Chapter 4

Thalamocortical Circuitry Matters

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Introduction

Until fairly recently, the thalamus was written off as merely a machine-like relay of peripheral information to the cortex. That is how textbooks still generally depict the thalamus, if they do so at all. However, work in the past few decades has made clear that the thalamus has complex intrinsic circuitry and connections with the cortex that belie any such simple function. Indeed, we now appreciate that the thalamus plays a major role in cortical functioning beyond the relay of peripheral information to the cortex. In this account, I start with an overview of thalamic circuitry. I then move on to details of thalamocortical and corticothalamic organization, starting with a cataloguing of synaptic types involved in this circuitry and finishing with speculations about what some of these details mean writ large. I will try to separate actual experimental data from speculation and hypothesis.

Overview of Thalamic Circuitry: The Cat's Lateral Geniculate Nucleus

The best-studied model of the functional circuitry of the thalamus remains the cat's lateral geniculate nucleus. Unfortunately, work on this 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 the study of the thalamus in these species catches up to the knowledge base amassed for the cat.

The schema of Figure 1A shows the main inputs to geniculate relay cells, with some pathways omitted for simplicity. To a first approximation, the circuitry shown here is conserved for the thalamus across nuclei and mammalian species, with the exception that for different nuclei, the retinal input would be replaced by a different information source to be relayed. Thus, for the ventral posterior nucleus, which relays somatosensory information, retinal input would be replaced by input from the medial lemniscus; for the medial geniculate nucleus, the input would be from the inferior colliculus; and so forth. Some exceptions to this general plan of thalamic circuitry are considered later in the chapter, and further details of thalamic circuitry can be found in Sherman and Guillery (1996, 2013).

Inputs to Geniculate Relay Cells

Although textbook accounts often mention only retinal inputs to geniculate relay cells, there are a number of other inputs. These include local inputs from interneurons and thalamic reticular cells, layer 6 of the visual cortex, and the brainstem, mostly from a midbrain area known as the *brainstem reticular formation*.[1] The left key in Figure 1A shows the neurotransmitters involved: glutamate by retinal and cortical input, γ-aminobutyric acid (GABA) by the interneurons and reticular cells, and mostly acetylcholine (ACh) by brainstem input. 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.

Postsynaptic Receptors on Relay Cells

All of the synapses onto relay cells shown in Figure 1A are standard chemical synapses. This means that they affect relay cells by releasing neurotransmitters that operate through various postsynaptic receptors. These receptors are of two main types, ionotropic and metabotropic, and both types are involved in the postsynaptic responses of relay cells. Examples of the relevant ionotropic receptors are alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) for glutamate, nicotinic for acetylcholine, and the $GABA_A$ receptor. Examples of metabotropic receptors are various metabotropic glutamate receptors, various muscarinic receptors for acetylcholine, and the $GABA_B$ receptor.

There are many differences between ionotropic and metabotropic receptors, and only some 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). Ionotropic receptors are simpler in construction and function, and the receptor protein itself usually contains the ion channel it controls. Binding of the neurotransmitter to the ionotropic receptor causes an alteration of the receptor shape, which in turn exposes and opens the ion channel. This allows ions to flow down their electrochemical gradients, leading to an excitatory postsynaptic potential (EPSP) or inhibitory postsynaptic potential (IPSP). Metabotropic receptor functioning is

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

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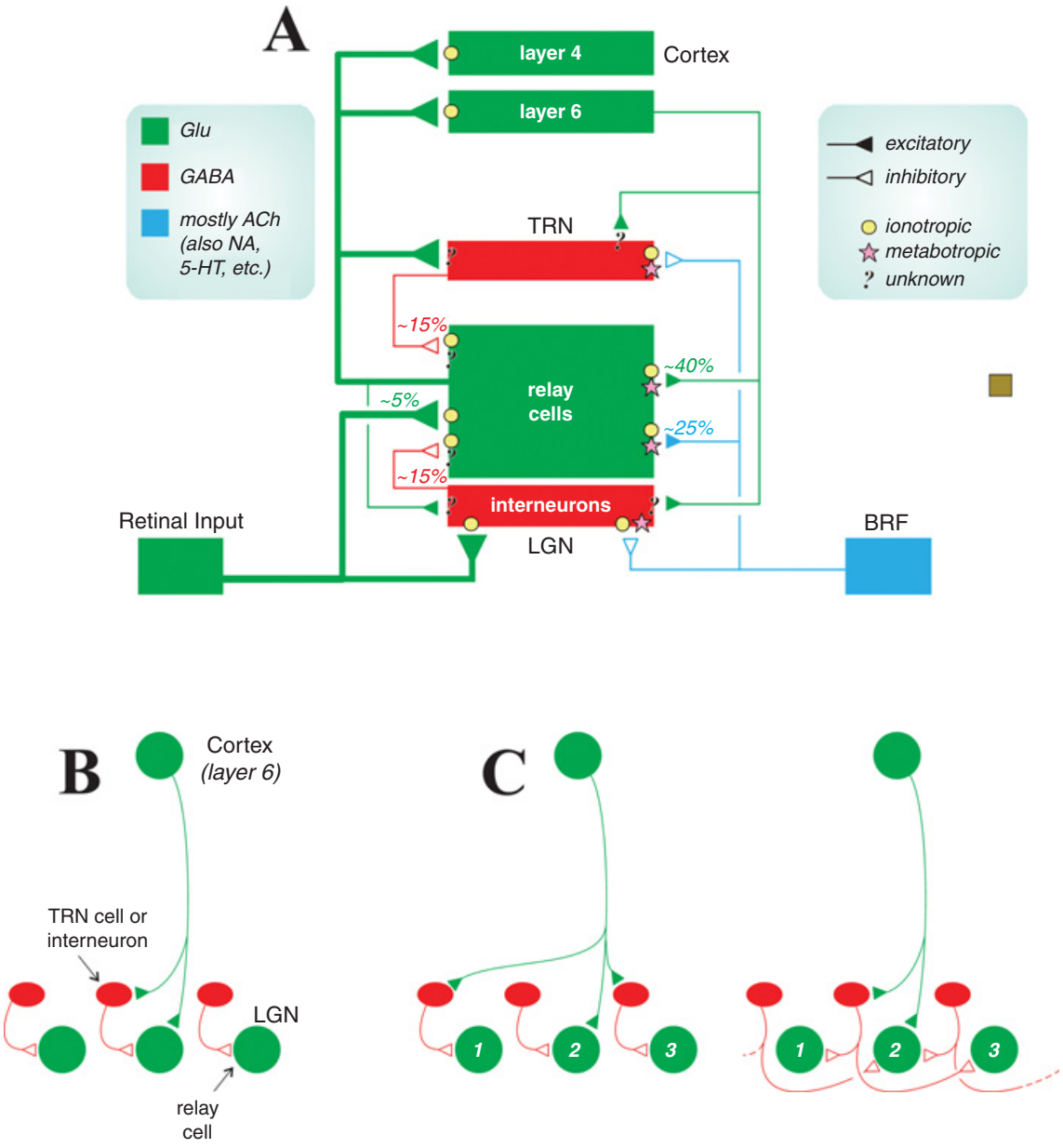

Figure 1 **Circuitry of the lateral geniculate nucleus.**

A. Major circuit features of the lateral geniculate nucleus with related postsynaptic receptors present on relay cells. Other thalamic nuclei seem to be organized along a similar pattern. The key to the left indicates the major transmitter systems involved, and that to the right indicates the postsynaptic receptors involved and whether the input is excitatory or inhibitory. The retinal input activates only ionotropic receptors (*yellow circles*), whereas all nonretinal inputs activate metabotropic receptors (*purple stars*) and often ionotropic receptors as well. The question marks related to interneurons indicate uncertainty of whether metabotropic receptors are involved. Percentages indicate, for each input to the relay cell, the relative number of synapses provided to that input. Abbreviations: *5-HT*, serotonin; *ACh*, acetylcholine; *BRF*, brainstem reticular formation; *GABA*, γ-aminobutyric acid; *Glu*, glutamate; *LGN*, lateral geniculate nucleus; *NA*, noradrenaline; *TRN*, thalamic reticular nucleus.

B and C. Two possible patterns among others for corticothalamic projection from layer 6.

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 (*cell 2*) and inhibit others (*cells 1 and 3*) through activation of interneurons or thalamic reticular cells. This could be done via several circuitry variants, and two examples are shown here. Further details in the text. Abbreviations for panels B and C are as in panel A.

more complicated because the receptor is indirectly linked to ion channels via second-messenger systems, and in thalamic relay cells, this usually involves a G-protein and ultimately opens or closes K^+ channels. Opening of K^+ channels causes K^+ to flow out of the cell, producing an IPSP, whereas closing of these channels stops leakage of K^+, leading to an EPSP.

Two other differences between receptor types bear emphasis. First, ionotropic PSPs typically occur with brief latencies (<1 msec) and durations (mostly over in 10 or a few 10s of msec), whereas metabotropic PSPs have longer latencies (~10 msec or so) and durations (100s of msec to several sec). Second, whereas the low firing rates of an afferent input, even a single action potential, can activate ionotropic receptors, higher

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firing rates are generally needed to activate metabotropic receptors. Apparently, this results from metabotropic receptors being located perisynaptically and thus farther from neurotransmitter release sites than are ionotropic receptors (Lujan et al., 1996), and thus higher firing rates are needed to release sufficient neurotransmitter to reach metabotropic receptors. However, as few as two action potentials separated by 100 msec or less in the afferent can begin to activate metabotropic glutamate receptors, although higher rates or more action potentials increasingly activate more of these receptors (Viaene et al., 2013).

Note that the extrinsic nonretinal inputs innervate not only relay cells but also interneurons and reticular cells, and individual axons usually do so via branches. The right key of Figure 1A shows the overall general effects of these extrinsic inputs on relay cells. Brainstem input, in general excites relay cells directly and inhibits interneurons and reticular cells, and often the same brainstem axon branches, to achieve all of these effects. This means that activity in this pathway excites relay cells both directly and indirectly, the latter by inhibiting inhibitory inputs to relay cells. This neat trick is achieved by cholinergic input activating different muscarinic (metabotropic or M) receptors on the different cell types. On relay cells, M1 receptors are activated, leading to prolonged EPSPs, whereas on interneurons and reticular cells, M2 receptors are activated, leading to prolonged IPSPs. However, these cholinergic inputs also activate nicotinic (ionotropic) receptors on all these target cells, producing a brief EPSP in them. As noted previously, activation of metabotropic receptors requires higher rates of firing of the afferent input, and so it is when these brainstem cholinergic inputs fire at higher rates that the muscarinic responses will begin to dominate and persist.

