, suprathreshold excitatory input in tonic or burst mode, a determination that dramatically affects the message relayed to the cortex.

Significance of Response Mode for Thalamocortical Relays

A major question for which we have only partial and largely hypothetical answers is: What is the functional significance

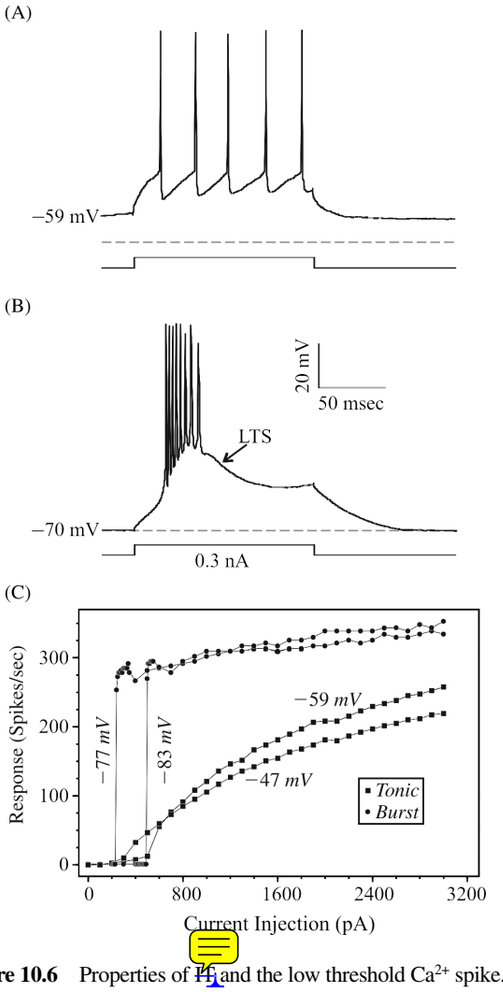

Figure 10.6 Properties of I_T and the low threshold Ca^{2+} spike. All examples are from relay cells of the cat's lateral geniculate nucleus recorded intracellularly in an *in vitro* slice preparation. **A,B:** Voltage dependency of the low threshold spike. Responses are shown to the same depolarizing current pulse delivered intracellularly but from two different initial holding potentials. When the cell is relatively depolarized (**A**), I_T is inactivated, and the cell responds in tonic mode, which is a stream of unitary action potentials to a suprathreshold stimulus. When the cell is relatively hyperpolarized (**B**), I_T is de-inactivated, and the cell responds in burst mode, which involves activation of a low threshold Ca^{2+} spike (LTS) with multiple action potentials (8 in this example) riding its crest. **C:** Input-output relationship for another cell. The abscissa is the amplitude of the depolarizing current pulse, and the ordinate is the firing frequency of the cell for the first 6 action potentials of the response, since this cell usually exhibited 6 action potentials per burst in this experiment. The initial holding potentials are shown, and −47 mV and −59 mV reflects tonic mode, whereas −77 mV and −83 mV reflects burst mode. Redrawn from Figure IV-6 of Sherman and Guillery (2006).

of the burst and tonic response modes for thalamic relay performance? One answer comes from a consideration of the fact that the only message reaching the cortex is in the form of action potentials and they are evoked differently in the two response modes. During tonic firing, action potentials

are directly evoked by an appropriate, suprathreshold depolarizing stimulus (e.g., an EPSP), and so a larger EPSP will evoke more firing. In other words, there is a relatively linear relationship between input (or EPSP) amplitude and firing rate. During burst firing, however, action potentials are not directly activated by the depolarizing input; instead they are activated by the large, depolarizing low threshold Ca^{2+} spike. Because this Ca^{2+} spike is all-or-none, a larger depolarizing input or EPSP will not evoke a larger Ca^{2+} spike, and thus the input-output relationship during burst firing is highly nonlinear, approximating a step function. These differences are illustrated in Figure 10.6C (Zhan et al., 1999).

Figure 10.7 shows related and additional effects of response mode. In this example, a geniculate relay cell is recorded intracellularly in an anesthetized cat while its responses to visual stimuli are monitored. These responses indicate how retinal input is relayed to the cortex. Because of the intracellular recording, it is possible to pass current into the cell either to depolarize its baseline level sufficiently to inactivate I_T (e.g., baseline depolarized to –65 mV in Figure 10.7A) and promote tonic firing or to hyperpolarize it (e.g., baseline depolarized to –75 mV in Figure 10.7B) so as to de-inactivate I_T and promote burst firing. The visual stimulus in this case is a drifting sinusoidal grating, providing a visual stimulus in which contrast varies sinusoidally with time at 2 Hz. Figure 10.7A, lower, shows that the tonic response profile is sinusoidal and accurately reflects the contrast changes in the stimulus. The response in burst mode (Figure 10.7B, lower) does not accurately reflect the contrast changes, showing the sort of nonlinear distortion that can largely be predicted by the cellular properties shown in Figure 10.6C.

This provides an obvious advantage for tonic firing because the nonlinear distortion caused by burst firing will limit the fidelity of the message relayed to the cortex. In other words, to faithfully reconstruct the visual world, the cortex is better served by tonic firing. What, then, is the purpose of burst firing? Two possible advantages have been suggested.

One advantage is related to spontaneous firing, which is much lower during burst firing (Figure 10.7A, B, upper histograms; Guido, Lu, & Sherman, 1992; Guido, Lu, Vaughan, Godwin, & Sherman, 1995). Actually, the higher spontaneous activity helps preserve linearity during tonic firing because the raised level of activity allows inhibitory components of the visual stimulus to be represented; without this, the response would "bottom out," reflecting rectification, which is itself a nonlinearity. There is another, perhaps more important, consequence of the difference in spontaneous activity levels. Spontaneous activity can be considered noise from the perspective of the cortex because, by definition, it represents firing in the geniculate relay cell that bears no relation to visual stimulation. The lower histograms in Figure 10.7A and B suggest that

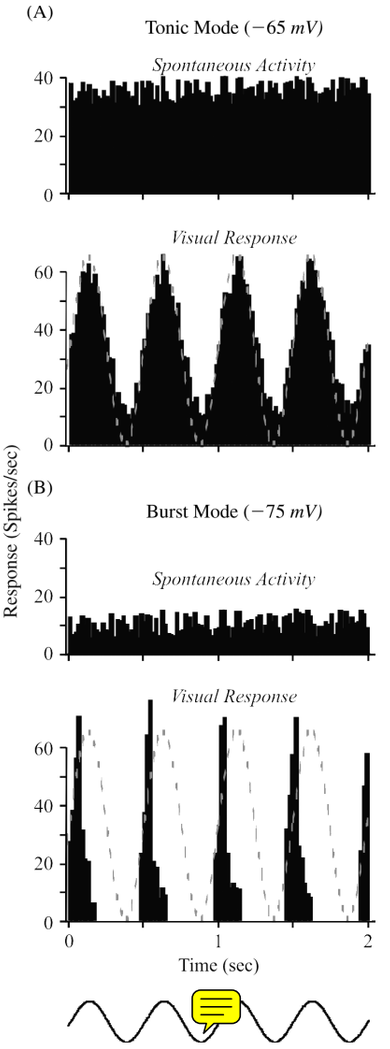

Figure 10.7 Responses of a representative relay cell in the lateral geniculate nucleus of a lightly anesthetized cat to a sinusoidal grating drifted through the cell's receptive field. The trace at the bottom reflects the sinusoidal changes in luminous contrast with time. Current was injected into the cell through the recording electrode to alter the membrane potential. Thus in **A,** the current injection was adjusted so that the membrane potential without visual stimulation averaged −65 mV, promoting tonic firing, because I_T is mostly inactivated at this membrane potential; in **B,** the current injection was adjusted to the more hyperpolarized level of −75 mV, permitting de-inactivation of I_T and promoting burst firing. Shown are average response histograms to the visual stimulus (bottom histograms in **A** and **B**) and during spontaneous activity with no visual stimulus (top histograms), plotting the mean firing rate as a function of time averaged over many epochs of that time. The sinusoidal changes in contrast as the grating moves across the receptive field are also shown as a dashed, gray curve superimposed on the responses in the lower histograms. Note that the response profile during the visual response in tonic mode looks like a sine wave, but the companion response during burst mode does not. Note also that the spontaneous activity is higher during tonic than during burst firing. Redrawn from Figure VI-2 of Sherman and Guillery (2006).

the signal relayed during both response modes to visual stimulation are roughly equal in extent, and so the lower noise during burst firing suggests that the signal-to-noise ratio is higher during burst firing. A higher signal-to-noise ratio, in turn, suggests better detectability of the stimulus in the response of the geniculate relay cell, and this has been demonstrated (Guido, Lu, et al., 1995).

