1.21 The Lateral Geniculate Nucleus and Pulvinar

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1.21.1 Abstract

Until fairly recently, the thalamus has largely been ignored as an interesting brain structure, and instead has been seen as a simple, machine-like relay of information to cortex. This view is now dramatically changed, largely from work on the visual thalamic relays, the lateral geniculate nucleus and the pulvinar. Two seminal observations helped to bring about this new appreciation. First, roughly 95% of synapses onto geniculate relay cells are nonretinal in origin and modulate the relay in a dynamic fashion linked to behavioral state. Much of this relates to control of response mode—*tonic* or *burst*. Second, the lateral geniculate nucleus and pulvinar are examples of two different types of relay: the lateral geniculate nucleus is a first order relay, transmitting information from a subcortical source (retina), while the pulvinar is mostly a higher order relay, transmitting information from layer 5 of one cortical area to another. Higher order relays seem to play a key role in cortical function via a cortico-thalamo-cortical route. Other examples of first and higher order relays also exist, and higher order relays represent the majority of thalamic volume. Thus, the thalamus not only provides a behaviorally relevant, dynamic control over the nature of information relayed, it also plays a key role in basic corticocortical communication.

1.21.2 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 visual cortex, chiefly to 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 of cortex. Fortunately, most of the detailed 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 general properties of thalamus.

The thalamus is a collection of adjacent nuclei located in the center of the brain. It is a paired structure, and in humans, each side is roughly the size of a walnut. Each of the various nuclei innervates one area of cortex or a small number of adjacent cortical areas. Unless otherwise specified, "cortex" used here refers to "neocortex" as opposed to "paleocortex" or "archicortex". It is important to keep in mind that virtually all information reaching 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 projection from one or more thalamic nuclei.

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 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 cortex, is known for all mammalian species so far 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 cortex but instead provide a GABAergic, inhibitory input to relay cells of the dorsal thalamus. Minor components of the ventral thalamus are the ventral division of the lateral geniculate nucleus, whose cells project to other brainstem sites but not the cortex, and the zona incerta, which provides a GABAergic innervation of some thalamic nuclei; these structures are 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.[1] The comparison of these thalamic nuclei serves to illuminate two very different purposes of thalamic relays: as shown in detail below, the lateral geniculate nucleus exemplifies *first order* relays, meaning that it relays subcortical (i.e., retinal) information to cortex, whereas pulvinar exemplifies *higher order* relays, meaning that it serves as part of a transthalamic route to relay information from one cortical area to another. Furthermore, in both cases, it is now clear that the complex cell and circuit functions of both types of thalamic nuclei belie any simple machine-like relay functions.

1.21.3 Thalamic Cell Types

Thalamus is comprised of 3 basic cell types: relay cells, interneurons, and cells of the thalamic reticular nucleus (**Fig. 1**) (for details, see Sherman and Guillery, 1996; Sherman and Guillery, 2013). Each of these may be further subdivided, but the complete classification of these cell types has yet to be done. Relay cells are glutamatergic, but interneurons and reticular cells 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[2].

Interneurons require some special mention, because they have unusual input/output properties. Details of their function can be found elsewhere (Sherman, 2004; Sherman and Guillery, 2013) and are only briefly summarized here. Interneurons have a conventional input/output route via an axon. However, in addition to the axonal output are many synaptic terminals emanating from distal dendrites (see inset to **Fig. 1**B). These dendritic terminals are both presynaptic, to a relay cell dendrite, and postsynaptic, to a retinal terminal. Because the local circuitry involving dendritic terminals is located distally on extremely thin dendritic processes (Hamos et al., 1985), these local circuits may be electronically isolated from each other and from the soma (Bloomfield and Sherman, 1989). As a result, it has been suggested that these cells can multiplex input/output processing separately among their dendritic outputs, which as a group are also processed separately from the axonal output, which would reflect activity of synaptic inputs located more proximally on the interneuron's dendrites (Sherman, 2004).

1.21.4 Cell Properties

Neurons throughout the central nervous system possess a bewildering variety of voltage- and time-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 and Guillery (Sherman and Guillery, 1996, 2006). The presence of these conductances means that

[1]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". Furthermore, rats and mice have a thalamic structure known as the "lateral posterior nucleus," but this is now thought of as homologous to the pulvinar of other mammals (Zhou et al., 2017) and will be referred to as such here.

[2]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 et al., 1997). This is not a property of rodents, because hamsters, guinea pigs, squirrels, etc., have interneurons throughout thalamus (e.g., Arcelli et al., 1997). However, this point has been questioned by evidence that the lateral posterior nucleus of the rat has a substantial fraction of interneurons (Li et al., 2003).

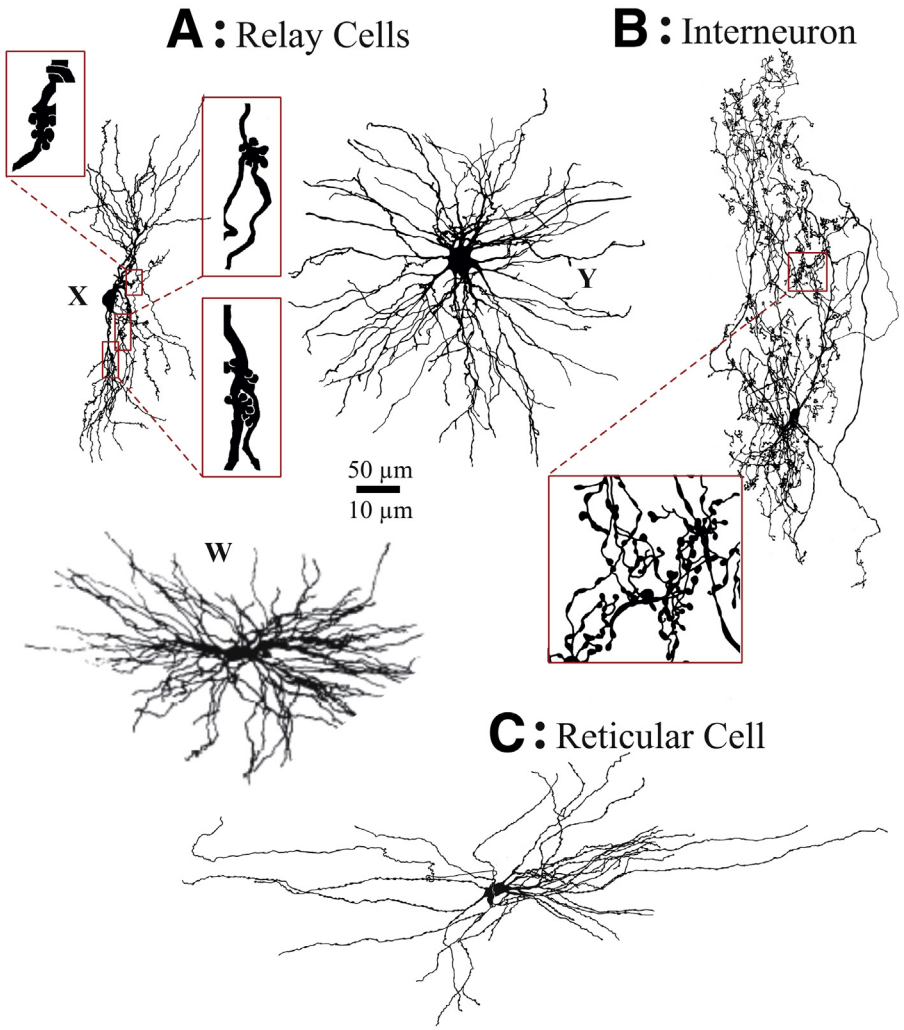

Figure 1 Tracings of representative cell types from the lateral geniculate nucleus and associated thalamic reticular nucleus of the cat. The data are from intracellular horseradish peroxidase fills performed *in vivo* in the author's laboratory after physiological identification of the cell. (A) Relay X, Y, and W cells. The insets for the X cell show examples of grape-like clusters appended to the dendrites near their proximal branch points; these reflect postsynaptic sites of retinal input. **(B)** Interneuron. The inset show synaptic terminals derived from dendrites. **(C)** Cell of the thalamic reticular nucleus. The scale bar indicates sizes for the main tracings as well as the insets in A and B.

membrane voltage and its temporal pattern, which together determine if and when each of these becomes activated, play important roles in relay cell excitability and thus the nature of information flow through the thalamic relay. 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 and Guillery, 1996, 2006; Sherman, 2001).

1.21.4.1 Properties of Na^+ and K^+ channels Underlying the Action Potential

Because the ionic events underlying the action potential are generally well understood, and because these are qualitatively so like those involving T-type Ca^{2+} channels, we shall start with a brief review of the action potential shown in Fig. 2A. The Na^+ channel has two voltage- and time-controlled gates, an *activation gate* and an *inactivation gate*. Both gates must be open for Na^+ to flow into the cell and depolarize it. The K^+ channel has only an activation gate. At normal resting potentials, say, −65 mV, the activation gate is closed, and so there is no entry of Na^+ (Fig. 2Ai). However a depolarization to, say, −55 mV, is sufficient to open the activation gate, leading to the upswing of the action potential (Fig. 2Aii). This depolarization leads, after about 1 msec, to closing of the inactivation gate, meaning that both depolarization and a period of time are needed for this process; this inactivation of the Na^+ channel, combined with activation of the somewhat slower K^+ channel, blocks further depolarization (Fig. 2Aiii) and serves to repolarize the cell to its original resting potential (Fig. 2Aiv). However, the Na^+ inactivation gate remains closed for another 1 msec or so, which underlies the refractory period during which no further action potentials can be evoked.