Whereas brainstem input, when more active, clearly excites relay cells directly and indirectly, the action of the layer 6 glutamatergic input is harder to predict, because all the target cells are excited. Thus, both monosynaptic excitation and disynaptic inhibition of relay cells are possible. However, the actual effect of this input on relay cells depends critically on details of circuitry, as illustrated in Figure 1B and C. Figure 1B shows the often-assumed configuration in which layer 6 activation monosynaptically excites relay cells and disynaptically inhibits them. Figure 1C shows a very different configuration: here, a layer 6 axon directly excites some relay cells (i.e., *cell 2*) and disynaptically inhibits surrounding ones (i.e., *cells 1* and *3*). Other patterns not shown in Figure 1B and C can also be imagined. Clearly, uncovering the details of this circuitry is key to understanding the function of this layer 6 corticothalamic pathway. It should be noted that if the pattern of Figure 1C exists, and evidence for this is available (Lam and Sherman, 2010; Wang et al., 2006; Legendy et al., 1978; Tsumoto et al., 1978), large-scale topographic excitation or suppression of this pathway, such as by optogenetics, lesion, chemical manipulation, and so forth, would obscure the details of Figure 1C and effectively not distinguish between Figure 1B and many other patterns, such as that in Figure 1C.

Thalamic Cell Properties

Neurons express many voltage- and time-gated ionic membrane conductances, and this includes thalamic relay cells. The action potential, which is based on voltage- and time-gated Na^+ and K^+ conductances, is the best-known example. There is also a variety of other Na^+, K^+, and Ca^{2+} conductances, and more detailed accounts can be found elsewhere (Jack et al., 1975; Hille, 1992; Levitan and Kaczmarek, 2002; Sherman and Guillery, 2006, 1996). Because of these conductances, membrane voltage and its temporal pattern play important roles in relay cell functioning. Although 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, 2006; Sherman, 2001; Sherman and Guillery, 1996). Because the properties of this Ca^{2+} channel are qualitatively so similar to those underlying the conventional action potential, we shall start with a brief review of the action potential shown in Figure 2A.

The Action Potential

The Na^+ channel has two voltage- and time-regulated gates, an *activation gate* and an *inactivation gate*. Both gates must be open for Na^+ to flow into the cell and depolarize it. When the activation gate is open, the channel is said to be *activated*; when closed, it is *de-activated*. Likewise for the inactivation gate: when open, the channel is *de-inactivated*, and when closed, *inactivated*. The K^+ channel has only an activation gate and thus can be *activated* or *de-activated*.

At normal resting potentials, the inactivation gate is open, but the activation gate is closed, preventing entry of Na^+ (Figure 2A[i]). From this level, a sufficient depolarization will open the activation gate, leading to the up swing of the action potential (Figure 2A[ii]). After about 1msec, this depolarizing spike inactivates the channel (i.e., the inactivation gate closes), meaning that *both* sufficient depolarization *and* sufficient time are needed for inactivation. This inactivation of the Na^+ channel, along with activation of the somewhat slower K^+ channel, prevents further depolarization (Figure 2A[iii]) and repolarizes the cell to its original resting potential (Figure 2A[iv]). However, even with this repolarization to the original level, the Na^+ channel remains inactivated for another 1 msec or so (i.e., the inactivation gate remains closed), after which the channel becomes de-inactivated (i.e., the inactivation gate opens); this underlies the refractory period of 1 msec or so during which no further action potentials can be evoked. In principle, this limits the cell's firing rate to 1 kHz, 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.

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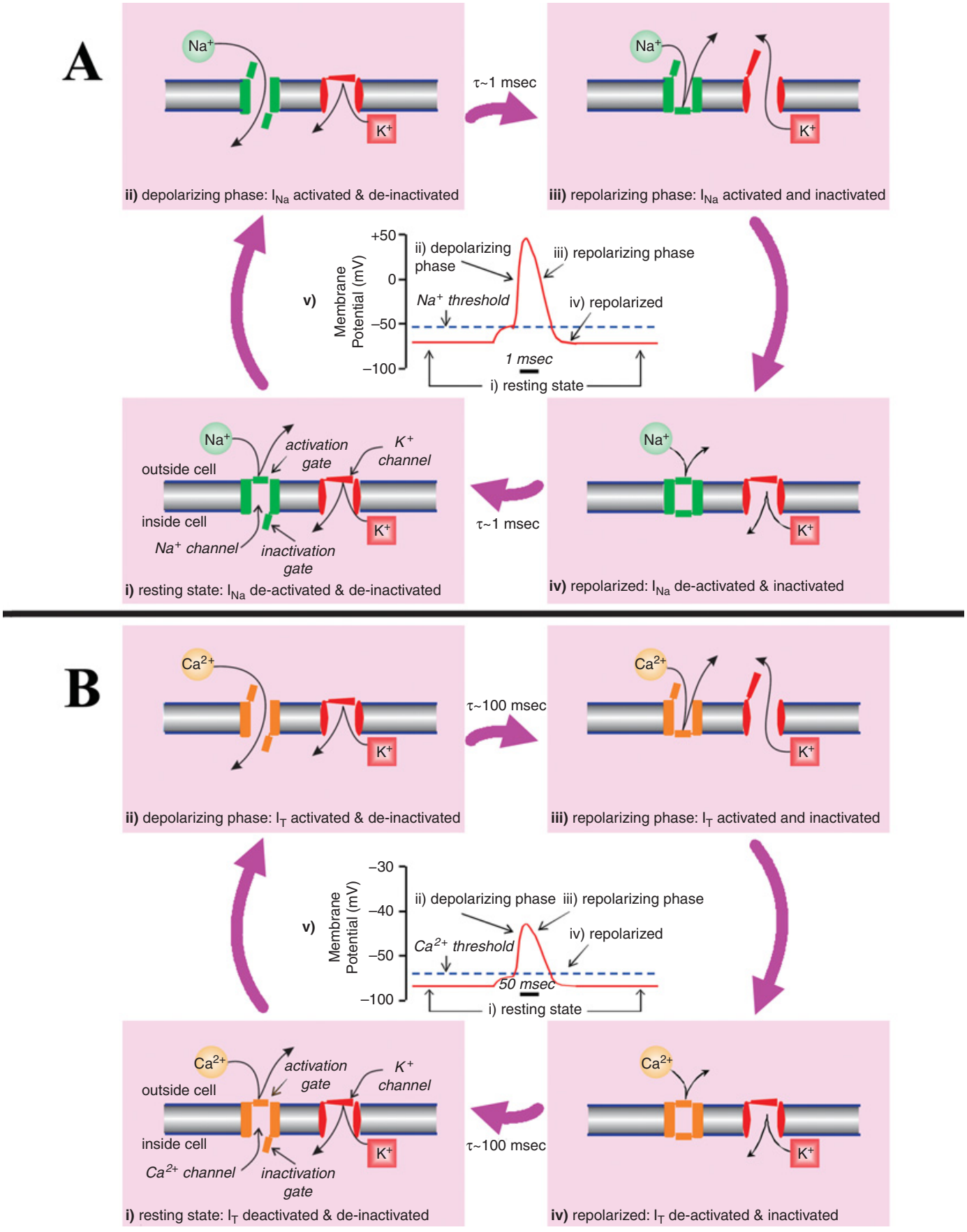

Figure 2 Schematic representation of qualitatively similar voltage- and time-gated ion channels underlying the conventional action potential and low-threshold Ca^{2+} spike.

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The Low-Threshold Ca^{2+} Spike

The voltage and time dependencies of T-type[2] Ca^{2+} channels are qualitatively like those of the Na^+ channels, with similar activation and inactivation gates (Sherman & Guillery, 2013; Sherman, 2001; Jahnsen and Llinás, 1984a, 1984b; McCormick and Huguenard, 1992). Figure 2B illustrates these properties. At rest, which is slightly more hyperpolarized than the example for the Na^+ channel in Figure 2A, the inactivation gate is open but the activation gate is closed; the channel is thus both de-inactivated and de-activated (Figure 2B[i]). Following sufficient depolarization, the activation gate opens, and Ca^{2+} flows into the cell, leading to a depolarizing spike, and so the Ca^{2+} channel is activated and de-inactivated (Figure 2B[ii]). This Ca^{2+} spike is often termed the *low-threshold spike* because the activation threshold for the Ca^{2+} channel is hyperpolarized with respect to that for the Na^+ channel underlying the action potential. After roughly 100 msec of depolarization, the Ca^{2+} channel inactivates[3] (Figure 2B[iii]), and this, combined with activation of a slower series of K^+ conductances, repolarizes the neuron (Figure 2B[iv]). However, the T-type Ca^{2+} channel remains inactivated (Figure 2B[iv]) for another 100 msec or so, after which time the original state of Figure 2B(i) 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. Most voltage- and time-gated conductances have rather long time constants for inactivation kinetics; thus, the T-type Ca^{2+} channel is rather typical in this regard, and the Na^+ channel underlying the action potential is a rather fast outlier. This means that to control most of these active channels requires rather long-lasting changes in membrane voltage.

T-type Ca^{2+} channels are common to neurons throughout the central nervous system. However, in the cases of both the Na^+ and Ca^{2+} channels discussed here, their density must be relatively high to generate an all-or-none propagating spike. The high density of Na^+ channels in the axon and often in the cell body and dendrites allows the propagation of the action potential. Regarding the T-type Ca^{2+} channels, their density in the soma and dendrites (but not along the axon!) of thalamic relay cells is typically high enough to support such spiking (Huguenard, 1996; Huguenard and McCormick, 1994). Because these Ca^{2+} channels are not found along the axon, such Ca^{2+} spikes are not propagated to any postsynaptic targets; however, the Na^+ action potentials they evoke at the axon hillock are so propagated. In most neurons outside of the thalamus, the density of these channels is too low for spiking, and so for these other neurons, activation of these channels leads to modest depolarizations that spread electrotonically.

Burst and Tonic Firing

The properties of T-type Ca^{2+} channels underlie two different response modes, *burst* or *tonic*, that characterize the firing properties of thalamic relay cells. Which of these response modes prevails at any time is an important variable in the nature of information transmission to the cortex (Sherman and Guillery, 2013; Sherman, 2001; Bezdudnaya et al., 2006; Swadlow and Gusev, 2001; MacLean et al., 2005).

Caption for Figure 2 (cont.)

A. For the action potential, (i)–(iv) depict 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. For the inward, depolarizing Na^+ current (I_{Na}) to flow, both gates must be open at the same time. The K^+ channel (here, an imaginary combination of 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, and Na^+ flows into the cell (i.e., I_{Na} flows). 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 approximately 1 msec ("approximately" 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 inactivated. (iv) Even though the initial resting potential is reached, the Na^+ channel remains inactivated because it takes approximately 1 msec of hyperpolarization for de-inactivation to occur. (v) Membrane voltage changes showing action potential corresponding to the events in (i)–(iv).

