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# The role of the thalamus in cortical function: not just a simple relay

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*Recent work on the visual thalamic relays provides two key properties reviewed here. First, ~95% of input to lateral geniculate relay cells is non-retinal and dynamically modulates the relay based on behavioral state, including attention. Part of this relates to control of a voltage-gated, low-threshold $Ca^{2+}$ conductance that controls the relay cell response mode (tonic or burst). Second, the lateral geniculate nucleus and pulvinar are examples of two relay types: the former is a first order relay, transmitting subcortical (retinal) information, while the latter is mostly a higher order relay, transmitting information from layer 5 of one cortical area to another. Higher order relays seem to be important to corticocortical communication, which challenges the dogma that such communication is based on direct cortico–cortical connections. Other examples of first order and higher order relays also exist. Interesting differences in functional circuitry between first and higher order thalamic relays are beginning to accumulate, which indicate extramodulatory functions for higher order relays. Thus, the thalamus provides a behaviorally relevant, dynamic control over the nature of information relayed, and also plays a key role in basic cortico–cortical communication.*

**Keywords:** Pulvinar, lateral geniculate nucleus, thalamocortical, corticothalamic, burst and tonic firing, first order thalamic nuclei, higher order thalamic nuclei

## INTRODUCTION

All information reaching the cerebral cortex is relayed by the thalamus and, thus, all cortical functions, including conscious thoughts, perceptions and voluntary movements, depend on information passed through the thalamus. The thalamus has long been seen as a simple, machine-like relay that faithfully passes information from subcortical pathways to the cortex, where the real processing was thought to begin. The role of a thalamic nucleus was defined in terms of the nature of the message passed (e.g. visual, auditory and somatosensory) rather than what the thalamic circuitry might contribute. In this older view, the only interesting roles played by the thalamus were related to sleep and certain pathological conditions, for example, epilepsy and pain. Here, I briefly and selectively review more recent findings that indicate a dynamic role for the thalamus in everyday behavior, leaving the relationships to sleep and pathological states to other authors (Steriade and Llinás, 1988; Steriade *et al.*, 1993; McCormick and Bal, 1997).

The neurons of the thalamus have complex functional properties that have an important role in how information is relayed to cortex. We need to understand how these properties in any given thalamic nucleus affect the transfer of information to cortex. There is significant evidence to indicate that, in general, there is a common pattern of functional properties for all thalamic relays (reviewed in Sherman and Guillery, 2006). However, there are also some differences between individual thalamic relays. We explore some of these differences here, looking particularly at two major distinguishable types of thalamic relay that have been classified as first order and higher order relays (Guillery, 1995; Guillery, 2003; Sherman and Guillery, 2004; Sherman and Guillery, 2006). The first order relays transmit information from ascending pathways to the cerebral cortex. They include the sensory pathways (auditory, visual, somatosensory and gustatory) and pathways from the mamillary bodies and cerebellum. The higher order relays transmit information about the motor outputs of one cortical area to another (higher) cortical area. This is information relayed by cortical layer 5 cells that have branches to thalamic nuclei. It is important to recognize that this is information that has already been processed in the cortex, either once for some relays, or more than once for others. Several recent studies have indicated that there might be structural and functional differences between the first order and higher order relays, and we first describe a generalized view that appears to apply to all thalamic relays, then consider differences between first and higher relays before considering the possible functional significance of these differences.

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## Circuit properties of thalamic relays

Before we consider features that might distinguish first order from higher order relays, it is necessary to consider the many common functional features throughout the thalamus. These have been studied in considerable detail, have been described previously (reviewed in Sherman and Guillery, 2006; Jones, 2006) and are summarized for a generalized thalamic nucleus for which the lateral geniculate nucleus serves as the model.

### COMMON CIRCUITRY CHARACTERISTICS OF THE THALAMUS

Fig. 1 schematically shows the main input to relay cells of the lateral geniculate nucleus. The input labeled 'driver' refers to