Another advantage of burst firing is that it more powerfully affects the cortex (Swadlow & Gusev, 2001; Swadlow, Gusev, & Bezdudnaya, 2002). This is because the thalamocortical synapse shows strong paired-pulse depression (Abbott, Varela, Sen & Nelson, 1997; Castro-Alamancos & Connors, 1997; Chung, Li, & Nelson, 2002; Gil, Connors, & Amitai, 1999; Lee & Sherman, 2007). This is shown in Figure 10.8A, where a facilitating layer 6 corticothalamic synapse (Reichova & Sherman, 2004) is also shown for comparison. For a depressing synapse, action potentials arriving with interspike intervals of less than 50 to 150 msec (see Figure 10.8B) or so will depress the postsynaptic responses resulting in a smaller EPSP. During tonic firing, interspike intervals are sufficiently high to keep the thalamocortical synapses in more or less a constant state of depression. However, the dynamics of burst firing result in a synapse with no depression. This is because, to burst, a cell must be in a sustained state of hyperpolarization for ≤100 msec or so (to de-inactivate T channels) before responding to a depolarizing EPSP, and so there can be no action potentials during this period; this imposes a requisite silent period on a cell before each burst meaning that, when the burst is evoked, the thalamocortical synapse is free of depression. Elegant experiments by Swadlow and colleagues (Swadlow & Gusev, 2001; Swadlow et al., 2002) have directly confirmed this (Figure 10.9).

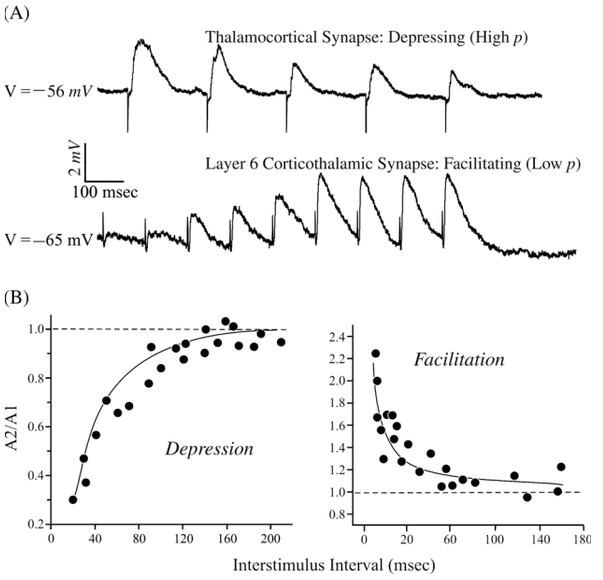

Figure 10.8 Examples of paired-pulse depression and paired-pulse facilitation. These recordings were made from *in vitro* slices of the mouse brain in which thalamocortical and corticothalamic projections are retained in the somatosensory system. When electrical stimulation is applied as a train of impulses at fixed frequency to afferents of a recorded cortical or thalamic cell, the resultant EPSPs decrease with stimulus number (paired-pulse depression) or increase (paired-pulse facilitation). **A:** Example of paired-pulse depression (upper trace; recording from a layer 4 cell and activating inputs from thalamus) and paired-pulse facilitation (lower trace; recording from thalamic relay cell and activating inputs from layer 6 of cortex). **B:** Time course of paired-pulse effects for the examples in **A.** The abscissa shows the interstimulus interval, and the ordinate, the measure of depression (left) or facilitation (right) expressed as the ratio of the amplitude of the second EPSP to the amplitude of the first. Unpublished data from laboratory of S.M. Sherman.

Hypothesis for Burst and Tonic Firing

To summarize the known functional consequences of firing mode (and there may be many other, undiscovered ones), tonic mode is associated with a more linear relay, while burst mode is associated both with superior signal detection and stronger cortical activation. This has led to the theory (Sherman, 1996, 2001; Sherman & Guillery, 2002, 2006) that burst mode may be involved in providing a strong "wake-up call" to the cortex that something has changed in the environment (e.g., the sudden appearance of a new visual stimulus), particularly in circumstances during which attention is not devoted to the relay under question (e.g., general drowsiness, or inattention, or for auditory thalamic relays while attention is diverted to visual stimuli). There are several very indirect lines of evidence in support of this. One is that bursting of thalamic relay cells increases with drowsiness (Massaux & Edeline, 2003; Ramcharan, Gnadt, & Sherman, 2000; Swadlow & Gusev, 2001). Another is that the initial cycle of a repeating visual tends more frequently to evoke bursting of geniculate relay cells (Guido & Weyand, 1995). Finally, studies of visual responses, including the use of natural visual scenes as stimuli, indicate that the best stimulus to evoke a burst is the replacement in the visual field of an inhibitory stimulus with an excitatory one, for instance, the replacement of a dark spot over the center of an on-center cell with a bright spot (Alitto, Weyand, & Usrey, 2005; Denning & Reinagel, 2005; Lesica & Stanley, 2004; Wang et al., 2007).

For this hypothesis to make sense, thalamic circuitry must be arranged in a manner that can efficiently control response mode, promoting the transition between burst and tonic firing under appropriate conditions. That is, there must be inputs to relay cells that effectively control membrane potential for a sufficiently long period (i.e., for at least 100 msec or so) to control the inactivation state of I_T. As the next section shows, this is indeed the case.

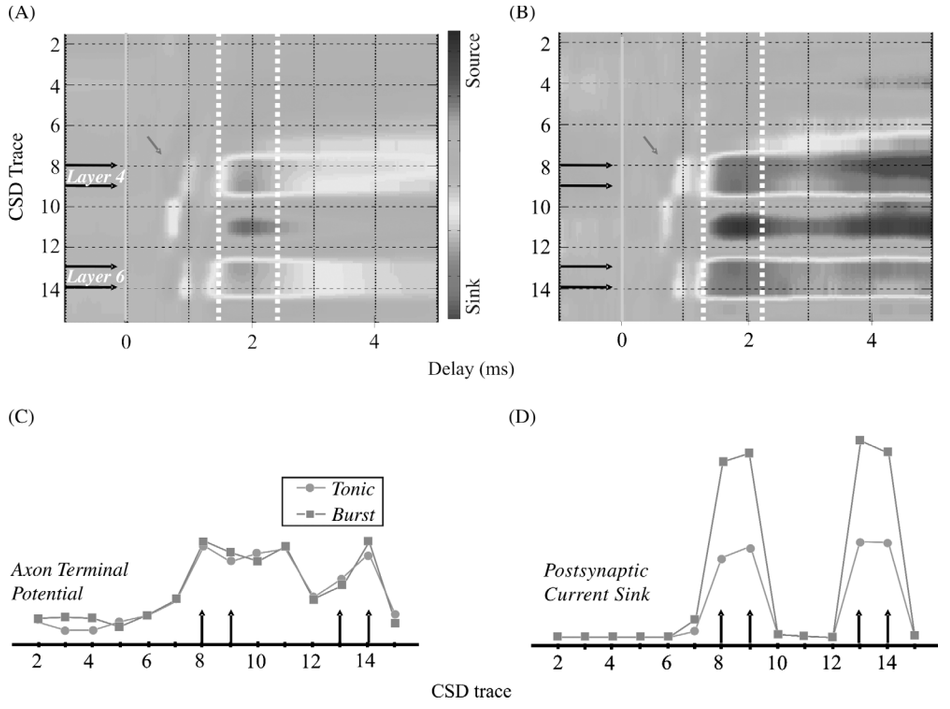

Figure 10.9 Current source density profiles in cortex generated from single spike in afferent thalamic neuron. Recordings were made simultaneously in an awake rabbit from a single neuron in the ventral posterior medial nucleus of the thalamus and from 16 probes at different depths along a column in the cortical target field of the recorded thalamic neuron. Spike triggered averaging was used to generate the synaptic sinks and sources as shown. **A,B:** Colorized current source density profile generated by tonic spike (**A,** ~120,000 thalamic action potentials) or first spike in burst (**B,** 2427 thalamic action potentials) in the thalamic afferent. The vertical orange line in each indicates the time of the action potential in the thalamic afferent. The red arrow in each shows the current source evoked by the terminals of the thalamic afferent, and note that this is the same for the tonic and burst spike. The depths of layers 4 and 6 are also indicated. The vertical dashed white lines show the initial 1 msec of the postsynaptic responses, with large sinks in layers 4 and 6. Note the denser sinks for the burst spike (**B**) compared to the tonic spike (**A**). **C,D:** amplitude (peak peak) of the axon terminal response (**C,** indicated by the red arrows in **A,B**) and the magnitude of the initial 1 msec of the postsynaptic current sink (**D**) plotted at different recording sites for both the tonic spike and first spike in a burst. Note that there is no difference in the corticothalamic terminal responses for these two spikes but that the peaks in layers 4 and 6 are greater for the burst spike. Redrawn from Figure 3 of Swadlow et al. (2002).