B. For the representation of actions of voltage-dependent T-type Ca^{2+} and K^+ channels underlying the low-threshold Ca^{2+} spike, the conventions are as in panel A, and so (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 and the Na^+ channel shown in panel 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 Ca^{2+} spike. (iii) The inactivation gate of the T-type Ca^{2+} channel closes after approximately 100 msec ("approximately" because, as for the Na^+ channel in panel 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, but after repolarization, it takes approximately 100 msec for de-inactivation to occur. Redrawn from Sherman and Guillery (2013).

[2] There are numerous types of Ca^{2+} channels found in neuronal membranes. The T-type channel is so named for its "transience." In addition are other, much higher-threshold Ca^{2+} channels that are located in dendrites and synaptic terminals (Johnston et al., 1996; Llinás, 1988; Hille, 1992). One involves the L-type Ca^{2+} channel (*L* for *long-lasting* because it slowly inactivates) and the other, the N-type channel (*N*, wryly, for *neither*, being neither T nor L type; it inactivates more rapidly than the L-type channel). Other types of high-threshold Ca^{2+} channels also exist (Wu et al., 1998; Hille, 1992; Snutch & Reiner, 1992).

[3] Control of the inactivation gate is a complex function of voltage and time (Jahnsen & Llinás, 1984b, 1984a; 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.

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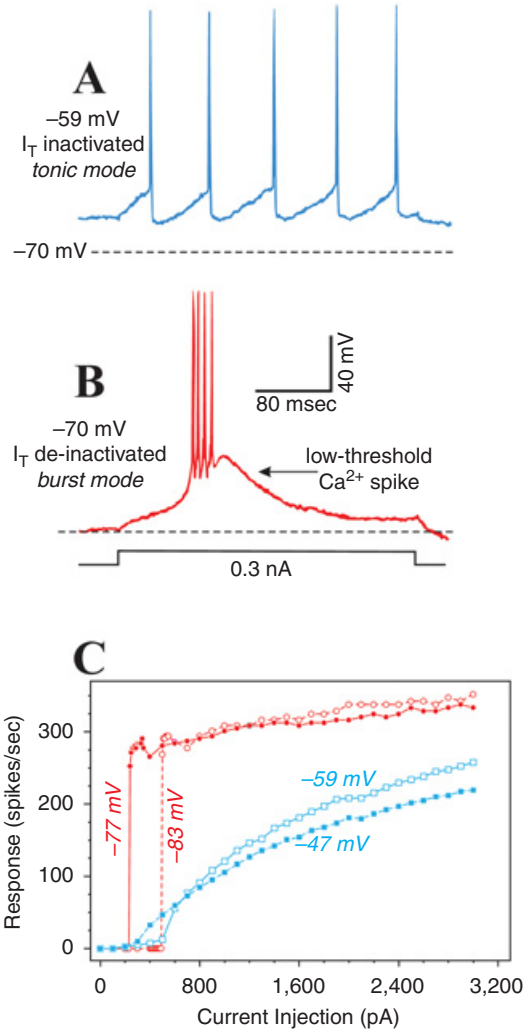

Figure 3 Properties related to T-type Ca^{2+} channels.

All examples are from relay cells of the cat's lateral geniculate nucleus recorded intracellularly in in vitro slice preparations.

A and B. Voltage dependency of the Ca^{2+} low-threshold spike. Responses are shown to the same depolarizing current injection delivered intracellularly from two different initial holding potentials. At a relatively depolarized level (A), most Ca^{2+} channels are 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. At a relatively hyperpolarized level (B), most Ca^{2+} channels are 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. Input–output relationship for another cell. The input variable is the amplitude of the depolarizing current pulse (labeled "Current Injection"), and the output is the firing frequency of the cell (labeled "Response"). To compare burst and tonic firing, the firing frequency was determined by the first six action potentials of the response because this cell usually exhibited six action potentials per burst in this experiment. The initial holding potentials are shown, and –47 mV and –59 mV reflect tonic mode, whereas –77 mV and –83 mV reflect burst mode. Redrawn from Sherman and Guillery (2013).

Burst and tonic firing properties. Figure 3 shows many of the properties that distinguish burst from tonic firing. Panels A and B of Figure 3 show that the same input (e.g., a current injection in this case, but it could also be an excitatory postsynaptic current [EPSC] from the retina in a geniculate relay cell) evokes a very different postsynaptic response during the two firing modes. When the cell is relatively depolarized (Figure 3A), the Ca^{2+} channels are mostly inactivated and thus play little or no role. Under these conditions, the depolarization evokes firing as long as it remains above threshold; this is tonic firing. When the same cell is relatively hyperpolarized (Figure 3B), these channels are de-inactivated, and the exact same depolarizing current injection now activates them, producing a spike upon which rides a brief burst of action potentials; this is burst firing.

Significance of burst and tonic firing. Burst and tonic firing modes are important for thalamic relay functions for at least three reasons. Figure 3C shows the first: tonic mode provides a more linear relay of information (Zhan et al., 1999). During tonic firing, there is a relatively direct relationship between the input depolarization (e.g., an EPSP) and evoked action potentials, and so the firing rate rises monotonically and thus fairly linearly with the size of the EPSP. However, during burst firing, action potentials are not evoked directly from the EPSP but, rather, from the Ca^{2+} spike, and because this is an all-or-none spike, once the EPSP is large enough to reach threshold for this spike, larger EPSPs do not evoke larger Ca^{2+} spikes, and so the input–output relationship is more like a step function, which is highly nonlinear. Second, burst firing can only occur after a period of hyperpolarization needed to de-inactivate the Ca^{2+} channels, and there can be no neuronal firing during such hyperpolarization. Therefore, the burst of action potentials occurs against a background of low spontaneous firing compared to tonic mode. Spontaneous firing can be regarded as noise, and as such, the signal-to-noise ratio of burst firing is considerably greater than that of tonic firing, so the thalamic response, and thus the signal that is passed to the cortex, is more detectable (Sherman, 1996). The third reason is again related to the requisite period of hyperpolarization and lack of action potentials before a burst can be evoked. Geniculocortical synapses show the property of paired-pulse depression (reviewed in Sherman and Guillery, 2013), meaning that an action potential produces a smaller EPSP if it follows another within about 100 msec or so. During tonic mode, when geniculate firing rates usually exceed 10 action potentials/sec, the geniculocortical synapse will usually be depressed; however, a burst of action potentials would arrive at the thalamocortical synapse after the requisite silent period of 100 msec or longer, which means that the thalamocortical synapse has been relieved of depression, and thus the postsynaptic response evoked would be greater. This, in turn, predicts that the first action potentials in a burst should evoke a greater response in the cortex than a typical tonic action potential, and this indeed occurs (Swadlow et al., 2002; Swadlow and Gusev, 2001).

These differences between firing modes suggest that burst firing produces a larger signal that is more readily detected in the cortex compared to tonic firing. However, the more linear input–output function during tonic firing suggests that it represents a more faithful relay mode for information transfer. These differences have led to the hypothesis that burst firing can provide a "wake-up call" to the cortex to strongly signal that a novel stimulus has occurred after a quiescent period. Once this signal has been detected, the circuitry can then be brought to bear to depolarize the relay cell (e.g., depolarization from corticogeniculate feedback that activates metabotropic

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glutamate receptors, leading to a prolonged depolarization to inactivate the underlying Ca^{2+} channels; see next section) to switch to tonic mode so that further details of the novel stimulus can be faithfully relayed (Sherman, 1996). This idea remains a hypothesis to be tested, and other hypotheses do exist (e.g., Kim et al., 2015).

One final point needs to be emphasized. Although burst and tonic firing modes are often referred to as completely distinct, there is a sort of intermediate stage. If a relay cell is held at a sufficiently depolarized level to inactivate virtually all T-type Ca^{2+} channels, the neuron's response is strictly in tonic mode. Likewise, if the neuron is held sufficiently hyperpolarized to bring an adequate number or density of these Ca^{2+} channels into play to activate a low-threshold spike, burst firing ensues. However, there exist less hyperpolarized levels at which some of these Ca^{2+} channels will be de-inactivated, but their density is insufficient to activate an all-or-none low-threshold spike. In this case, activation of these Ca^{2+} channels will evoke a relatively small depolarization that propagates only electrotonically but that can nonetheless affect the neuron's responsiveness (Deleuze et al., 2012; Alitto et al., 2019).

Control of burst and tonic firing. A relay cell's firing mode is dictated by its recent voltage history: sufficiently long relative depolarization produces tonic firing, and hyperpolarization produces burst firing. Because of the temporal requirement, it would appear that activation of metabotropic receptors presents the most efficient route for controlling firing mode. Figure 1A shows the likely candidates. Layer 6 feedback activates metabotropic glutamate receptors on relay cells that depolarize them sufficiently in time and amount to promote tonic firing, and evidence for this exists (Godwin et al., 1996; Andolina et al., 2013). Likewise, $GABA_B$ receptors on relay cells activated from thalamic reticular neurons (Ulrich et al., 2007; Huguenard and Prince, 1994; Crunelli and Leresche, 1991; Soltész et al., 1989) and possibly interneurons would hyperpolarize them sufficiently in time and amount to promote burst firing. Figure 1C shows how a likely corticogeniculate circuit would depolarize some cells (e.g., *cell 2*) to promote tonic firing and hyperpolarize others (e.g., *cells 1* and *3*) to promote burst firing.

Glutamatergic Drivers and Modulators

Despite the many different inputs to relay cells, it is the retinal input alone that carries the main information relayed to the cortex. A consideration of receptive field properties underscores this fact because these properties of the relay cell identify the information it relays. This is shown in Figure 4. The receptive fields of geniculate relay cells are remarkably like those of their retinal afferents, having basically the same monocularly driven, center/surround configuration (Usrey et al., 1999; Hubel and Wiesel, 1961). In contrast, these relay cell receptive fields are unlike those of extraretinal afferents: the receptive fields of corticogeniculate afferents are characteristically binocularly driven and selective for orientation and often direction, properties typical of visual cortical neurons (Gilbert, 1977), and brainstem inputs are not plausible sources of such clear center/surround properties. If retinal input alone provides the information to be relayed, then the nonretinal inputs must have another function. Clearly, then, retinogeniculate and layer 6 corticogeniculate inputs, which are both glutamatergic, have very different functions.