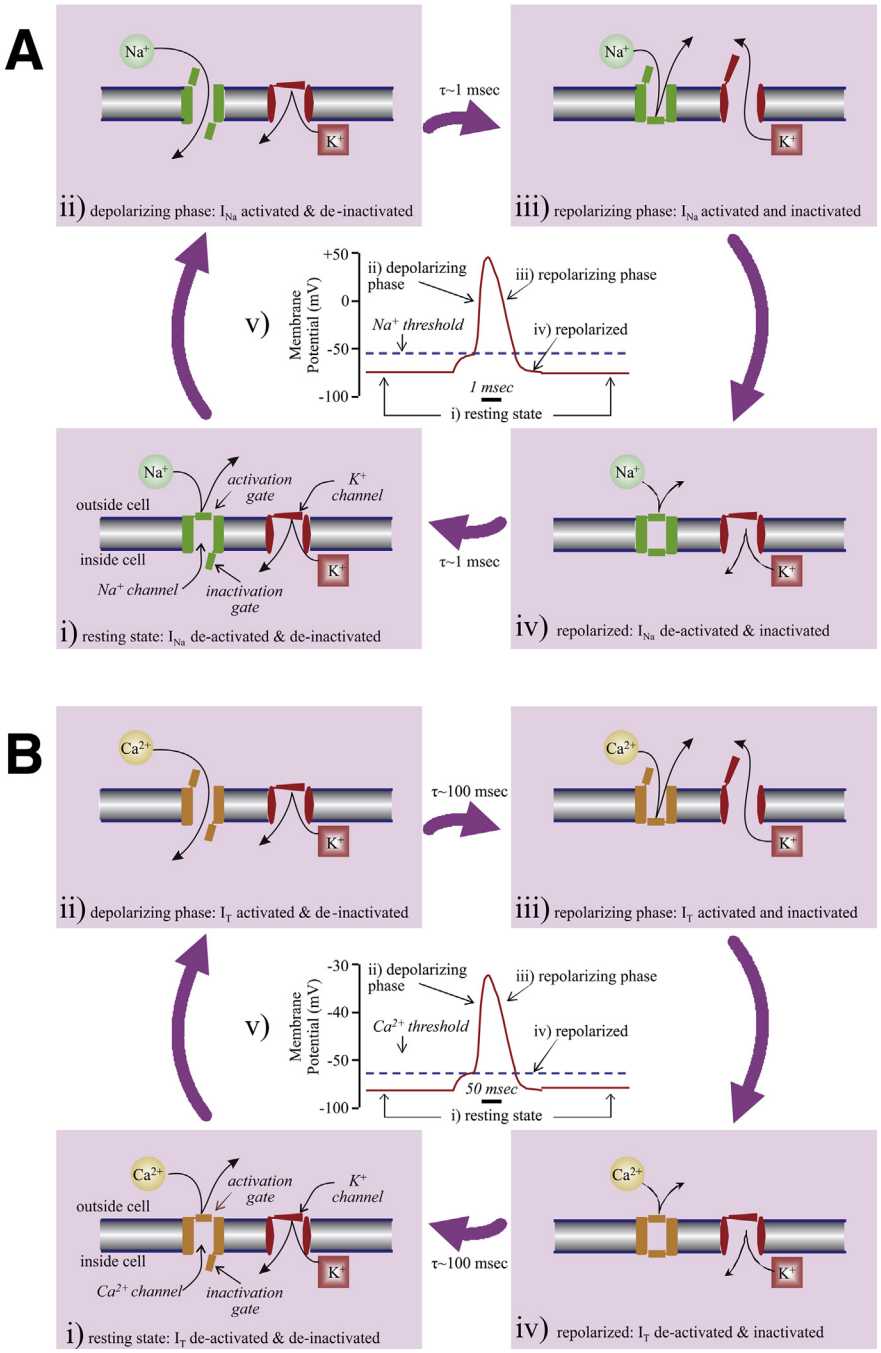

Figure 2 Schematic representation of voltage-dependent ion channels underlying the conventional action potential and the low-threshold Ca^{2+} spike. **(A)** For the action potential, (i–iv) show the channel events, and (v) shows the effects on membrane potential. The Na^+ channel has two voltage-dependent 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 with slower kinetics than for the Na^+ gates, and when it opens at depolarized levels, an outward, hyperpolarizing K^+ current is activated. (i) At the resting membrane potential, the activation gate of the Na^+ channel is closed, and so it is de-activated, but the inactivation gate is open, and so it is also de-inactivated. The single gate for the K^+ channel is closed, and so the K^+ channel is also de-activated. (ii) 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. (iii) 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. (iv) Even though the initial resting potential is reached, the Na^+ channel remains inactivated because it takes roughly 1 msec of hyperpolarization for de-inactivation. (v) Membrane voltage changes showing action potential corresponding to the events in i–iv. (B) For the representation of actions of voltage-dependent T (Ca^{2+}) and K^+ channels underlying the low-threshold Ca^{2+} spike, the conventions are as in A; (i–iv) Show the channel events, and (v) shows the effects on membrane potential. Note the strong qualitative similarity between the behavior of the T-type Ca^{2+} channel here and the Na^+ channel shown in A, including the presence of both activation and inactivation gates with similar relative voltage dependencies. (i) At a membrane potential more hyperpolarized than the normal resting potential, the activation gate of the T-type Ca^{2+} channel is closed, but the inactivation gate is open, and so the channel is both de-activated and de-inactivated. The K^+ channel is also de-activated. (ii) With sufficient depolarization to reach its threshold, the activation gate of the T-type Ca^{2+} channel opens, allowing Ca^{2+} to flow into the cell. This depolarizes the cell, providing the upswing of the low-threshold spike. (iii) The inactivation gate of the T-type Ca^{2+} channel closes after roughly 100 msec ("roughly," because, as for the Na^+ channel in A, closing of the channel is a complex function of time and voltage), inactivating the T-type Ca^{2+} channel, and the K^+ channel also opens. (iv) These combined actions repolarize the cell. Redrawn from Sherman and Guillery (2013).

This also limits the cell's firing rate to 1 KHz in theory, but in practice, other factors limit the firing of most cells to a few hundred hertz. An important point worth emphasizing here is that the inactivation gate has both voltage and time requirements: inactivation requires sufficient depolarization for at least about 1 msec; de-inactivation requires sufficient hyperpolarization, again for at least about 1 msec.

1.21.4.2 Properties of T-type Ca^{2+} Channels

Fig. 2B shows that the voltage and time dependency for the T-type Ca^{2+} channels are qualitatively like those of the Na^{+} channels, with activation and inactivation gates (Jahnsen and Llinás 1984a,b; McCormick and Huguenard, 1992; Sherman, 2001; Sherman and Guillery, 2013). At rest, which at roughly −70 mV here is slightly more hyperpolarized than the above example, the inactivation gate is open but the activation gate is closed; the channel is thus both de-inactivated and de-activated (Fig. 2Bi). Following depolarization to threshold for the activation gate (to roughly −65 mV), the gate opens and Ca^{2+} flows into the cell, leading to the upswing of the all-or-none Ca^{2+} spike; now, the T type Ca^{2+} channel is activated and de-inactivated (Fig. 2Bii). 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 msec of depolarization, the T type Ca^{2+} channel inactivates[3] (Fig. 2Biii), and this, combined with activation of a slower series of K^{+} conductances, repolarizes the neuron Fig. 2Biv). However, the T type Ca^{2+} channel remains inactivated (Fig. 2Biv) for another 100 msec or so, after which time the original state of Fig. 2Bi is restored. The two gates of the T type Ca^{2+} channel have opposite voltage dependencies, but while the activation gate responds quickly to voltage change, the inactivation gate is slower, requiring roughly 100 msec of polarization change to open or close. Note that the roughly 100 msec of hyperpolarization needed to de-inactivate the T type Ca^{2+} channel provides a refractory period limiting low threshold Ca^{2+} spiking to roughly 10 Hz.

As noted, this behavior of the T type Ca^{2+} channel is qualitatively identical to that of the Na^{+} channel underlying conventional action potentials, but there are three important quantitative differences: (1) the regime of the voltage dependency of the T type Ca^{2+} channel is 5–10 mV more hyperpolarized; (2) the inactivation kinetics of the T type Ca^{2+} channel are much slower; and (3) T type Ca^{2+} channels are found in the dendrites and soma but not in the axons, where Na^{+} channels are common. This last point means that it is only action potentials that convey the information relayed to cortex.

It should be noted that T-type Ca^{2+} channels are found broadly in neurons throughout the central nervous system. In order to generate an all-or-none spike that propagates throughout the somadendritic membranes, the density of these channels must be relatively high. In thalamic relay cells this density is high enough to support such spiking, but in most cells, the density of these channels is too low for spiking, and thus activation of these channels leads to modest depolarizations that spread electrotonically.

1.21.4.3 Properties of Burst and Tonic Firing

This behavior of T type Ca^{2+} channels underlies the two different response modes, *tonic* or *burst*, that are expressed by thalamic relay cells. How information is relayed to cortex depends heavily on which response mode is in use (Sherman, 2001; Swadlow and Gusev, 2001; MacLean et al., 2005; Bezdudnaya et al., 2006; Sherman and Guillery, 2013). This is because the same input (e.g., an EPSP from retina) will evoke a very different response in the relay cell during tonic versus burst firing (see Fig. 3A and B). For a given level of sustained hyperpolarization, leading to a related level of T type Ca^{2+} channel de-inactivation, the all-or-none evoked low threshold Ca^{2+} spike is fairly constant in amplitude (Fig. 3C). However, the more initially hyperpolarized the cell in amplitude and time, the more T-type Ca^{2+} channels are de-inactivated, and thus a larger low threshold spike providing more action potentials is evoked (Fig. 3D). 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 (Fig. 3E). 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 spike is all-or-none, a larger EPSP does not elicit a larger low threshold spike or a higher firing (Fig. 3E). The response during burst firing as illustrated in Fig. 3E resembles a step function, which is highly nonlinear.

The advantage for tonic firing is pretty clear: if cortex is to reproduce faithfully the visual scene, the sort of nonlinear distortion seen during burst firing would hamper this process. While less obvious perhaps, there are at least three advantages for burst firing (Sherman, 2001; Swadlow and Gusev, 2001; MacLean et al., 2005; Bezdudnaya et al., 2006; Sherman and Guillery, 2013). First, because burst firing is associated with lower spontaneous activity, itself the result of relative hyperpolarization associated with the burst firing mode, and spontaneous activity, which by definition is unrelated to any visual stimulus, can be considered noise with respect to analyzing a visual scene. However, because the burst itself represents a high rate of firing in response to a visual stimulus, burst firing has a higher signal-to-noise ratio and thus subserves better stimulus detectability. Second, burst firing enhances the efficacy of the retinogeniculate synapse (Alitto et al., 2019). Third, burst firing leads to a much greater postsynaptic response in cortex (Swadlow and Gusev, 2001; Swadlow et al., 2002). This last point follows from the nature of the thalamocortical synapse, which is a depressing synapse (Beierlein and Connors, 2002; Viaene et al., 2011c): the firing rate during tonic mode is sufficiently

[3]Control of inactivation gate is a complex function of voltage and time (Jahnsen and Llinás 1984a,b; Zhan 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 msec is required for these actions.

