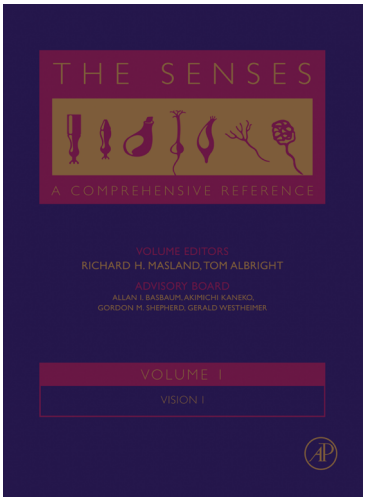

S M Sherman, The Visual Thalamus. In: Allan I. Basbaum, Akimichi Kaneko, Gordon M. Shepherd and Gerald Westheimer, editors The Senses: A Comprehensive Reference, Vol 1, Vision I, Richard Masland and Thomas D. Albright. San Diego: Academic Press; 2008. p. 557-576

1.28 The Visual Thalamus

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1.28.1 Introduction

The two major thalamic nuclei involved in visual processing are the lateral geniculate nucleus and the pulvinar. The lateral geniculate nucleus relays retinal input to the visual cortex, chiefly to the primary visual cortex. The pulvinar innervates most or all visual cortical areas, and what it is relaying has been something of a mystery, although this account makes the case that it is involved chiefly in relaying information between visual areas. Fortunately, most of the details regarding cell and circuit properties are common to thalamic relay nuclei, and so before considering these two visual relay nuclei in detail, it is worth standing back and considering some generally properties of thalamus.

The thalamus is a collection of adjacent nuclei located in the center of the brain. It is a paired structure, each side roughly the size of a walnut. Each of the various nuclei innervates one area of the cortex (unless otherwise specified, cortex use here refers to neocortex) or a small number of adjacent cortical areas. It is important to keep in mind that virtually all information reaching the cortex, and thus attentional and other cognitive levels, must first be relayed by thalamus. Also, as far as we know, every cortical area receives a thalamic projection.

Strictly speaking, thalamus has two broad divisions: dorsal thalamus and ventral thalamus. Dorsal thalamus includes the relay nuclei, namely, the bulk of thalamus in which neurons that project to the cortex are located. These relay nuclei can typically be distinguished by cytoarchitectonic criteria. Generally, homologous nuclei can be discerned across mammals, and so a lateral geniculate nucleus, which relays retinal information to the cortex, is known for all mammalian species so far

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studied, but in some cases, identification of homologous nuclei across species remains elusive. The ventral thalamus includes as its chief component the thalamic reticular nucleus, which is a thin shell of neurons that lies generally lateral to the dorsal thalamus, like a shield, extending somewhat dorsally, ventrally, and anteriorly. These reticular cells do not project to the cortex but instead provide a gamma-aminobutyric acid (GABA)ergic, inhibitory input to relay cells of the dorsal thalamus. A minor component of the ventral thalamus is the ventral division of the lateral geniculate nucleus, whose cells project to other brainstem sites but not the cortex; the ventral division of the lateral geniculate nucleus is not considered further. For simplicity in what follows below, unless otherwise indicated, thalamus refers just to the dorsal thalamus, and lateral geniculate nucleus refers just to its dorsal division.

The main thalamic relays of visual information are the lateral geniculate nucleus and pulvinar. (Strictly speaking, this includes the lateral posterior nucleus and is often referred to as the lateral posterior/pulvinar complex, but for the sake of brevity, we shall refer to this simply as the pulvinar.) The main purpose of this chapter is to disabuse readers of the old notions about these thalamic nuclei: namely that the lateral geniculate nucleus is a simple, machine-like relay of retinal information to the primary visual cortex, and the pulvinar is a mysterious entity that innervates extrastriate visual areas and is somehow involved in attention (LaBerge, D. and Buchsbaum, M. S., 1990; Olshausen, B. A. *et al.*, 1993; Anderson, C. H. *et al.*, 2005; Van Essen, D. C., 2005). It is now clear that the complex cell and circuit functions of the thalamus, including the lateral geniculate nucleus, belie any simple relay functions. These thalamic nuclei act as gateways for information flow to the cortex, gateways that are dynamically modulated. Furthermore, we can now seriously consider a relatively new hypothesis for the function of pulvinar as a central element in information transfer between cortical areas involving a corticothalamocortical route. Related to this is the recent appreciation that, as noted above, while all thalamic relays share most basic cell and circuit functions, certain differences between the lateral geniculate nucleus and pulvinar identify them as members of two different kinds of relay found throughout thalamus.

1.28.2 Thalamic Cell Types

The thalamus consists of three basic cell types: relay cells, interneurons, and cells of the thalamic reticular nucleus (for details, see Sherman, S. M. and Guillery, R. W., 1996; 2006). Each of these may be further subdivided, but the complete classification of these cell types has yet to be done. Relay cells are glutamatergic, and the latter two cell types are GABAergic, providing a major inhibitory input to relay cells. Interneurons are located within the main dorsal thalamic relay nuclei, intermixed with relay cells, and the ratio of interneurons to relay cells is roughly 1:3. This ratio is similar throughout thalamus in all mammals with a peculiar exception. That is, outside of the lateral geniculate nucleus, the thalamus of rats and mice are essentially devoid of interneurons, but, curiously, the lateral geniculate nucleus in these animals does have a normal complement of interneurons (Arcelli, P. *et al.*, 1997). This is not a property of rodents, because hamsters, guinea pigs, squirrels, etc., have interneurons throughout thalamus (e.g., Arcelli, P. *et al.*, 1997). However, this point has been questioned recently by evidence that the lateral posterior nucleus of the rat has a substantial fraction of interneurons (Li, J. L. *et al.*, 2003).

1.28.3 Cell Properties

As we learn more about neurons throughout the central nervous system, it is clear that they possess a bewildering variety of voltage-gated ionic membrane conductances, and thalamic relay cells are no exception. The voltage-gated Na^+ conductance underlying the action potential is perhaps the best-known example. Other examples include various voltage-gated K^+ and Ca^{2+} conductances, and a more detailed listing can be found in Sherman S. M. and Guillery R. W. (1996; 2006). The presence of these conductances means that membrane voltage and its temporal pattern, which together determine whether and when each of these becomes activated, play an important role in relay cell excitability and thus the gating of information flow. While most of these conductances are ubiquitous to neurons everywhere, one in particular, a voltage-gated Ca^{2+} conductance that operates via T-type Ca^{2+} channels, is particularly important to relay cell function and relatively specific to thalamic neurons (for details, see Sherman, S. M. and Guillery, R. W., 1996; Sherman, S. M., 2001; Sherman, S. M. and Guillery, R. W., 2006).

1.28.3.1 Properties of T-Type Ca^{2+} Channels

Figure 1 shows the voltage and time dependency for the T channels (Jahnsen, H. and Llinás, R., 1984a; 1984b;

