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## 4

# What Is the Function of the Thalamus?

*S. Murray Sherman*

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What is the function of the thalamus? This may seem an odd question to pose because we know that virtually all information reaching the cortex, and thus conscious perception, passes through the thalamus. Thus an easy answer to the question is that the thalamus serves as a relay for the flow of information to the cortex. But if thalamus is a simple relay, as has been suggested on the basis of receptive field studies, which indicate that the receptive fields of relay cells projecting to the cortex are little different from those of their sensory afferents (reviewed in Sherman and Guillery 1996, 2001), why do we even have one? That is, why does the retina not project directly to the cortex instead of relaying through the lateral geniculate nucleus? The same question could be posed for the primary somatosensory and auditory relays. While I cannot answer any of these posed questions in detail or with any confidence, I can suggest insights that indicate that the relay role of the thalamus is complex and dynamically changing in ways that influence the nature of information reaching the cortex. Furthermore, based on a new interpretation of a variety of data, I can suggest that the thalamus does not merely relay information up to the cortex but also serves a vital role in cortico-cortical communication. To arrive at these conclusions, I shall review some of the intrinsic properties of thalamic relay cells as well as some of the functional circuitry of the thalamus and thalamocortical interactions. Although most of our knowledge of thalamic function derives from study of the lateral geniculate nucleus, the main principles described below appear to apply to all of thalamus.

### The Low-Threshold $\text{Ca}^{2+}$ Spike

Like any respectable neuron, the thalamic relay cell is endowed with a rich variety of gated membrane conductances, mostly gated by voltage (for details, see