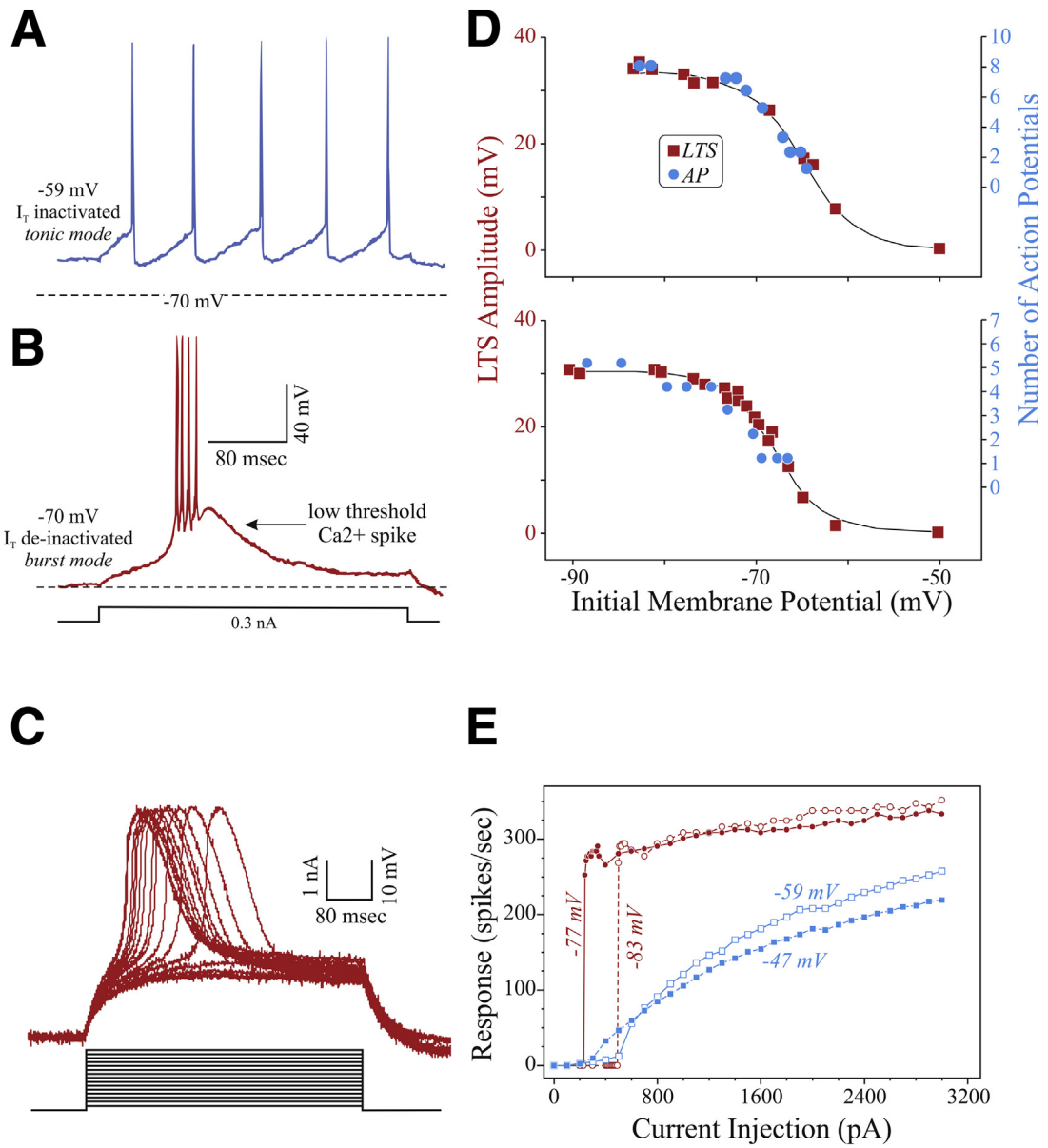

Figure 3 Properties of I_T and the low threshold Ca^{2+}spike. All examples are from relay cells of the cat's lateral geniculate nucleus recorded intracellularly in *in vitro* slice preparations. (A,B) Voltage dependency of the low Ca^{2+} threshold spike. Responses are shown to the same depolarizing 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 with a stream of unitary action potentials as long as the stimulus is suprathreshold for firing. This is the *tonic mode* of firing. When the cell is relatively hyperpolarized (B), I_T is de-inactivated, and the current pulse activates a low threshold Ca^{2+} spike with four action potentials riding its crest. This is the *burst mode* of firing. (C) All-or-none nature of low threshold Ca^{2+} spikes measured in the presence of TTX (to eliminate action potentials) in another geniculate cell neuron that was initially hyperpolarized, and current pulses were injected into the neuron starting at 200 pA and incremented in 10 pA steps. Smaller (subthreshold) pulses led to pure resistive-capacitive responses, but all larger (suprathreshold) pulses led to a low threshold spike. Much like conventional action potentials, the low threshold spikes are all the same amplitude regardless of how far the depolarizing pulse exceeded activation threshold, although there is latency variability for smaller suprathreshold pulses. (D) Voltage dependency of amplitude of low threshold spike and number of action potentials in the burst response. Examples for two neurons are shown, and the upper cell is the same cell as shown in C. The more hyperpolarized the cell before being activated (*Initial Membrane Potential*), the larger the low threshold spike (*LTS*; *red squares* and *curve*), and the more action potentials (*AP*) in the burst (*blue circles*). The number of action potentials was measured first and then TTX was applied to isolate the low threshold spike for measurement. (E) Input-output relationship for another cell. The input variable is the amplitude of the depolarizing current pulse, and the output is the firing frequency of the cell. To compare burst and tonic firing, the firing frequency was determined by the first 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 reflect tonic mode, whereas −77 mV and −83 mV reflect burst mode. Redrawn from Sherman and Guillery (2006).

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 de-inactivate the T type Ca^{2+} channels) 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.

There is an important proviso regarding these different firing modes. Burst and tonic firing are often described as distinct firing modes, but a kind of intermediate stage also exists. The extremes are clear: if a relay cells is sufficiently depolarized, all T-type Ca^{2+} channels are inactivated, and the neuron's response is strictly in tonic mode; if the neuron is sufficiently hyperpolarized to de-inactivate an adequate population of T-type Ca^{2+} channels to generate a low threshold spike, burst firing ensues. However, at a less hyperpolarized level, some of these Ca^{2+} channels will be de-inactivated, but their density is insufficient to activate an all-or-none low-threshold spike, so instead their activation by a depolarizing input such as an EPSP will evoke a relatively small non-propagating depolarization that will affect the neuron's responsiveness (Deleuze et al., 2012; Alitto et al., 2019).

1.21.4.4 Hypothesis for Burst and Tonic Firing

These properties of burst and tonic firing have led to the following hypothesis (Sherman, 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 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 in the environment, a change that perhaps 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 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. This could be accomplished by the layer 6 feedback that could depolarize the relevant relay cells, thereby inactivating their T type Ca^{2+} channels, which switches firing mode from burst to tonic.

Several recent observations support this hypothesis (Weyand et al., 2001; Alitto and Usrey, 2004; Lesica and Stanley, 2004; Denning and Reinagel, 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. Note that such stimuli occur more often during responses to natural scenes than in response to artificial stimuli such as drifting gratings or flashing spots (Lesica and Stanley, 2004; Lesica et al., 2006). 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.

1.21.5 Lateral Geniculate Nucleus

An important proviso to this section is the observation that the best studied thalamic nucleus in terms of understanding its functional circuitry remains the cat's lateral geniculate nucleus. It remains a useful model for the mammalian thalamus writ large and will serve that purpose here. However, work on the cat's lateral geniculate nucleus has come to a virtual stop, with very few laboratories continuing to study the cat brain, and so we have not much advanced our knowledge of thalamic circuitry in the past decade or so. Relevant work today centers on the use of mice or monkeys, and it will be some time before study of the thalamus in these species catches up to the knowledge base amassed for the cat.

1.21.5.1 Anatomical Features

Fig. 4A schematically shows the main inputs to geniculate relay cells. 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 and Guillery (1996, 2013).

Retinal input is one of several to geniculate relay cells. Nonretinal inputs derive from local GABAergic sources (interneurons and reticular cells), layer 6 of visual cortex, which provides a feedback, glutamatergic input, and from the brainstem, mostly from cholinergic cells in a midbrain area known as the brainstem reticular formation.[4] 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.

[4]Other terms often applied to this area include "pedunculopontine tegmental nucleus" or "parabrachial region". We prefer "brainstem reticular formation," because, in many or most species, the cells that innervate thalamus from this area do not have a clear nuclear boundary and instead are found scattered around the brachium conjunctivum.