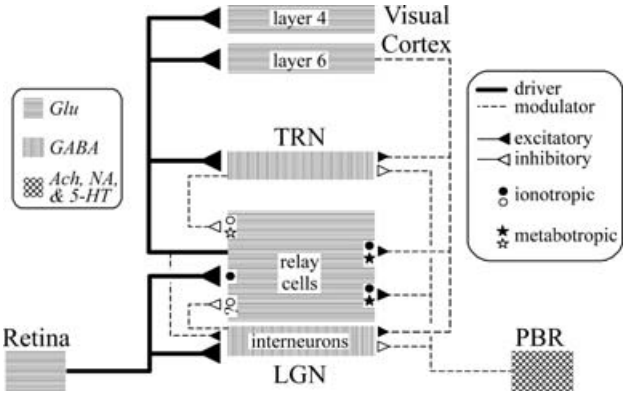


**Fig. 1. Inputs to relay cells of the lateral geniculate nucleus, showing transmitters and postsynaptic receptors (ionotropic and metabotropic).** *Abbreviations*: ACh, acetylcholine; GABA, γ-aminobutyric acid; Glu, glutamate; LGN, lateral geniculate nucleus; PBR, parabrachial region; TRN, thalamic reticular nucleus. Further details in text. Adapted from (Sherman, 2005).

the input carrying the information that is transferred to the cortex. For the lateral geniculate nucleus, this is the retinal input; for the somatosensory and auditory thalamic relays these are the lemniscal and inferior collicular inputs, respectively. These inputs are glutamatergic. Three other kinds of input are shown that are common to all other thalamic relays. These are local, inhibitory GABAergic inputs that derive from intrinsic interneurons (except in rats and mice) and from cells of the nearby thalamic reticular nucleus, a glutamatergic input from layer 6 of cortex that is mostly feedback, and ascending inputs from the brainstem. Most of the latter group come from the midbrain parabrachial region and are cholinergic, but, as indicated in Fig. 1, there are also noradrenergic inputs from the parabrachial region, scattered amongst the cholinergic inputs, and serotonergic inputs from the dorsal raphé nucleus.

An exception to this pattern for interneurons occurs in rats and mice (Arcelli *et al.*, 1997). In these species, interneurons occur in the lateral geniculate nucleus but are, essentially, missing from the rest of thalamus. However, this property is not common to all rodents because the thalamus of squirrels, guinea pigs and hamsters has interneurons throughout. The reason for this unusual distribution of interneurons in mice and rats and the functional significance are unknown. Nonetheless, this observation calls into question the widespread use of mice and rats to study the thalamus.

The inputs shown in Fig. 1 are common to thalamic nuclei for which sufficient information is available, although much of thalamus is still *terra incognita* with regard to some of these inputs. Other inputs are not shown in Fig. 1, because these are not generally found throughout thalamus. For example, the lateral geniculate nucleus receives histaminergic inputs from the tuberomamillary nucleus of the hypothalamus, GABAergic inputs from the nucleus of the optic tract and cholinergic inputs from the parabigeminal nucleus of the midbrain, and it is not clear if other thalamic nuclei receive similar or functionally comparable inputs.

### DRIVERS AND MODULATORS

Perhaps the most important point about any thalamic relay is the distinction between afferents that carry the message that is passed to cortex and the many other afferents, that carry information that is not directly passed on to cortex, but that modulate the way in which the message is transmitted. The afferents carrying the main information are the drivers, and the others are the modulators (reviewed in Sherman & Guillery, 1998, 2004, 2006). Fig. 1 shows some of the features that distinguish driver afferents from modulators. One difference is the postsynaptic receptors, which are ionotropic for the driver inputs but also include metabotropic receptors for the modulator inputs. Also, there are anatomical differences: the driver inputs have primarily thick axons that end in especially large terminals that make multiple synaptic contacts, whereas the non-retinal inputs involve thin axons with small terminals that make single synaptic contacts. In addition, driver inputs frequently innervate relay cells in complex synaptic arrangements known as 'triads', whereby the driver terminal contacts a GABAergic terminal from the dendrite of a GABAergic interneuron and both of these terminals contact the same relay cell dendrite (Ralston, 1971; Famiglietti and Peters, 1972; Hamos *et al.*, 1985; Sherman, 2004). Typically, these triads are embedded in more complex synaptic zones known as glomeruli. Normally, each synapse is surrounded closely by glial processes, but in a glomerulus the synapses have no individual glial ensheathment, but rather the entire complex is surrounded by glial processes. A glomerulus has a single driver terminal and many smaller terminals from either brainstem or interneuronal sources (Guillery, 1971; Sherman and Guillery, 2006). Table 1, which summarizes data on many thalamic nuclei from many laboratories (Wilson *et al.*, 1984; Hamos *et al.*, 1987; McCormick and Von Krosigk, 1992; Bourassa *et al.*, 1995; Bourassa and Deschênes, 1995; Salt and Eaton, 1996; Rockland, 1996; Godwin *et al.*, 1996; Rockland, 1998; Turner and Salt, 1998; Turner and Salt, 2000; Salt and Binns, 2001; Rockland and Knutson, 2001; Guillery and Sherman, 2002; Salt, 2002; Sherman and Guillery, 2004; Reichova and Sherman, 2004; Castro-Alamancos, 2004; Guillery, 2005; Sirota *et al.*, 2005; Sherman and Guillery, 2006) offers a more complete list of differences between the driver and modulator inputs (see also below).