CIRCUIT PROPERTIES OF THALAMIC RELAY NEURONS

Fortunately, the detailed circuit properties of the thalamus are largely conserved among thalamic nuclei. To be sure, there are some differences in circuitry among thalamic nuclei. Certain ones will be discussed next. Because we know most about the lateral geniculate nucleus, this serves as a convenient model for all of the thalamus. Figure 10.10 schematically shows the main circuitry involving geniculate neurons, including the main transmitters and classes of postsynaptic receptor involved. (These circuit details are reviewed in Sherman & Guillery, 1996, 2004, 2006).

Basic Anatomical Circuits

Relay cells receive input from retinal axons and, in turn, project to visual cortex, mostly to layer 4 but also to layer 6. Also intimately associated with relay cells are two types of local, GABAergic neurons that provide inhibitory input to relay cells: these are local interneurons and cells of the nearby thalamic reticular nucleus. Interneurons live among relay cells throughout the relay nuclei of the thalamus, and the ratio is roughly three relay cells to every interneuron across nuclei and species, with one curious exception (Arcelli, Frassoni, Regondi, De Biasi, & Spreafico, 1997). That is, while the lateral geniculate nucleus of the rat and mouse contain roughly 25% interneurons, the rest of the thalamus in these species contain almost no interneurons. This is not a rodent property because the thalamus of other rodent species, like squirrels, guinea pigs, and so on, contains normal numbers of interneurons.

There are two major sources of extrinsic input to geniculate circuitry (see Figure 10.10). One is a feedback glutamatergic projection from layer 6 of the visual cortex, and the other is a mostly cholinergic input from

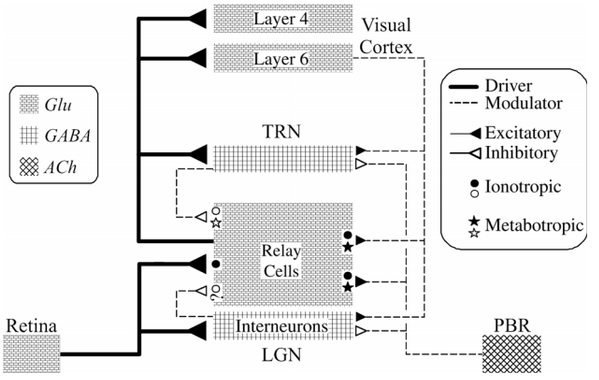

Figure 10.10 Schematic view of details of the main connections of the lateral geniculate nucleus. Indicated are the inhibitory or excitatory nature of the synapses, the postsynaptic receptors activated by each input on relay cells, and the neurotransmitters involved. ***Abbreviations:*** *ACh,* acetylcholine; *GABA,* γ-aminobutyric acid; *Glu,* glutamate; *LGN,* lateral geniculate nucleus; *PBR,* parabrachial region; *TRN,* thalamic reticular nucleus.

the parabrachial region of the midbrain. In both cases, individual axons branch to innervate all three thalamic cell classes: relay cells, interneurons, and reticular cells. Not shown for simplicity are various serotonergic, noradrenergic, GABAergic, and dopaminergic inputs from the brain stem and histaminergic inputs from the tuberomamillary nucleus of the hypothalamus. This is partly to avoid unnecessary complication and also because the functional significance of these other inputs is just beginning to be understood. (see Sherman & Guillery, 1996, 2004, 2006). Thus, not only do relay cells receive inputs from the retina, which represents the main input relayed to the cortex, but they also receive inputs from other sources as well.

Postsynaptic Receptors on Relay Cells

It is clear from Figure 10.10 that nonretinal inputs can influence retinogeniculate transmission. All of these inputs to relay cells operate via conventional chemical synapses, and thus their postsynaptic effects are largely controlled by postsynaptic receptors. These, too, are illustrated in Figure 10.10, and they are divided into two main groups: ionotropic and metabotropic. Examples of ionotropic receptors for the transmitter systems shown are AMPA receptors for glutamate, the $GABA_A$ receptor, and nicotinic receptors for acetylcholine; the equivalent metabotropic receptor examples are various metabotropic glutamate receptors, the $GABA_B$ receptor, and various muscarinic receptors for acetylcholine.

Details of differences between these receptor classes are many (Brown et al., 1997; Conn & Pin, 1997; Mott & Lewis, 1991; Nicoll, Malenka, & Kauer, 1990; Pin & Duvoisin, 1995; Recasens & Vignes, 1995), but two major differences are particularly relevant here. First, excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) generated via ionotropic receptors tend to be very brief, on the order of 10 msec or a few 10s of msec, whereas those via metabotropic are much more sustained, lasting 100s of msec to several seconds. Second, metabotropic receptors tend to be less sensitive in the sense that afferent firing rates usually need to be higher before they are activated; this is because these receptors tend to be a bit eccentrically located in the synapse with respect to ionotropic receptors (Lujan, Nusser, Roberts, Shigemoto, & Somogyi, 1996; Somogyi, Tamas, Lujan, & Buhl, 1998), and so more transmitter must be released to reach them. With these differences in mind, it is interesting that retinal input activates only ionotropic receptors (mostly AMPA), whereas all of the nonretinal inputs activate metabotropic receptors, often in addition to activation of ionotropic receptors. One input for which the postsynaptic receptor is not as clear is the input from interneurons to relay cells: clearly $GABA_A$ receptors are involved, but there have as yet been no definitive tests for the presence or absence of $GABA_B$ receptors for this input.

Consequences of Type of Postsynaptic Receptor

The fact that only ionotropic receptors are activated by retinal input is good for transfer of temporal information. That is, because the evoked EPSPs are brief, temporal summation does not occur until relatively high rates of firing in the retinal afferents, and thus it is possible to evoke a single EPSP for every retinal action potential for reasonable high rates of firing, thereby representing each input action potential as an EPSP in a one-to-one manner. Put another way, if retinal inputs activated metabotropic glutamate receptors, the sustained EPSPs would summate at lower firing rates, and no longer would postsynaptic responses ultimately relayed to the cortex be a precise copy of the retinal input. The representation of EPSPs evoked via metabotropic glutamate receptors would act like a low pass temporal filter, and temporal information would be lost. In this regard, the activation of metabotropic receptors, because of their long time course, would seem to provide a poor substrate for effective information transfer but an excellent one for modulation.

In contrast, the sustained PSPs evoked by nonretinal inputs to relay cells means that sufficient activation of these inputs will provide rather lengthy effects on membrane potential, and thus excitability, of the relay cell. In this way, these nonretinal inputs will serve to modulate the gain or effectiveness of retinogeniculate transmission. Other consequences of these nonretinal inputs can be seen in their control of voltage gated ion channels, and a good

example of this is their ability to control response mode—burst or tonic—of the relay cell.

Control of Response Mode

Recall from the previous description of T channel behavior that inactivation or de-inactivation requires a change in membrane potential to be sustained for at least roughly 100 msec. PSPs activated via ionotropic receptors are poorly suited to this, because they are too brief. Thus, for instance, an AMPA- or nicotinic-mediated EPSP is too brief to inactivate many T channels for a cell in burst mode, and a $GABA_A$-mediated IPSP is too brief to relieve many T channels of their inactivation for a cell in tonic mode. However, the sustained PSPs of metabotropic receptors, lasting ≥100s of msec, are ideally suited to control response mode. Thus activation of metabotropic glutamate receptors via layer 6 corticogeniculate input or muscarinic receptors via parabrachial input produces an EPSP sustained enough to inactivate T channels and switch relay cell firing mode from burst to tonic; likewise, activation of $GABA_B$ receptors produces an IPSP sustained enough to de-inactivate T channels and switch relay cell firing mode from tonic to burst.

Further Details of Effects of Corticogeniculate or Parabrachial Inputs

Another consequence of the postsynaptic receptor is that it often determines whether a given neurotransmitter acts in an excitatory or inhibitory manner. In the case of the circuitry shown in Figure 10.10, cholinergic inputs excite relay cells while they inhibit interneurons and reticular cells. This is achieved by two types of muscarinic receptors (McCormick, 1992). Those on relay cells are mostly of the M1 type, and activation of M1 receptors leads to closing of K^+ channels, reducing the outward leakage of K^+ ions and thereby resulting in an EPSP. Those on the GABAergic cells are mostly of the M2 type, and activation of M2 receptors leads to opening of K^+ channels, increasing the outward leakage of K^+ ions and thereby resulting in an IPSP. This allows cholinergic inputs to the thalamus to perform a neat trick: they directly excite relay cells while they indirectly disinhibit them. As a result, increasing activity of parabrachial neurons leads to more depolarized relay cells, making them more responsive to retinal input and biasing them toward the tonic firing mode. Indeed, parabrachial cells become more active with increasing vigilance (Datta & Siwek, 2002; Steriade & Contreras, 1995), and more vigilance is associated with increased retinogeniculate transmission and a shift toward tonic firing (Massaux & Edeline, 2003; Ramcharan et al., 2000; Swadlow & Gusev, 2001).