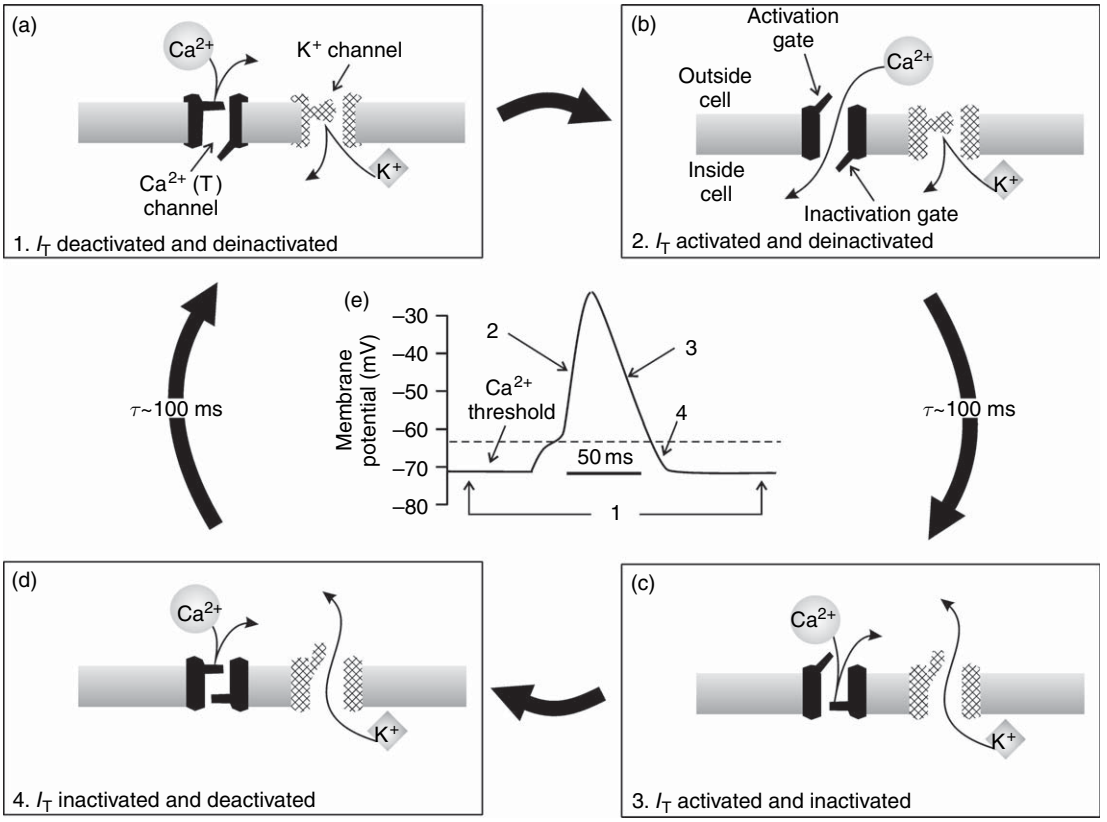

Figure 1 Schematized view of actions of voltage-dependent T (Ca^{2+}) and K^+ channels underlying low-threshold Ca^{2+} spike. Panels (a)–(d) show the sequence of channel events, and the central graph (e) shows the effects on membrane potential. The T channel has two voltage-dependent gates: an activation gate that opens with depolarization and closes at hyperpolarized levels and an inactivation gate that shows the opposite voltage dependency. The K^+ channel shown actually represents several such channels having a single gate that opens during depolarization; thus, these channels do not inactivate. (a) I_T deactivated and deinactivated. At a relatively hyperpolarized resting membrane potential (~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 deinactivated. The single gate for the K^+ channel is closed. (b) I_T activated and deinactivated. With sufficient depolarization to reach its threshold, the activation gate of the T channel opens, and Ca^{2+} flows into the cell. Thus, the T channel is activated and, for the time being, remains deinactivated. This further depolarizes the cell, providing the rise of the low-threshold spike. (c) I_T activated and inactivated. The inactivation gate of the T channel closes after being depolarized for roughly 100 ms (roughly, because closing of the channel is a complex function of voltage and time), and the K^+ channel also opens. Thus, the continued depolarization inactivates the T channel, although the activation gate remains open. These actions stop the influx of Ca^{2+} and allow the efflux of K^+, serving to repolarize the cell. (d) I_T inactivated and deactivated. Even though the initial resting potential is reached, the T channel remains inactivated, because it takes roughly 100 ms (roughly having the same meaning as above) of hyperpolarization to deinactivate it; thus, the T channel is inactivated and deactivated. It also takes a bit of time for the various K^+ channels to close. Note that the behavior of the T channel is qualitatively exactly like the Na^+ channel involved with the action potential, but with several quantitative differences: the T channel is slower to inactivate and deinactivate, and it operates in a more hyperpolarized regime.

Sherman, S. M., 2001; Sherman, S. M. and Guillery, R. W., 2006). These channels have two voltage gates, because they can be both activated and inactivated by voltage. At rest (roughly −70 mV), the inactivation gate is open, but the activation gate is closed; the channel is thus both deinactivated and deactivated (Figure 1(a)). Following depolarization to threshold for the activation gate (to roughly −65 mV), the activation gate opens and I_T is generated via entry of Ca^{2+} into the cell, leading to the upswing of the all-or-none Ca^{2+} spike; now, the T channel is activated and deinactivated (Figure 1(b)). This Ca^{2+} spike is often termed the low-threshold spike, because its activation threshold is hyperpolarized with respect to that for the action potential. After roughly 100 ms of depolarization, the T channel inactivates (control of the inactivation gate is a complex function of voltage and time (Jahnsen, H. and Llinás, R., 1984a; 1984b; Zhan, H. J. *et al.*, 1999) so that

the more depolarized (or hyperpolarized), the more quickly the gate closes (or opens), but the important point is that under normal conditions, roughly 100 ms is required for these actions) (Figure 1(c)), and this, combined with the activation of a slower series of K^+ conductances, repolarizes the neuron. However, the T channel remains inactivated (Figure 1(d)) for another 100 ms or so, after which time the original state shown in Figure 1(a) is returned. The two gates of the T channel have opposite voltage dependencies, but while the activation gate responds quickly to voltage change, the inactivation gate is slower, requiring roughly 100 ms of polarization change to open or close. Note that the roughly 100 ms of hyperpolarization needed to deinactivate the T channel provides a refractory period, limiting low-threshold Ca^{2+} spiking to 10 Hz.

Note also that this behavior of the T channel is qualitatively identical to that of the Na^+ channel underlying conventional action potentials, although there are two important quantitative differences: the regime of the voltage dependency of the T channel is 5–10 mV more hyperpolarized, and the inactivation kinetics of the T channel are much slower. Also, T channels are not found in the axons. The last point means that it is only action potentials that convey the information relayed to the cortex.

1.28.3.2 Properties of Burst and Tonic Firing

This behavior of T channels underlies the two very different response modes, tonic or burst, that are expressed by thalamic relay cells. How information is relayed to the cortex depends heavily on which response mode is in use (Sherman, S. M. 2001; Swadlow, H. A. and Gusev, A. G., 2001; MacLean, J. N. *et al.*, 2005; Bezdudnaya, T. *et al.*, 2006; Sherman, S. M. and Guillery, R. W., 2006). This is because the same input (e.g., an excitatory postsynaptic potential (EPSP) from retina) will evoke a very different response in the relay cell during tonic versus burst firing (Figures 2(a) and 2(b)). During tonic firing mode, the EPSP directly elicits action potentials, and so a larger EPSP elicits a higher firing rate, forming a fairly linear input/output relationship (Figure 2(c)). However, during bursting, the relationship is highly nonlinear, because the input or EPSP no longer directly elicits action potentials; instead, it elicits the low-threshold spike, which in turn elicits the action potentials, but because the low-threshold

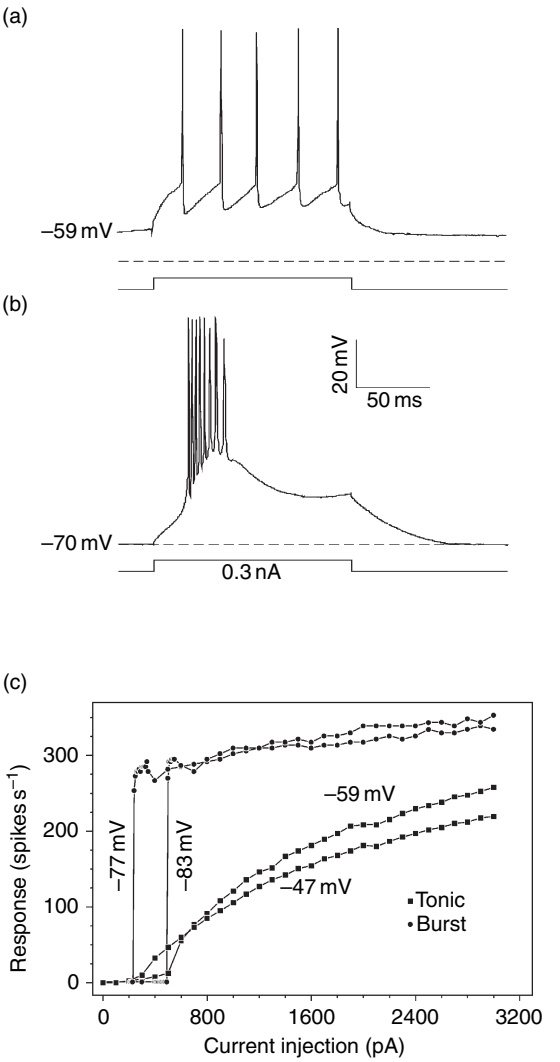

Figure 2 Properties of burst and tonic firing modes for relay cells of the lateral geniculate nucleus of the cat recorded intracellularly *in vitro*. (a, b) Voltage dependency of the low-threshold spike for one cell. Responses are shown to the same depolarizing current pulse administered intracellularly but from two different initial holding potentials. I_T is inactivated with relative depolarization (a), and the response is a succession of unitary action potentials for the duration of the suprathreshold stimulus. This is the *t*onic mode of firing. I_T is deinactivated with relative hyperpolarization (b), 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 cell. The abscissa plots the amplitude of the depolarizing current pulse, and the ordinate plots the evoked firing frequency based on the first six action potentials of the response, since this cell usually exhibited six action potentials per burst in this experiment. The initial holding potentials are shown: −47 and −59 mV reflect tonic mode, whereas −77 and −83 mV reflect burst mode. Redrawn from Sherman, S. M. and Guillery, R. W. 2001. Exploring the Thalamus. Academic Press.

spike is all-or-none, a larger EPSP does not elicit a larger low-threshold spike or a higher firing.