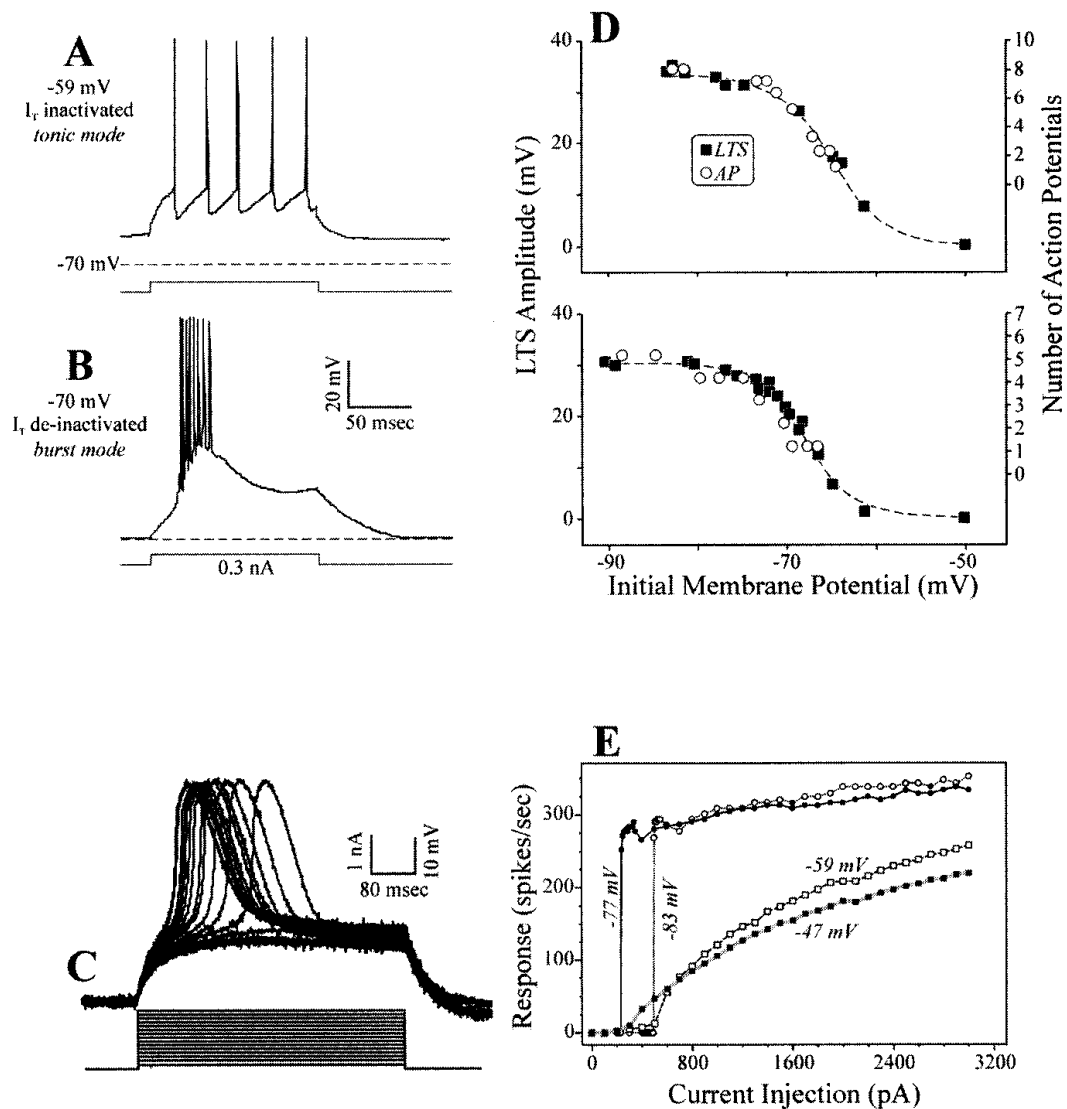


Figure 4-1. Voltage dependent properties of  $I_T$  and the low-threshold spike (LTS) shown in relay cells of the cat's lateral geniculate nucleus recorded intracellularly in an in vitro slice preparation. (A, B) Voltage dependency of the LTS. Responses are shown to the same depolarizing current pulse delivered intracellularly from two different initial holding potentials. When the cell is relatively depolarized (A),  $I_T$  is inactivated, and the cell responds to the suprathreshold stimulus with a stream of unitary action potentials. This is the tonic mode of firing. When the cell is sufficiently hyperpolarized to de-inactivate  $I_T$  (B), the current pulse activates an LTS with eight action potentials riding its crest. This is the burst mode of firing. (C) The all-or-none nature of LTSs activated from hyperpolarized cells in the presence of TTX. Current pulses were injected starting at 200 pA in amplitude and incremented in 10-pA steps. Smaller (subthreshold) pulses led to pure resistive-capacitive responses, but all larger (suprathreshold) pulses led to an LTS. Much like conventional action potentials, the LTSs are all the same amplitude regardless of the amplitude of suprathreshold depolarizing pulses, although there is latency variability for smaller suprathreshold pulses. Redrawn from Zhan et al. (1999). (D) Voltage dependency of amplitude of LTS and burst response. Examples for two cells are shown. The more hyperpolarized the cell before being activated (initial membrane potential), the larger the LTS and the more action potentials (AP) in the burst. The number of action potentials were measured first and then TTX was applied to isolate the LTS

McCormick and Huguenard 1992; Sherman and Guillery 1996, 2001). However, one that seems particularly important to relay functions and that has received considerable attention is the voltage-gated  $\text{Ca}^{2+}$  conductance underlying the *low-threshold spike*. This involves T-type  $\text{Ca}^{2+}$  channels that can exist in three states: *inactivated*, when the membrane has been relatively depolarized (beyond about  $-60$  to  $-65$  mV) for  $>50$ – $100$  msec<sup>1</sup>; *de-inactivated*, when the membrane has been relatively hyperpolarized (beyond about  $-60$  to  $-65$  mV) for  $>50$ – $100$  msec; and *activated*, which occurs when the channels are de-inactivated and then the membrane is sufficiently depolarized (e.g., via an EPSP). Activation of the channels opens them and leads to an inward current,  $I_T$ , carried by influx of  $\text{Ca}^{2+}$ , and this, in turn, leads to a largely all-or-none depolarization, which is the low-threshold spike. This spike is usually large enough to evoke a burst of conventional action potentials that ride its crest. This property of the low-threshold spike is ubiquitous for the thalamus: every relay cell of every thalamic nucleus of every mammalian species so far studied displays this property.

The properties of the T channel are qualitatively very similar to the more familiar  $\text{Na}^+$  channel associated with the action potential, since this  $\text{Na}^+$  channel has the same three states and is both voltage- and time-gated. However, there are three quantitative differences: (1) The  $\text{Ca}^{2+}$  channel operates in a regime more hyperpolarized by roughly 20 mV. (2) The time constants for inactivation and de-inactivation are almost two orders of magnitude slower for the  $\text{Ca}^{2+}$  channel. An interesting aspect of this is that once the membranes repolarize after an action potential, the  $\text{Na}^+$  channel takes roughly 1 msec to de-inactivate, and this determines the absolute refractory period. After the membranes repolarize following a low-threshold spike, the  $\text{Ca}^{2+}$  channel takes roughly 100 msec to de-inactivate, and thus the limit to the frequency of low threshold spiking is about 10 Hz (Mukherjee and Kaplan 1995; Smith et al. 2000). (3) The  $\text{Na}^+$  channels are found all along the axon, permitting propagation of the action potential down the axon to cortex, whereas the  $\text{Ca}^{2+}$  channels are found in appreciable numbers only in the soma and dendrites. Thus the only message reaching the cortex from relay cells is via action potentials. However, although the low-threshold spike does not propagate down the axon, it does propagate to the axon hillock and thus affects the firing of action potentials.

Figure 4-1 shows some of the features of the low-threshold spike from in vitro recording of cells of the cat's lateral geniculate nucleus. When a

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for measurement. Redrawn from Zhan, Cox, and Sherman (2000). (E) Input-output relationship for one 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 six action potentials of the response, since this cell usually exhibited six action potentials per burst in this experiment. The initial holding potentials are shown, and  $-47$  mV and  $-59$  mV reflects tonic mode, whereas  $-77$  mV and  $-83$  mV reflects burst mode. Redrawn from Zhan et al. (2000).

thalamic relay cell receives a depolarizing pulse (or EPSP), its response depends on its initial level of membrane polarization since this determines the state of  $I_T$ . If the cell is relatively depolarized with  $I_T$  inactivated (figure 4-1A), the response is a tonic stream of unitary action potentials; this represents the *tonic mode* of firing. If relatively hyperpolarized with  $I_T$  de-inactivated (figure 4-1B),  $I_T$  becomes activated, producing a low-threshold spike and burst of action potentials; this represents the *burst mode* of firing.

As noted, the low-threshold spike is evoked in an all-or-none manner, and this means that from any level of  $I_T$  de-inactivation, an evoked low-threshold spike is relatively invariant in size, meaning that larger suprathreshold depolarizations (or EPSPs) do not evoke larger low-threshold spikes (figure 4-1C). However, more initial hyperpolarization, on average, de-inactivates more  $Ca^{2+}$  channels (and thus more  $I_T$ ), producing a larger low-threshold spike (figure 4-1D). This, in turn, produces a larger burst of action potentials relayed to the cortex (figure 4-1D).

Two obvious differences between firing modes can be deduced so far. First, note that tonic firing persists as long as the stimulus applied is suprathreshold, while the burst evoked would be the same for a wide range of stimulus durations. This has to do partly with the long refractory period for the low-threshold spike noted above. Second, during tonic firing, one would expect a larger EPSP to produce a higher firing rate, and it does (figure 4-1E). However, a larger EPSP does not produce a larger low-threshold spike or burst of action potentials, so there is a very nonlinear relationship between input and output during burst firing (figure 4-1E).