The situation with corticogeniculate inputs is more complex. These inputs to relay cells and local GABAergic cells are all excitatory, and thus the circuitry shown in Figure 10.10 suggests that corticogeniculate input directly excites relay cells but indirectly inhibits them, and it is not clear from this perspective what purpose this serves or what effect corticogeniculate input has on the firing mode of relay cells. However, as Figure 10.11 indicates, Figure 10.10 may be misleading in terms of the specifics of corticogeniculate circuitry because it does not reveal important details. Figure 10.11 shows two distinct variants of this circuitry involving the thalamic reticular nucleus; one can imagine similar variants involving interneurons and, of course other variants are possible.

The variant shown in Figure 10.11A is an example of classical feed forward inhibition. It might seem puzzling because increased activity leads to both depolarization and (indirect) hyperpolarization of the relay cell, with perhaps minimal effect on the relay cell's membrane potential. This would have very little effect on T channel inactivation and thus little effect on response mode. However, the resultant increase in synaptic conductance would reduce input resistance of the relay cell, and this and other subtle effects pointed out by Chance, Abbott, and Reyes (2002) would result in a reduced retinogeniculate EPSP amplitude. In other words, this form of feedforward inhibition acts as an effective means of gain control for retinogeniculate transmission.

The variant shown in Figure 10.11B has quite a different functional significance. This is no longer an example of feedforward inhibition, but instead, an active corticogeniculate axon will directly excite some relay cells and indirectly

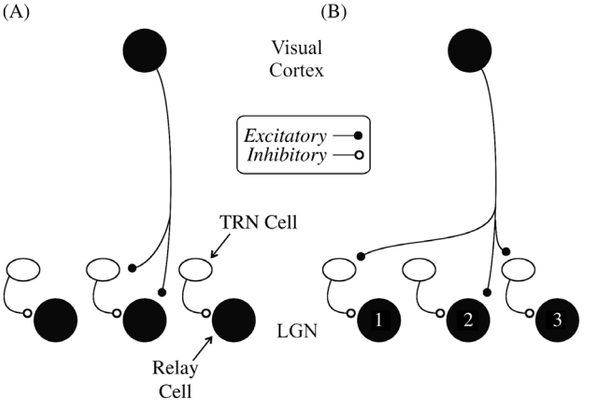

Figure 10.11 Schematic view of different possible corticothalamic circuits involving the thalamic reticular nucleus that have quite different effects on relay cells. **A:** Feedback inhibitory arrangement. **B:** Arrangement in which activation of layer 6 cell monosynaptically excites some relay cells (e.g., cell 2) and disynaptically inhibits others (e.g., cells 1 and 3).See text for details.

inhibit others. In this specific example, increased activity in the corticogeniculate axon will depolarize geniculate cell 2, biasing it toward tonic firing, and hyperpolarize cells 1 and 3, biasing them toward burst firing. Evidence exists that activation of layer 6 corticogeniculate input can have dramatic effects on response mode, switching some relay cells from burst to tonic firing, and others, in the opposite direction (Wang, Jones, Andolina, Salt, & Sillito, 2006).

Role of Interneurons

Interneurons are particularly interesting cells because, among other properties, they have both axonal (F1) and dendritic (F2) output terminals. The axonal outputs seem to innervate both X and Y relay cells and other interneurons on proximal dendritic shafts with conventional, simple synapses. The dendritic outputs target relay X cells in complex synaptic arrangements known as triads (see Figures 10.12 and 10.13).

Triadic Circuits

The F2 dendritic outputs of interneurons enter into a complex synaptic arrangement known as triads (see Figures 10.12 and 10.13). In the most common form, a retinal terminal contacts an F2 terminal, and both of these terminals contact the same relay X cell, usually on a grape-like appendage (Hamos et al., 1985; Wilson et al., 1984). This would appear to be a form of simple feedforward inhibition, but a consideration of the postsynaptic receptors involved suggests a more interesting possibility. Release of GABA from the F2 terminal results in inhibition in the relay cell, and the rate of GABA release is strongly determined by the retinal input to the F2 terminal. The retinal input is glutamatergic. As noted, the retinal input to the relay cell acts via ionotropic receptors, but recent evidence (Cox & Sherman, 2000; Govindaiah & Cox, 2004) suggests that the retinal input to the F2 terminal operates mainly via metabotropic glutamate receptors (Figure 10.13).

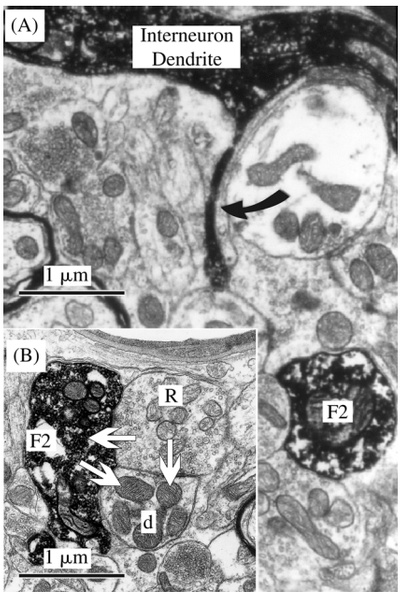

Figure 10.12 Electron micgrographs showing some properties of F2 terminals based on intracellular labeling with horseradish peroxidase of an interneuron in the cat's lateral geniculate nucleus. **A:** F2 terminal appended to interneuron dendrite via long, thin process (arrow). **B:** Section through triad. A retinal terminal (R) synapses onto an F2 terminal and a relay cell dendrite (d), and the F2 terminal synapses onto the same dendrite. The arrows show the direction of the synapses, pointing from presynaptic to postsynaptic elements. Figure reassembled from Hamos et al. (1985).

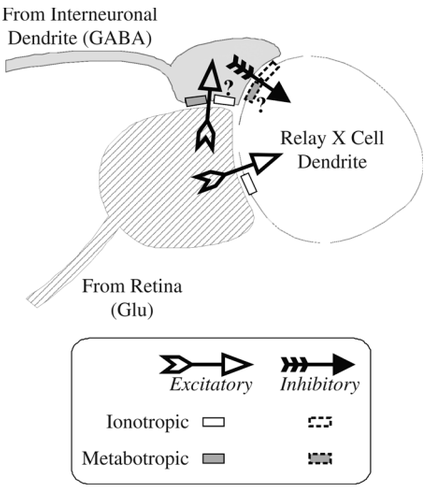

Figure 10.13 Schematic view of a synaptic triad. Arrows indicate direction of synaptic function, pointing from presynaptic to postsynaptic elements. The question marks indicate that the presence of the receptor indicated is unclear. ***Abbreviations:*** *GABA,* γ-aminobutyric acid; *Glu,* glutamate.

In Figure 10.13, arrows indicate the direction of synaptic function, pointing from presynaptic to postsynaptic elements. The question marks indicate that the presence of the receptor indicated is unclear.

Also as noted, metabotropic receptor activation requires higher firing rates in the afferent. The implication here is that, at low firing rates, relay cells will be depolarized via the retinal input, but the feedforward circuit via the F2 terminal will not be activated, and so there will be no feedforward hyperpolarization. As the firing rate in the retinal afferent increases, more and more of the feedforward inhibition will be brought into play to offset the increasing, direct depolarization.

There are two possible and related implications to this (Sherman, 2004). First, one function of this circuit is to extend the operating range of the retinogeniculate circuit.