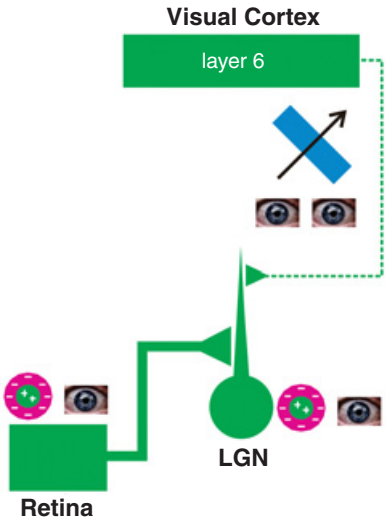

Figure 4 Different functions for glutamatergic retinal and cortical inputs to the lateral geniculate nucleus.

The receptive field of the retinal input (monocular, center/surround) is very similar to that of the geniculate relay cell, whereas the cortical cell's receptive field (binocular, specificity for orientation, direction, etc.) is not. This suggests that the retinal input carries the information to be relayed, whereas the cortical input has a very different function. See text for details.

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 information-bearing drivers (so called because one of their properties is the very strong postsynaptic drive of their target relay cells), whereas all the nonretinal inputs serve to modulate retinogeniculate transmission (reviewed in Sherman and Guillery, 1998, 2013). A modulatory function for GABAergic and classic modulatory afferents like cholinergic, noradrenergic, and so forth is clearly not a novel idea. However, it follows from this argument that the cortical layer 6 feedback input, which, like the retinal input, is glutamatergic, is also a modulator.

Drivers and Modulators in Thalamus

The concept of a division of glutamatergic inputs being classified as drivers or modulators originated with consideration, as just discussed, of the very different properties of retinal versus layer 6 cortical input to geniculate relay cells (Sherman and Guillery, 1998). This spawned experiments identifying different properties among glutamatergic afferents in the thalamus and cortex, which in turn led to their classification into drivers and modulators (reviewed in Sherman and Guillery, 2013). Many properties distinguish glutamatergic drivers from modulators in the thalamus, and the number will likely increase as we learn more about this issue. The following list, which is not meant to be exhaustive, summarizes seven distinguishing features in a roughly decreasing order of importance:

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1. Drivers activate only ionotropic receptors; modulators activate metabotropic receptors as well.
2. Driver synapses show a high probability of neurotransmitter release and paired-pulse depression; modulator synapses show the opposite properties of low release probability and paired-pulse facilitation (Dobrunz and Stevens, 1997; Dittman et al., 2000; Branco and Staras, 2009)
3. Drivers evoke larger initial EPSPs than do modulators.
4. Driver inputs show less convergence onto their targets than do modulators.
5. Driver inputs produce a small minority (2–5%) of the synapses onto thalamic relays cells, whereas layer 6 cortical input produces 30–50% of such synapses (Wang et al., 2002; Van Horn et al., 2000; Van Horn and Sherman, 2007).
6. Drivers tend to form larger terminals on more proximal dendrites than do modulators.
7. Drivers tend to have thicker axons and denser terminal arbors than do modulators.

The main point is that not all anatomical pathways are functionally equivalent, acting in some sort of anatomical democracy so that the numerically largest glutamatergic input is the most important. This old notion is strongly challenged by a consideration of the lateral geniculate nucleus, where the number of layer 6 cortical synaptic inputs exceeds that of retinal inputs by roughly an order of magnitude, and the conclusion based on this notion of information magnitude being determined by the size of the input is that the layer 6 input provides relay cells with information to be fed back to the cortex, whereas the retinal input is too small to be of much importance. Clearly, this conclusion is wrong. Thus, if one is to understand the functional organization of the thalamus, and especially the identity of the input being relayed to the cortex, one must identify and characterize the driver input.

Drivers and Modulators in the Cortex

The classification of drivers and modulators among glutamatergic circuits has been extended to the cortex (reviewed in Sherman and Guillery, 2013). This includes thalamocortical (Mo and Sherman, 2019; Lee and Sherman, 2012; Covic and Sherman, 2011; Viaene et al., 2011a, 2011b, 2011c; Lee and Sherman, 2008), local intraareal corticocortical (Lam and Sherman, 2019; DePasquale and Sherman, 2012; Lee and Sherman, 2008, 2009), and interareal corticocortical pathways (Petrof et al., 2015; Covic and Sherman, 2011; DePasquale and Sherman, 2011, 2013).

The three-dimensional scatterplot of Figure 5 shows certain quantitative features of this classification for the thalamus and cortex. Each point represents a single thalamic or cortical neuron recorded in a mouse brain slice for which a glutamatergic input was identified as driver or modulator. The scatterplot suggests three conclusions. First, the driver-versus-modulator 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 only two main classes of glutamatergic synapse have been described in the thalamus and cortex, although there is evidence that driver synapses in the cortex may be further subdivided (Viaene et al., 2011c). Third, the basic properties of a glutamatergic driver or modulator synapse appear to be fundamentally the same in the thalamus and cortex.

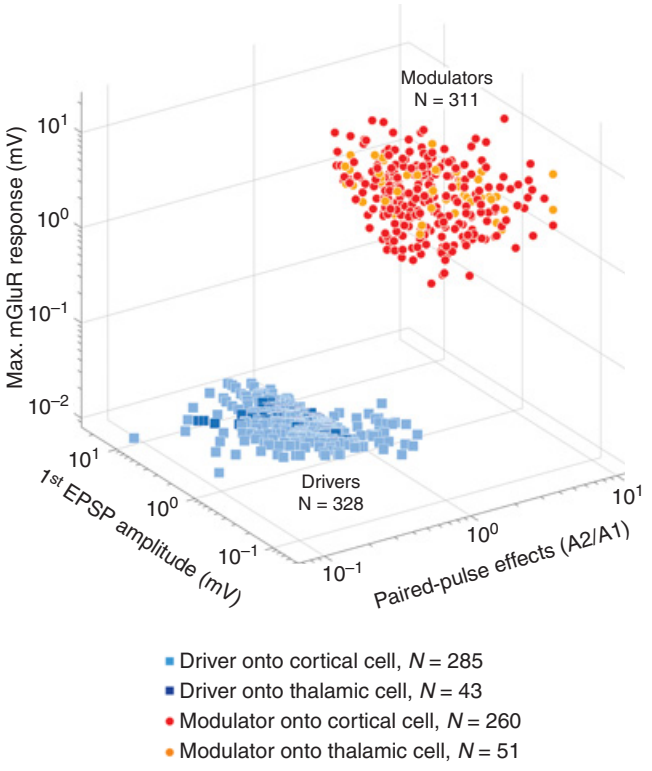

Figure 5 Three-dimensional scatterplot for inputs classified as driver or modulator to cells of thalamus and cortex; data from in vitro slice experiments in mice from the author's laboratory.

Each point is a single cell for which a glutamatergic input was identified as driver or modulator, and the key below the graph indicates whether the cell was thalamic or cortical. The parameters for the three axes 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 depolarization or hyperpolarization evoked during the 300-msec postsynaptic response period to tetanic stimulation in the presence of AMPA and NMDA blockers. Pathways tested here include various inputs to the thalamus from the cortex and subcortical sources, various thalamocortical pathways, and various intracortical pathways. From Sherman (2016).

Why Have Glutamatergic Modulators?

Given the presence of so many classic modulatory systems (e.g., cholinergic, noradrenergic, serotonergic), what is the point of adding glutamatergic modulators to the mix? I suggest an answer based both on topography and the control of the modulation. 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 the 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, and so forth. Only glutamatergic modulatory pathways possess a high degree of topography, and such topographic

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modulation is needed for processes that require localized effects, such as focal or covert attention, adaptation, and learning and memory. Furthermore, classic modulatory systems originate subcortically and thus do not have the benefit of thalamocortical processing, which is the source of most of the glutamatergic inputs discussed here, and such processing would obviously be important for modulation related to higher cognitive functioning.

First and Higher Order Thalamic Relays

A major function of a thalamic relay is determined by its driver input. Thus, we can define the function of the lateral geniculate nucleus or the ventral posterior nucleus as relaying retinal or medial lemniscal information, respectively. However, until recently, the driver inputs of many thalamic relays were undefined, and thus their functions in this sense had been unclear. We now know that a major source of driver input to many thalamic nuclei originates in layer 5 of various cortical areas (Prasad et al., 2020; Kita and Kita, 2012; Bourassa and Deschênes, 1995; Bourassa et al., 1995; Deschênes et al., 1994; Economo et al., 2018; reviewed in Sherman and Guillery, 2013). This is illustrated in Figure 6A, using the visual system as an example. Figure 6B generalizes the patterns of Figure 6A to the thalamus more broadly.

Thalamic relays can be divided based on the source of their driver input: *first order* relays receive driver input from a subcortical source, whereas *higher order* relays receive driver input from layer 5 of the cortex (Sherman and Guillery, 2013; Guillery, 1995). 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. A first order example is the lateral geniculate nucleus, which receives driving subcortical input from the retina, and a higher order example is the pulvinar, which receives driving input from layer 5 of the visual cortex (Figure 6A). This pattern is not limited to the visual