The distinction between drivers and modulators is clear for the main sensory relays and, even though the retinal (also lemniscal or inferior collicular) inputs contribute $<10\%$ of the synaptic inputs to the relay cells (reviewed in Sherman and Guillery, 2006; Jones, 2006), we can recognize that functionally these are the drivers. Neither the inputs from cortical layer 6, nor those from the brainstem, which, together, represent $>50\%$ of the synapses in the relevant thalamic nuclei, carry basic information that is transmitted to cortex, and the same is true for the local GABAergic inputs. All of these modulate the relay of the driver input. For many thalamic nuclei the distinction between drivers and modulators is functionally less obvious than it is for the main sensory relay nuclei, but knowing the characteristic morphological and functional properties of drivers in several first order thalamic nuclei allows us to recognize the drivers in other, more mysterious, generally higher order relays like the mediodorsal nucleus, the laterodorsal nucleus and the pulvinar.

## Functional properties of relay neurons

Relay neurons, like neurons throughout the brain, exhibit several voltage-gated ionic conductances across their membranes. The best known are the $Na^+$ and $K^+$ conductances

**Table 1**. Drivers and Modulators

| **Subcortical driver (e.g., retinal) to FO** | **Layer 5 driver to HO** | **Modulator: layer 6** | **Modulator: PBR** | **Modulator: TRN & Int** |
|---|---|---|---|---|
| Determines relay cell receptive field | *Determines relay cell receptive field | Does not determine relay cell receptive field | Does not determine relay cell receptive field | Does not determine relay cell receptive field |
| Activates only ionotropic receptors | Activates only inonotropic receptors | Activates metabotropic receptors | Activates metabotropic receptors | TRN: Activates metabotropic receptors; Int: † |
| Large EPSPs | Large EPSPs | Small EPSPs | † | TRN: small IPSPs; Int: † |
| Large terminals on proximal dendrites | Large terminals on proximal dendrites | Small terminals on distal dendrites | Small terminals on proximal dendrites | Small terminals; TRN: distal; Int: proximal |
| Terminals often central component of triads | Terminals often central components of triads | Terminals do not end in triads | Terminals do not end in triads | TRN: not triadic; Int: not central in triads |
| Each terminal forms multiple contacts | Each terminal forms multiple contacts | Each terminal forms single contact | Each terminal forms single contact | Each terminal forms single contact |
| Little convergence onto target | *Little convergence onto target | Much convergence onto target | † | † |
| Very few synapses onto relay cells (~5%) | Very few synapses onto relay cells (~5%) | Many synapses onto relay cells (~30%) | Many synapses onto relay cells (~30%) | Many synapses onto relay cells (~30%) |
| Often thick axons | Often thick axons | Thin axons | Thin axons | Thin axons |
| Glutamatergic | Glutamatergic | Glutamatergic | Cholinergic | GABAergic |
| Synapses show paired-pulse depression (high p) | *Synapses show paired-pulse depression (low p) | Synapses show paired-pulse facilitation | † | † |
| Well localized, dense terminal arbors | Well localized, dense terminal arbors | Well localized, dense terminal arbors | Sparse terminal arbors | Well localized, dense terminal arbors |
| Branches innervate extrathalamic targets | Branches innervate extrathlamic targets | Subcortically known to innervate thalamus only | † | Subcortically known to innervate thalamus only |
| Innervates dorsal thalamus but not TRN | Innervates dorsal thalamus but not TRN | Innervates dorsal thalamus and TRN | Innervates dorsal thalamus and TRN | TRN: both; Int: dorsal thalamus only |