That is, if the retinal input fires at a high enough frequency to cause the relay cell to fire at its maximum frequency, thereby saturating its response, further increases in retinal firing cannot be represented in the relay. This triadic circuit would ensure that higher firing rates would be needed than without the circuit for the relay cell's response to saturate. Second, this also means that as the firing rate in the retinal afferent increases, the gain of the retinogeniculate transmission is reduced, and furthermore, because the metabotropic response lasts so long, estimated to be several seconds in this example (Govindaiah & Cox, 2004), this reduced gain will continue for a period even if the retinal input reduces its firing level. Since retinal firing level generally increases monotonically with contrast in the visual stimulus, periods of higher stimulus contrast will produce a short, several second period of reduced visual sensitivity. This phenomenon, known as contrast gain control, is a central feature of the visual system (Geisler & Albrecht, 1995; Määttänen & Koenderink, 1991; Ohzawa, Sclar, & Freeman, 1982). While there is evidence for contrast gain control having neuronal substrates in the retina and the cortex (Beaudoin, Borghuis, & Demb, 2007; Ohzawa et al., 1982; Bernardete, Kaplan, & Knight, 1992; Truchard, Ohzawa, & Freeman, 2000), this may also occur via thalamic processing (Sherman, 2004).

Functioning of the Interneuron

The F2 terminals are connected to each other and to the stem dendrite via long, thin processes (typically >10 μm in length and <1 μm in diameter; see Figure 10.12A). Modeling (Bloomfield & Sherman, 1989) suggests that, if there are not significant active processes in the membranes involved, a significant proviso, then any membrane potential changes generated in the F2 terminal (e.g., from activation of metabotropic glutamate receptors) would effectively decay before reaching the stem dendrite and thus have no discernable effects on other F2 terminals or on the cell body. This modeling further suggests that synaptic inputs that effectively control the axonal output are essentially limited to the soma itself and proximal dendrites. The hypothesis, then, is that the interneuron massively multiplexes, with an axonal output controlled in a conventional means via proximal inputs and dendritic outputs controlled locally and independently via direct inputs onto these F2 terminals (Sherman, 2004).

Generality of Circuit Properties

While Figures 10.10 through 10.13 refer specifically to the lateral geniculate nucleus, with minor exceptions, the principles they represent seem to be found throughout the thalamus. An important proviso is that these properties have been documented regarding thalamic nuclei for which sufficient information is available, but there are some that have not been much studied to date. Most of our knowledge is based on studies of thalamic nuclei that project mainly to layer 4 of the cortex, but some nuclei, such as the midline and interlaminar nuclei (see Figure 10.1) project largely to layer 1, and very little is known of their detailed cell and circuit properties.

DRIVERS AND MODULATORS

A glance at Figure 10.10 reveals a common situation in brain circuitry that is often ignored or overlooked. That is, relay cells receive inputs from many different sources, but these do not act as some sort of anatomical democracy to equally affect relay cell responses. In fact, only one of these inputs, the retinal for the lateral geniculate nucleus and equivalent for other nuclei (e.g., lemniscal input for the ventral posterior nucleus and inferior collicular input for the medial geniculate nucleus), represents the actual input to be relayed to the cortex. In the case of the lateral geniculate nucleus, for example, the receptive fields of the relay cells represent the information relayed to the cortex, and these receptive fields have the same center/surround configuration as their retinal inputs but are very different from the orientation and direction selective receptive fields of layer 6 cells, not to mention the lack of clear visual receptive fields for parabrachial inputs (reviewed in Sherman & Guillery, 1996, 2006).

The retinal input stands alone in terms of being the main information source to be relayed, but it also differs from nonretinal input along a number of anatomical, physiological, and pharmacological properties, and these differences extend to other thalamic nuclei. This has led to the conclusion that these form two different types of input exemplified by retinal and nonretinal input, and termed *drivers* (for the retinal equivalent because these provide a uniquely powerful drive of relay cells) and *modulators* (for the nonretinal equivalent because these chiefly modulate thalamic transmission of driver input; Sherman & Guillery, 1998). Table 10.1 summarizes these differences (reviewed in Sherman & Guillery, 1998, 2004, 2006); the 13 criteria in Table 10.1, in a roughly decreasing order of importance, are:

1. As already suggested for the lateral geniculate nucleus, drivers determine the main receptive field properties of the relay cell; modulator input does not.
2. Also as already noted, drivers activate only ionotropic receptors; modulators activate metabotropic as well as ionotropic receptors.

TABLE 10.1 Drivers and modulators in LGN plus layer 5 drivers

Criteria	Retinal (Driver)	Layer 5 to HO (Driver)	Modulator: Layer 6	Modulator: PBR	Modulator: TRN and Int
1	Determines relay cell receptive field	Determines relay cell receptive field*	Does not determine relay cell receptive field	Does not determine relay cell receptive field	Does not determine relay cell receptive field
2	Activates only ionotropic receptors	Activates only ionotropic receptors	Activates metabotropic receptors	Activates metabotropic receptors	TRN: Activates metabotropic receptors; Int:†
3	Large EPSPs	Large EPSPs	Small EPSPs	†	TRN: small IPSPs; Int:†
4	Large terminals on proximal dendrites	Large terminals on proximal dendrites	Small terminals on distal dendrites	Small terminals on proximal dendrites	Small terminals; TRN: distal; Int: proximal
5	Each terminal forms multiple contacts	Each terminal forms multiple contacts	Each terminal forms single contact	Each terminal forms single contact	Each terminal forms single contact
6	Little convergence on to target	Little convergence on to target*	Much convergence on to target	†	†
7	Very few synapses on to relay cells (~5%)	Very few synapses on to relay cells (~5%)	Many synapses on to relay cells (~30%)	Many synapses on to relay cells (~30%)	Many synapses on to relay cells (~30%)
8	Often thick axons	Often thick axons	Thin axons	Thin axons	Thin axons
9	Glutamatergic	Glutamatergic	Glutamatergic	Cholinergic	GABAergic
10	Synapses show paired-pulse depression (high p)	Synapses show paired-pulse depression (high p)*	Synapses show paired-pulse facilitation (low p)	†	†
11	Well localized, dense terminal arbors	Well localized, dense terminal arbors	Well localized, dense terminal arbors	Sparse terminal arbors	Well localized, dense terminal arbors
12	Branches innervate subtelencephalic targets	Branches innervate subtelencephalic targets	Subcortically known to innervate thalamus only	†	Subcortically known to innervate thalamus only
13	Innervates dorsal thalamus but not TRN	Innervates dorsal halamus but not TRN	Innervates dorsal thalamus and TRN	Innervates dorsal thalamus and TRN	TRN: both; Int: dorsal thalamus only

• Very limited data to date.
• †No relevant data available.

3. Drivers evoke very large excitatory postsynaptic potentials; modulators generally evoke much smaller excitatory or inhibitory postsynaptic potentials.
4. Drivers form very large terminals on proximal dendrites; modulators usually form small terminals, and these can be on proximal or distal dendrites.
5. Each driver terminal forms multiple large synapses; each modulator terminal usually forms a single, small synapse.
6. Driver inputs show little convergence, meaning, for example, that one or a small number of retinal axons converge to innervate each geniculate relay cell; where evidence is available, modulator inputs show considerable convergence.
7. Driver inputs produce a small minority (~5%) of the synapses onto relays cells; many modulator inputs produce larger synaptic numbers (e.g., the local GABAergic, cortical, and parabrachial modulator inputs in Figure 10.10 each produce about 30% to 40% of the synapses).
8. Drivers have thick axons; modulators have thin axons.
9. Drivers are glutamatergic; modulators can use a variety of neurotransmitters.
10. Driver synapses show high release probability and paired-pulse depression; modulator synapses that have been tested so far show the opposite properties of low release probability and paired-pulse facilitation (see Figure 10.8).
11. Driver terminal arbors are well localized with a dense array of terminals; modulator terminal arbors can be either well-localized and dense or relatively poorly localized and sparse.

12. Branches of driver axons tend to innervate extrathalamic targets as well as the thalamus (e.g., many or all retinogeniculate axons branch and also innervate midbrain targets); those modulator inputs so far tested innervate the thalamus only.
13. Driver inputs innervate relay cells and interneurons in the dorsal thalamus but do not innervate the thalamic reticular nucleus; modulator inputs innervate relay cells, interneurons, and reticular cells.

This driver/modulator distinction is clear not just in the lateral geniculate nucleus, but also in other thalamic relays for which sufficient information is available, such as the ventral portion of the medial geniculate nucleus (the primary auditory thalamic relay) and the ventral posterior nucleus (the primary somatosensory thalamic relay). The main point, again, is that not all anatomical pathways are functionally equivalent, and if we are to understand the functional organization of the thalamus and what it is that is being relayed, we must identify and characterize the driver input. This may also apply outside of the thalamus. This point is considered further in the next section.