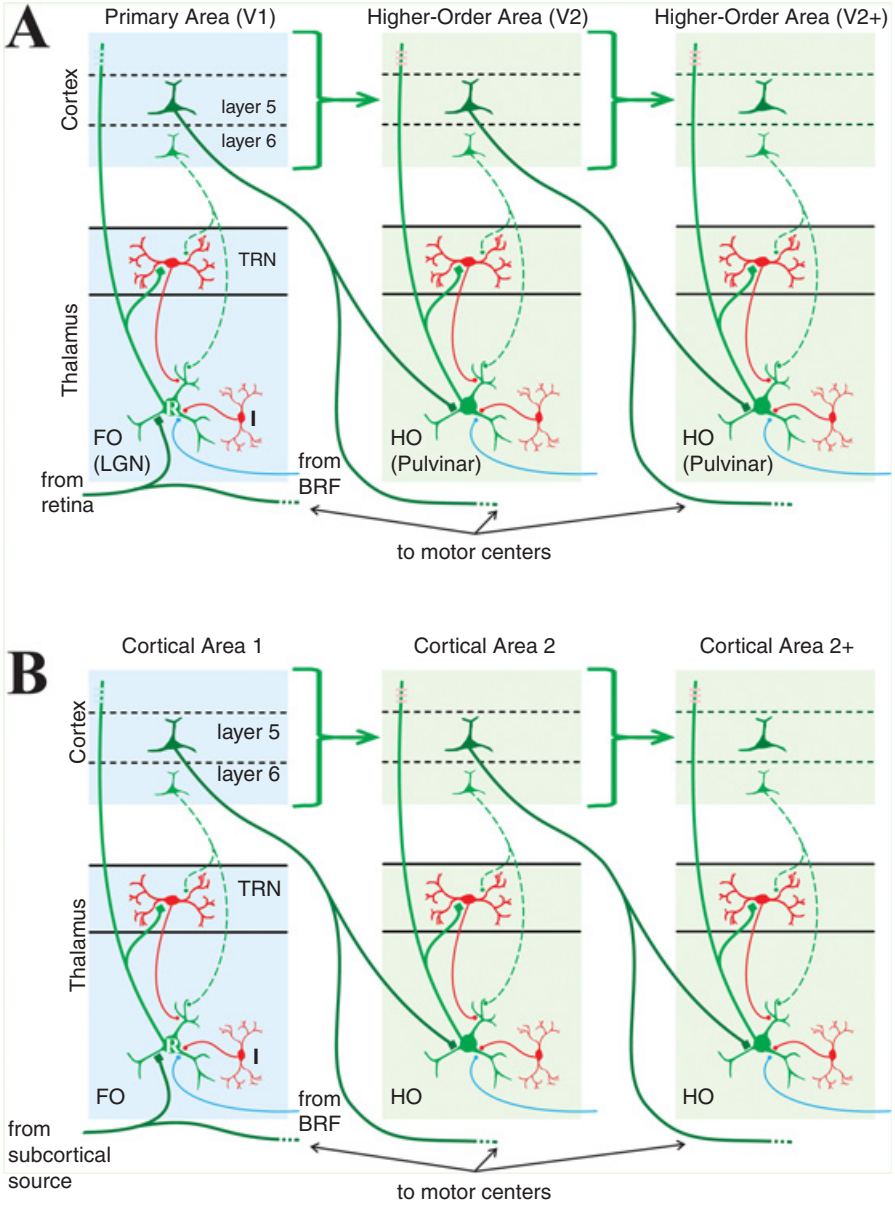

Figure 6 Schematic diagram showing organizational features of first and higher order thalamic relays.

A. Examples from the visual system. The first order nucleus (FO; lateral geniculate nucleus) relays subcortical (retinal) input to the primary visual cortex. A higher order nucleus (HO; pulvinar) relays information from layer 5 of one visual cortical area to another; this is a transthalamic corticocortical circuit. This relay can be between first and higher order visual areas or between two higher order visual areas. The important difference between first and higher order relays is the driver input, which is subcortical (retinal) for a first order thalamic nucleus and from layer 5 of the cortex for a higher order one. Note that both types of thalamic nuclei receive an input from layer 6 of the cortex, which is modulatory and mostly feedback, but higher order nuclei additionally receive a layer 5 input from the 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.

B. Generalization for thalamus from example in the visual system shown in panel A.

Abbreviations: *BRF*, brainstem reticular formation; *FO*, first order; *HO*, higher order; *I*, interneuron; *LGN*, lateral geniculate nucleus; *R*, relay cell; *TRN*, thalamic reticular nucleus. Redrawn from Sherman (2005).

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system, as shown in Figure 6B: for the somatosensory system, the ventral posterior nucleus is first order, and the posterior medial nucleus is higher order; for the auditory system, the ventral division of the medial geniculate nucleus is first order, and the dorsal division is higher order (details reviewed in Sherman and Guillery, 2013). This classification has been extended to most of the thalamus, and in this regard, most of the thalamus, by volume, is higher order (Sherman and Guillery, 2013). It appears that all thalamic nuclei receive a corticothalamic projection from layer 6 that is a modulator, but higher order relays receive another cortical input, a driver input from layer 5 (Figure 6).

As indicated in Figure 6, the non-driver inputs to first and higher order thalamic relays are similar, with some quantitative differences, some of which are noted later in the discussion. One implication is that all thalamic relays receive a modulator layer 6 corticothalamic projection, but higher order relays receive another cortical input, from layer 5, that is a driver. Another implication is that higher order relays serve as a thalamic hub in transthalamic corticocortical communication. Figure 6 also shows that cortical areas connected via transthalamic pathways also have direct connections. This parallel organization has been seen for direct and transthalamic connections in the mouse between V1 and V2, S1 and S2, A1 and A2 (reviewed in Sherman and Guillery, 2013), and S1 and M1 (Mo and Sherman, 2019; Petrof et al., 2015).

It should be clear from Figure 6 that higher order relays are organized to provide a route for corticocortical communication. Given the preponderance of higher order relays in the thalamus (Sherman and Guillery, 2013; Prasad et al., 2020), such transthalamic circuits likely play an important and only recently recognized role in overall cortical functioning. The patterns seen in Figure 6 raise three critical questions for which we now have no clear answers:

- How often is this parallel pattern of direct and transthalamic connections seen between cortical areas, or how often are cortical areas connected by just one or the other?
- What is different in the nature of the messages sent via the direct versus transthalamic pathways?
- Why is one path of corticocortical communication routed through the thalamus?

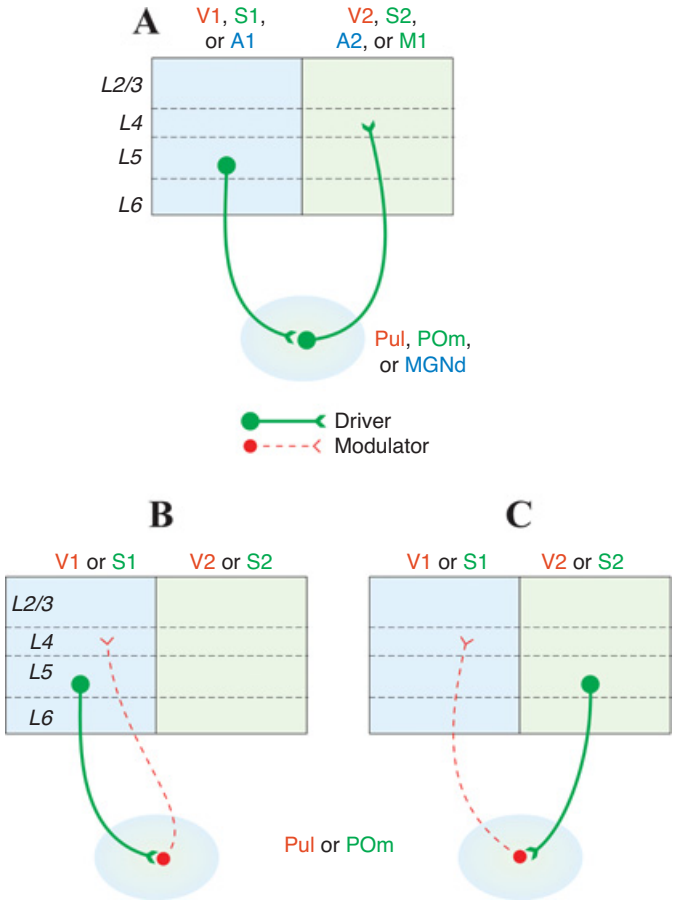

Figure 7 Feedforward and feedback transthalamic circuits identified to date in the mouse.

A. Examples of feedforward transthalamic circuits. These are from primary to secondary cortical areas (visual, V1 and V2; somatosensory, S1 and S2; auditory, A1 and A2) through higher order thalamic relays (pulvinar [Pul] for vision, posterior medial nucleus [POm] for somatosensation, dorsal division of the medial geniculate nucleus [MGNd] for audition); also, there is a transthalamic pathway from S1 to M1 via POm. All inputs shown are driver. The color coding shows the cortical and thalamic relationships.

B and C. Examples of feedback transthalamic circuits; color coding and abbreviations as in panel A. Note that the thalamocortical inputs here are modulatory.

B. Feedback from primary sensory area to itself.

C. Feedback from secondary sensory area to primary sensory area.
Abbreviations: *MGNd*, dorsal division of medial geniculate nucleus; *POm*, posterior medial nucleus; *Pul*, pulvinar.

Feedforward versus Feedback Transthalamic Pathways

The transthalamic pathways shown in Figure 6 represent feedforward examples that ascend a cortical hierarchy. Figure 7A shows feedforward transthalamic pathways that have been identified to date in the mouse cortex (Sherman and Guillery, 2013; Mo and Sherman, 2019), and these are color coded in the diagram. These include V1 to V2 via the pulvinar; S1 to S2 and S1 to M1, both via the posterior medial nucleus; and A1 to A2 via the dorsal division of the medial geniculate nucleus.

The possibility that transthalamic circuits may be involved in feedback corticocortical communication remains a possibility that, to date, has received little attention. Recent evidence for a transthalamic feedback circuit has been presented for the visual cortex and the somatosensory cortex (Miller-Hansen and Sherman, 2022) and is summarized in Figure 7B and C. In both cases, the feedback targets the primary sensory cortex. Figure 7B shows a layer 5 driving input from V1 or S1 to the higher order thalamic relay, the pulvinar or the posterior medial nucleus, with the latter providing a modulatory input back to V1 or S1. Figure 7C shows a feedback arrangement starting with a driving input from layer 5 of V2 or S2 to the pulvinar or the posterior medial nucleus and, from there, a modulatory input to V1 or S1. What is particularly interesting in the transthalamic pathways shown in Figure 7 is that the feedforward ones provide driving input to the target cortical area, whereas the feedback ones provide modulatory input to the target cortical area. The

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examples so far are few, and so we need many more examples to test the generality of these patterns.