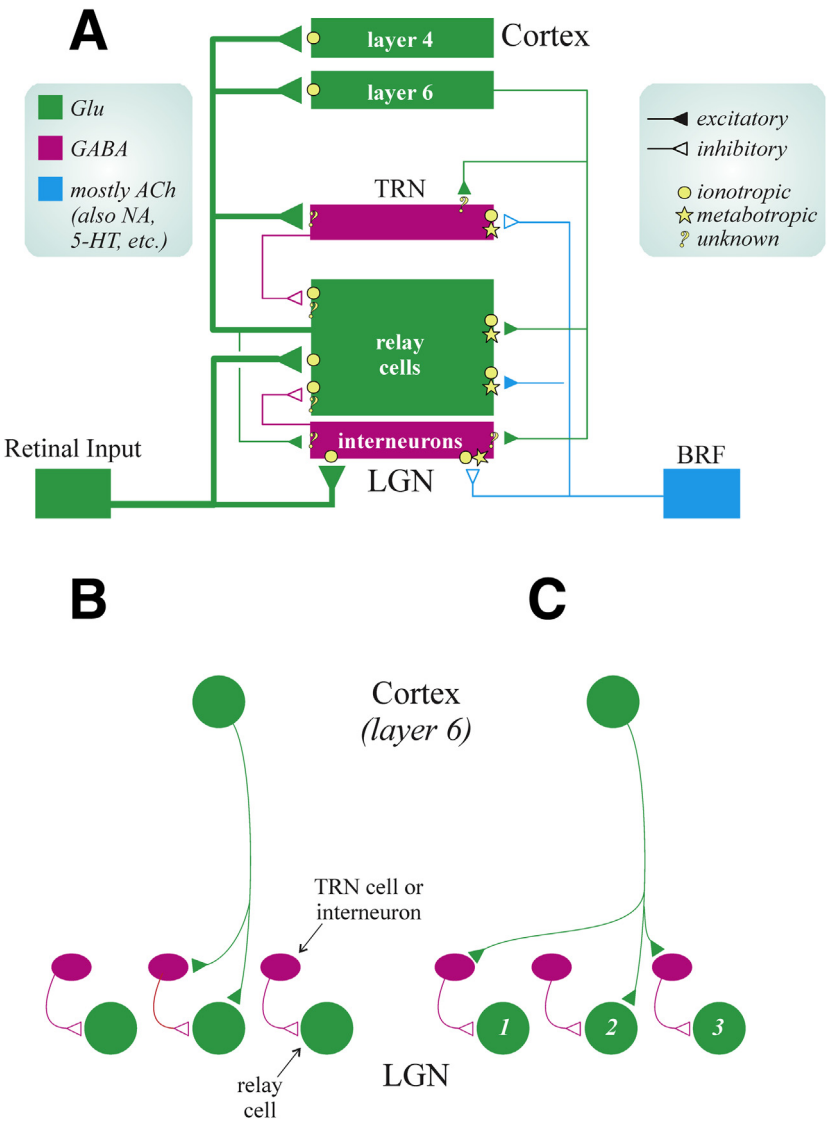

Figure 4 Details of circuitry of lateral the geniculate nucleus. (A) Schematic view of major circuit features of the lateral geniculate nucleus with related postsynaptic receptors present on relay cells. Other thalamic nuclei seem to be organized along the same pattern. The key to the left indicates the major transmitter systems involved, and that to the right, the postsynaptic receptors involved and whether the input is excitatory or inhibitory. 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. 5-HT, serotonin; ACh, acetylcholine; BRF, brainstem reticular formation; GABA, γ-aminobutyric acid; Glu, glutamate; LGN, lateral geniculate nucleus; TRN, thalamic reticular nucleus. (B,C) Two patterns among others possible for corticothalamic projection from layer 6 to cells of the thalamic reticular nucleus, geniculate interneurons, and geniculate relay cells. (B) Pattern of simple excitation and feedforward inhibition. (C) More complicated pattern in which activation of a cortical axon can excite some relay cells directly and inhibit others through activation of reticular cells. Abbreviations as in A.

1.21.5.2 Functional Features

Fig. 4 makes clear that, while the retina may provide the main source of information relayed to cortex, many nonretinal pathways innervate relays 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. Fig. 4A 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.

1.21.5.2.1 Ionotropic and Metabotropic Receptors

Differences between ionotropic and metabotropic receptors are many, and only certain ones are considered here (for details, see Nicoll et al., 1990; Mott and Lewis, 1994; Pin and Duvoisin, 1995; Recasens and Vignes, 1995; Brown et al., 1997; Viaene et al., 2013). **Fig. 5** illustrates differences relevant to this account. Ionotropic receptors (**Fig. 5**A) 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 occur with brief latencies (<1 msec) and durations (mostly over in 10 or a few 10 s of msec). Metabotropic receptor functioning is more complicated (**Fig. 5**B), 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

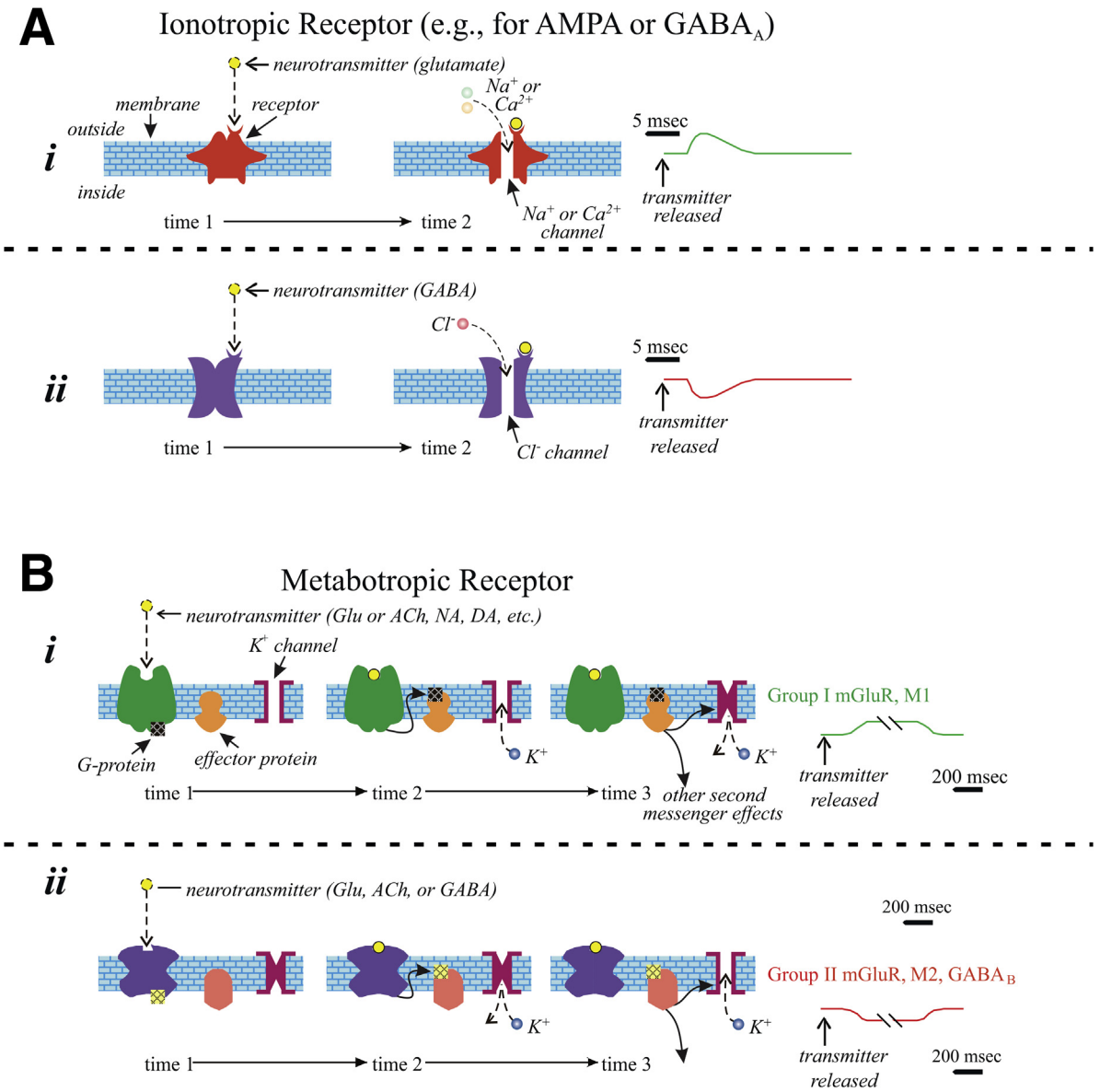

Figure 5 Schematic depiction of ionotropic and metabotropic receptors, each type shown repeatedly at different times (*time 1* and *time 2* for the ionotropic receptors, and *time 1*, *time 2*, and *time 3* for the metabotropic receptors). (A) For the ionotropic examples, *time 1* represents the period before binding to the neurotransmitter, and *time 2* is the period after binding. The binding causes a conformational change that opens the ion channel, which forms the central core of the receptor complex. (B) For the metabotropic receptors, *time 1* is the period before neurotransmitter binding, and just after binding (*time 2*) a G-protein is released from the postsynaptic receptor complex, and the G-protein reacts with an effector protein to produce a cascade of biochemical reactions eventually resulting in opening or closing of an ion channel, usually a K^+ channel (*time 3*). Redrawn from Sherman and Guillery (2013).

of K^+ is stopped, leading to an EPSP. One important difference with activation of ionotropic receptors is that these PSPs related to metabotropic receptors typically have a long latency (~10 msec or so) and duration (100 s of msec to several sec).

From the pattern of postsynaptic receptors associated with the various inputs onto relay cells (Fig. 4A), we can see 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 type Ca^{2+} channel (i.e., to close the inactivation gate) requires 100 msec or so of sustained depolarization; likewise, to de-inactivate it (i.e., to open the inactivation gate) requires 100 msec or so of sustained hyperpolarization. This means that the fast excitatory or inhibitory postsynaptic potentials seen with ionotropic receptors are ill suited to affect the inactivation gate; even action potentials, despite their large amplitude, appear too briefly to effectively inactivate the T type Ca^{2+} channel. In contrast, the sustained postsynaptic potentials of metabotropic receptors are ideally suited to inactivate or de-inactivate T type Ca^{2+} channels. It thus follows that retinal input by itself, with its fast excitatory postsynaptic potentials, is less likely to directly affect T type Ca^{2+} channels.

This seems appropriate in the sense that burst or tonic firing is thought to be largely dependent on behavioral state (Sherman, 2001; Bezdudnaya et al., 2006), 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 mode, 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 de-inactivate the T type Ca^{2+} channels, and when this stimulus is replaced by an excitatory one (e.g., a bright spot), a burst is evoked (Lesica and Stanley, 2004; Alitto et al., 2005; Denning and Reinagel, 2005). However, this is likely due to inhibitory circuits involving interneurons or reticular cells, or both, and perhaps involving $GABA_B$ receptors, and is not likely to represent retinal inputs alone. Indeed, evidence exists (reviewed in Sherman and Guillery 1996; Sherman and Guillery 2013) that metabotropic glutamate receptors activated from layer 6 of cortex and muscarinic receptors activated from the brainstem reticular formation produce long, slow excitatory postsynaptic potentials that inactivate the T type Ca^{2+} 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 Fig. 4A, it is not yet known whether these inputs activate $GABA_B$ receptors on relay cells.

1.21.5.2.2 Role of Inputs From Brainstem Reticular Formation and Layer 6 of Cortex

Fig. 4A shows that increased activity in brainstem inputs depolarize relay cells directly; this is accomplished largely through the activation of nicotinic and M1 (muscarinic) receptors. In addition, increased brainstem activity inhibits reticular cells and interneurons, mainly through activation of M2 (muscarinic) receptors, thereby disinhibiting relay cells (McCormick and Prince, 1986; McCormick and Pape, 1988; McCormick 1989, 1992). Thus, increased brainstem activity results in more depolarized relay cells, which not only makes them more excitable, but also serves to inactivate their T type Ca^{2+} channels, biasing relay cell responses to tonic mode. This observation is consistent with evidence that brainstem neurons become more active and relay cells become less bursty with increasing vigilance, from slow wave sleep through drowsiness to full attention (Steriade and Contreras, 1995; Datta and Siwek, 2002).