## Role of Firing Modes in Thalamic Relays

Insights into the significance of these two relay modes come largely from studies of visual response properties of neurons in the lateral geniculate nucleus of lightly anesthetized and awake, behaving cats and monkeys. Studies of behaving animals make clear that both response modes are useful in relaying information to cortex, although in the fully alert animal, tonic firing is more common (McCarley, Benoit, and Barrionuevo 1983; Guido and Weyand 1995; Ramcharan, Gnadt, and Sherman 2000).<sup>2</sup> Both firing modes have also been described during thalamic recording in alert humans (Lenz et al. 1998; Radhakrishnan et al. 1999; Magnin, Morel, and Jeanmonod 2000). Studies of lightly anesthetized animals provide a more quantitative appreciation of the information relayed during both modes.

An analysis of raw information content relayed suggests that the amount is roughly the same during tonic and burst firing (Reinagel et al. 1999). However, the nature of the information differs (Sherman 1996), and that can

be appreciated from responses to sinusoidal gratings drifting through the receptive field (figure 4-2A, B, *lower sections*). Here, during intracellular recording in vivo, response mode can be controlled by current injection that biases the membrane polarization to more depolarized to create tonic firing or more hyperpolarized for burst firing. During tonic firing, the response profile is sinusoidal, mirroring the input (as predicted from figure 4-1E) and reflecting a high degree of linear summation. During burst firing to the same stimulus, the response profile deviates from a sinusoidal shape, reflecting nonlinear distortion. Figure 4-2C shows for a population of geniculate cells in the cat that there is a dramatic difference in linearity between firing modes: tonic firing always results in better linearity.

There seems to be an obvious advantage for improved linearity with tonic firing: if the cortex is to reconstruct the outside world accurately, it requires information relayed through the thalamus to have minimal nonlinear distortion. What, then, might be an offsetting advantage for burst firing? Again, the neural responses provide a clue. Note that spontaneous activity is considerably higher during tonic firing (figure 4-2A, B, *upper sections*). The higher spontaneous activity actually helps sustain linearity by preventing inhibitory visual stimuli from bottoming out the response, leading to a nonlinearity via rectification of the response. It is more interesting that we can think of the spontaneous activity as background noise against which the signal—the visual response—must be detected. A glance at figure 4-2A, B suggests that the signal-to-noise ratio is higher during burst firing, which, in turn, suggests better signal detectability during burst firing. Detectability was assessed by the construction of receiver operating characteristic curves (for details, see Green and Swets 1966; Swets 1973; Macmillan and Creelman 1991), and the result (figure 4-2D) shows a dramatic advantage for burst firing on this measure (Guido et al. 1995).

Other, more subtle differences between burst and tonic firing exist (see, e.g., Mukherjee and Kaplan 1995; Sherman 1996; Smith et al. 2000), and more dramatic ones may emerge, but at present the most salient differences for relay function are these differences in linearity and detectability: tonic firing is better for linearity, and burst firing is better for signal detection. A speculative hypothesis that incorporates these differences goes as follows. If a group of geniculate cells has receptive fields in an unattended part of visual field—unattended because the animal is attending elsewhere, is using another sensory modality, is drowsy, and so on—these relay cells might be held in burst mode so they can more efficiently signal the presence of a novel, potentially interesting or threatening stimulus. Once the stimulus is detected, the response mode may be shifted to tonic to enable a more accurate analysis of the newly detected stimulus. For this speculative hypothesis to be plausible, there must be efficient ways for the brain to control the response mode of thalamic relay cells according to behavioral state.