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

that underlie the conventional action potential, but other conductances exist for these and other ions (Sherman and Guillery, 2006). One that is particularly interesting is a voltage-gated conductance based on T-type $Ca^{2+}$ channels ('T' for 'transient') that are found in the membranes of the cell body and dendrites but not the axon (Jahnsen and Llinás, 1984a; Jahnsen and Llinás, 1984b). When these channels are open, $Ca^{2+}$ flows into the cell and this ion flow is known at $I_T$ (T current), which depolarizes the cell. It is found widely in cells throughout the brain, but the density of T channels in the membranes of the dendrites and cell bodies of thalamic relay cells make $I_T$ in these cells exceptional. That is, T channels here are so dense that $I_T$, once initiated, generally becomes self-generating, or autocatalytic, resulting in an all-or-none depolarization that propagates through the cell body and dendrites but not the axons: this is known as the low-threshold ($Ca^{2+}$) spike. So far, every relay cell of every thalamic nucleus in every animal studied shows this behavior and such behavior is occurs only rarely in a few other brainstem and cortical neurons (reviewed in Sherman and Guillery, 2006). For most other neurons in the brain, T channels are too sparse to generate an all-or-none spike. As detailed below, this behavior of T channels in thalamic relay cells is qualitatively the same as that of $Na^+$ channels underlying the action potential. Fig. 2 summarizes the detailed properties of the T channel (Jahnsen and Llinás, 1984a; Jahnsen and Llinás, 1984b; Smith *et al.*, 2000; Sherman, 2001; Sherman and Guillery, 2006). It has two voltage- (and time)-activated gates: an activation gate and an inactivation gate (Fig. 2B). Both channels must be open for $Ca^{2+}$ to flow into the cell in the sequence as follows: (1) at resting membrane potentials (ca. −70 mV; Fig. 2E), the activation gate is closed and the inactivation gate is open (Fig. 2A); (2) if the membrane is depolarized to a certain threshold (ca. −65 mV; Fig. 2E), the activation gate opens, leading to cell depolarization (Fig. 2B). This is the upswing of the low threshold spike in Fig. 2E; (3) After ∼100 msec of depolarization, the inactivation gate closes and a slower set of voltage-gated $K^+$ channels open (Fig. 2C); (4) the result of T-channel inactivation and outflow of $K^+$ ions is a repolarization of the cell (Fig. 2D), leading to closing of the activation gate; (1) after ∼100 msec of this hyperpolarization leading to repolarization, the inactivation gate opens and the T channel reverts to the original form in this sequence. Fig. 2E shows the voltage changes in the cell related to this sequence. To summarize, the activation gate responds very rapidly to voltage changes, opening with depolarization and closing with hyperpolarization within ∼1 msec. The inactivation gate is much slower, requiring ∼100 msec of depolarization to close and ∼100 msec of hyperpolarization to open. The 100 msec times indicated are approximate, because inactivation and de-activation are complex functions of voltage and time so that the more the cell is depolarized, the faster $I_T$ inactivates, and the more the cell is hyperpolarized, the faster $I_T$ de-inactivates (Zhan *et al.*, 1999).

## TONIC AND BURST FIRING MODES

The significance of the T-channel properties of relay cells is that their activation state determines which of two very different response modes, *tonic* or *burst*, characterizes the