The advantage for tonic firing is pretty clear: if the cortex is to faithfully reproduce the visual scene, the sort of nonlinear distortion seen during burst firing would hamper this process. While less obvious perhaps, there are at least two advantages for burst firing (Sherman, S. M., 2001; Swadlow, A. G. and Gusev, A. G., 2001; MacLean, J. N. *et al.*, 2005; Bezdudnaya, T. *et al.*, 2006; Sherman, S. M. and Guillery, R. W., 2006). First, because burst firing is associated with lower spontaneous activity but the burst itself represents a high rate of firing, burst firing has a higher signal-to-noise ratio and thus better stimulus detectability. Second, burst firing leads to a much greater postsynaptic response in the cortex. The second point follows from the nature of the thalamocortical synapse, which is a depressing synapse: the firing rate during tonic mode is sufficiently high to maintain the synapse in a depressed state, but the silent intervals before each burst (due to the requisite period of hyperpolarization needed to deinactivate I_T) completely relieves the synaptic depression. The overall implication is that, while tonic firing is better for stimulus reconstruction, burst firing is better for the detection of novel stimuli, and associated with this improved detectability is a much stronger cortical response.

1.28.3.3 Hypothesis for Burst and Tonic Firing

These properties of burst and tonic firing have led to the following hypothesis (Sherman, S. M., 2001). To the extent that burst firing is better for stimulus detection, it could be the mode more often seen when the information that the thalamic cell relays is not well attended to (due to drowsiness, attention directed elsewhere, etc.); under these conditions, the burst evoked by a novel stimulus would more likely get through to the cortex and be recognized as a signal than if the cell were firing tonically. In this sense, the burst is a sort of wake-up call that something has changed and that something should be attended to so that its importance can be evaluated. The idea here is not necessarily that bursting provides a stronger overall signal to the cortex than does tonic firing, but rather that bursting overcomes any disadvantage regarding stimulus detectability or cortical activation imposed by inattention. Once the burst activates cortical circuits, the relay cell would then switch to tonic firing so that the novel stimulus can be properly evaluated.

Several recent observations support this hypothesis (Weyand, T. G. *et al.*, 2001; Lesica, N. A. and Stanley, G. B., 2004; Alitto, H. J. *et al.*, 2005; Denning, K. S. and Reinagel, P., 2005). Both tonic and burst firing are seen in awake, behaving animals, including humans, with switching between modes. Bursting is seen relatively rarely in alert animals and more commonly in drowsy animals. Furthermore, recent receptive field studies of the lateral geniculate nucleus show that the type of visual stimulus most likely to evoke a burst is one that switches from inhibition to excitation, such as a dark region covering the receptive field of an on-center cell that is replaced by a bright spot. This indicates that the burst signals a significant change in the form of a novel stimulus just appearing. However, these observations, while supporting the hypothesis, do not constitute proof of its validity. Much more research will be needed to accept or reject the hypothesis.

1.28.4 Circuit Properties

Figure 3 schematically shows the main inputs to thalamic relay cells. The model used here is the lateral

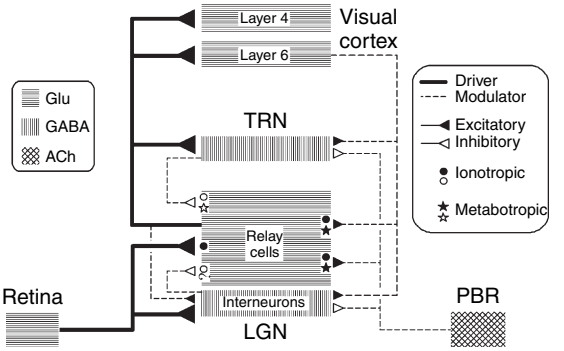

Figure 3 Schematic view of major circuit features of the lateral geniculate nucleus with related receptors present on relay cells. Other thalamic nuclei seem to be organized along the same pattern. The key to the left indicates the major transmitter systems involved. The retinal input activates only ionotropic receptors (circles), whereas all nonretinal inputs activate metabotropic receptors (stars) and often ionotropic receptors as well. The question mark related to input from interneurons indicates uncertainty whether metabotropic receptors are involved. Thick solid and thin dashed lines indicate driver and modulator inputs, respectively. Filled and open icons for synaptic terminals indicate excitatory and inhibitory inputs, respectively. ACh, acetylcholine; GABA, gamma-aminobutyric acid; Glu, glutamate; LGN, lateral geniculate nucleus; PBR, parabrachial region of the brainstem; TRN, thalamic reticular nucleus.

geniculate nucleus, because the circuitry shown here is essentially repeated throughout thalamus. For simplicity, certain pathways are omitted, but some that appear to be differentially distributed between the lateral geniculate nucleus and pulvinar are considered below. For details of these other inputs, see Sherman S. M. and Guillery R. W. (1996; 2006).

1.28.4.1 Anatomical Features

Figure 3 shows that retinal input is one of several to geniculate relay cells. Nonretinal input derives from local GABAergic sources (interneurons and reticular cells), layer 6 of the cortex, which provides a feedback, glutamatergic input, and from the brainstem, mostly from cholinergic cells in a midbrain area known as the parabrachial region. (Another term often applied to this area is pedunculopontine tegmental nucleus. We prefer parabrachial region, because, in many or most species, the cells that innervate thalamus from this area do not have a clear nuclear boundary, and they are found scattered around the brachium conjunctivum.) Thus, the main extrinsic, nonretinal inputs to geniculate relay cells derive from the cortex and brainstem. Note that the local, GABAergic inputs are also innervated by the same cortical and brainstem sources that innervate relay cells. Thus, these extrinsic inputs can affect relay cells directly or indirectly via local GABAergic circuitry.

1.28.4.2 Functional Features

Figure 3 makes clear that, while the retina may provide the main input relayed to the cortex, many nonretinal pathways innervate relay cells, presumably to modulate retinogeniculate transmission. All of these synapses onto relay cells are standard chemical synapses, meaning that they affect relay cells by releasing neurotransmitters that operate through various postsynaptic receptors on the relay cells. These receptors come in two main flavors: ionotropic and metabotropic. Figure 3 shows that a combination of ionotropic and metabotropic receptors is involved in postsynaptic responses of relay cells. Examples of the relevant ionotropic receptors are AMPA and NMDA for glutamate, nicotinic for acetylcholine, and the $GABA_A$ receptor. For metabotropic receptors, examples are various metabotropic glutamate receptors, various muscarinic receptors for acetylcholine, and the $GABA_B$ receptor.

Ionotropic and metabotropic receptors. Differences between ionotropic and metabotropic receptors are many, and only certain ones are considered here (for details, see Nicoll, R. A. *et al.*, 1990; Mott, D. D. and Lewis, D. V., 1994; Pin, J. P. and Duvoisin, R., 1995; Recasens, M. and Vignes, M., 1995; Brown, D. A. *et al.*, 1997; Conn, P. J. and Pin, J. P., 1997). Ionotropic receptors are simpler in construction and function, and the receptor protein itself usually contains the ion channel it controls. Typically, when transmitter binds to the ionotropic receptor, the receptor changes shape, thereby opening the ion channel. This, in turn, allows ions to flow down their electrochemical gradients, leading to an EPSP or IPSP. These ionotropic PSPs typically occurs with brief latencies (<1 ms) and durations (mostly over in 10 or a few tens of milliseconds). Metabotropic receptor functioning is more complicated, because the receptor is linked to ion channels via second messenger systems, which in thalamic relay cells usually involves a G protein and ultimately opens or closes K^+ channels. When K^+ channels open, K^+ flows out of the cell, producing an IPSP, and when K^+ channels close, leakage of K^+ is stopped, leading to an EPSP. One important difference with the activation of ionotropic receptors is that these PSPs related to metabotropic receptors typically have a long latency (~10 ms or so) and duration (hundreds of a millisecond to several seconds).

Figure 3 also shows the pattern of postsynaptic receptors associated with the various inputs onto relay cells. Note that retinal inputs activate only ionotropic receptors (mostly AMPA but also NMDA), whereas all nonretinal inputs activate metabotropic and often also ionotropic receptors. The fast EPSPs activated by retinogeniculate synapses means that for relatively high firing rates in the retinal afferent, it is possible to evoke a single, separate EPSP for each retinal action potential. Put another way, if retinogeniculate synapses activated metabotropic glutamate receptors, the resultant prolonged EPSPs would temporally summate at relatively low firing rates in the afferent; this would act like a low-pass temporal filter, and the result would be a loss of higher-frequency temporal information. Thus, the lack of metabotropic glutamate receptors associated with retinal input maximizes the faithful relay of temporal information. The nonretinal inputs, by activating metabotropic receptors, can achieve sustained changes in membrane potential and thus relay cell excitability, thereby modulating the gain of retinogeniculate transmission.