FIRST AND HIGHER ORDER THALAMIC RELAYS

There are two aspects of functional organization of thalamic nuclei that should be considered. One is the actual relay mechanisms, which are related to the cell and circuit properties defined earlier. The other is a determination of what, exactly, is being relayed by a given nucleus. This second functional property seems clearly defined for some nuclei, such as lateral geniculate nucleus, which relays retinal input, but until recently has not been so clear for many other nuclei, such as the pulvinar or medial dorsal nucleus. From the previous section, it should be clear that understanding this second property boils down to identifying the driver input to any particular nucleus. The recent ability to identify driver inputs to many heretofore rather mysterious nuclei, like the pulvinar or medial dorsal nucleus, has led to the further suggestion that, based on the origin of driver inputs, subcortical or cortical, thalamic nuclei can be identified as *first order* or *higher order.*

Division of Thalamic Relays into First Order and Higher Order

This distinction is well characterized by comparing the two main visual thalamic relays, the lateral geniculate nucleus and pulvinar (see Figure 10.14A). These two nuclei have the same general pattern of modulator inputs from local GABAergic neurons, the brain stem, and layer 6 of cortex. Data that have accumulated over the past few decades make it clear that the pulvinar receives its driver input from layer 5 of one cortical area and projects it to another (reviewed in Guillery, 1995; Guillery & Sherman, 2002a; Sherman & Guillery, 2006). This means that all thalamic nuclei receive a modulator projection from layer 6 that is mostly feedback but that some in addition receive a driver projection from layer 5 (instead of a subcortical driver, such as from the retina) that is feedforward (Van Horn & Sherman, 2004). As indicated in Figure 10.14A, this feedforward layer 5 input places these higher order thalamic nuclei in the middle of a cortico-thalamo-cortical route of information flow.

The main sensory thalamic relays can be divided into first order and higher order. In addition to the lateral geniculate nucleus (first order) and the pulvinar (higher order) for vision, there is the ventral posterior nucleus (first order) and the posterior nucleus (higher order) for somesthesis, and the ventral division of the medial geniculate nucleus (first order) and its dorsal division (higher order) for hearing (reviewed in Guillery, 1995; Guillery & Sherman, 2002a; Sherman & Guillery, 2006). Other thalamic relays have also been so identified: the medial dorsal nucleus is mostly or wholly a higher order relay innervating prefrontal cortex; the ventral anterior and lateral nuclear complex, which innervates motor cortex, includes first order circuits based on cerebellar inputs and higher order circuits based on inputs from layer 5 of the motor cortex; and so on. While not all of the thalamus has been so identified yet as regards this division, it seems clear that most of the thalamic volume is involved in higher order relays.

There is an important proviso to this, namely, that while first order nuclei seem fairly purely first order, those designated as higher order may have first order components as well. For instance, while most of the pulvinar receives layer 5 input from various regions of the visual cortex and thus appears to participate as a higher order relay in a cortico-thalamo-cortical circuit, parts of pulvinar are innervated by the superior colliculus. It is not entirely clear whether this colliculo-pulvinar pathway is a driver or modulator (or something else heretofore not described), but there is some anatomical evidence that at least some of the colliculo-pulvinar terminalis are quite large, suggesting that they are drivers (Kelly, Li, Carden, & Bickford, 2003). If so, then the pulvinar would represent a mixture of mostly higher order relays with some first order relays. Likewise, the posterior medial nucleus, which receives input from layer 5 of somatosensory cortex, also receives some direct spinothalamic input, but it is not known whether this latter input is a driver or modulator. A similar proviso exists for the dorsal portion of the medial geniculate nucleus, which we defined previously as a higher order nucleus: this receives input from the "belt" region of the inferior colliculus, but again,

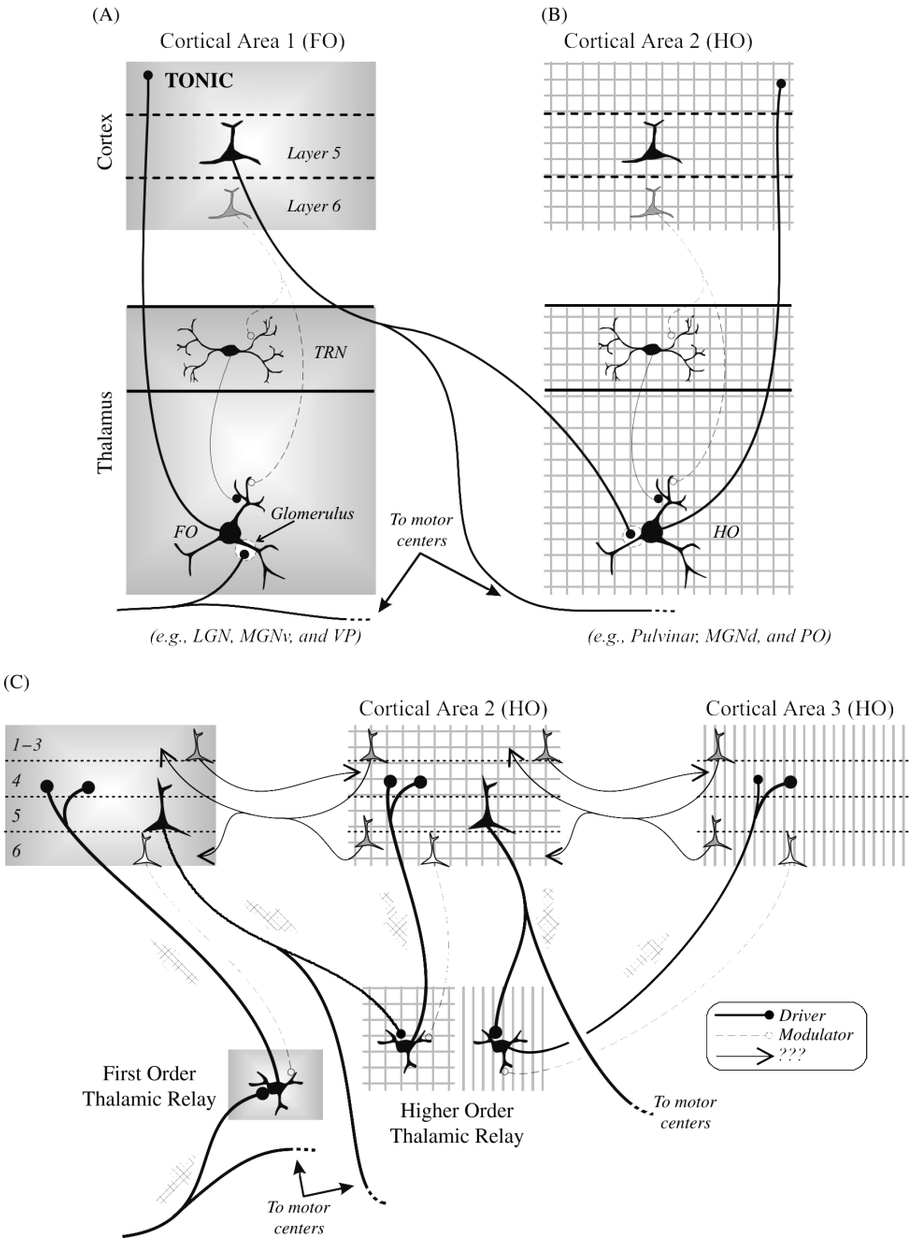

Figure 10.14 Schematic diagrams showing organizational features of first and higher order thalamic nuclei. **A,B:** Distinction between first order and higher order thalamic nuclei. A first order nucleus (**A**) represents the first relay of a particular type of subcortical information to a first order or primary cortical area. A higher order nucleus (**B**) relays information from layer 5 of one cortical area to another. This relay can be between first and higher order cortical areas as shown or between two higher order cortical areas. **C:** Role of higher order thalamic nuclei in cortico-cortical communication via cortico-thalamo-cortical circuits involving a projection from layer 5 of cortex to a higher order thalamic relay to another cortical area. As indicated, the role of the direct corticocortical projections, driver or modulator or other, is unclear. Note in **A-C** that the driver inputs, both subcortical and from layer 5, are typically from branching axons, the significance of which is elaborated in the text. ***Abbreviations:*** *FO,* first order; *HO,* higher order; *LGN,* lateral geniculate nucleus; *MGNv* or *MGNd,* ventral or dorsal division of medial geniculate nucleus; *PO,* posterior nucleus; *TRN,* thalamic reticular nucleus; *VP,* ventral posterior nucleus.

it is not known if this is a driver or modulator. Finally, the medial dorsal nucleus, which has much layer 5 input from the prefrontal cortex also has input from the superior colliculus, and although this latter input is described as if it were a driver (Sommer & Wurtz, 2004a, 2004b), insufficient evidence exists as to its identity. Given the possibility that some thalamic nuclei defined here as higher order may also have first order components operating in parallel, we refer below to first order and higher order thalamic "relays" rather than "nuclei."