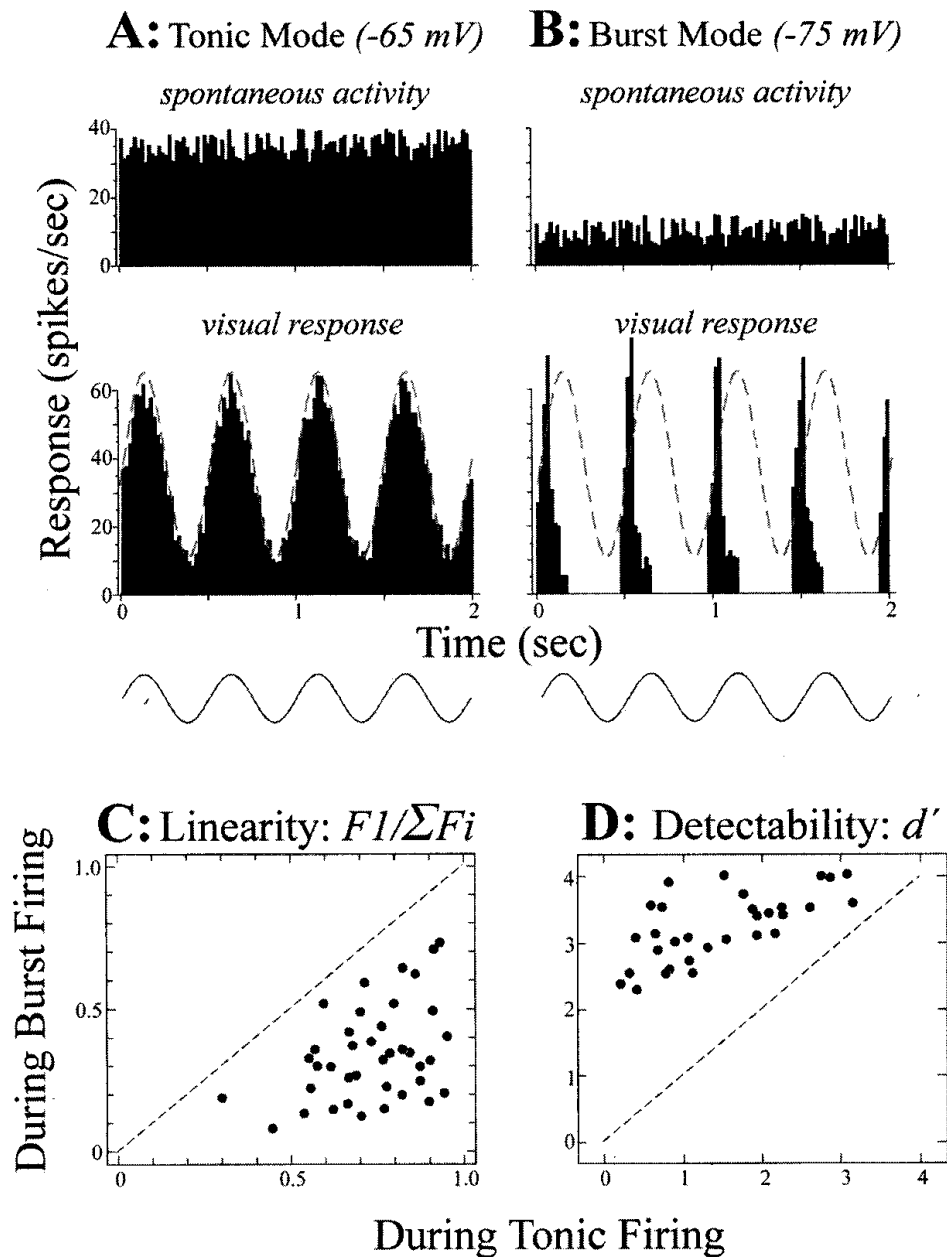


Figure 4-2. Tonic and burst responses of relay cells from the cat's lateral geniculate nucleus to visual stimulation during in vivo recording. (A, B) Average response histograms of responses of one cell to four cycles of drifting sinusoidal grating (bottom) and during spontaneous activity (top). The sinusoidal contrast changes resulting from the drifting grating are shown below the histograms. The cell was recorded intracellularly, and current injected through the recording electrode was used to bias membrane potential to more depolarized ( $-65$  mV), producing tonic firing (A), or more hyperpolarized ( $-75$  mV), producing burst firing (B). (C, D) Response linearity (C) and signal detectability (D) during tonic and burst firing (for details of how many of the data points were derived, see Guido, Lu, and Sherman 1992; Guido et al. 1995). Each point in the scatter plots reflects data from one relay cell of the cat's lateral geniculate nucleus recorded in vivo during visual stimulation, and the plots compare the response during tonic firing on the abscissa versus burst firing on the ordinate. The dashed

## Control of Response Mode

The obvious place to look for ways to control response mode is in thalamic circuitry, since synaptic inputs to relay cells can alter membrane potential and thereby control the state of  $I_T$ . These inputs affect relay cells by releasing neurotransmitters that act on the postsynaptic cell via various postsynaptic receptors. These receptors come in two basic classes: ionotropic and metabotropic. Examples of the former receptors in thalamic functioning are AMPA and NMDA (for glutamate),  $GABA_A$ , and nicotinic (for acetylcholine); examples of the latter receptors are metabotropic glutamate,  $GABA_B$ , and muscarinic (for acetylcholine). The differences between ionotropic and metabotropic receptors are critical in their ability to control response mode.

### *Ionotropic and Metabotropic Receptors*

Details of differences between these receptor types can be found elsewhere (Nicoll, Malenka, and Kauer 1990; Mott and Lewis 1994; Pin and Bockaert 1995; Pin and Duvoisin 1995; Recasens and Vignes 1995; Brown et al. 1997; Isaac et al. 1997), and only some are briefly outlined here. Transmission via ionotropic receptors is simpler and, as a result, much faster. The receptor itself is a complex, transmembrane protein that usually has an ion channel embedded within it. Binding of the neurotransmitter leads to a conformational change in the receptor that exposes the ion channel, thereby allowing flow of charged ions into or out of the cell. This leads to a postsynaptic potential (PSP) that is very fast, typically with a latency  $<1$  msec and a peak duration of 10–20 msec or less. Metabotropic receptors have a rather indirect link, usually via G-proteins and second messenger pathways, to ion channels. For these, binding of the neurotransmitter unleashes a cascade of biochemical reactions that eventually leads to opening or closing of an ion channel, which in the case of thalamic relay cells is usually a  $K^+$  channel. Opening the channel increases the flow of  $K^+$  out of the cell, producing an IPSP, while closing the channel does the opposite, producing an EPSP. But the PSPs are slow, typically with a latency  $\geq 10$  msec and a duration of hundreds of msec or longer.

As noted in the section “The Low-Threshold  $Ca^{2+}$  Spike” above, to change the firing mode of a thalamic relay cell requires sustaining for  $\geq \sim 100$  msec a

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line of slope 1 is also shown in each plot. Linearity (C) was determined from Fourier analysis, and a linearity index was created by dividing the first Fourier component, which is linear, by the sum of the higher order distortion components. Thus the higher the index, the more linear the response. Note that every single cell shows more linearity during tonic firing. For detectability (D),  $d'$  values were determined from receiver operating characteristic curve analysis (for details, see Green and Swets 1966; Swets 1973; Macmillan and Creelman 1991). Note that every single cell shows better detectability during burst firing.



hyperpolarization (to switch to burst mode) or depolarization (to switch to tonic mode). Fast PSPs via ionotropic receptors are ill suited to do this, although it is possible with temporal summation for activation of ionotropic receptors to manage the job. However, activation of metabotropic receptors seems ideally suited to control response mode because the PSPs evoked are sustained enough to do the job.