This pattern of receptors also has implications for the control of firing mode. Recall that to inactivate the T channel (i.e., to close the inactivation gate) requires 100 ms or so of sustained depolarization; likewise, to

deinactivate it (i.e., to open the inactivation gate) requires 100 ms or so of sustained hyperpolarization. This means that the fast EPSPs or inhibitory postsynaptic potentials (IPSPs) seen with ionotropic receptors are ill-suited to affect the inactivation gate; even action potentials, despite their amplitude, are terminated too quickly to effectively inactivate the T channel. In contrast, the sustained postsynaptic potentials of metabotropic receptors are ideally suited to inactivate or deinactivate T channels. It thus follows that retinal input by itself, with its fast EPSPs, is less likely to directly affect T channels. Even evoked action potentials are too fast to have much affect on the inactivation state of these channels.

This seems appropriate in the sense that burst or tonic firing is thought to be largely dependent on behavioral state (Sherman, S. M., 2001), and one would expect that to be mainly the function of the nonretinal inputs to relay cells that do not carry the main information to be relayed. Although visual stimuli can also affect firing rate, this, too, seems to be due to nonretinal afferents. That is, a visual stimulus that inhibits a geniculate cell for a sufficient time (e.g., a dark stimulus falling on the center of an on-center cell) can deinactivate the T channels, and when this stimulus is replaced by an excitatory one (e.g., a bright spot), a burst is evoked (Lesica, N. A. and Stanley, G. B., 2004; Alitto, H. J. *et al.*, 2005; Denning, K. S. and Reinagel, P., 2005). However, this is likely due to inhibitory circuits involving interneurons or reticular cells, or both, and perhaps also involving $GABA_B$ receptors, and is not likely to represent retinal inputs alone. Indeed, evidence exists (reviewed in Sherman, S. M. and Guillery, R. W., 1996; 2006) that metabotropic glutamate receptors activated from layer 6 of the cortex and muscarinic receptors activated from the parabrachial region produce long, slow EPSPs that inactivate the T channels and switch relay cells from burst to tonic firing mode. Likewise, activation of $GABA_B$ receptors from reticular inputs does the opposite: it produces a sustained inhibitory postsynaptic potential that switches firing modes from tonic to burst. Interneurons may also participate in this, but as indicated by the question mark in Figure 3, it is not yet known whether or not these inputs activate $GABA_B$ receptors on relay cells.

Role of parabrachial and cortical inputs. Figure 3 shows that increased activity in parabrachial inputs depolarizes relay cells directly. In addition, increased parabrachial activity inhibits reticular cells and interneurons, thereby disinhibiting relay cells. Thus, increased parabrachial activity results in more depolarized relay cells, which not only makes them more excitable, but also serves to activate their T channels, biasing relay cell responses to tonic mode. This is consistent with evidence that parabrachial neurons become more active and relay cells become less bursty with increasing vigilance, from slow-wave sleep through drowsiness to full attention (Steriade, M. and Contreras, D., 1995; Datta, S. and Siwek, D. F., 2002).

Understanding the consequence of the layer 6 cortical input is much more difficult. Figure 3 suggests that this input directly excites relay cells while it indirectly inhibits them, but in fact, the actual effect of this input depends on details of the circuit that are generally unknown. This is illustrated in Figure 4, which shows two variants of many possible for the relevant circuit. Figure 4(a) shows individual corticogeniculate axons innervating a reticular cell and a relay cell, with the reticular cell innervating the same relay cell. This is an example of feedforward inhibition. The consequence of increased corticogeniculate activity might be little or no net effect on the relay cell's membrane voltage (and T-channel inactivation or deinactivation) if the excitatory and inhibitory inputs are balanced. However, as pointed out by Chance F. S. *et al.* (2002), while this may not affect membrane voltage, the increased synaptic conductance among other factors will reduce relay cell excitability to other (i.e., retinal) inputs; thus, in the lateral geniculate nucleus, activation of this circuit would reduce the gain of retinogeniculate transmission.

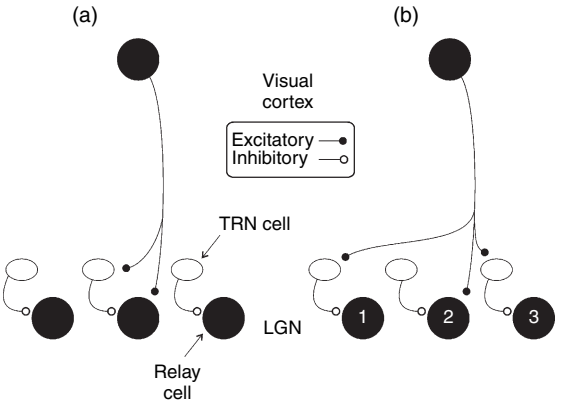

Figure 4 Two patterns among others possible for corticothalamic projection from layer 6 to cells of the thalamic reticular nucleus and geniculate relay cells. (a) Pattern of simple excitation and feedforward inhibition. (b) More complicated pattern in which activation of a cortical axon can excite some relay cells directly and inhibit others through activation of reticular cells. Further details in text. LGN, lateral geniculate nucleus; TRN, thalamic reticular nucleus.

The circuit of Figure 4(b) has very different consequences. Here, activation of the corticogeniculate axon purely excites one or a few relay cells (e.g., cell 2) and purely inhibits others (e.g., cells 1 and 3). Note that this circuit does not involve feedforward inhibition. Also, note that the final effect on relay cell membrane voltage is such that the activation of the corticogeniculate axon would promote tonic firing in cell 2 and burst firing in cells 1 and 3. This means that layer 6 increased corticogeniculate input can have very different and localized effects. Recent evidence is in support of this pattern (Wang, W. *et al.*, 2006). Figure 4 illustrates the importance of a much better understanding of these functional circuits at the single-cell level than we have at present. The example of Figure 4 includes just reticular cells, but one can easily imagine a similar circuit involving interneurons.

1.28.5 The Lateral Geniculate Nucleus

While the above sections describe properties that are applicable to the lateral geniculate nucleus, there are certain features of processing information that are specific to or more readily studied in this nucleus.

1.28.5.1 Parallel Processing

Relay cells in the lateral geniculate nucleus can be divided into at least three functional classes (Sherman, S. M., 1982; Shapley, R. and Lennie, P., 1985; Casagrande, V. A. and Norton, T. T., 1991; Hendry, S. H. C. and Reid, R. C., 2000; Casagrande, V. A. and Xu, X., 2004). Each of these geniculate classes represents a thalamic link in separate streams of retinogeniculocortical processing. That is, there are equivalent distinct classes of retinal ganglion cells that project to the lateral geniculate nucleus, and each retinal class seems to innervate a single class of geniculate relay cell to maintain separate, parallel streams of information to the cortex. In general, the receptive field properties that distinguish these cell types are similar for retina and the lateral geniculate nucleus, because geniculate receptive fields are essentially the same as their retinal inputs. These classes have been best studied in the cat, where they are called X, Y, and W cells, and in the monkey, where they are called parvocellular (P), magnocellular (M), and koniocellular (K). There appears to be a link in homology here between X and P cells, Y and M cells, and W and K cells. Homologies to these parallel cell classes have also been suggested for other species (Casagrande, V. A. and Norton, T. T., 1991; Van Hooser, S. D. *et al.*, 2003; Casagrande, V. A. and Xu, X., 2004).

1.28.5.1.1 The cat lateral geniculate nucleus

X and Y cells. X and Y cells are each a fairly homogeneous class, with both anatomical and receptive field correlates. Anatomically, retinal X cells are known as beta cells and Y cells as alpha cells (Boycott, B. B. and Wässle, H., 1974). Beta cells have smaller cell bodies with smaller dendritic arbors and thinner caliber axons. Similar relationships exist for geniculate X and Y cells (LeVay, S. and Ferster, D., 1977; Friedlander, M. J. *et al.*, 1981). Geniculate X cells have smaller cell bodies with thinner axons, and their dendritic arbors are elongated perpendicular to the geniculate laminar borders (see below for geniculate layers), whereas those of Y cells are organized into a roughly spherical shape. Also, X cells tend to have grape-like appendages near proximal dendritic branch points, whereas Y-cell dendrites are generally smooth. This is interesting, because these appendages on the X cells mark the postsynaptic target of the retinal inputs, whereas on Y cells, retinal inputs terminate directly onto proximal dendritic shafts (Wilson, J. R. *et al.*, 1984; Hamos, J. E. *et al.*, 1986).

The receptive fields of both cell types in retina and the lateral geniculate nucleus are organized into classic center/surround regions. There are roughly equal numbers of on- and off-center cells. However, X cells have smaller receptive fields and respond to higher spatial and lower temporal frequencies (Sherman, S. M., 1982; Shapley, R. and Lennie, P., 1985). These center/surround regions for both X and Y cells exhibit linear summation, but the Y cells, in addition, have small, nonlinear subunits in their receptive fields that produce a doubling response (i.e., a response to both onset and offset to both bright and dark spots) to visual stimuli (Enroth-Cugell, C. and Robson, J. G., 1966; Hochstein, S. and Shapley, R. M., 1976).