Implications for Cortical Functioning

The concept of higher order relays offering a cortico-thalamo-cortical route for information processing should be seen in the context of the traditional view best expressed by Van Essen and colleagues (Felleman & Van Essen, 1991; Van Essen, Anderson, & Felleman, 1992), namely, that cortical areas communicate with one another via a plethora of direct cortico-cortical connections. In the visual cortex of rhesus monkeys, for instance, this view states that information is brought to the primary visual cortex by the lateral geniculate nucleus, and once it reaches the cortex, it stays there, being processed by the 30-odd visual areas of the cortex through a series of several parallel feedforward routes involving 4 or 5 hierarchical levels. This scheme also has feedback and lateral connections, and the direction of all of these pathways are defined by criteria dependent mostly on the laminar pattern of the cortico-cortical terminations. The cortico-thalamo-cortical pathways may be seen as a complementary or even alternate route for information processing by the cortex, and in this context means that the thalamus is not there just to bring information from the periphery to the cortex but also serves a central role in ongoing cortical processing.

One way to try to gain insight into the functional significance of these various pathways is to recall the example of the lateral geniculate nucleus: not all inputs to relay cells are information bearing (i.e., drivers). It is interesting to speculate that the driver/modulator distinction that is so valuable in elucidating functional pathways through the thalamus might also apply beyond the thalamus, especially in the cortex. If so, then it would be appropriate to consider which of the direct cortico-cortical and indirect cortico-thalamo-cortical pathways, which are all glutamatergic pathways, are drivers or modulators.

Drivers and Modulators in Various Thalamic and Cortical Circuits

The retinogeniculate synapse can serve as the prototypical glutamatergic driver, and the layer 6 thalamocortical synapse, the prototypical glutamatergic modulator. By these criteria, evidence exists that thalamocortical synapses, both from first order and higher order relay cells, have driver properties (Lee & Sherman, 2007). Likewise, the layer 5 cortico-thalamic synapses have driver properties (Guillery, 1995; Reichova & Sherman, 2004). Thus the cortico-thalamo-cortical pathways involving higher order thalamic relays appear to be a functional information routes. In other words, as shown in Figure 10.14C, first order relays bring information of a certain type (e.g., visual) from a subcortical site (e.g., the retina) to the cortex for the first time, and higher order relays are used to pass on this information up the cortical hierarchy as it is processed.

Less is known about the direct cortico-cortical synapses. These pathways have been defined almost strictly by anatomical criteria, and the assertion that all, or at least all of the feedforward cortico-cortical projections, are drivers and not modulators (or perhaps something entirely different) is not founded on empirical data. Evidence is now available that the driver/modulator classification works for at least one specific cortical circuit. Figure 10.15 shows that layer 4 cells in the visual cortex receive geniculate inputs with driver properties: these inputs provide the basic receptive field properties of their target cortical cells, and their synaptic properties, including paired-pulse depression of large EPSPs and lack of metabotropic receptor activation are also driver characteristics (Lee & Sherman, 2007). These same layer 4 cells receive another glutamatergic input from branches of layer 6 corticogeniculate axons, and this synaptic input has modulator characteristics, including paired-pulse facilitation of small EPSPs and the presence of metabotropic receptor activation (Lee & Sherman, 2007). The numbers are also interesting because in both pathways the driver inputs to geniculate relay cells and layer

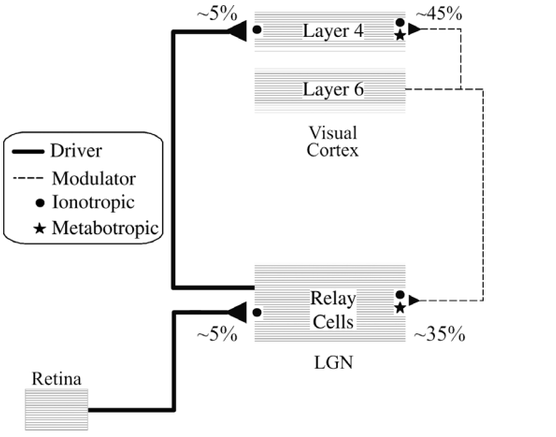

Figure 10.15 Schematic view of selected driver and modulator pathways, the percentages reflecting the relative number of synapses associated with each input.

4 cortical cells operate over very few (but powerful) synapses, representing only ~5% of the total (Ahmed, Anderson, Douglas, Martin, & Nelson, 1994; Latawiec, Martin, & Meskenaite, 2000; Van Horn, Erişir, & Sherman, 2000), whereas the glutamatergic modulators inputs operate over many more (but weak) synapses, being about 35% of the input to relay cells and about 45%, to layer 4 cells (Ahmed et al., 1994; Ahmed, Anderson, Martin, & Nelson, 1997; Erişir, Van Horn, & Sherman, 1997; Van Horn et al., 2000).

Thus, while the thalamo-cortico-thalamic circuits involving higher order thalamic relays appears to be a functioning circuit to transmit information between cortical areas, it remains to be determined just what functional properties characterize the direct cortico-cortical projections.

Nature of Information Relayed by the Thalamus

As shown in Figure 10.14, a curious but potentially important fact is that many and perhaps all driver inputs to thalamic relay cells involve branching axons, with one branch innervating relay cells, and the other, extrathalmic subcortical targets (reviewed in Guillery, 2003, 2005; Guillery & Sherman, 2002b; Sherman & Guillery, 2006). Thus, many or all retinogeniculate axons branch to innervate the pretectum and superior collicus (Sur, Esguerra, Garraghty, Kritzer, & Sherman, 1987; Tamamaki, Uhlrich, & Sherman, 1994), and many or all layer 5 corticothalamic axons likewise branch to innervate other brain stem targets, sometimes reaching into the spinal cord (reviewed in Guillery, 2003, 2005; Guillery & Sherman, 2002b; Sherman & Guillery, 2006). Note that, unlike the layer 5 corticothalamic axons, which do not innervate the thalamic reticular nucleus but do branch innervate extrathalamic targets, layer 6 corticothalamic axons innervate the thalamic reticular nucleus but do not extend beyond the thalamus.

Guillery (2003, 2005) reviewed these data and pointed out that the major extrathalamic targets of driver afferents to the thalamus appear to be motor targets, as if the messages actually sent to the cortex via the thalamus represent a sort of efference copy of motor commands, starting perhaps as very crude, preliminary commands that are updated and improved on as the message ascends the cortical hierarchy via the ascending cortico-thalamo-cortical circuits. The idea of efference copy is that a command sent to a motor center to initiate movement is copied to other brain areas, such as the cortex, so that these motor commands can be accounted for in the animal's experience (for details, see Andersen, Snyder, Bradley, & Xing, 1997; Nelson, 1996; Thier & Ilg, 2005; Webb, 2004). Further details of these ideas of efference copy as regards thalamic circuitry can be found in Guillery (2003, 2005).

Direct Cortico-Cortical versus Cortico-Thalamo-Cortical Circuits

Figure 10.16 summarizes the main conclusions to be derived from an understanding of the existence of higher order thalamic relays. Figure 10.16A shows the conventional view. Here, information is relayed from the periphery by appropriate thalamic nuclei (e.g., the lateral geniculate or ventral posterior nuclei) to primary sensory cortex. From there, the information is processed by direct cortico-cortical connections through several hierarchical levels, including sensorimotor areas, and finally reaches motor cortex, from which a motor command is sent out of the cortex. This view has definite entry and exit points for information processing—the primary sensory cortex and motor cortex, respectively. It also has no definite role for most of the thalamus that we have identified as higher order (labeled by question marks).

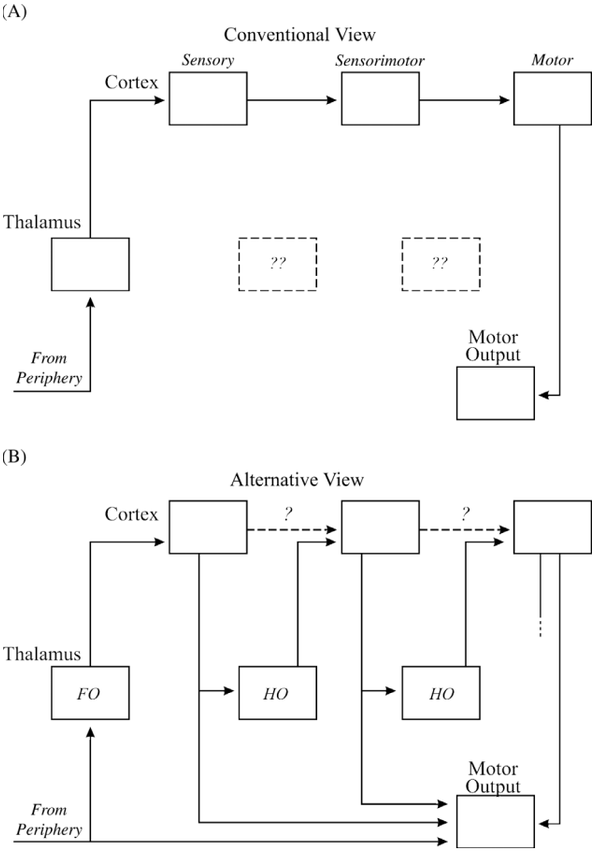

Figure 10.16 Comparison of conventional view (**A**) with the alternative view proposed here (**B**). The question marks in **A** indicate higher order thalamic relays, for which no specific function is suggested. The question marks in **B** indicate uncertainty about the role of the direct corticocortical connections (see text for details). ***Abbreviations:*** *FO,* first order; *HO,* higher order. Further details in text.