Understanding the consequence of the layer 6 cortical input is much more difficult, because the details of the circuitry remain largely elusive. Fig. 4B and C shows two variants among many possible. Fig. 4B shows individual corticogeniculate axons innervating a reticular cell and 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 type Ca^{2+} channel inactivation or de-inactivation) if the excitatory and inhibitory inputs are roughly balanced. However, as pointed out by Chance et al. (Chance et al., 2002), while this may not much affect membrane voltage, the increased synaptic conductance among other factors will reduce relay cell excitability to other (e.g., retinal) inputs; thus in the lateral geniculate nucleus, activation of this circuit would reduce the gain of retinogeniculate transmission.

The circuit of Fig. 4C 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 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 corticogeniculate feedback can have very different and localized effects. Recent evidence is in support of this pattern (Wang et al., 2006; Lam and Sherman, 2010). It is also important to note that any macroscopic manipulation of the layer 6 feedback that obscures the topography of Fig. 4C, such as a large scale chemical or physical ablation of the pathway or similarly large scale excitation (e.g., via optogenetics), would affect the projection as if it were organized as in Fig. 4B. Thus, the vast majority of studies of corticogeniculate function that have employed macroscopic manipulation have plausibly obscured a major function of this feedback. Thus, Fig. 4B and C illustrates the importance of a much better understanding of these functional circuits at the single cell level than we have at present.

1.21.5.3 Parallel Processing

Relay cells in the lateral geniculate nucleus can be divided into at least three functional classes (Cleland et al., 1971; Sherman 1982, 1985; Shapley and Lennie, 1985; Casagrande and Norton, 1991; Usrey et al., 1999; Hendry and Reid, 2000; Casagrande and Xu, 2004). Each of these represents a thalamic link in separate streams of retino-geniculo-cortical 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 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 and Norton, 1991; Van Hooser et al., 2003; Casagrande and Xu, 2004).

1.21.5.3.1 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 and Wässle, 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 and Ferster, 1977; Friedlander 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 (see **Fig. 1**A). 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 et al., 1984; Hamos et al., 1987).

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 and Spear, 1982; Shapley and Lennie, 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 and Robson, 1966; Hochstein and Shapley, 1976). Based on receptive field properties, hypotheses have been developed for the distinct function of the X and Y pathways. One of these hypotheses suggests that X cells provide maximum acuity for detailed vision, while Y cells are more important for motion detection and processing of low spatial frequencies (Sherman, 1985).

1.21.5.3.2 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, 1982; Sherman, 1985; Berson et al., 1998; Isayama 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 geniculate layers (see **Fig. 1**A) (Stanford et al., 1983). The receptive fields of these cells, both in retina and the lateral geniculate nucleus, are also quite varied but tend to be large and poorly responsive. Indeed, Cleland and Levick (Cleland and Levick 1974a,b) 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(s) of the W pathway(s), functions that remains mostly a mystery.

1.21.5.4 The Monkey Lateral Geniculate Nucleus

1.21.5.4.1 P and M Cells[5]

Among retinal ganglion cells, P cells (also called midget cells) are smaller than are M cells (also called parasol cells), and this size differential also holds in the lateral geniculate nucleus, as the names (***P***arvocellular and ***M***agnocellular) imply (Rodieck, 1979; Leventhal et al., 1981). Their receptive fields both in retina and the lateral geniculate nucleus have the classic center/surround configuration, but P cells have smaller receptive fields (Casagrande and Norton, 1991; Hendry and Reid, 2000; Casagrande and Xu, 2004). M cells are much more sensitive to luminance contrast and moving stimuli, but, whereas M cells show no wavelength sensitivity, P cells in diurnal monkeys show sensitivity for green and red wavelengths. It is worth noting that in owl monkeys, which are nocturnal and are thus not so reliant on color vision, P cells show little wavelength sensitivity (Ogden, 1975; Jacobs et al., 1993; O'Keefe et al., 1998). As is the case for the cat, there has been much speculation concerning the role of these P and M pathways in the monkey.

[5]We use this terminology for these cells because P cells project to the parvocellular geniculate layers, and M cells, to the magnocellular layers. Later, we refer to K ganglion cells as those innervating the koniocellular geniculate layers.

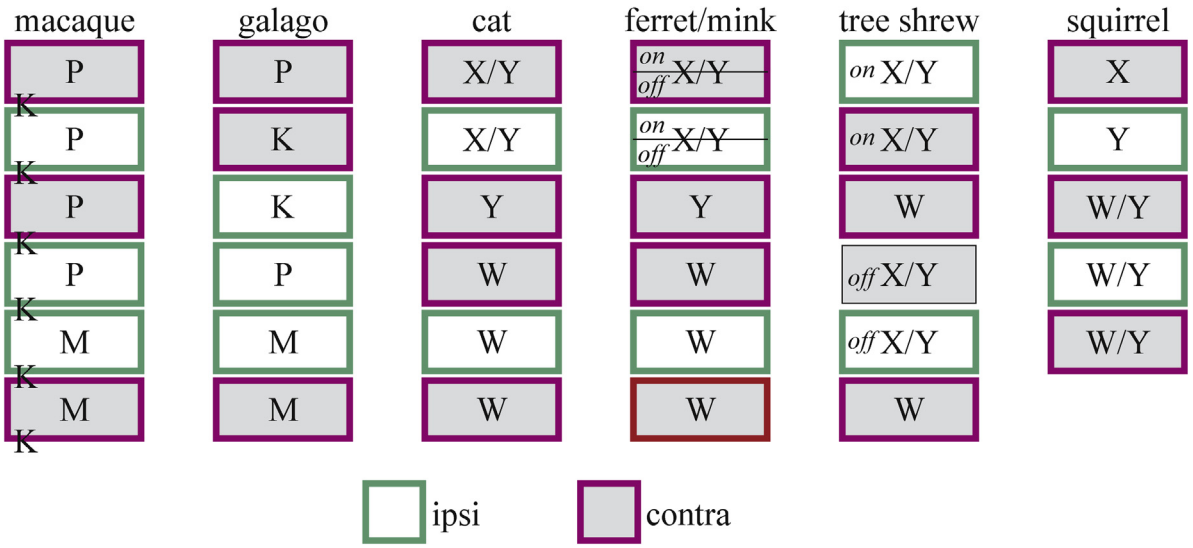

Figure 6 Schematic rendering of layers and distribution of cell types in the lateral geniculate nucleus of six different species (Kaas et al., 1972; Sherman and Spear, 1982; Sherman, 1985; Casagrande and Norton, 1991; Hendry and Calkins, 1998; Van Hooser, Heimel and Nelson, 2003). The magenta boxes show layers innervated by the contralateral eye (*contra*), and the green boxes show the input from the ipsilateral eye (*ipsi*). The X, Y, and W pathways are shown for cat, ferret, mink, tree shrew and squirrel, and the magnocellular (M), parvocellular (P) and koniocellular (K) pathways are shown for macaque monkey and galago. Where there is a clear segregation of on and off center (*on*, *off*) cells for the mink and ferret, this is also indicated. From Sherman and Guillery (2006).

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 important for motion detection (Casagrande and Norton, 1991; Hendry and Reid, 2000; Casagrande and Xu, 2004).

1.21.5.4.2 K Cells

Like W cells, K cells probably include many distinct cell classes, and like W cells, are grouped together here, because their complete classification remains to be done. As the name (***K***oniocellular) 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 et al., 1997; Martin, 1998; Silveira et al., 1999; Hendry and Reid, 2000; Szmajda et al., 2008; Roy et al., 2009; Briggs and Usrey, 2009; Cheong et al., 2013.

1.21.5.5 Laminar Relationships of the Lateral Geniculate Nucleus

Layering is a constant feature of the lateral geniculate nucleus in all mammals so far studied. In some species (e.g., cat and monkey), the layering is obvious, because cell-poor interlaminar zones exist to demarcate the layers. In other species (e.g., mouse and rat), 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.

Fig. 6 summarizes the laminar patterns for several representative mammalian species to illustrate the sort of bewildering variation present. 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 most ventral layers have only W cells (Sherman 1982, 1985). In the rhesus monkey, P and M cells separate into four dorsal parvocellular layers[6] and two ventral magnocellular layers. The K cells are found in all the interlaminar zones but also extend into the ventral regions of the parvocellular layers (Casagrande and Norton, 1991; Hendry and Reid, 2000; Casagrande and Xu, 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 and McConnell, 1982; Stryker and Zahs, 1983), and yet the closely related cat has these on- and off-center cells congregated in single layers. Geniculate lamination does 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.

[6]Textbooks refer to four parvocellular layers, but actually, four such layers exist only for representation of central portions of visual space; for more peripheral representations, the two parvocellular layers for each eye merge, leading to two parvocellular layers for peripheral vision, one for each eye (Le Gros Clark, 1949).

1.21.6 Visual Cortex

There is also a laminar correlation regarding the cortical target zones of the various cell types (Ferster and LeVay, 1978; Blasdel and Lund, 1983; Humphrey et al. 1985a,b; Casagrande and Xu, 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 layers 2/3. 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 layers 2/3. 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.

1.21.7 Glutamatergic Drivers and Modulators

Fig. 4A 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 cortex. A consideration of receptive field properties helps to demonstrate this fact, because the responses of the relay cell to visual stimulation identifies 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 with only minor, subtle differences (Hubel and Wiesel, 1961; Usrey et al., 1999). Geniculate receptive fields do not closely match any other extraretinal afferent: receptive fields of corticogeniculate afferents, which show selectivities for orientation and often direction typical of cortical cells (Gilbert, 1977), are quite different, and brainstem 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 its properties is the very strong postsynaptic drive of their target relay cells), 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 (reviewed in Sherman and Guillery, 1998; Sherman and Guillery, 2013). It follows from this that the cortical layer 6 feedback input, which, like the retinal input, is glutamatergic, is also a modulator, and this is further explored in the following section. Modulation can take many forms, including, for example, the abovementioned consequences of metabotropic receptor activation that lead to overall changes in relay cell excitability and that serve to control the tonic/burst transition, which Fig. 4C suggests for the cortical input. In addition, the circuit suggested by Fig. 4B can operate to control the gain of retinogeniculate transmission.