Based on receptive field properties, hypotheses have been developed for the distinct function of the X and Y pathways. X cells are thought to provide maximum acuity for detail vision, while Y cells are more important for motion detection and processing of low spatial frequencies (Sherman, S. M., 1985).

W cells. W cells remain a poorly understood cell group and probably represent a heterogeneous group with several distinct classes. However, for convenience and because the final classification and

functional correlates of W cells are lacking, they are considered together here (for further details of these cells, see Sherman, S. M., 1982; Berson, D. M. *et al*., 1998; 1999; Isayama, T. *et al*., 2000). Retinal W cells generally have small to medium-sized cell bodies with long, sparsely branched dendrites, but the morphological features of this group are so varied that any generality must be qualified. W cells so far described in the lateral geniculate nucleus have medium-sized cell bodies and dendritic arbors oriented parallel to the layers (Stanford, L. R. *et al*., 1983). The receptive fields of these cells, both in retina and in the lateral geniculate nucleus, are also quite varied but tend to be large and poorly responsive. Indeed, Cleland B. G. and Levick W. R. (1974) have named them sluggish; some have center/surround configuration, others have poorly defined borders with on/off responses throughout, some have directional selectivity, and some have some wavelength sensitivity. To date, there has not been much speculation regarding the function of the W pathway(s), and this remains a mystery.

1.28.5.1.2 The monkey lateral geniculate nucleus

P and M cells. In the retina (Rodieck, R. W., 1979; Leventhal, A. G. *et al*., 1981), P cells (called midget cells) are smaller than M cells (called parasol cells), and this size differential also holds in the lateral geniculate nucleus, as the names (Parvocellular and Magnocellular) imply. Their receptive fields both in retina and in the lateral geniculate nucleus have the classic center/surround configuration, but P cells have smaller receptive fields (Casagrande, V. A. and Norton, T. T., 1991; Hendry, S. H. C. and Reid, R. C., 2000; Casagrande, V. A. and Xu, X., 2004). M cells are much more sensitive to luminance contrast and moving stimuli, but, while M cells show no wavelength sensitivity, P cells show sensitivity for green and red wavelengths. One exception to this are owl monkeys, which are crepuscular, like cats, and, like cats, are thus not so reliant on color vision. For these animals, P cells show little wavelength sensitivity (O'Keefe, L. P. *et al*., 1998). As is the case for the cat, there has been much speculation concerning the role of these cell types in the monkey. Common suggestions are that P cells are important for color discrimination in monkeys with diurnal behavioral patterns, especially for red/green distinctions, and may also be involved in high acuity vision, whereas M cells provide for better luminance contrast sensitivity and are also important for motion detection (Casagrande, V. A. and Norton, T. T., 1991; Hendry, S. H. C. and Reid, R. C., 2000; Casagrande, V. A. and Xu, X., 2004).

K cells. Like W cells, K cells probably include many distinct cell classes, and also like W cells, are grouped together here, because their complete classification remains to be done. As the name (Koniocellular) implies, these are smaller than M or P cells in both the retina and the lateral geniculate nucleus. Not much is known of their receptive field properties, but some of these cells are thought to be responsible for yellow/blue wavelength discrimination. For a fuller account of K cells, see Martin P. R. *et al*. (1997), Martin P. R. (1998), Silveira L. C. L. *et al*. (1999), and Hendry S. H. C. and Reid R. C. (2000).

1.28.5.2 Laminar Relationships

1.28.5.2.1 Lateral geniculate nucleus

Layering is a constant feature of the lateral geniculate nucleus in all mammals so far studied. In some species (e.g., cats and monkeys), the layering is obvious, because cell-poor interlaminar zones exist to demarcate the layers. In other species (e.g., rats), such zones do not exist, so the layering is less obvious but still present. Each of these layers receives an input from one or the other eye. Geniculate laminar patterns vary greatly among species, but this ocular division between sets of layers seems to be one constant.

In addition to ocular dominance, the various cell types are distributed with varying levels of laminar specificity. In the cat, X and Y cells commingle in the dorsal two layers (called the A layers); the next ventral layer (layer C) has only Y cells; and the ventral few layers have only W cells (Sherman, S. M., 1982). In the rhesus monkey, P and M cells separate into four dorsal parvocellular layers and two ventral magnocellular layers. The K cells not only are found in all the interlaminar zones but also extend into the ventral regions of the parvocellular layers (Casagrande, V. A. and Norton, T. T., 1991; Hendry, S. H. C. and Reid, R. C., 2000; Casagrande, V. A. and Xu, X., 2004). In the mink and ferret, the A layers (containing commingled X and Y cells) further separate into sublayers containing only on- or off-center cells (LeVay, S. and McConnell, S. K., 1982; Stryker, M. P. and Zahs, K. R., 1983), and yet the closely related cat has these on- and off-center cells commingled in single layers. Figure 5 summarizes the laminar patterns for several representative mammalian species to illustrate the sort of bewildering variation present. Geniculate lamination does

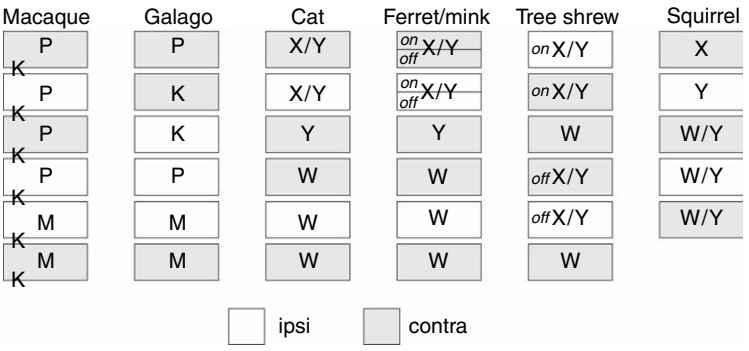

Figure 5 Schematic rendering of layers and distribution of cell types in the lateral geniculate nucleus of six different species (Kaas, J. H. *et al.*, 1972; Sherman, S. M. and Spear, 1982; Sherman, S. M., 1985; Casagrande, V. A. and Norton, T. T., 1991; Hendry, S. H. and Calkins, D. J., 1998; Van Hooser, S. D. *et al.*, 2003). The shaded boxes show layers innervated by the contralateral eye (contra), and the unshaded boxes show the input from the ipsilateral eye (ipsi). The X, Y, and W pathways are shown for the cat, the ferret/mink, the tree shrew, and the squirrel, and the magnocellular (M), parvocellular (P), and koniocellular (K) pathways are shown for the macaque and the galago. Where there is a clear segregation of on- and off-center (*on*, *off*) cells, this is also indicated. From Sherman, S. M. and Guillery, R. W. 2006. Exploring the Thalamus and its Role in Cortical Function, 2nd edn. MIT Press.

correlate with cell type, but the nature and extent of this correlation varies widely across species, and it is difficult to discern any special significance to these correlations.

1.28.5.2.2 Visual cortex

There is also a laminar correlation regarding the target zones of the various cell types (Ferster, D. and LeVay, S., 1978; Blasdel, G. G. and Lund, J. S., 1983; Humphrey, A. L. *et al.*, 1985; Casagrande, V. A. and Xu, X., 2004). In the cat, geniculate X-cell axons innervate the ventral part of layer 4, while those of Y cells innervate the upper part. Geniculate W cells mostly innervate layer 3. A similar arrangement holds for the monkey: P cells innervate the ventral half of layer 4 (sometimes called layer 4Cβ), M cells innervate the dorsal half of layer 4 (sometimes called 4Cα), and K cells mostly innervate layer 3. Thus, through the first stage of processing, the three parallel pathways are kept fairly independent, although what happens further centrally with regard to these pathways is not at all clear.