Some Differences between First and Higher Order Thalamic Nuclei

Figure 6 suggests that the only difference between first and higher order thalamic nuclei is the nature of their driver input: subcortical for first order and cortical layer 5 for higher order. However, several differences, mostly quantitative, between them have been documented. These are simply listed as follows:

- Higher order nuclei have relatively fewer driver synapses than do first order nuclei, at roughly 2% of all synapses versus 7% (Van Horn and Sherman, 2007; Van Horn et al., 2000; Wang et al., 2002). This suggests more modulation of higher order relay cells.
- Serotonergic and cholinergic inputs from the brainstem depolarize all first order relay cells, but a significant minority (1/4 to 1/3) of those in higher order nuclei are hyperpolarized by these inputs; this results from different postsynaptic receptors to these neurotransmitters (Varela and Sherman, 2008; Varela and Sherman, 2007).
- Higher order thalamic nuclei receive substantial GABAergic inputs from the zona incerta, substantia nigra, basal ganglia, and pretectal region that do not extensively innervate first order nuclei (Bokor et al., 2005; Gulcebi et al., 2011; Lavallée et al., 2005; Kuramoto et al., 2011; Sakai et al., 1996).
- Bursting based on activation of T-type Ca^{2+} channels is more frequent among higher order relay cells (Ramcharan et al., 2005; Sherman, 2001). This may be related to the previously noted points that higher order relays receive more hyperpolarizing inputs via GABAergic, serotonergic, and cholinergic innervation, which serves to de-inactivate T-type Ca^{2+} channels in more relay cells, thereby promoting more burst firing.
- First order nuclei appear to be strictly first order, meaning that they all receive subcortical driver inputs, but nuclei identified as higher order appear to include some first order circuits. Thus, the superior colliculus seems to provide driving input to some cells of the pulvinar and medial dorsal nucleus, as does the spinal trigeminal nucleus for some cells of the posterior medial nucleus (Groh et al., 2013; Kelly et al., 2003; Berman and Wurtz, 2010; Sommer and Wurtz, 2004; Mo et al., 2017).
- First order relays innervate the cortex in a feedforward manner because they are the first relay of a particular kind of information to the cortex and predominantly innervate primary cortical areas. However, as indicated by Figure 7, some relay cells of the pulvinar, posterior medial nucleus, and dorsal division of the medial geniculate nucleus innervate primary visual, somatosensory, and auditory cortices, as well as higher areas, indicating that some higher order inputs to the cortex are links in feedback circuitry.
- First order relay cells generally transfer information from one or a few driver inputs without further significant elaboration of the information carried (but see Bickford et al., 2015; Litvina and Chen, 2017), whereas evidence exists for such elaboration for some higher order relay cells, where single neurons in the posterior medial nucleus or pulvinar are innervated both by layer 5 and subcortical driver inputs (Groh et al., 2014). This is a critical issue and needs indisputable confirmation because current ideas of thalamic processing do not include the elaboration of information based on a significant convergence of driver inputs.

Do Driver Afferents to the Thalamus Carry Efference Copy Information?

Efference Copies

Every eye movement creates a sensory signal on the retina that the visual scene has moved in the opposite direction. We typically scan scenes with rapid eye movements known as *saccades* three to five times per second, and yet we do not normally perceive the world as spinning about when this occurs. This is because neural circuits are set up to anticipate these eye movements and eliminate the sensory consequences of them from our perception. All self-generated movements, not just eye movements, create such circuits. Such a process is required to disambiguate sensory stimulation due to self-generated movements from that caused by actual changes in the environment, an absolute requirement for any organism moving about in its environment. This requires a prediction, or "forward model," of what will occur because of the impending motion, but any sensory feedback that can indicate the position of the eyes or any joint would occur after the movement and be too late for this purpose (Sommer and Wurtz, 2008).

These anticipatory circuits depend on efference copies (also known as *corollary discharges*), which are messages sent from motor areas of the brain back into appropriate sensory processing streams to anticipate impending self-generated behaviors. Details of efference copies can be found elsewhere (Wolpert and Flanagan, 2010; Sommer and Wurtz, 2008; Crapse and Sommer, 2008a, 2008b); here, the focus is on the possible role of efference copies in thalamocortical processing.

Coordinated motor performance of any motile animal without efference copies is implausible. Indeed, the presence of efference copies was predicted in the nineteenth century (von Graefe, 1854). It took nearly another century for experimental evidence to be found for efference copies in fishes and flies (Sperry, 1950; von Holst and Mittelstaedt, 1950), and this indicates that it must occur widely in the animal kingdom and be a core part of our early evolutionary heritage. It thus logically follows that any message generated anywhere in the central nervous system that leads to a change in motor behavior must have associated with it an efference copy. In the next section, I suggest that branching axons associated with thalamocortical relationships might serve a role in the processing of some efference copies.

Axonal Branching

Axonal branching is a ubiquitous feature of the central nervous system. Because of the high safety factor in propagating action potentials in mammalian axons, it seems clear that the exact same temporal pattern of action potentials will be conducted along all branches of the axon to its terminations (Raastad and

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Shepherd, 2003; Cox et al., 2000). This does not mean that the message has the same effect on all of its targets because different synaptic properties at different targets likely exist, and these lead to postsynaptic variation in responses. Nonetheless, a branching axon is the most efficient and effective way to share a single message with multiple targets.

Some Axonal Branching Could Subserve Efference Copies

Over a century ago, Cajal (1911) emphasized the omnipresence of branching axons in the central nervous system. Figure 8A is a reproduction of one of his drawings from Golgi impregnations in which he pointed out that every primary afferent entering the spinal cord branches, with one branch innervating the ventral horn, where motoneurons live, and the other ascending to the brain. Figure 8B is a version of this pattern shown more schematically. The branch carrying the message toward motoneurons can be considered a motor command, but the branch ascending to the brain carries the exact same message. This ascending message is conventionally thought of as a sensory message, conveying information about a change in skin depression, a joint angle, and so forth. However, this message is also an exact copy of a message targeting motor neurons, that is, a motor message, and a copy of a motor message is a definition of an efference copy. An important point about the ascending axon branch is that it carries a single message. This message can be interpreted by some postsynaptic targets as sensory information and by others as an efference copy.

Axonal Branching of Driver Afferents to Thalamus

Figure 6 shows that axons providing the driver inputs to both first and higher order relay cells branch, with extrathalamic branches innervating targets in the brainstem and spinal cord that are often motor in nature (Sherman and Guillery, 2013; Guillery, 2003, 2005). Figure 9 shows specific examples of this. Most or all retinogeniculate axons branch to innervate the pretectum and/or superior colliculus (Sur et al., 1987; Tamamaki et al., 1995), areas involved in the control of head and eye movements, pupillary size, focusing, and so forth (Figure 9A). Other examples in Figure 9 include cerebellar axons innervating the ventral anterior/ventral lateral complex of the motor thalamus and branching to innervate bulbospinal control centers (Figure 9B), and layer 5 pyramidal tract axons from the motor cortex that branch to innervate the thalamus plus many motor targets in the brainstem, as well as entering the spinal cord (Figure 9C).

So far, the evidence is that all layer 5 corticofugal axons branch to innervate numerous targets, and those that innervate the thalamus also innervate extrathalamic targets; these latter targets include supraspinal control centers and often the spinal cord itself. In any case, this branching pattern of driver inputs to the thalamus, with some extrathalamic branches targeting subcortical motor structures, seems to be a ubiquitous feature of thalamic circuitry. An interesting feature of these layer 5 corticothalamic axons is that regardless of the cortical area of origin, the layer 5 projections to the thalamus all have extrathalamic branches, and most or all of these innervate the superior colliculus (Prasad et al., 2020; Economo et al., 2018).

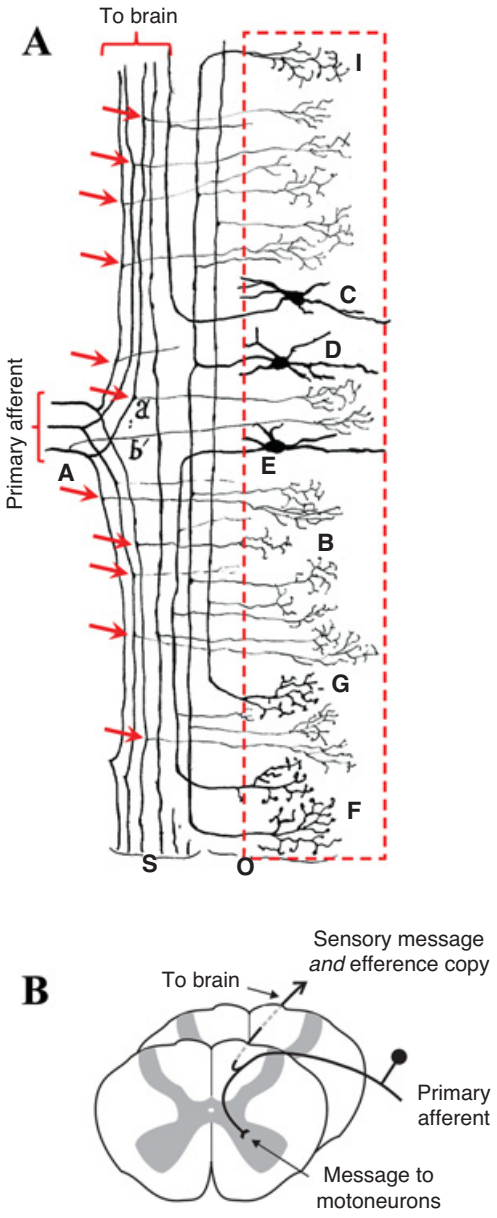

Figure 8 **Examples of branching primary afferents to spinal cord.**

A. 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.

B. Schematic interpretation of panel A. From Sherman (2016).

One interpretation of this pattern of branching driver afferents to the thalamus shown in Figure 6 is that the messages relayed by the thalamus can relate to motor commands and thus serve as efference copies. However, as explained by the example of Figure 8B, these messages can be interpreted by different targets groups in different ways, with only some postsynaptic circuitry treating them as efference copies.

Logic of Cortically Related Efference Copies

These ideas of efference copies related to thalamic afferents may at first seem unfettered and purely speculative, but there is a plausible line of reasoning that supports this hypothesis. The