The role of circuit elements has in the past often been tied to the neurotransmitters involved. The old idea is that information is carried between neurons and brain areas by glutamatergic axons and that classical modulator input (e.g., cholinergic, noradrenergic, serotonergic, etc.) affects how information is processed; in this theoretical framework, inhibitory input (e.g., GABAergic input) serves to control excitability in local circuitry. However, it is now clear that glutamatergic inputs can be classified into two quite distinct functional types: drivers and modulators (Sherman and Guillery 1998, 2013). The classification is clear (see below), but the functional significance is still being explored. The main hypothesis is that the glutamatergic drivers do represent the pathways that carry information, as originally suggested for all glutamatergic pathways, whereas the glutamatergic modulators modulate. How these differ from classical modulator pathways is considered below. Table 1 summarizes some key differences between glutamatergic driver and modulator inputs (Sherman and Guillery 1998, 2013).

1.21.7.1 Glutamatergic Drivers and Modulators in Thalamus

The idea of dividing drivers from modulators among glutamatergic pathways originated with consideration of circuitry of the lateral geniculate nucleus (Sherman and Guillery, 1998). Fig. 4A shows that relay cells receive two glutamatergic inputs: from retina and layer 6 of cortex. As noted above, it is clear from an assessment of receptive field properties of the various inputs that the information-bearing, or driver, input to geniculate relay cells is the retinal input. The cortical input, rather than providing basic

Table 1 Glutamatergic driver and modulator inputs

Criteria	*Driver*	*Modulator*
Criterion 1	Activates only ionotropic receptors	Activates ionotropic and metabotropic receptors
Criterion 2	Synapses show paired-pulse depression (high *p*)[a]	Synapses show paired-pulse facilitation (low *p*)
Criterion 3	Larger initial EPSPs	Smaller initial EPSPs
Criterion 4	Little or no convergence onto target	Much convergence onto target
Criterion 5	Minority of glutamatergic inputs	Majority of glutamatergic inputs
Criterion 6	Large terminals on proximal dendrites	Small terminals on distal dendrites
Criterion 7	Thick axons with dense terminal arbors	Thin axons with delicate terminal arbors

[a]Probability of neurotransmitter release; see text for details.

information to be relayed to cortex, instead modulates various aspects of retinogeniculate transmission (reviewed in Sherman and Guillery, 2013): thus the layer 6 input is a modulator.

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 and Guillery, 2013). The 7 criteria in **Table 1**, in a roughly decreasing order of importance, are:

1. Drivers activate only ionotropic receptors; modulators activate metabotropic receptors as well.
2. Driver synapses show high release probability and paired-pulse depression, meaning that an action potential in a given terminal 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 10s of msec that the next one will be smaller (depressed); modulator synapses show the opposite properties of low release probability and paired-pulse facilitation.
3. Drivers evoke larger initial EPSPs; modulators evoke smaller initial EPSPs.
4. Driver inputs show less convergence onto their targets than do modulator inputs. Estimates for a typical geniculate relay cells suggest that 1–3 retinal inputs converge compared to a hundred or more of cortical inputs (Sherman and Koch, 1986; Usrey et al., 1999).
5. Driver inputs produce a small minority (2%–5%) of the synapses onto thalamic relays cells, whereas layer 6 cortical inputs produce 30%–50% of such synapses (Van Horn et al., 2000; Wang et al., 2002; Van Horn and Sherman, 2007).
6. Drivers form larger terminals on proximal dendrites; modulators form smaller terminals more distally.
7. Drivers have thicker axons and denser terminal arbors; modulators have thinner axons with sparser terminal arbors.

These driver/modulator classification criteria 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. Furthermore, if one is to understand the functional organization of the thalamus, and especially the identity of the input being relayed to cortex, 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 point described below is that this driver/modulator distinction also applies to cortex and may apply more broadly within the central nervous system.

Regarding criterion 5 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 to explain this. First, despite the small number of inputs anatomically, these are especially powerful and effectively drive relay cells. Second, a relatively small but powerful number of synapses may be all that is needed to relay basic information, whereas many more, individually weaker synapses can be combined in different ways to provide a wide range of 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 only anatomical information regarding the distribution of glutamatergic inputs (which used to be the basis for determining the strength or importance of an input), the number of synapses from cortex is much greater than that from retina. Such anatomical data in isolation might lead one to the mistaken conclusion that the cortical input is the more important and thus represents the information being relayed (back to itself!), 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.[7]

1.21.7.2 Glutamatergic Drivers and Modulators in Cortex

The classification of drivers and modulators among glutamatergic circuits, initiated for thalamic circuitry, has been extended to cortex (reviewed in Sherman and Guillery, 2013), including thalamocortical (Lee and Sherman 2008, 2012; Covic and Sherman, 2011; Viaene et al. 2011a,b; Viaene, Petrof and Sherman, 2011c; Mo and Sherman, 2019), local intra-areal corticocortical (Lee and Sherman, 2008; Lee and Sherman, 2009; DePasquale and Sherman, 2012; Lam and Sherman, 2019), and interareal corticocortical pathways (Covic and Sherman, 2011; DePasquale and Sherman 2011, 2013; Petrof et al., 2015).

Fig. 7 illustrates quantitative features of this classification for both thalamus and cortex. Each point in the three-dimensional scatterplot represents a single neuron in a slice of mouse brain for which we were able to identify a glutamatergic input as driver or modulator. The color code indicates whether the recorded cell was thalamic or cortical. The three axes of the graph represent three of the criteria from **Table 1** for which we obtained quantified parameters: the first EPSP amplitude evoked at just above threshold electrical activation, a measure of paired-pulse effects, and the amplitude of any evoked metabotropic glutamate receptor component. Three conclusions can be drawn from **Fig. 7**. First, the classification is clearly robust. Thus, whereas the functional significance of the duality of glutamatergic synapses may still be open to question, the presence of this duality seems quite clear. Second, so far

[7]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.

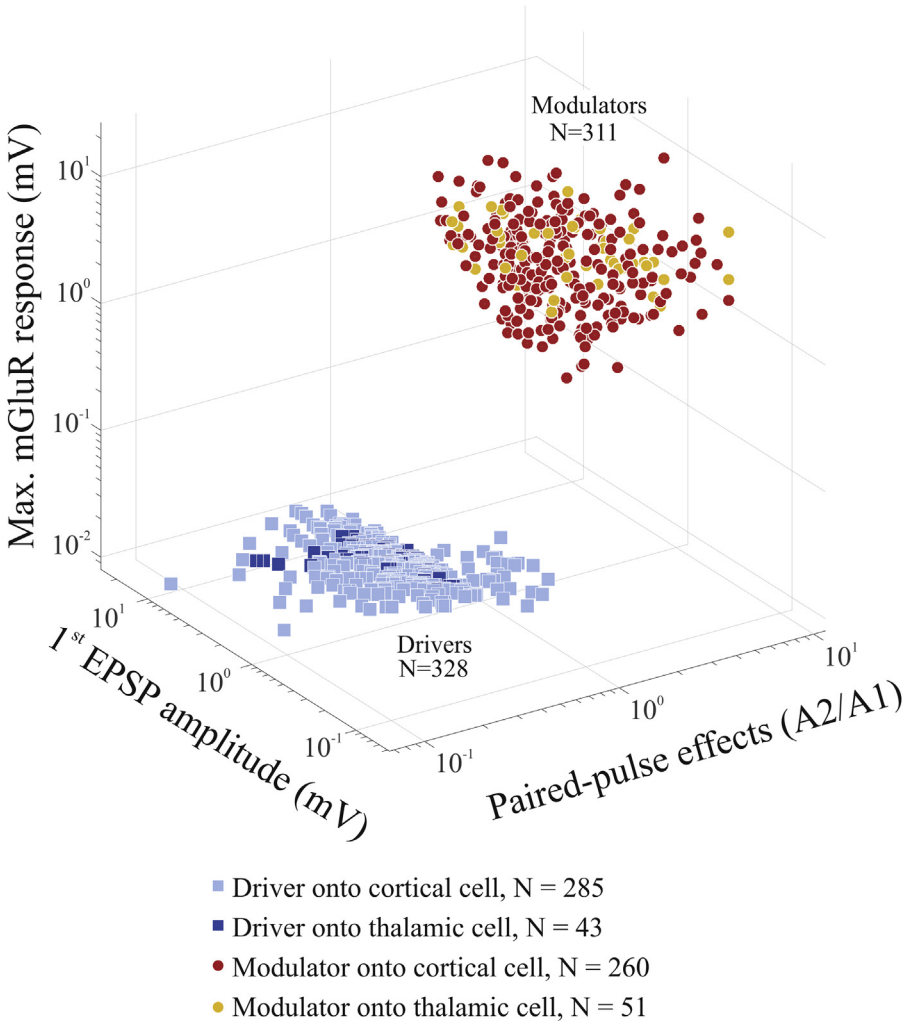

Figure 7 Three-dimensional scatterplot for inputs classified as driver or modulator to cells of thalamus and cortex; data from *in vitro* slice experiments in mice from the author's laboratory. The three parameters are: (1) the amplitude of the first EPSP elicited in a train at a stimulus level just above threshold; (2) a measure of paired-pulse effects (the amplitude of the second EPSP divided by the first; A2 divided by A1) for stimulus trains of 10–20 Hz; and (3) a measure of the response to synaptic activation of metabotropic glutamate receptors, taken as the maximum voltage deflection (i.e., depolarization or hyperpolarization) during the 300 msec postsynaptic response period to tetanic stimulation in the presence of AMPA and NMDA antagonists. Pathways tested here include various inputs to thalamus from cortex and subcortical sources, various thalamocortical pathways, and various intracortical pathways. From Sherman (2016)

only two types of glutamatergic synapse have been described in thalamus and cortex, although there is evidence that driver synapses in cortex may be further subdivided (Viaene et al., 2011c). This may seem somewhat surprising, because given the number of apparently independent parameters shown in **Table 1**, it is possible to combinatorially create many more classes, which we frankly expected to find in the more complex circuitry of cortex. Perhaps further investigation of glutamatergic pathways will reveal more classes. Third, the basic properties of a glutamatergic driver or modulator synapse appear to be fundamentally the same in thalamus and cortex.