1.28.6 Drivers and Modulators

Figure 3 illustrates a fundamentally important point that is often overlooked: all inputs to geniculate relay cells are not equal. That is, the retinal input alone represents the main information actually relayed to the cortex. A consideration of receptive field properties helps demonstrate this fact, because the responses of the relay cell to visual stimulation identify the information relayed. It is clear that the receptive fields of geniculate relay cells are remarkably like those of their retinal afferents, having the same center/surround configuration and with only minor, subtle differences (reviewed in Sherman, S. M., 1985). Geniculate receptive fields do not closely match any other extrageniculate afferent: receptive fields of corticogeniculate afferents, which show selectivities for orientation and often direction typical of cortical cells (Gilbert, C. D., 1977), are quite different, and parabrachial inputs are not plausible sources of such clear center/surround properties. If it is the retinal input that provides the information to be relayed, then the nonretinal inputs must have another function. This, plus a number of morphological, pharmacological, and physiological differences that distinguish retinal and nonretinal afferents to relay cells, has led to the idea that these can be functionally divided: the retinal inputs are the drivers (so called because one of their properties is the very strong postsynaptic drive of their target relay cells; see Table 1), while all the nonretinal inputs are the modulators, the idea being that the driver input is the information-bearing input, while the modulators serve to modulate retinogeniculate transmission (Sherman, S. M. and Guillery, R. W., 1998; 2006). Modulation can take many forms, including, for example, the above-mentioned consequences of metabotropic receptor activation that lead to overall

Table 1 Drivers and modulators in lateral geniculate nucleus (LGN) plus layer 5 drivers

Criteria	*Retinal (driver)*	*Layer 5 to higher order (driver)*	*Modulator: layer 6*	*Modulator: PBR*	*Modulator: TRN and Int*
1	Determines relay cell receptive field	Determines relay cell receptive field[a]	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; Interneuron: [b]
3	Large EPSPs	Large EPSPs	Small EPSPs	[b]	TRN: small IPSPs; Interneuron: [b]
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; Interneuron: 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 onto target	Little convergence onto target[a]	Much convergence onto target	[b]	[b]
7	Very few synapses onto relay cells (~5%)	Very few synapses onto relay cells (~5%)	Many synapses onto relay cells (~30%)	Many synapses onto relay cells (~30%)	Many synapses onto 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*)[a]	Synapses show paired-pulse facilitation (low *p*)	[b]	[b]
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	[b]	Subcortically known to innervate thalamus only
13	Innervates dorsal thalamus but not TRN	Innervates dorsal thalamus but not TRN	Innervates dorsal thalamus and TRN	Innervates dorsal thalamus and TRN	TRN: both; Interneuron: dorsal thalamus only

[a]Very limited data to date.
[b]No relevant data available.
EPSP, excitatory postsynaptic potential; PBR, parabrachial region of the brainstem; TRN, thalamic reticular nucleus.

changes in relay cell excitability and that serve to control the tonic/burst transition. In addition, the circuit suggested by Figure 4(a) can operate to control the gain of retinogeniculate transmission.

Many properties distinguish drivers from modulators in thalamus, and the number will likely increase as we learn more about this issue. Table 1, which is not meant to be exhaustive, summarizes some important features (see also Sherman, S. M. and Guillery, R. W., 2006). Layer 5 drivers (the second column in Table 1) are considered below. The 13 criteria in Table 1, in a roughly decreasing order of importance, are as follows:

1. Drivers determine the main receptive field properties of the relay cell; modulators do not.
2. Drivers activate only ionotropic receptors; modulators activate metabotropic receptors as well.
3. Drivers evoke large EPSPs; modulators evoke smaller EPSPs or IPSPs.
4. Drivers form large terminals on proximal dendrites; modulators usually form small terminals throughout the dendritic arbor.
5. Each driver terminal forms multiple large synapses; each modulator terminal usually forms a single, small synapse.
6. Driver inputs show little convergence so that one or a small number of driver axons converge onto the postsynaptic target neuron; where evidence is available, modulator inputs show considerable convergence.
7. Driver inputs produce a small minority (~5%) of the synapses onto thalamic relays cells; many modulator inputs produce larger synaptic numbers (e.g., the cortical and parabrachial modulator inputs in Figure 3 each produces about 30% 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, meaning that a given action potential is likely to result in transmitter release and that, with the initiation of a train of action potentials, there is a period after each evoked postsynaptic potential lasting for tens of a millisecond that the next one will be smaller (depressed); modulator synapses that have been tested so far show the opposite properties of low release probability and paired-pulse facilitation.
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 thalamus (e.g., many or all retinogeniculate axons branch and also innervate midbrain targets); those modulator inputs so far tested innervate thalamus only.
13. Driver inputs innervate relay cells and interneurons in dorsal thalamus but do not innervate the thalamic reticular nucleus; modulator inputs innervate relay cells, interneurons, and reticular cells.

This driver/modulator distinction can be applied, not just to the lateral geniculate nucleus, but also to all 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, acting in some sort of anatomical democracy, and if one is to understand the functional organization of the thalamus and what it is that is being relayed, one must identify and characterize the driver input. As we shall see, identifying the driver to the lateral geniculate nucleus is clear, but it is not so obvious for the pulvinar. An important possibility raised below is that this driver/modulator distinction may also apply outside of thalamus.

Regarding criterion 7 above, it may seem surprising at first that the main information to be relayed is responsible for such a small minority of synapses onto relay cells, but two factors may help explain this. First, despite the small number of inputs anatomically, these are especially powerful and effectively drive the relay cells. Second, if a relatively small but powerful number of synapses are needed to relay the basic information, many more, individually weaker synapses that can be combined in different ways are needed to provide a wide range of subtle modulatory effects.

One last point needs to be emphasized with respect to geniculate circuitry that should be considered when evaluating any circuits in the central nervous system. With anatomical information alone, such as numbers of synapses from subcortical sites, the number from the parabrachial region (~30%) is considerably greater than that from retina (5–10%). Such anatomical data in isolation might lead one to the mistaken conclusion that the parabrachial input is

the more important and thus represents the information being relayed, while the retinal input, being so small, performs some vague, lesser function that might not even merit inclusion in some schematic illustrations of geniculate circuitry. The key lesson here is that anatomical data, on their own, can be very misleading when trying to unravel functional circuits. With regard to information processing through thalamus, a most important issue is to identify what is being relayed, and to do so, it is potentially misleading to treat all pathways as equal: one must instead separately identify drivers from modulators. Look through any textbook on neuroscience, and perhaps even this volume, and you are likely to find examples of schematically illustrated circuits that are based on anatomy alone, as if all inputs were drivers in the sense the term has been used here. If the concept of drivers and modulators has validity beyond thalamus, many of these suggested circuits need to be reconsidered.

1.28.7 First- and Higher-Order Relays: The Lateral Geniculate Nucleus and Pulvinar

There are two ways to think about the function of the thalamus. One is to consider the properties of thalamic circuitry as they affect relay functions. For one example, how do the modulators affect retinogeniculate transmission? The other is to consider what it is that a thalamic nucleus is actually relaying. Put another way, we can define the function of lateral geniculate nucleus or the ventral posterior nucleus as relaying retinal or medial lemniscal information, respectfully. It is this latter aspect of thalamic functioning, which really boils down to identifying the driver input, that chiefly concerns us in this section.

1.28.7.1 Layer 5 Corticothalamic Inputs as Drivers

Identifying the function of a thalamic nucleus by identifying the driver input may seem obvious and trivial for well-studied relays like the lateral geniculate nucleus, but there are many other less-well-understood relays with unknown functions because, until recently, their driver inputs were undefined. Examples are the pulvinar and medial dorsal nucleus. We now know that a major source of driver input to thalamic relays like these is layer 5 of the cortex. This is illustrated in Figure 6.

First- and higher-order relays. Figure 6(a) illustrates key elements of this organization (details reviewed in Sherman, S. M. and Guillery, R. W., 2006). All thalamic nuclei receive a feedback corticothalamic projection from layer 6, and they also have inputs from the thalamic reticular nucleus; not shown for simplicity are inputs to relay cells from interneurons and the parabrachial region (Figure 3). However, while some thalamic nuclei relay subcortical driver inputs to the cortex (Figure 6(a)), others instead relay driver inputs that arise from cortical layer 5, and this appears to be feedforward (Figure 6(b); see Van Horn, S. C. and Sherman, S. M., 2004). We refer to the type of thalamic relay of Figure 6(a) as first order, because this is the first relay of a particular type of subcortical information (e.g., retinal) to the cortex, and that of Figure 6(b) as higher order, because this relays information already in the cortex but from one cortical area to another.

The lateral geniculate nucleus and pulvinar as first- and higher-order relays. Clearly, in this scheme, the lateral geniculate nucleus is a first-order nucleus. As noted above, examples of other first-order nuclei are the ventral posterior nucleus for somesthesis and the ventral (or lemniscal) portion of the medial geniculate nucleus for sounds. The pulvinar is mostly a higher-order nucleus. We say "mostly" here, because a small part of the pulvinar appears to relay driver information from the superior colliculus (Kelly, L. R. *et al.*, 2003), which would make this portion of the pulvinar first order. Examples of other higher-order thalamic nuclei are most of the posterior medial nucleus for somesthesia, most of the medial and dorsal (or nonlemniscal) portion of the medial geniculate nucleus for hearing, and the medial dorsal nucleus, which widely innervates the prefrontal cortex. Again, most here refers to the fact that some of these nuclei may contain first-order circuits: there is a spinothalamic zone of the posterior medial nucleus and an inferior collicular input to the nonlemniscal part of the medial geniculate nucleus. This possible complex organization of higher-order nuclei has to be clarified, and it will not be considered further here, but it does point up a potential shortcoming of classically defined, cytoarchitectonic boundaries for functional thalamic relays.