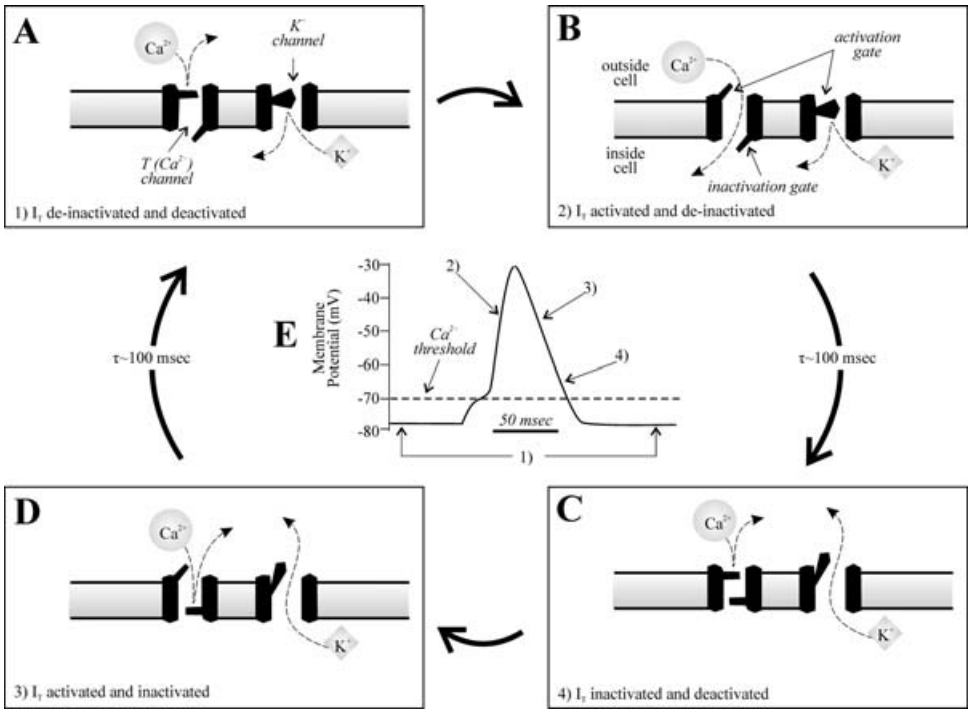


**Fig. 2. States in voltage dependency of T channel and associated $K^+$ channel(s).** (A-D) The sequence of events is shown clockwise from A. (E) Membrane voltage changes. (A) At relatively hyperpolarized resting membrane potential (∼−70 mV), the activation gate of the T channel is closed, but because the inactivation gate is open, the T channel is deactivated and de-inactivated. The $K^+$ channel is also deactivated. (B) Sufficient depolarization opens the activation gate of the T channel, allowing $Ca^{2+}$ to enter and depolarize the cell. This provides the upswing of the low threshold spike. (C) Depolarization for ∼100 msec or more closes the inactivation gate of the T channel and the $K^+$ channel opens. These actions repolarize the cell. (D) Although the initial resting potential is reached, the T channel remains inactivated, because it takes ∼100 msec of hyperpolarization to de-inactivate it; it also takes some time for the various $K^+$ channels to close. (E) Membrane voltage changes showing low threshold spike. Adapted from (Sherman and Guillery, 2006).

response of the relay cell to its driver input (Sherman, 2001; Sherman and Guillery, 2004; Sherman and Guillery, 2006). Fig. 3 shows some features of these response modes. If the relay cell has been relatively depolarized for >100 msec (as in Fig. 3A at −59 mV), IT is inactivated and has no role in the response. Thus, a depolarizing pulse injected into the cell (or a suitably large EPSP) evokes a steady stream of unitary action potentials for as long as the cell membranes are depolarized beyond firing threshold and there is no IT evoked. This is tonic firing. In contrast, if the same cell is sufficiently hyperpolarized for >100 msec (as in Fig. 3B at −70 mV), IT is deinactivated and primed for action. Now the same depolarizing pulse activates IT and a low-threshold spike that is sufficiently large to evoke a burst of several action potentials. This is burst firing. The important point is that the same depolarization (or EPSP) evokes two different signals sent to cortex (represented by the patterns of action potentials that flow up the thalamocortical axons) based on firing mode. This, in turn, reflects the recent voltage history of the cell, because the voltage history determines the inactivation state of IT. T channels are not present to any extent in axons, so only action potentials reach cortex and any actions of IT in the relay cell are transmitted to cortex indirectly through its effects on action potential patterns.