### Thalamic Circuitry and Receptor Types

Figure 4-3 summarizes for the lateral geniculate nucleus most of the inputs to relay cells and the receptor types they activate (reviewed in Sherman and

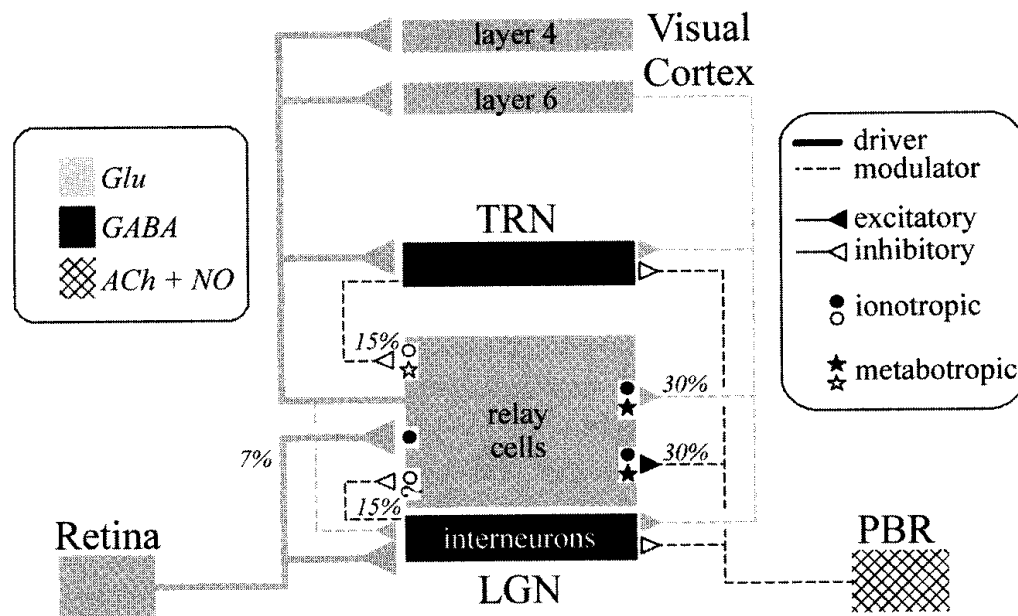


Figure 4-3. Circuitry of the lateral geniculate nucleus showing inputs to relay cells plus neurotransmitters and related receptors. Other thalamic nuclei seem to be organized along the same pattern (Sherman and Guillery 1996, 2001). The retinal input activates only ionotropic receptors, whereas all nonretinal inputs activate metabotropic receptors and often ionotropic receptors as well. The question mark related to interneuronal input indicates uncertainty whether metabotropic receptors are involved. The percentages indicate approximate contribution of each of the inputs to relay cells in terms of the number of actual synapses provided. Not shown for simplicity are other small modulatory inputs to geniculate relay cells; these include noradrenergic inputs from the parabrachial region, serotonergic inputs from the dorsal raphé nucleus, and histaminergic inputs from the tuberomammillary nucleus of the hypothalamus (for details, see Sherman and Guillery 1996, 2001). The relative number of synapses onto relay cells from various inputs is also shown. *Abbreviations:* ACh, acetylcholine; GABA,  $\gamma$ -aminobutyric acid; Glu, glutamate; LGN, lateral geniculate nucleus; NO, nitric oxide; PBR, parabrachial region of the brainstem; TRN, thalamic reticular nucleus.

Guillery 1996, 2001). Other thalamic nuclei have similar patterns of circuitry. What is striking about the pattern shown in figure 4-3 is that retinal input, which is the primary sensory input to be relayed to the cortex, activates only ionotropic receptors, whereas all of the nonretinal afferent pathways activate metabotropic receptors (and often ionotropic as well). The retinal input is glutamatergic, and the nonretinal inputs include a glutamatergic feedback input from layer six of the cortex, a cholinergic input from the brainstem parabrachial region, and a GABAergic input from intrinsic interneurons and cells of the adjacent thalamic reticular nucleus. Omitted for simplicity are much smaller inputs that also activate metabotropic receptors: a noradrenergic input, also from the parabrachial region, a serotonergic input from the dorsal raphé nucleus, and a histaminergic input from the tuberomamillary nucleus of the hypothalamus (reviewed in Sherman and Guillery 1996, 2001).

This pattern has several implications. The fact that retinal inputs activate only ionotropic receptors means that the EPSPs used in retinogeniculate transmission are relatively fast. Thus retinal input itself is less likely to change response mode, and this makes sense because the bulk of control should be the responsibility of pathways that reflect the dynamic needs of the system, not the primary sensory input to be relayed. Also, the slow EPSPs related to metabotropic receptors cannot reflect fast changes in the afferent input pattern. In fact, these slow PSPs act like a low pass temporal filter, filtering out fast input signals. Thus the association of only ionotropic receptors with retinal input helps preserve fast-changing temporal events in the signals relayed to the cortex, and this seems ideal for sensory transmission.