The key to this division of thalamic relays into first and higher order is the observation that the layer 5 inputs to relay cells have the same properties as do the subcortical drivers (e.g., retinal input to the lateral geniculate nucleus and medial lemniscal input to the ventral posterior nucleus). Support for

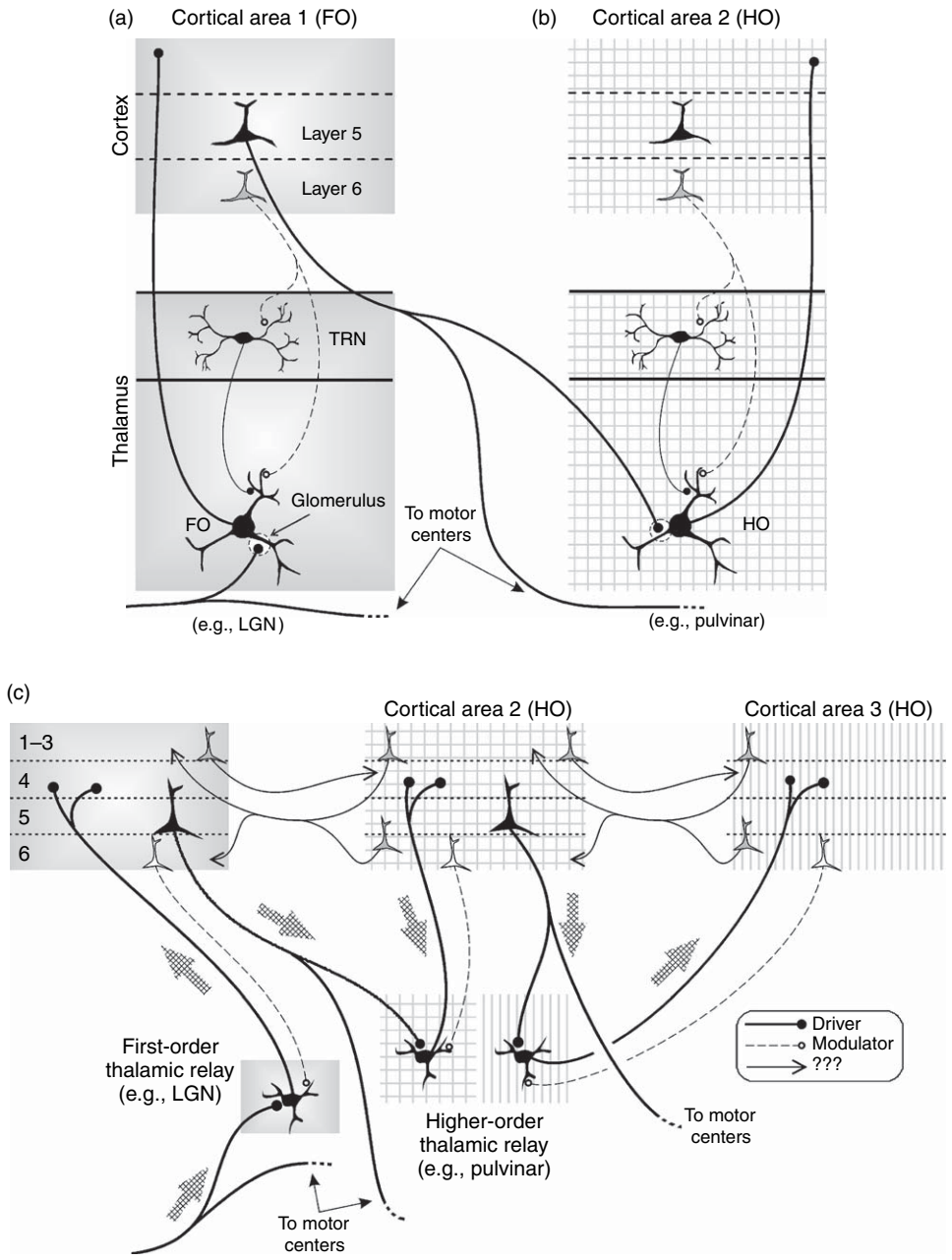

Figure 6 Schematic diagrams showing organizational features of first- and higher-order thalamic nuclei. (a, b) Distinction between first- and higher-order thalamic nuclei. A first-order nucleus (a) represents the first relay of a particular type of subcortical information to a first-order or primary 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. The important difference between them is the driver input, which is subcortical (a) for a first-order thalamic nucleus and from layer 5 of cortex (b) for a higher-order one. Note that all thalamic nuclei receive an input from layer 6 of cortex, which is mostly feedback, but higher-order nuclei in addition receive a layer 5 input from cortex, which is feedforward. (c) Role of higher-order thalamic nuclei in corticocortical communication. This involves 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. FO, first order; HO, higher order; LGN, lateral geniculate nucleus; TRN, thalamic reticular nucleus. Redrawn from Sherman, S. M. 2005. Thalamic relays and cortical functioning. Prog. Brain Res. 149, 107–126.

this can be found in Table 1: note from the first two columns of Table 1 that the layer 5 input to higher-order relays matches retinogeniculate input on all criteria; in contrast, the second and third columns show that the corticothalamic inputs from layers 5 and 6 differ on all criteria (Reichova, I. and Sherman, S. M., 2004; Sherman, S. M. and Guillery, R. W., 2006; Lee, C. C. and Sherman, S. M., unpublished).

1.28.7.2 Branching of Driver Afferents to Thalamus

Figures 6(a) and 6(b) also shows that the driver inputs to both first- and higher-order relay cells are delivered mostly or wholly via branching axons, with one branch innervating thalamic relay cells and the other innervating extrathalamic targets in the brainstem and spinal cord that are generally motor in nature (Guillery, R. W., 2003; 2005; Sherman, S. M. and Guillery, R. W., 2006). For instance, most or all retinogeniculate axons branch to innervate the pretectum and/or superior colliculus, and, likewise, most or all layer 5 corticothalamic axons branch to innervate motor targets in the pons, midbrain, medulla, and sometimes even spinal cord. However, drivers do not branch to innervate the thalamic reticular nucleus. This is in contrast to most modulator inputs, which do branch to innervate the thalamic reticular nucleus but often have no extrathalamic targets. Limited data are consistent with a similar arrangement for relays of somatosensory and auditory information (reviewed in Guillery, R. W., 2003; 2005; Sherman, S. M. and Guillery, R. W., 2006), and so are not limited to the lateral geniculate nucleus and pulvinar. Guillery R. W. (2003; 2005) has described this feature of driver afferents and suggested what its functional significance might be; this is briefly outlined below.

One interpretation of this pattern of branching to innervate extrathalamic motor targets is that the information actually relayed by thalamus relates to motor commands, starting with first-order relays as perhaps quite crude commands that are constantly upgraded with further cortical processing and effected via higher-order layer 5 cortical outputs. If so, then even first-order sensory processing involves processing of motor commands, a notion that stands conventional views of early visual processing on its head. That is, conventionally, the primary visual cortex (V1) is generally viewed as a purely sensory structure, and this view seems at odds with the idea that V1 is processing motor information. Furthermore, as already noted, V1 (and, indeed all cortical areas so far studied) has a layer 5 projection that branches to innervate pulvinar and extrathalamic motor targets, so that even the corticofugal outputs of V1 have a motor tag according to this perspective. The conventional wisdom that V1 or any other visual, auditory, or somatosensory area is purely sensory is challenged by the observation that all of these areas have a motor output.

1.28.7.3 Role of Higher-Order Thalamic Relays in Corticocortical Processing

Figure 6(c) illustrates the suggested role played by higher-order thalamic relays. After initially reaching the cortex via a first-order relay, such as the lateral geniculate nucleus, information is then passed on to higher-order cortical areas through higher-order thalamic relays. This can involve a number of hierarchical levels of both cortical and thalamic processing. The obvious question raised here is: if the corticothalamocortical pathways involving higher-order thalamic nuclei represent a significant information route, what of the direct corticocortical projections? The answer, simply, is not yet available, but to help clarify the issue here, it is useful to consider three obvious hypotheses, among others.

One possibility is that all direct corticocortical pathways are modulators, in which case all information between cortical areas is relayed via the thalamus. One conclusion that could be drawn here is that all new information that reaches the cortex, whether originating from a subcortical source such as the retina or from another cortical area, benefits from a thalamic relay. That is, for the same reason that retinal information is relayed by the lateral geniculate nucleus and does not project directly to the visual cortex, information from one cortical area to another is relayed through thalamus. Benefits could include gating properties of the thalamus, the burst/tonic transition, etc.

One problem with this hypothesis is that higher-order relays such as the pulvinar may not have enough neurons to relay all of the requisite information needed for cortical processing. Although the pulvinar is the largest thalamic nucleus and dwarfs the lateral geniculate nucleus, Van Essen D. C. (2005) points out that pulvinar neurons may be insufficient in number to relay all information needed for corticocortical communication. A very small percentage of visual cortical neurons are represented by the layer 5 efferents that could provide the afferent link in the corticothalamocortical pathway (Callaway, E. M. and Wiser, A. K., 1996), and these numbers do not

seem to pose a limitation on the role of the pulvinar as a central relay structure between cortical areas. Unfortunately, we as yet have no answer to this general question, because we simply do not know the nature or neural coding of this information that is passed on, and our ignorance here is such that we cannot rule out the possibility that the small number of layer 5 efferent cells is sufficient to this task. It is also possible that the full extent of information processed in a cortical area requires an additional, corticocortical route, the case to which we now turn.