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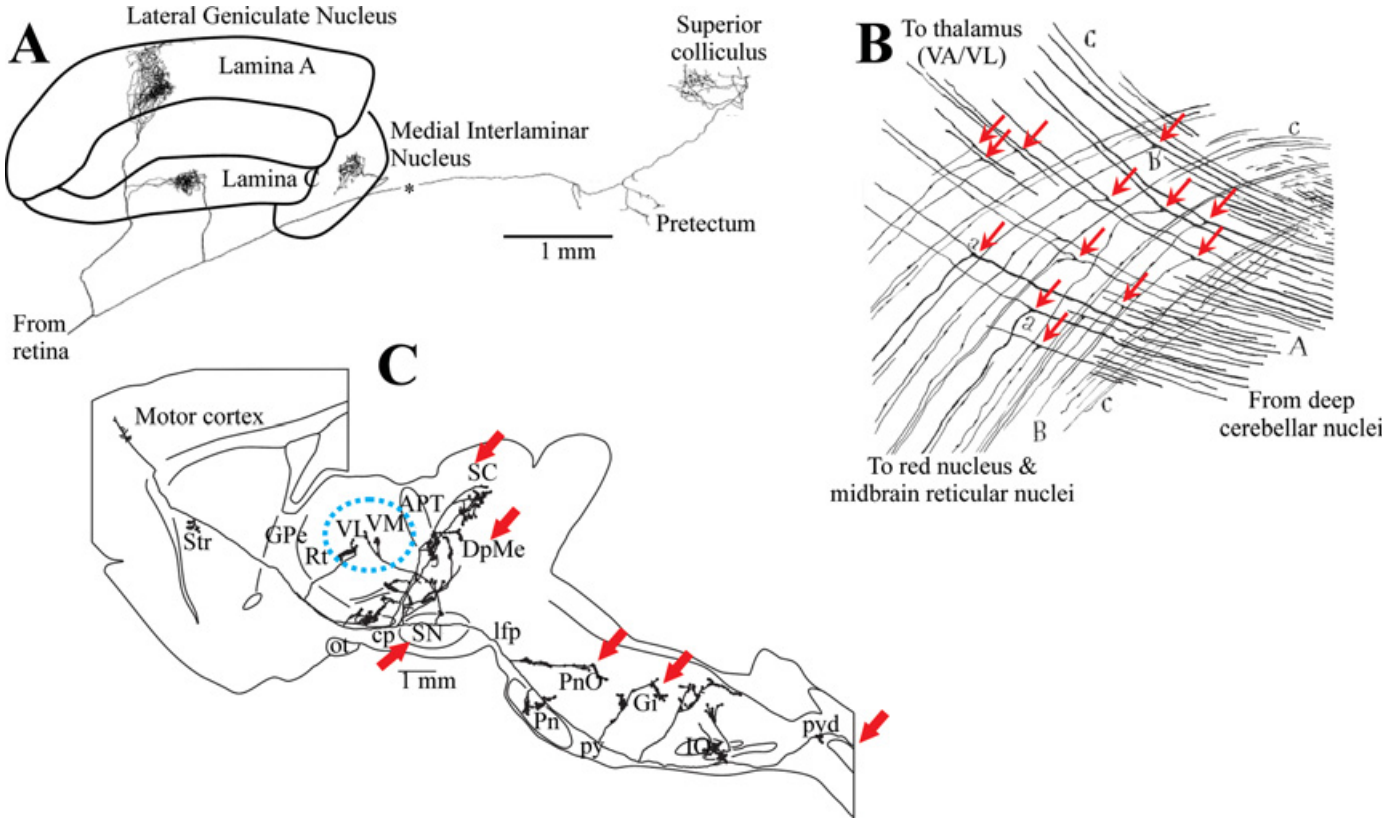

Figure 9 **Examples of branching axons of driver inputs to the thalamus.**

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 the 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 the thalamus are indicated by the dashed blue circle, and brainstem motor regions are indicated by red arrows. Abbreviations: *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. From Sherman (2016).

cortex clearly evolved to affect behavior in more flexible and effective ways than had been possible with only subcortical circuitry. Nonetheless, much behavior is accomplished without significant cortical participation: think of chewing gum, breathing, or walking up a familiar flight of stairs. Yet the cortex is required for many high-level behaviors, such as when attention is focused on a new task. But the only effective pathway for the cortex to affect behavior is through its layer 5 projections to the brainstem and spinal motor centers. The cortex, with all of its beautiful circuitry and computational power, would be pretty useless without these layer 5 outputs.

Thus, the cortex influences behavior by using layer 5 projections, meaning that the messages carried by these axons in at least some cases are read as motor commands. If the cortex does act to create a new behavior, it follows that it must also create a related efference copy to be fed back into the cortical circuitry so that further cortical processing can disambiguate the environmental effects of any new movement from independent environmental changes. The branches from these layer 5 axons that innervate the thalamus seem like an ideal candidate for an efference copy route because, as noted, the branch to the thalamus carries an exact copy of the message also being transmitted to subcortical motor centers.

It should also be noted again that an efference copy, to be effective, must create a forward model of the expected behavior, and this must occur with minimal latency. Therefore, any efference copies generated downstream from these layer 5 outputs, for instance, from target brainstem or spinal centers, might be too late by the time they reach the cortex. Again, the idea is that layer 5 corticofugal branches that innervate the thalamus seem to fit the bill quite nicely.

Although evidence does indicate that virtually every layer 5 axon that innervates the thalamus branches to innervate other subcortical sites, the obverse is not the case: some of the layer 5 corticofugal axons avoid targeting the thalamus (Economo et al., 2018). This indicates an important proviso to these ideas about efference copies because if these neurons carry a motor message like other layer 5 corticofugal projections, their innervation patterns offer no clear route for an efference copy back to the cortex that can quickly produce the needed forward model. At least three possible explanations for this pattern can be proposed. First, these projections that avoid the thalamus may modulate rather than drive their subcortical targets and thus

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would not carry a message requiring an efference copy. Second, perhaps an efference copy originates from one of their targets, such as the superior colliculus (see later discussion), and the extra synaptic delay still permits a timely efference copy. Indeed, evidence exists for efference copies being sent from the superior colliculus to the thalamus (Sommer and Wurtz, 2004). Third, these ideas about efference copies may simply be wrong.

Other Aspects of Layer 5 Corticofugal Projections

The evolution of the cortex occurred without coevolution of motor circuitry to which the cortex has unique access. That is, except in rare examples in primates, there is no direct pathway from the cortex to motoneurons (Isa et al., 2013; Rathelot and Strick, 2009). This means that layer 5 outputs of the cortex must operate through older circuitry in the brainstem and spinal cord if they are to influence behavior.

Bursting in Layer 5 Corticofugal Cells

Both tonic and burst firing also exist in layer 5 corticofugal cells that in many ways resemble these different firing modes in thalamic relay cells, although different Ca^{2+} channels are involved (Larkum et al., 1999, 2007; Llano and Sherman, 2009; Suzuki and Larkum, 2020). One similarity is that these layer 5 cells must be suitably hyperpolarized for a period of time to de-inactivate the Ca^{2+} channels so that a burst can be evoked, and during such hyperpolarization, these cells would not fire action potentials. Because the layer 5 inputs to higher order thalamic relay cells have driver characteristics showing paired-pulse depression (Sherman, 2016; Sherman and Guillery, 2013), and because the requisite period of hyperpolarization and lack of firing would relieve such depression, it follows that a burst would maximally activate the corticothalamic synapses, just as bursting thalamic relay cells do so in the cortex (Swadlow et al., 2002; Swadlow and Gusev, 2001). Perhaps this acts as a "wake-up call" for the transthalamic pathway much as it does for thalamocortical processing, as suggested previously.

Several unresolved issues arise with this speculation. One is that bursting in these cells, as in thalamic relay cells, likely involves nonlinear distortion in the message being transmitted. Second, because these layer 5 projections involve branching to many extrathalamic motor sites as well as the thalamus, what is the implication of this strong activation of these sites by the bursts? Is this a way to "jump-start" the initial phase of a motor action? Clearly, there is a great deal we need to learn about the properties of these layer 5 corticofugal cells, especially because they are the sole means by which the cortex can influence behavior.

We have discussed earlier how the burst/tonic transition in thalamic relay cells might be controlled (e.g., via layer 6 feedback circuitry). There are several pieces of evidence for the control of bursting in these layer 5 cells, largely from the work of Matthew Larkum and his colleagues (Suzuki and Larkum, 2020; Larkum et al., 1999, 2004). Bursting in these cells occurs when there is conjoint synaptic activation of their apical dendritic tufts in layer 1 and input to more proximal dendrites. The summed resultant depolarization, which typically involves a backpropagating action potential, is sufficient to activate the Ca^{2+} spike in the apical dendrite, thereby producing a burst. This requires coupling between the apical dendritic tufts in layer 1 and the main shaft of the apical dendrite. This coupling can be broken by anesthetics but, more interestingly, also by blockers of metabotropic receptors for either acetylcholine (i.e., muscarinic receptors) or glutamate (i.e., metabotropic glutamate receptors) (Suzuki and Larkum, 2020). It thus follows that cholinergic input from the basal forebrain, which corresponds mostly to overall behavioral state, or that from glutamatergic modulators, which can provide more specific and topographic control of activity in these layer 5 corticofugal cells, can provide necessary conditions for bursting in these cells. Given the importance of these layer 5 cells for the execution of cortical control of behavior, it is of obvious importance to better understand the response properties of these cells and, in particular, the inputs that activate metabotropic glutamate receptors that control bursting.

Layer 5 Projections to the Midbrain

It seems reasonable to assume that in doing so, the cortex would preferentially operate through circuits more advanced in evolutionary terms rather than having to "reinvent the wheel" by accessing older circuitry in the spinal cord and brainstem. In this regard, the most advanced sensorimotor center in nonmammalian vertebrates is the optic tectum and associated midbrain regions, structures that remain in mammals as a major center for controlling head and body movements (Stein et al., 2009; Stein and Gaither, 1983; Gaither and Stein, 1979; Suzuki et al., 2019).

From this perspective, we suggest that the most efficient way for the cortex to influence many or most behaviors is by operating through these midbrain circuits. It is thus particularly interesting that most or all cortical areas for which layer 5 projections have been defined innervate the midbrain (Prasad et al., 2020; Kita and Kita, 2012; Bourassa and Deschênes, 1995; Bourassa et al., 1995; Deschênes et al., 1994; Economo et al., 2018). Also, these studies indicate that most or all layer 5 axons that innervate the midbrain branch to innervate the thalamus.

Layer 5 Projections and Attention

Mechanisms underlying attention have long been a main focus of neuroscience research. A detailed discussion of the neuronal bases of attention is beyond the scope of this account, and many excellent reviews on the subject are available (Nobre et al., 2014; Maunsell and Treue, 2006; Posner, 2012; Desimone and Duncan, 1995; Petersen and Posner, 2012; Reynolds and Chelazzi, 2004). Much research on underlying mechanisms of attention has been directed at putative bottom-up and/or top-down circuits that enable a brain region, typically cortical, to enhance processing of the attended object (Awh et al., 2012; Desimone and Duncan, 1995). Mechanisms for this that have been identified to date include, among others, enhanced responses to attended stimuli (Lee and Maunsell,

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2010; Suzuki et al., 2019; Mineault et al., 2016; Maunsell and Treue, 2006); less noise correlation in firing among neurons in the attending circuit (Cohen and Maunsell, 2009); coherent, rhythmic neuronal firing across cortical areas (Fries, 2005; Suzuki et al., 2019; Chalk et al., 2010; Miller and Buschman, 2013;); and enhancement of thalamocortical synaptic efficacy (Suzuki et al., 2019; Briggs et al., 2013).

Why does attention reduce cognitive abilities to unattended objects? The explanation for attentional mechanisms is that it enables our brains to focus on environmental events of particular importance to our survival. For instance, a rabbit traveling through bushland might attend with its visual system on the lookout for hovering hawks. However, attention comes at a price because that rabbit, by emphasizing visual stimuli, may be less responsive to auditory cues that could signal a stalking fox. Even within vision, there may be a price to be paid: by concentrating on upper visual fields where hawks fly, the rabbit might miss observing the fox in its lower visual field. This raises the question: Given the extensive cortical circuitry subserving its enormous computational power, why cannot all areas of the cortex function all the time in an attentive-like mode so that the rabbit can be maximally sensitive to all sensory stimuli simultaneously? I believe that an evolutionary perspective offers a plausible answer to this question (Sherman and Usrey, 2021).