The concentration of metabotropic receptors with nonretinal inputs means that these pathways are well designed to control response mode. The direct inputs to relay cells from layer six of the cortex and from the parabrachial region are able to produce sustained EPSPs via activation of metabotropic receptors, and this should effectively switch firing mode from burst to tonic. Some evidence for this exists. Activation of metabotropic glutamate receptors from firing of corticogeniculate axons does indeed promote tonic firing (McCormick and von Krosigk 1992; Godwin, Vaughan, and Sherman 1996) in geniculate relay cells, as does activation of inputs from the parabrachial region (Lu, Guido, and Sherman 1993). The opposite—a switch from tonic to burst firing—is possible from activation of GABA<sub>B</sub> receptors, which can be achieved from reticular cells and possibly from interneurons. While experimental evidence for this has not yet been gathered, it seems a plausible scenario. Note that external control of firing mode by this scenario rests with cortical and brainstem input (see figure 4-3): directly, they depolarize relay cells to effect tonic firing; indirectly, via reticular (and possibly also interneuronal) input, they hyperpolarize to effect burst firing.

## Drivers and Modulators

Afferent inputs to thalamic relay cells are not all the same but can be divided into at least two functionally distinct groups: drivers and modulators (Sherman and Guillery 1998). Drivers are the inputs that convey the basic information to be relayed to the cortex. In the lateral geniculate nucleus, this is the retinal input, and in other primary sensory relay nuclei, drivers can also be clearly defined as the medial lemniscal afferents for the ventral posterior nucleus (the primary somatosensory relay) and the inferior collicular afferents for the ventral part of the medial geniculate nucleus (the primary auditory relay). Drivers can also be clearly recognized for some other thalamic relays, but in many, the identity of the drivers is not yet obvious. By definition, any afferents that are not drivers are modulators. Their job is to provide modulation of the thalamic relay. An example of modulation is the control of response mode as described in the previous paragraph. A more detailed description of the distinction between drivers and modulators can be found elsewhere (Sherman and Guillery 1998), but a brief summary of these differences is as follows (see figure 4-3; see also Sherman and Guillery 1996, 1998, 2001):

- The driver (retinal) afferents innervate relay cells and interneurons but fail to innervate the thalamic reticular nucleus, whereas the modulator (nonretinal) afferents innervate the thalamic reticular nucleus as well.
- Driver inputs activate only ionotropic receptors, whereas modulator inputs activate metabotropic receptors as well and sometimes do so exclusively.
- Driver axons exhibit a morphology known as type 2 (Guillery 1966), having thick axons with richly branched, flowery, dense terminal arbors. Most modulatory inputs have type-1 axons (Guillery 1966), which involve thin axons with few preterminal branches and terminals *en passant* or on short side branches.
- Driver synaptic terminals are larger than any others in the geniculate neuropil, and they contact proximal dendrites, often in glomeruli and exhibiting triadic arrangements with terminals from interneurons.
- Driver axons often (perhaps always, as is the case for retinal axons) branch to innervate extrathalamic structures; at least some modulatory afferents (i.e., from cortex and the thalamic reticular nucleus) innervate only thalamic structures; whether brainstem modulatory afferents branch to innervate extrathalamic targets is not presently known.

The numbers of synapses provided by drivers versus modulators is also interesting (see figure 4-3). In the lateral geniculate nucleus, the driver (retinal) input provides only 5 to 10 percent of synaptic input to relay cells, and limited evidence from other sensory thalamic relays also indicates that the driver inputs provide a small minority of synapses there as well. It has been argued elsewhere (Sherman and Guillery 1998, 2001) that this makes sense because

bringing the basic information to a thalamic nucleus does not require as much synaptic investment as would be required for fine modulation of the relay.

A further interesting speculation is that this idea of driver inputs to an area being small in number may not be limited to the thalamus. For example, it now seems clear that the main information is brought to layer-four cells in the visual cortex by geniculocortical axons (Reid and Alonso 1995, 1996; Ferster, Chung, and Wheat 1996; Chung and Ferster 1998), yet these provide only about 5 to 10 percent of the synaptic inputs to these cells (Ahmed et al. 1994; Latawiec, Martin, and Meskaneite 2000). Perhaps the similarity of these numbers with those of retinal inputs to relay cells is a coincidence, but maybe not, and perhaps it signifies a general property of drivers in the central nervous system. For example, an analysis of synaptic counts on spinal motoneurons indicates that Ia afferents, which constitute a major driver input, provide <5 percent of the synaptic terminals to these cells (reviewed on p. 462 of Henneman and Mendell 1981). It will be interesting to see how general beyond the sensory thalamic relays this finding is that driver inputs constitute a small minority of synapses.

An important point that is reiterated below is that in many areas of the brain there is a tendency to equate functional importance with the size of the input to an area. This, of course, completely ignores the fact that different inputs may be functionally quite different and thus cannot be compared anatomically. If that strategy were applied to the lateral geniculate nucleus, one would come to the silly conclusion that retinal input is of minor importance to a thalamic nucleus that relays brainstem parabrachial information to the cortex!

## First- and Higher-Order Relays

### *Layer-Six versus Layer-Five Corticothalamic Inputs*

Guillery (1995) first refocused attention on a long-known curiosity about thalamic relays: that while all seem to receive a generally reciprocal, modulatory feedback from layer six of the cortex, some in addition receive an input from layer five. These latter thalamic relays do not have an obvious subcortical driver input, and the suggestion has been offered that their driver inputs come instead from layer five of certain cortical areas (Guillery 1995; Sherman and Guillery 1998, 2001). Examples of nuclei that receive layer-five afferents are the pulvinar,<sup>3</sup> the posterior medial nucleus,<sup>4</sup> the magnocellular division of the medial geniculate nucleus (as opposed to the ventral division, which receives inferior collicular input), the medial dorsal nucleus, and others (for details, see Guillery 1995; Sherman and Guillery 1996, 2001). It is not clear if the layer-five innervation supplies the entirety of each of these nuclei or only certain as-yet-undefined segments, and there may be sparse layer-five input to certain primary

sensory nuclei like the ventral posterior nucleus. It is clear that the layer-five afferents are quite unlike layer-six afferents but bear a striking anatomical resemblance to driver afferents as described for the main sensory relays (compare with the driver/modulator bulleted list above; for details, see Sherman and Guillery 1996, 1998, 2001; Vidnyánszky et al. 1996):