The second hypothesis is that the corticothalamocortical pathways involving higher-order thalamic nuclei serve a modulatory role with all information carried by direct corticocortical projections. For instance, Van Essen D. C. and co-workers (Olshausen, B. A. *et al.*, 1993; Anderson, C. H. *et al.*, 2005; Van Essen, D. C., 2005) have suggested that pulvinar projections to the cortex serve to regulate attentional responses, which, in turn, implies that these projections could act as modulators. However, evidence does exist that the relevant synapses in corticothalamocortical pathways – namely, the layer 5 corticothalamic projections and the higher-order thalamocortical projections – are drivers (Reichova, I. and Sherman, S. M., 2004) (Agmon, A. and Connors, B. W., 1991; Stratford, K. J. *et al.*, 1996; Castro-Alamancos, M. A. and Connors, B. W., 1997; Gil, Z. *et al.*, 1999; Lee, C. C. and Sherman, S. M., unpublished).

The third and final hypothesis is that the higher-order corticothalamocortical and direct corticocortical pathways represent two parallel, largely independent, and complementary routes of information flow. One example of this would be that the very large corticocortical projection handles all of the details of information that must be analyzed about the environment, and the corticothalamocortical projections inform the target cortical area about motor commands initiated by the source area. This is a more limited form of information but is essential, because higher-order cortical areas must maintain a real-time appreciation of how motor commands affect sensory processing. For example, higher-order visual cortical areas need to be able to factor in eye movements that cause the visual world to move on the retina and not view these as movement in the environment. This example of the limited sort of information carried by the corticothalamocortical pathways is consistent with the motor branches of the layer 5 axons described above.

Two further points need to be emphasized here. First, even if both pathways are involved in information flow, there is an important distinction to be made. Whatever information is carried by direct corticocortical connections, this remains in the cortex and is thus different in kind from information carried by the layer 5 outputs to higher-order thalamic nuclei, because as noted above, these layer 5 axons branch to carry the same information to various extrathalamic, subcortical targets. Second, even if some corticocortical projections carry information, the massive potential problem remains to determine which pathways are modulators and which are drivers. This assumes that the driver/modulator distinction makes sense for intracortical pathways, and some recent evidence suggests the plausibility of this. That is, Lee C. C. and Sherman S. M. (unpublished) have shown that, while both first- and higher-order thalamocortical inputs to layer 4 cells in mice have driver synaptic characteristics, intracortical layer 6 inputs to the same layer 4 cells have modulator characteristics. Identifying the subset of drivers among these direct corticocortical pathways, even if the subset proves to be small, along with a full appreciation of the corticothalamocortical pathways, would allow the creation of a more complete and accurate hierarchical scheme for cortical processing.

1.28.7.4 Overview

To help appreciate cortical processing according to the conventional view and how this departs from the alternative view offered here, Figure 7 shows schematically how different these are. In the conventional view, information is relayed by the thalamus to the sensory cortex and passes within the cortex to the sensorimotor and then to the motor cortex before an output is generated to motor centers (Figure 7(a)). This provides no specific role for most of thalamus, which we have defined as higher order, although there are suggestions that some of these thalamic nuclei could play a modulatory role related to attention (Olshausen, B. A. *et al.*, 1993; Anderson, C. H. *et al.*, 2005; Van Essen, D. C., 2005). The alternative view (Figure 7(b)) differs from the beginning, since initial information to be relayed via a first-order thalamic nucleus is a copy of information sent to motor structures. From the primary cortex, information can be relayed to other cortical areas via higher-order thalamic nuclei, and this continues through the various hierarchical stages. Also, these pathways involve layer 5 corticothalamic axons that branch to innervate extrathalamic motor structures. The role of direct corticocortical pathways remains unclear in this view, but it is plausible that there are

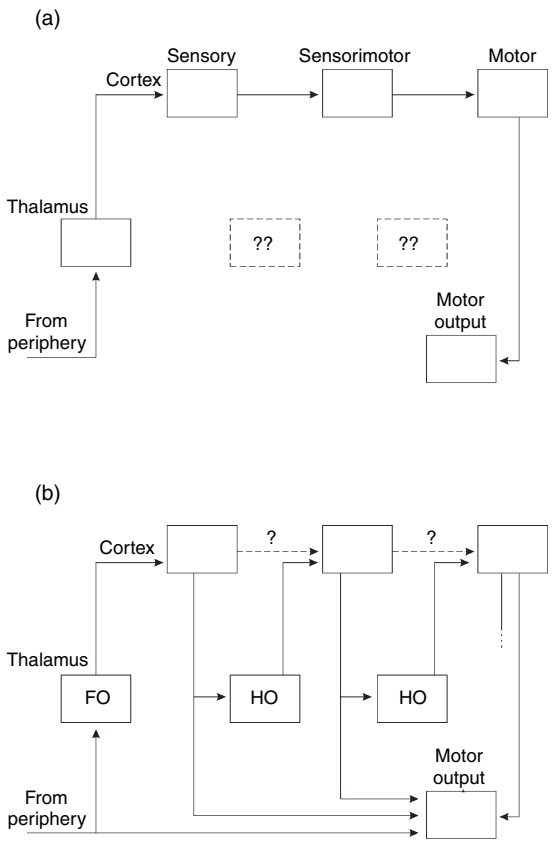

Figure 7 Comparison of conventional view (a) with the alternative view proposed here (b). The role of the direct corticocortical connections in (b) (dashed lines) is questioned (see text for details). FO, first order; HO, higher order. Further details in text. Reproduced from Sherman, S. M. 2005. Thalamic relays and cortical functioning. Prog. Brain Res. 149, 107–126.

two information routes operating independently and in parallel: one is the direct corticocortical route and the other the corticothalamocortical route.

It seems most likely that higher-order thalamic nuclei play an important and hitherto unappreciated role in corticocortical communication. Thus, thalamus is not there just to get information to the cortex in the first place but rather continues to play a role in further cortical processing of that information. What is less clear is the role of direct corticocortical pathways and their relationship to the corticothalamocortical pathways. If the driver/modulator has relevance for these pathways, and that is a major proviso, then it will be essential to identify which of these pathways, if any, are drivers. Only then can we have a clearer understanding of processing among the related cortical areas.

1.28.8 Conclusions

We have progressed from the days when the thalamus was seen as a dull, machine-like relay, providing interesting behaviors only during epilepsy or slow-wave sleep. To a large extent, this misconception grew out of the success of the receptive field approach to the study of sensory systems, particularly vision. Studies of the retina showed that receptive fields become increasingly complicated as one ascends synaptic hierarchies, leading ultimately to the classic center/surround receptive field of ganglion cells projecting to the lateral geniculate nucleus. This process continues across synaptic hierarchies in the cortex, providing cortical receptive fields with exquisite sensitivity to orientation, direction and speed of movement, spatial frequency, stereoscopic depth, etc. This receptive field elaboration in retina and the cortex is ultimately used to encode the sensory environment. The one synapse in the visual system across which no significant receptive field elaboration occurs is the retinogeniculate synapse, since the same basic center/surround organization is seen in retinal afferents and their target geniculate relay cells. This led to the notion that the lateral geniculate nucleus specifically and thalamus more generally represents an uninteresting, simple relay.

We can now turn that view on its head. Indeed, while the rest of the visual and other sensory systems can be ascribed to the same function – that is receptive field elaboration – the thalamus has a completely unique role to play in information processing. Recent appreciation of the complex cell and circuit properties of thalamus makes it clear that it is anything but simple and uninteresting in its functioning. These properties serve to regulate the flow of information to the cortex through mechanisms such as gain control of the retinogeniculate synapse (or equivalent for other nuclei) and the burst/tonic transition, functions that are probably just the tip of the iceberg. Furthermore, we can now see that thalamus is not there just to get information to the cortex but continues to play a significant role in corticocortical communication.

The challenge for students of the visual system is at least twofold. One is to gain a better appreciation of how and under what conditions information is affected before being relayed by the lateral geniculate nucleus or pulvinar to the cortex. The other is to address questions about the pulvinar. One of the great problems here is that we have no complete map of pulvinar that includes a full demarcation of what

regions of pulvinar innervate which regions of the cortex and which are innervated by each cortical area, with a separate mapping of layer 5 and 6 inputs. Given these variables and the presence of more than 30 visual cortical areas with which the pulvinar is involved, it may be that more than a hundred separate pulvinar regions remain to be discovered. This is a daunting task and should be seen as one of the major challenges for future studies of the visual system.

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