Figure 10.16B shows the alternative view offered here. By this view, from the beginning, the information from the periphery brought to first order thalamic relays is carried via branching axons that also innervate motor structures, suggesting the possibility that these primary messages relayed to the cortex are also some form of crude motor command. The further processing of information at the cortical level involves cortico-thalamo-cortical pathways using higher order thalamic relays. Here, too, the corticothalamic limb involves branching axons that also innervate motor structures as if the motor commands are being updated and refined by this cortical processing.

There are two other points to notice about Figure 10.16B. First, there is no single entry to or exit from the cortex for information processing. Even the cortex regarded as solely sensory (e.g., primary visual cortex) has a layer 5 output to motor structures: indeed, as far as we know, all cortical areas have such a layer 5 output. Thus, electrical activation of the primary visual cortex in the monkey generates eye movements (Tehovnik, Slocum, & Schiller, 2003). In this regard, the very concept of a cortical area being either sensory or motor needs to be reconsidered. Second, Figure 10.16B raises the question of the direct cortico-cortical projections. Do they function as drivers, modulators, a combination, or something entirely different?

One possibility is that a partial combination of panels A and B of Figure 10.16 is closer to the truth. That is, the cortico-cortical and cortico-thalamo-cortical circuits may represent two relatively independent parallel streams of information processing. One possibility is that the larger (anatomically) direct cortico-cortical route may reflect the major bulk of the basic information processing, while the cortico-thalamo-cortical route may be a means of each cortical area informing its upstream partner about motor commands it initiated so that this will not lead to confusion in how the outside world is represented. An example of this is the problem presented by eye movements: such movements create a visual stimulus on the retina of the visual environment moving in the opposite direction, and the the visual cortex must be able to distinguish between such self-generated stimuli and those actually initiated in the visual environment. The cortico-thalamo-cortical pathways may provide just this sort of information. However, the actual role of the various pathways, direct cortico-cortical and cortico-thalamo-cortical, remains unknown, and while there is some experimental evidence that the synapses in the cortico-thalamo-cortical circuit are all drivers, the actual synaptic function of direct cortico-cortical pathways remains to be determined.

SUMMARY

There are two main points to be made here. First, that the thalamus is not a simple, machine-like relay, but instead its cell and circuit properties control the flow of information to the cortex in dynamic and state-dependent ways. Second, in addition to getting information to the cortex in the first place, the thalamus continues to play a role in processing that information via cortico-thalamo-cortical circuits involving higher order thalamic relays. One of the challenges to understanding how the cortex processes information is to understand the relative function of the direct cortico-cortical and indirect cortico-thalamo-cortical circuits.

Thalamic Relay Functions

The fact that relay cells receive ~95% of their input from modulatory sources clearly indicates that many thalamic relay functions are under strong dynamic control. We are just beginning to understand this, and much of the control seems to be affected through control of membrane voltage. As is indicated in Figures 10.10 and 10.11, external modulatory inputs (e.g., feedback cortical and brain stem inputs) operate directly and indirectly via local GABAergic neurons to provide push-pull control of the membrane voltage. The example of how this interacts with the voltage—and time-gated Ca^{2+} T channel has been detailed and, in addition to the ubiquitous Na^{+} channel underlying the classic action potential, this may be the best understood example of effects of membrane potential on relay cell functions. However, relay cells exhibit other voltage- and time-gated ion channels, including various K^{+} channels, other Ca^{2+} and Na^{+} channels, and mixed cation channels, and these are understood much less well (for further details, see Huguenard & McCormick, 1994; Sherman & Guillery, 2006). This plus the fact that all of these channels likely have complex interactions with one another indicates that there is still much to learn about the effects of membrane voltage on thalamic relay cell functions.

The synaptic triad involving dendritic outputs of interneurons provides another interesting but not well-understood relay function. A hypothesis has been advanced that this circuit helps to maintain a larger dynamic range of input/output relationships for the relay cell that involves controlling gain of the retinogeniculate synapse, a process that could also support the mechanism of contrast gain control. This is yet another idea that requires more data.

Significance of Driver and Modulators and Higher Order Thalamic Relays

The importance of the driver/modulator distinction in the thalamus seems fairly clear and straightforward. One can

partly define the function of a thalamic relay by defining its driver input, and thus we can now argue that much of the function of heretofore rather mysterious nuclei like the pulvinar or medial dorsal nucleus is to relay information originating in layer 5 of the cortex. This, in, turn, defines higher order relays.

Another more subtle implication of this distinction is related to the concept of labeled lines: Whatever the cause of a particular neuron firing, the result is always interpreted based on the most likely natural cause. For example, pressure applied to the side of the eyeball creates the perception of light and dark spots in the visual field because of the resultant effect on photoreceptors; it is not perceived as increased intraocular pressure. The cortex must always interpret the firing of relay cells as being due to driver input. Thus, for the lateral geniculate nucleus, every relay cell response must be interpreted as being due to retinal input and not cortical or brain stem. There is some evidence in anesthetized cats that practically every action potential seen in a geniculate relay cell can be attributed to a retinal spike (Cleland, Dubin, & Levick, 1971), so this concept is not so difficult to accept.

A final and perhaps most profound implication of the driver/modulator concept is that it dictates that, not only are all inputs to a neuron not equal functionally, but in terms of information transfer versus modulation, only a very small subset of inputs to the thalamus are drivers. This distinction seems quite robust in the thalamus and offers a very different way of looking at information transfer. One important issue is the extent to which this distinction, so clear in the thalamus, can be extrapolated elsewhere, such as the cortex. Most cortico-cortical pathways, especially between areas, are glutamatergic, and it may be significant that metabotropic glutamate receptors are common in the cortex (Caleo et al., 2007). This means that some as yet undetermined subset of these pathways activate metabotropic glutamate receptors (Lee & Sherman, 2007), and as noted, this seems an important property of modulators. Thus, it seems plausible that many cortical pathways are modulatory. Nonetheless, such is our general ignorance of the functional properties of cortical circuitry and particularly of cortico-cortical projections between areas, that these pathways may require a classification scheme completely different from or in addition to the driver/modulator categories.

First Order and Higher Order Thalamic Relays

The major implication of the division of the thalamus into first and higher order relays is that, via the latter, cortico-cortical communication may depend heavily on the thalamus, a thalamic function previously unknown. It is possible that *all* cortico-cortical communication is via cortico-thalamo-cortical circuits and that all direct cortico-cortical pathways are modulatory. If so, this would mean that all information entering a cortical area, whether from the periphery (e.g., retina) or another cortical area, must pass through the thalamus. In other words, retinal information does not innervate the cortex directly but passes through a thalamic relay (i.e., the lateral geniculate nucleus) and this applies to cortico-cortical communication as well.

A more plausible implication has been suggested earlier. That is, while some undetermined fraction of cortico-cortical pathways are not information bearing, many are, and the direct cortico-cortical and indirect cortico-thalamo-cortical circuits represent two parallel paths of information processing. More data are needed to sort this out.

Nature of Driver Inputs to Thalamic Relay Cells

A curious fact about many, and perhaps all, of the subcortical and layer 5 driver inputs to thalamic relay cells is that they are comprised of branching axons, with the extrathalamic branch innervating motor centers (see Figure 10.14; Guillery, 2003). The significance of this has been discussed in some detail by Guillery (2003, 2005) and will not be repeated here. Nonetheless, this anatomical fact does suggest that much of the evolution of the thalamus and the cortex has involved getting information to the cortex about motor commands and their updating.

The thalamus has come a long way from when it was seen as an uninteresting structure whose only role was to relay information simply and consistently from the periphery to the cortex. We now understand that these relay functions are quite complicated and that the thalamus continues to play a role beyond simply getting information to the cortex from the periphery. Nonetheless, we are just beginning to understand these broader and more interesting functions of the thalamus. The challenge is to continue along these lines with more research focused on these subjects.

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