- They innervate dorsal thalamic nuclei but fail to innervate the thalamic reticular nucleus with collateral branches even though they pass through this region *en route* to their dorsal thalamic target.
- Where studied, layer-five inputs activate only ionotropic receptors on relay cells, whereas layer-six inputs activate metabotropic receptors as well.
- Their axons are thick, with type-2 morphology and terminal fields, while layer-six afferents have type-1 morphology.
- Their synaptic terminals are quite large and seem to innervate proximal dendrites, often in glomeruli and exhibiting triadic arrangements with terminals from interneurons.
- Many, if not all, branch to innervate extrathalamic targets.

The above list matches point-for-point the earlier list that distinguishes drivers from modulators. It thus seems reasonable to regard these layer-five afferents as drivers in the same sense that we consider retinal afferents as the drivers for the lateral geniculate nucleus. If so, this may offer an important insight into the function of these relays with layer-five inputs, because no obvious subcortical driver inputs had been previously suggested.

### *Two Types of Thalamic Relay*

Thus some thalamic relays receive their driver input from subcortical sources, like the retina, brainstem, and so on, and relay this information to the cortex, whereas others receive their main driver input from the cortex itself and relay this information to another cortical area. Some relay nuclei, like perhaps pulvinar, may receive both subcortical and layer-five driver inputs, but unless individual relay cells receive both types—a genuine possibility, but one that is ignored here due to our ignorance on the subject—functionally, the subcortical and layer-five relays can be considered as distinct types. We can consider the former type of relay as *first order* because it represents a first pass of the relevant information into the cortex and the latter as *higher order*, because it represents a relay of information that has already reached cortex but from one cortical area to another (see figure 4-4 and Guillery 1995).

It is interesting that when thought of this way, each of the main sensory systems has both types of relay: for vision, the lateral geniculate nucleus is the first-order relay, and most of the pulvinar is the higher-order relay; for somesthesia, the ventral posterior nucleus is the first-order relay, and the medial portion of the posterior complex is the higher-order relay; and for audition, the ventral part of the medial geniculate nucleus is the first-order

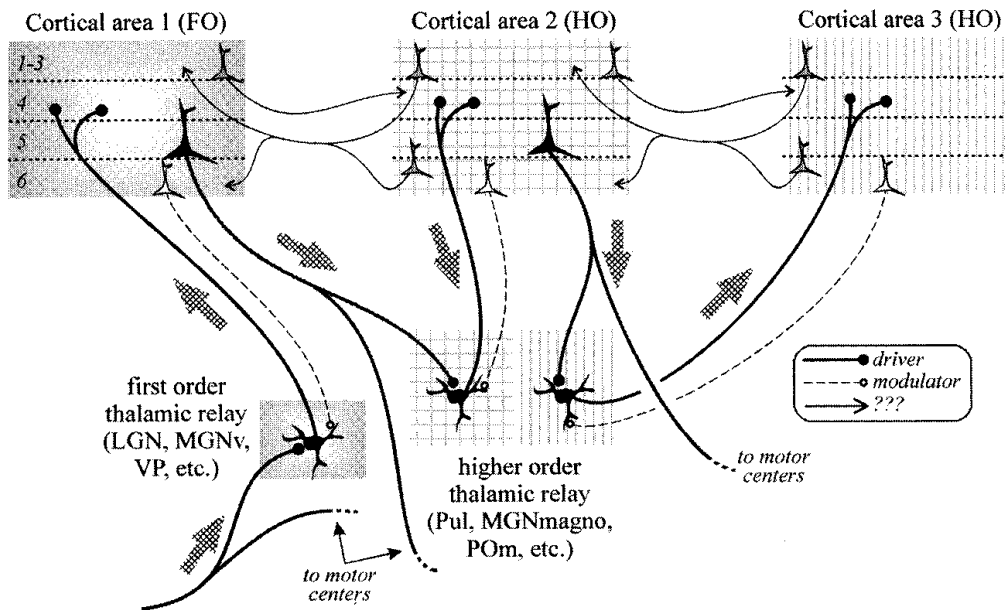


Figure 4-4. Schema of the hypothesis that corticocortical information flow involves a higher-order thalamic relay. The first-order relay (e.g., lateral geniculate nucleus) relays a driver (e.g., retinal) input to primary cortex (e.g., V1). From here, information is relayed among cortical areas via corticothalamocortical paths involving different regions of a higher-order thalamic nucleus (e.g., the pulvinar) routes. Thick, dark pathways represent the drivers, and thin, lighter pathways with dashed lines represent the modulators. The nature of direct corticocortical projections (thin solid lines) is ambiguous as to identity as driver or modulator. *Abbreviations:* FO, first order; HO, higher order; LGN, lateral geniculate nucleus; MGNmagno, magnocellular region of medial geniculate nucleus; MGNv, ventral region of medial geniculate nucleus; POm, posterior medial nucleus; Pul, pulvinar; VP, ventral posterior nucleus.

relay, and the magnocellular part is the higher-order relay. Olfactory information reaches the cortex in an unusual way that makes it difficult to fit into this duality, but much olfactory information is ultimately relayed to the cortex via the medial dorsal nucleus. It is interesting that much of the medial dorsal nucleus, a very large thalamic relay that innervates the frontal cortex, is a higher-order relay. How far this neat duality can be applied for other types of information relayed through the thalamus remains to be determined.