As noted earlier, the cortex evolved without the evolution of motor circuitry to which it has unique access. This means that cortical areas can only influence behavior by projections from layer 5 that activate older motor centers in the brainstem and spinal cord. These older motor centers may be seen as a bottleneck through which the cortex must operate. This presents a problem. If, as suggested previously, every cortical area operated at maximum capacity to turn its inputs into layer 5 motor commands, these would all compete for control through the same subcortical intermediaries, and chaos would ensue. There clearly needs to be some selective process that ensures that only the cortical areas engaged in analyzing those environmental objects that are the most important, or the most crucial to survival, are permitted to control subcortical motor centers. This is where "attention" comes in. Somehow, via top-down or bottom-up processes (Awh et al., 2012; Desimone and Duncan, 1995), the appropriate region or regions of cortex are engaged, and their layer 5 corticofugal projections are allowed to dominate subcortical motor regions; other areas of cortex (and their layer 5 outputs) dealing with less critical environmental events are suppressed.

Attention is not just cortical. Most of the literature on attention is concerned only with cortical contributions thereof. However, an evolutionary perspective suggests a more complex view. Just as attention seems necessary to ensure that the appropriate cortical regions take control of behavior, more primitive species had to deal with the same problem but without a cortex. For example, the highest level of behavioral control for nonmammalian vertebrates would be various brainstem motor areas, and I have argued earlier that the highest level of motor control for nonmammalian vertebrates is located in the midbrain. These centers, like the mammalian cortex, also had to operate through older bulbospinal and spinal centers, and the same problem as suggested earlier had to be overcome: that is, to avoid chaos, something like attentional mechanisms would be required to filter out inappropriate midbrain centers from controlling behavior (Sherman and Usrey, 2021).

One general rule of the evolution of the nervous system is that these older circuits are not discarded as newer ones evolve, and furthermore, these older circuits continue to function in current species, including humans. Indeed, for example, the mammalian superior colliculus has been shown to be involved in various attentional and other cognitive processes (Suzuki et al., 2019; Basso and May, 2017; Krauzlis et al., 2013; Wang et al., 2020; Herman et al., 2018; Wang and Krauzlis, 2018). It thus seems likely that the attentional mechanisms in our brains are not limited to cortical circuitry but involve older, subcortical circuits as well, and these all must operate in a coordinated fashion.

Concluding Remarks

Figure 10 contrasts the conventional view of thalamocortical processing (Figure 10A) with the alternative view offered here (Figure 10B). The conventional view is that information from the periphery is initially relayed by the thalamus to the sensory cortex and passes up a cortical hierarchy from sensory areas to sensorimotor areas and finally to some executive motor area from which an output is finally produced to activate motor centers and affect behavior (Figure 10A). Also, it is only at this final stage of sensorimotor processing that an efference copy is created, but the circuitry of Figure 10A offers no plausible route for this information to reach the cortex in a timely manner, a *sine qua non* for continued effective cortical involvement in ongoing behavior. Another problem with Figure 10A is that it provides no specific role for most of the thalamus (indicated by question marks), which we have defined as higher order. Perhaps even more important as a criticism, the circuitry of Figure 10A seems an implausible result of evolution. That is, anytime 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 Figure 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 (Figure 10B) differs significantly and does so from the very beginning of the sensorimotor processing stream. The initial information to be relayed via a first order thalamic nucleus is a copy of the information sent to motor structures. From the primary cortex, information can be relayed to other cortical areas not only via direct projections but also via higher order thalamic nuclei, and this continues through the various hierarchical stages. Also, these transthalamic pathways involve layer 5 corticothalamic axons that branch to innervate extrathalamic motor structures. Thus, this circuitry provides a credible route for efference copies to be effectively incorporated into further cortical processing.

Figures 6 and 10B show that most or all driving inputs to the thalamus, even to first order relays, branch to innervate extrathalamic motor centers. The branches related to first order relays are perhaps quite crude commands that are

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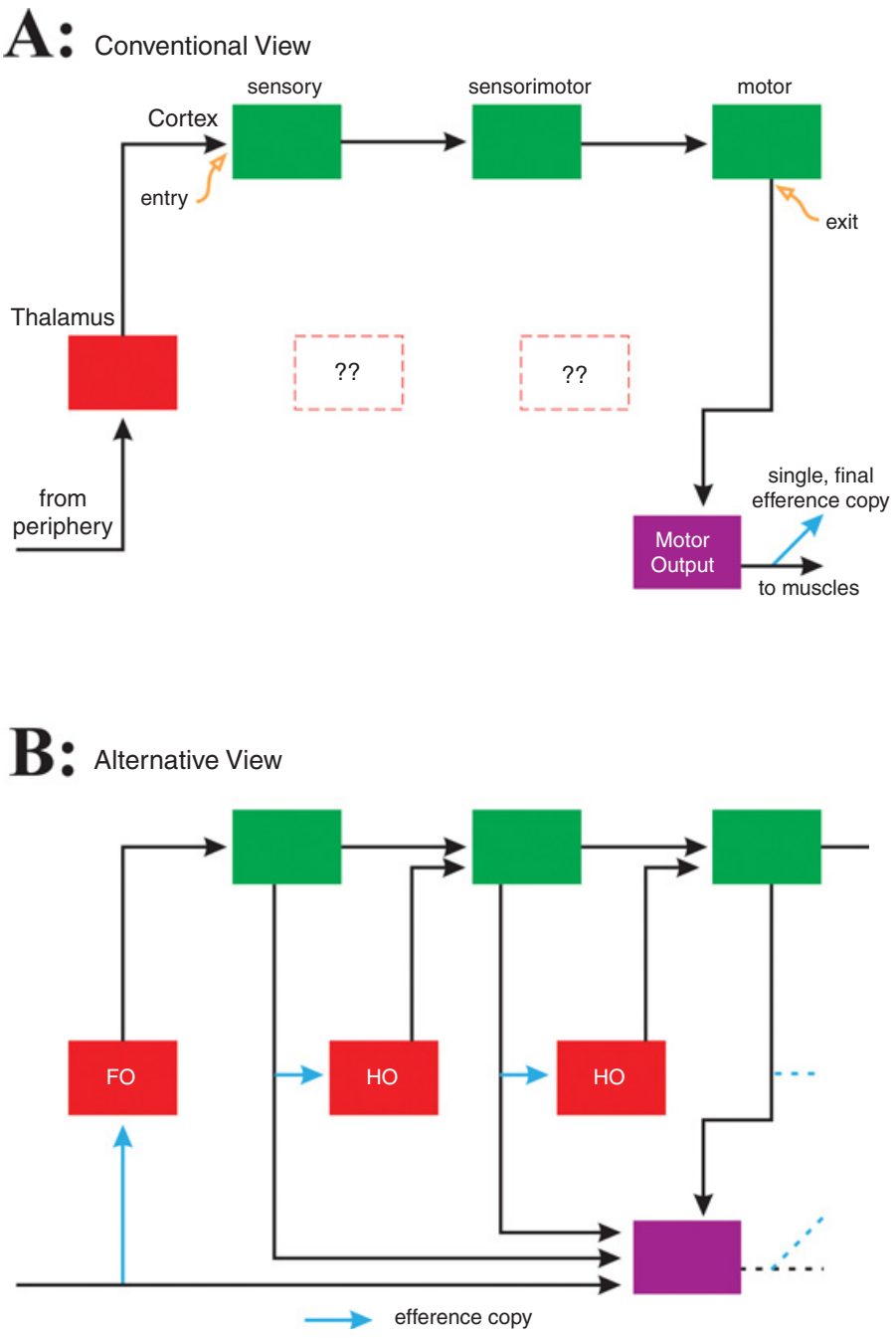

Figure 10 Comparison of conventional view (A) with the alternative view proposed here (B).

Abbreviations: *FO*, first order; *HO*, higher order. Further details in the text. Reproduced from Sherman (2005).

constantly upgraded with further cortical processing and effected via higher order layer 5 cortical outputs. An observation consistent with but far from proving this scenario was made in monkeys trained to pursue a moving target that suddenly appeared in their visual fields (Osborne et al., 2007). After fixing the target, each monkey pursued it with smooth eye movements, but the accuracy of the smooth pursuit was initially poor and improved asymptotically over the next 50–100 msec of pursuit.

This interpretation clearly stands the conventional view 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 (Prasad et al., 2020; Kita and Kita, 2012; Bourassa and Deschênes, 1995; Bourassa et al., 1995; Deschênes et al., 1994; Economo et al., 2018), so 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 thus challenged by this observation that all of these areas have motor outputs. Indeed, as suggested previously, the idea that evolution would produce cortical areas that have no fairly immediate motor effect seems unlikely. By this way of

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thinking, the current view that some cortical areas are "sensory" and others "motor" is misleading. Finally, Figure 10B offers a more plausible route for efference copies to be integrated into cortical processing.

The bottom line is that higher order thalamic nuclei play an important and still largely unappreciated role in corticocortical communication. Thus, the 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 different roles of the direct and transthalamic corticocortical pathways, their relationship to each other, and why one route involves a thalamic relay.

Outstanding Questions

I conclude this chapter with a list of questions, the answers to which are as yet unavailable but that I consider to be of special importance.

1. Why do we have a thalamus?
2. Among glutamatergic inputs in the thalamus, those of modulators greatly outnumber those of drivers, measured either by the number of afferent axons or the number of synaptic terminals, but what are the relative numbers for cortical circuitry?
3. How common is the pattern whereby two cortical areas are connected in parallel by both direct and transthalamic pathways, or are some connected only by one or the other? Does this pattern apply equally to feedforward and feedback transthalamic pathways?
4. What is different in the nature of the messages carried by direct versus transthalamic corticocortical pathways?
5. Why do the messages carried by transthalamic pathways pass through a thalamic relay?
6. Given that some layer 5 corticofugal axons that innervate subcortical motor centers have branches that innervate higher order relays and others lack these branches, what are the functional differences between these two types of layer 5 cells? Do they send different messages to the lower motor centers?
7. What is the significance of the pattern of branching axons that provide driver input to the thalamus and also innervate extrathalamic targets? (Remember that the suggestion that these relate to efference copies is merely a hypothesis.)
8. Why does attention reduce awareness of unattended features in the environment?
9. What is the significance of bursting in layer 5 corticofugal cells, and how is it controlled?

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