1.21.7.3 Purpose of Glutamatergic Modulators

One might ask: Given the presence of so many classic modulatory systems (e.g., cholinergic, noradrenergic, serotonergic, etc.), what is the point of adding glutamatergic modulators to the mix? The answer may have to do with topography. That is, the classical modulatory systems have little or no topography in their projections patterns, affecting much of the neuraxis when active, although recent evidence does indicate some topography in the cholinergic input from the basal forebrain to cortex (Zaborszky et al., 2018). Thus, for the most part, the function of classic modulatory systems seems more related to overall behavioral state: alertness, sleep, etc. Only glutamatergic modulatory pathways possess a high degree of topography. Furthermore, the classic modulatory pathways, which derive from brainstem structures, necessarily reflect only brainstem processing, whereas, the glutamatergic modulators

discussed here benefit from processing in thalamus and cortex. Such topographic modulation controlled by cortex and thalamus is needed for cognitive processes that require localized effects, such as focal or covert attention, adaptation, learning and memory, etc.

1.21.8 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 the 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, which chiefly concerns us in this section.

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 thalamic relays with unknown functions because, until recently, their driver inputs were undefined. Clearly, identifying the driver input to a thalamic nucleus reveals a key functional property of that nucleus: thus we appreciate that the main function of the lateral geniculate nucleus is to relay retinal information to cortex. The pulvinar is an example of a nucleus for which, until fairly recently, its driver inputs were undefined. We now know that a major source of driver input to pulvinar emanates from layer 5 of various areas of visual cortex. This is illustrated in Fig. 8.

Based on the source of driver input, subcortical or layer 5 of cortex, we now divide thalamic relays into *first order* and *higher order*(-Guillery, 1995; Sherman and Guillery, 2013): the former receive subcortical driver input, such as retina for the lateral geniculate nucleus, whereas the latter receive such input from layer 5 of cortex, such as layer 5 visual cortical input to pulvinar. These layer 5 inputs to relay cells have the same properties as do the subcortical drivers, such as retinal input to the lateral geniculate nucleus and medial lemniscal input to the ventral posterior nucleus (Sherman and Guillery, 2013). Fig. 8 illustrates key elements of this organization (details reviewed in Sherman and Guillery, 2013). All thalamic nuclei receive a feedback corticothalamic projection from layer 6 that is a modulator, but higher order relays receive another cortical input, a driver input from layer 5 that is often organized in a feedforward manner as illustrated in Fig. 8.

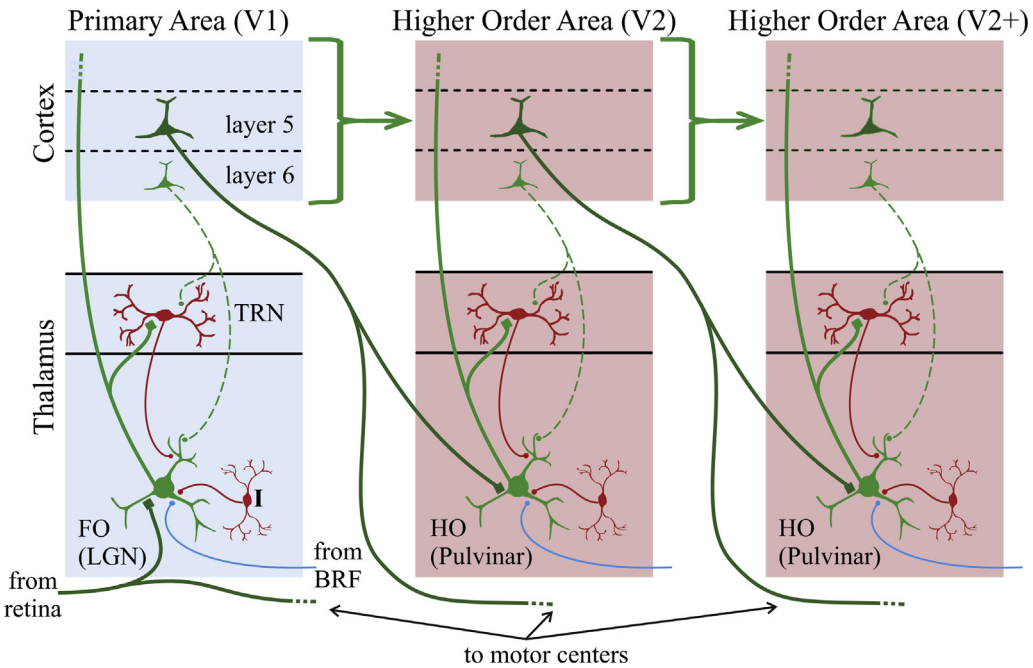

Figure 8 Schematic diagram showing organizational features of first and higher order thalamic nuclei in the visual system. A first order nucleus (FO; lateral geniculate nucleus) represents the first relay of a particular type of subcortical information to a first order or primary cortical area. A higher order nucleus (HO; pulvinar) relays information from layer 5 of one cortical area to another cortical area. 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 (retinal) for a first order thalamic nucleus and from layer 5 of cortex for a higher order one. Note that all thalamic nuclei receive an input from layer 6 of cortex, which is modulatory and mostly feedback, but higher order nuclei in addition receive a layer 5 input from cortex, which in these examples is feedforward. Note also 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; V1, primary visual cortex; V2, secondary visual cortex. Redrawn from Sherman (2005).

Fig. 8 shows first and higher order thalamic relays for the visual system, but equivalent circuitry has been demonstrated for other cortical processing. For somatosensory cortex, the ventral posterior nucleus is a first order relay (like the lateral geniculate nucleus), and the posterior medial nucleus is a higher order relay (like the pulvinar); for the auditory cortex, the ventral division of the medial geniculate nucleus is first order, and the dorsal division, higher order (Sherman and Guillery, 2013). In each case, there is both direct and transthalamic connectivity organized in parallel between cortical areas. Similar direct and transthalamic (through the posterior medial nucleus) corticocortical connectivity has been demonstrated from primary somatosensory cortex to primary motor cortex (Petrof et al., 2015; Mo and Sherman, 2019). We have estimated that the majority of thalamus by volume is configured as higher order relays (Sherman and Guillery, 2013).

The transthalamic connectivity shown in Fig. 8 is depicted as a feedforward circuit, and the above examples of such feedforward transthalamic circuits have been demonstrated. The possibility that transthalamic circuits may be involved in feedback corticortical communication remains a possibility that to date has not been much explored. Recent evidence for a transthalamic feedback circuit has been recently presented (Miller and Sherman, 2019).

There is an important proviso to this division of thalamic nuclei into first and higher order. Those nuclei identified as first order so far seem to be completely first order, meaning that all driver inputs are of subcortical origin. As an example of this, the lateral geniculate nucleus receives no innervation from layer 5 of cortex (only layer 6) and thus has no higher order circuitry. However, this seems not to be the case necessarily for nuclei identified as higher order. For instance, the pulvinar as an overall nucleus has many complex divisions. This includes regions receiving input from layer 5 of cortex, rendering these regions as higher order, but at least some pulvinar neurons appear to relay driver information from the superior colliculus (Kelly et al., 2003), which would make those relay cells first order. For this reason, it may be clearer to refer to these thalamic entities within conventional nuclear borders as first or higher order "relays," reflecting the properties of single relay cells, rather than referring to the entire nucleus as higher order.

1.21.9 Branching of Driver Afferents to Thalamus

Fig. 8 also shows that the driver inputs to both first and higher order relay cells arrive 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 often motor in nature (Guillery 2003, 2005; Sherman and Guillery, 2013). For instance, most or all retinogeniculate axons branch to innervate the pretectum and/or superior colliculus, areas involved in the control of head and eye movements, pupillary size, focusing, etc. Likewise, most or all layer 5 corticothalamic axons branch to innervate motor targets in the pons, midbrain, medulla, and sometimes even spinal cord; see Fig. 9 for these and other examples. This branching pattern of driver inputs to thalamus, with some extrathalamic branches targeting subcortical motor structures, seems to be a ubiquitous feature of thalamic circuitry. However, drivers do not branch to innervate the thalamic reticular nucleus. This is in contrast to the layer 6 modulator inputs, which do branch to innervate the thalamic reticular nucleus but generally have no extrathalamic targets. Limited data are consistent with a similar arrangement for relays of somatosensory and auditory information (Guillery 2003, 2005; Sherman and Guillery, 2013).

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 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, 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 (Prasad et al., 2019), 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.

1.21.10 Role of Higher Order Thalamic Relays in Corticocortical Processing

Fig. 8 illustrates the suggested role played by higher order thalamic relays. After initially reaching 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 circuits illustrated in Fig. 8 raise at least three questions:

- How common is the pattern of parallel direct and transthalamic connections between cortical areas, or, how often are cortical areas connected only by one or the other pathway?
- What is different in the nature of information represented by each pathway?
- Why does one of the pathways involved in cortico-cortical communication involve a thalamic relay?

At present, there are no clear answers to these questions, but such answers seem key to further understanding of cortical functioning, and thus explicitly raising the questions is a requisite first step in this process.