## Implications for Corticocortical Communication

The visual world in carnivores and primates is analyzed by many different areas of cortex (more than thirty in monkeys) in the occipital, parietal, and temporal lobes (for reviews, see Van Essen 1985; Felleman and Van Essen 1991; Van Essen, Anderson, and Felleman 1992). Attempts to understand how these areas communicate with one another in visual analysis has to date focused almost entirely on direct corticocortical connections, which are rich

and often reciprocal (see figure 2 of Van Essen, Anderson, and Felleman 1992 for details). Strategies exist to distinguish feedforward from feedback pathways among these connections (Felleman and Van Essen, 1991). The basic notion here, which is challenged later in this chapter, is that visual information enters the striate cortex from the lateral geniculate nucleus, and in a more or less hierarchical set of feedforward connections, the information is passed from the striate cortex to higher and higher areas, with many feedback connections, the function of which remains obscure. Note that, according to this view, once the information reaches the cortex from the lateral geniculate nucleus, it stays within the cortex, being routed effectively only amongst cortical areas. Among other drawbacks, this view of visual processing has little regard for the pulvinar, which is a much larger thalamic structure than is the lateral geniculate nucleus and which seems to innervate all of the extrastriate visual areas.

Apparently, the main and perhaps sole reason this view is so widely held is due to the very massive nature of direct corticocortical connections. Indeed, each cortical area receives the vast majority of its extrinsic afferents from other cortical areas and rather little from subcortical structures, like the thalamus. But this linking of functional importance of a pathway with its size is the very thinking that, as I suggested at the end of this section's chapter on drivers and modulators, would lead one to conclude that retinal input to the lateral geniculate nucleus is functionally of little consequence.

An alternative view of corticocortical communication is offered here to contrast with the traditional one. For cortical afferents, just as for those of the thalamus, it may be that drivers and modulators exist. The drivers carry the main information, and identifying them among afferents to a cortical area becomes supremely important. Perhaps the driver inputs are a small minority, as in the thalamus. Then a blind concentration on large pathways, which describes most direct corticocortical connections, may be misleading. That is, perhaps only a small minority of these direct pathways are drivers, with the rest being modulators.

The most extreme view, which I offer here for clarity, is that *none* of the direct corticocortical projections is a driver, and instead they are all modulators. The drivers, then, are the thalamocortical afferents. By this extreme version, the information route for corticocortical communication travels from layer five of one area down to a higher order thalamic relay (i.e., pulvinar for visual cortical communication) and then back up to the target cortical area (see figure 4-4). Just as retinal information passes through a thalamic relay before reaching the cortex, a more general rule may be that *any* new information coming into a cortical area, whether originating subcortically or in another cortical area, benefits from a thalamic relay.

A less extreme and perhaps more plausible hypothesis is that one important route for corticocortical communication via drivers involves a relay through higher-order thalamic nuclei, but that another route involves some of the direct

corticocortical connections, presumably a minority, the rest being modulatory. If so, there remains an important difference between corticocortical drivers and those involving corticothalamocortical routes. Information carried by the former stays strictly within the cortex, but that carried by the latter pathway also informs other parts of the subcortical central nervous system. Whatever the ultimate accuracy of this hypothesis, it does draw attention to the need to avoid treating all connections among cortical areas as functionally equivalent.

## Conclusions

We are far from a definitive answer to the question posed: What is the function of the thalamus? However, recent research offers several glimpses of partial answers. This is probably just the tip of the iceberg, meaning that as we learn more about thalamic relays, we are likely to see more and more key functions attributed to the thalamus. The suggestions here take two forms.

First, the complex cell and circuit properties of thalamic nuclei leave little doubt that the relay of information to the cortex is an active and mutable process. Clearly, these thalamic relays can affect the nature of information arriving in the cortex. How these different relay properties are controlled is a related issue of great importance. Specific suggestions have been offered here about how circuit properties control a voltage-dependent conductance,  $I_T$ , in relay cells to control responsiveness, and how this could affect the nature of information relayed to the cortex. However, this control of tonic and burst response modes is likely to be just one of many mechanisms by which thalamic relays can control the flow of information to cortex.

Second, not only do thalamic relays play an active role in relaying information to the cortex, they may also play a key role in corticocortical communication. The discovery that many thalamic regions seem to receive their driving input from layer five of cortex itself leads to the suggestion that much of corticocortical communication involves a route through the thalamus, with the same advantages of having a thalamic relay for this route as exists for relaying, say, retinal information to the cortex. As a corollary, the direct connections among cortical areas need to be reconsidered with regard to the nature of these pathways and the possibility that many, and perhaps all, are modulatory in nature. Thus the full impact of the thalamus may be much more than simply controlling the flow of information to the cortex: it may remain an active partner in all cortical computations.

### *Notes*

1. Actually, the state of the T channel is a complex function of voltage and time, so stronger polarizations take less time to affect the change in the channel's inactivation state.



2. We are dealing here only with the function of thalamic relays in the behaving animal. During sleep and in certain pathological conditions, relay cells tend to burst rhythmically at frequencies varying up to about 10 Hz, and large assemblies of these cells manage to synchronize their firing. This is very different from the bursting seen in lightly anesthetized and behaving animals, which is nonrhythmic (Steriade and McCarley 1990; Steriade, McCormick, and Sejnowski 1993; Ramcharan, Gnadt, and Sherman 2000).

3. For simplicity, the term *pulvinar* includes the lateral posterior nucleus in carnivores.

4. Terminology across species can often be confusing. The primate equivalent to the medial portion of the posterior complex in rodents and carnivores is the anterior or "oral" part of pulvinar. The nonprimate terminology is used here, and so the pulvinar (which includes what is sometimes called the lateral posterior nucleus) is a structure associated essentially only with vision.

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