There are a number of testable hypotheses one can imagine that explain the circuitry outlined in Fig. 8. It is beyond the scope of this account to consider such hypotheses in detail. One that has been described elsewhere involves the patterns indicated in Figs. 8

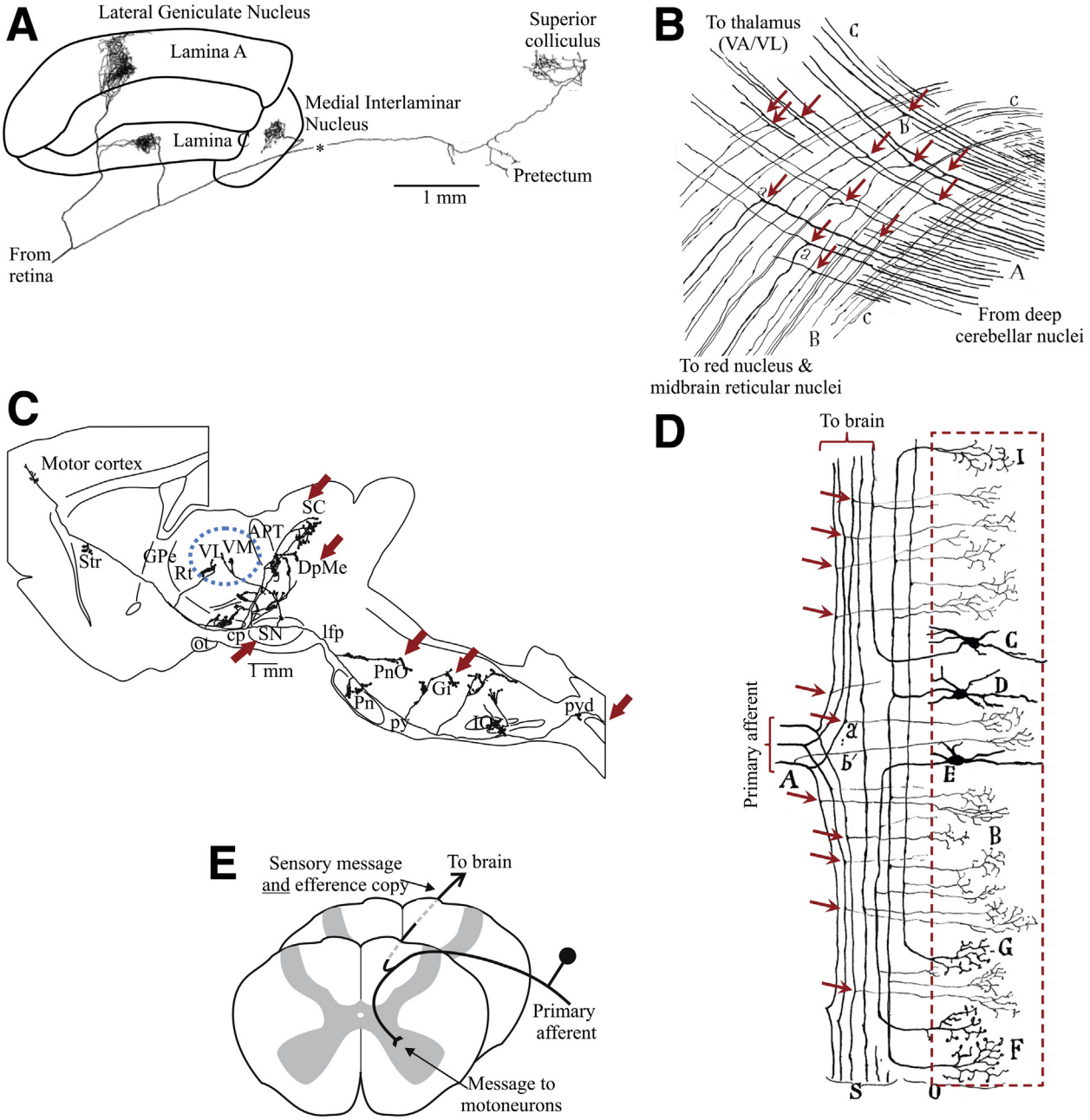

Figure 9 Examples of branching axons of driver inputs to thalamus. (A) Example from retinogeniculate axon of cat; redrawn from Tamamaki et al. (1995). (B) Cajal illustration (Cajal, 1911) showing that innervation of the ventral anterior-ventral lateral (VA-VL) thalamic complex from cerebellum involves axons that branch (red arrows) to innervate other brainstem structures as well. (C) Example from layer 5 pyramidal tract cell of rat motor cortex; redrawn from Kita and Kita (2012). Branches innervating thalamus are indicated by the dashed blue circle, and brainstem motor regions are indicated by red arrows. DpMe, deep mesencephalic nuclei; Gi, gigantocellular reticular nucleus; GPe, Globus pallidus external segment; ic, internal capsule; IO, inferior olive; MIN, medial interlaminar nucleus (part of the lateral geniculate nucleus); Pn, pontine nucleus; PnO, pontine reticular nucleus, oral part; py, medullary pyramid; pyd, pyramidal decussation; Rt, reticular thalamic nucleus; SC, superior colliculus; SN, substantia nigra; Str, striatum; VL, ventrolateral thalamic nucleus; VM, ventromedial thalamic nucleus. (D) Cajal illustration (Cajal, 1911) of primary axons entering the spinal cord and branching to innervate the spinal gray matter and brain areas. The red arrows indicate branch points. (E) Schematic interpretation of D. From Sherman (2016).

and 9 (for details, see Guillery, 2003; Guillery, 2005; Sherman and Guillery, 2013; Sherman, 2016). Namely, if driver inputs to thalamus involve branching axons, with some extrathalamic branches carrying messages to motor centers, it follows that the messages relayed by thalamus are exact copies of such motor messages. Copies of motor messages are efference copies, and thus the information relayed to thalamus can be read by some of the cortical targets as efference copies. If so, then the transthalamic projections inform the target cortical area about motor commands initiated by the source area.

The branching pattern of the primary afferent shown in Fig. 9E serves to illustrate this point. The branch headed to the ventral gray matter in the spinal cord can be regarded as influencing motoneurons and is thus carrying a motor command. The branch ascending in the spinal cord to the brain is usually seen as carrying a sensory message, such as a change in a joint angle, skin depression, etc. But because of the branching, this ascending message can also be viewed as a copy of a motor command, which is the definition of an efference copy. The ascending branch carries a single message, but this can be interpreted by some postsynaptic targets as purely sensory information and by others as an efference copy. Likewise, the information relayed through higher order thalamic relays can be interpreted by some neurons in the cortical target area as the result of processing in the originating cortical area (e.g., sensory processing if the layer 5 innervation emanates from a sensory cortical area) and by other neurons as an efference copy.

1.21.11 Overview

To help appreciate cortical processing according to the conventional view and how this departs from the alternative view offered here, Fig. 10 shows schematically how different these are. In the conventional view, new information from the periphery is initially relayed by thalamus to sensory cortex and passes within cortex to sensorimotor and then motor cortex before an output is generated to motor centers (Fig. 10A). This provides no specific role for most of thalamus, which we have defined as higher order. Perhaps

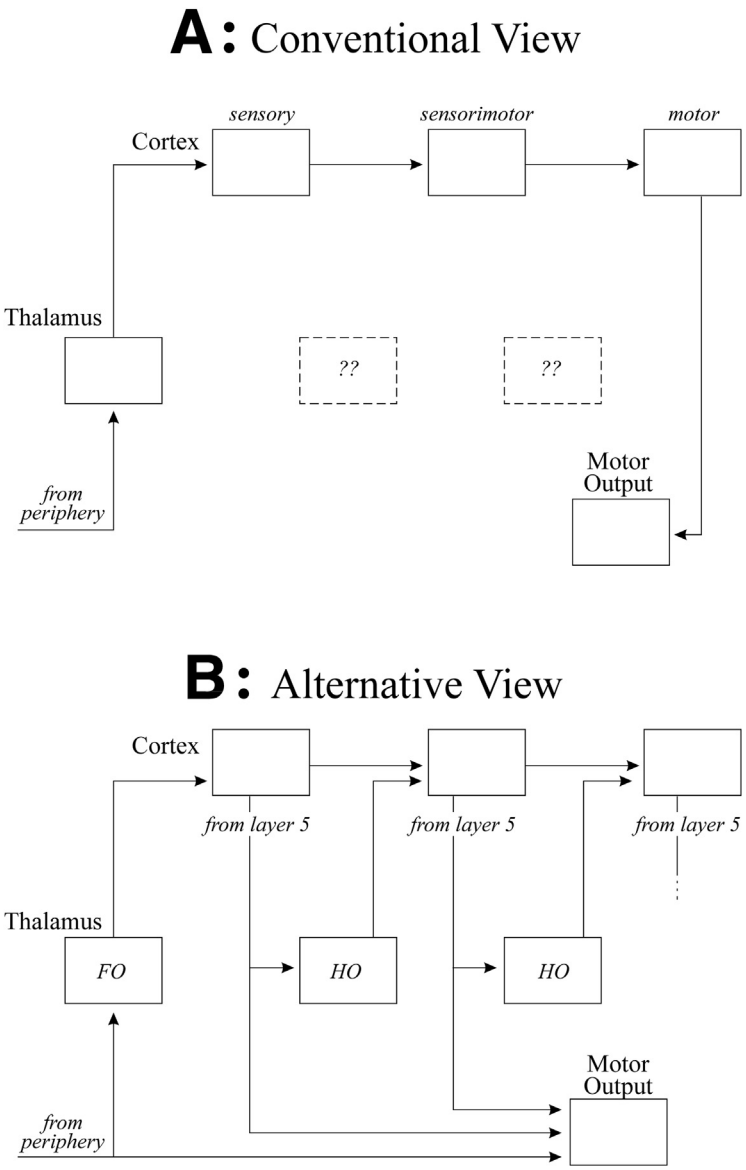

Figure 10 Comparison of conventional view (A) with the alternative view proposed here (B). FO, first order; HO, higher order. Reproduced from Sherman (2005).

more damning, the circuit of Fig. 10A seems an implausible result of evolution. That is, any time a new sensory receptor or circuit evolves, it will have no survival value if it lacks a fairly immediate motor output. Whereas an intelligent designer might design a circuit like Fig. 10A, it seems unlikely that evolution would produce one that takes so long to yield a relevant behavioral response to a sensory stimulus. The alternative view (Fig. 10B) 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 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.

Another feature of Fig. 10B that bears emphasis is that, so far, every cortical area studied for the feature has a layer 5 output that targets motor structures, including each of the primary sensory areas (reviewed in Sherman and Guillery, 2013). Indeed, as suggested above, the idea that evolution would produce cortical areas that have no fairly immediate motor effect seems unlikely. By this way of thinking, the current view that some cortical areas are "sensory," and others, "motor" is misleading.

The bottom line is that higher order thalamic nuclei play an important and still largely unappreciated role in corticocortical communication. Thus, thalamus is not there just to get information to 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 different roles of the direct and transthalamic corticocortical pathways and their relationship to each other.

1.21.12 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 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 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 make it clear that it is anything but simple and uninteresting in its functioning. These properties serve to regulate the flow of information to cortex through mechanisms such as gain control of the retinogeniculate synapse (or equivalent for other nuclei), the burst-tonic transition, etc. These functions are probably just the tip of the iceberg. Furthermore, we can now see that thalamus is not there just to get peripheral information to 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 cortex. The other is to address questions about the pulvinar and its role in transthalamic corticocortical communication. 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 cortex and which are innervated by each cortical area, with a separate mapping of layer 5 and layer 6 inputs. Given these variables and the presence of more than 30 visual cortical areas in monkeys and humans 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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