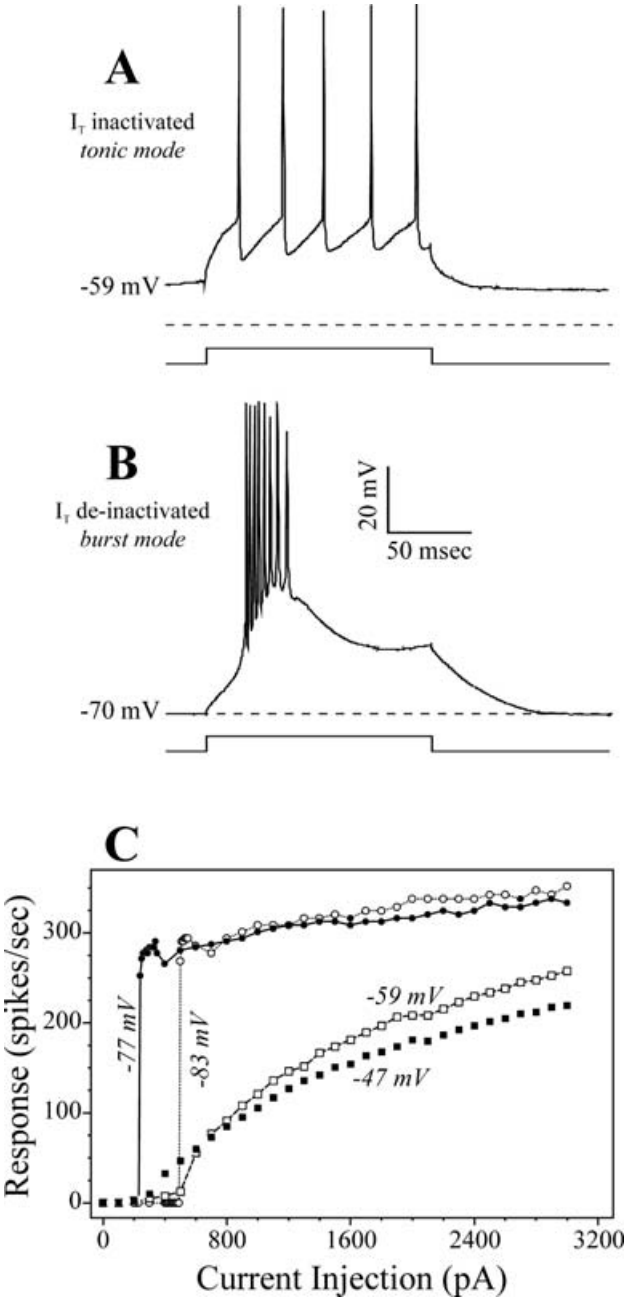


**Fig. 3. Properties of IT and the low threshold spike.** All examples are from relay cells of the cat lateral geniculate nucleus recorded intracellularly in an *in vitro* slice preparation. (A,B) Voltage dependency of the low threshold spike. Responses are shown to the same depolarizing current pulse delivered intracellularly from two different initial holding potentials. Relative depolarization (A) inactivates IT and the cell responds with a stream of unitary action potentials. This is tonic mode. Relative hyperpolarization de-inactivates IT and the cell responds with a low threshold spike and eight action potentials at its crest. This is burst mode. (C) Input–output relationship for another cell, showing relationship between the amplitude of the depolarizing current pulse and the firing frequency of the cell for the first six action potentials evoked. The initial holding potentials are shown. −47 mV and −59 mV reflects tonic mode, whereas −77 mV and −83 mV reflects burst mode. Adapted from (Sherman and Guillery, 2006).

The different patterns of firing associated with tonic and burst firing have important consequences for thalamic relay functions. One consequence is a relationship between the input (or EPSP) and the generation of action potentials. In tonic mode, when IT is absent, action potentials are evoked directly from the input depolarization (or EPSP). Therefore, the larger the depolarization, the more action potentials evoked. Thus, there is a relatively direct, linear relationship between input and output during tonic firing (Fig. 3C). However, with burst firing, the input depolarization (or EPSP) does not evoke action potentials directly, but rather it evokes the low threshold spike, which, in turn, evokes action potentials. Because the low threshold spike is all-or-none, it does not get larger with larger input depolarizations and so the input–output relationship during burst firing is non-linear, characterized mostly by a step function (Fig. 3C). This difference is also seen, for example, in responses of neurons of the lateral geniculate nucleus to visual stimuli: these responses show much more non-linear distortion during burst firing than during tonic firing in a manner that is consistent with Fig. 3C (Sherman, 2001; Sherman and Guillery, 2004; Sherman and Guillery, 2006).

Burst firing typically occurs against a much lower rate of background or spontaneous firing than does tonic firing, and, since spontaneous activity can be considered as noise against which a signal delivered by the driver input must be detected, this leads to a much higher signal-to-noise ratio and thus higher signal detectability during burst firing (Guido *et al.*, 1995). Another interesting issue about the different firing patterns derives from the temporal requirements of burst firing. A burst requires a low-threshold spike, which, in turn, requires activation of IT; this can only happen if IT is first de-inactivated, which takes ~100 msec or more of continuous hyperpolarization. This last requirement means that a burst only occurs after the cell has been silent for ≥100 msec. During tonic firing, the cell typically fires irregularly in a roughly Poisson pattern at rates averaging 20–50 or more spikes $sec^{-1}$, meaning that silent periods tend to be much shorter. This is important because the thalamocortical synapse shows the property of paired-pulse depression (Castro-Alamancos and Connors, 1997; Gil *et al.*, 1999; Chung *et al.*, 2002; Beierlein and Connors, 2002), so for ~50–100 msec after an EPSP is evoked at a synapse, the next EPSP is smaller; EPSPs spaced further apart than this

show no depression. Thus, burst firing, with its requisite silent period before the burst, activates thalamocortical synapses that are completely relieved of depression, whereas tonic firing typically involves a depressed synapse. The consequence of this is that bursts provide a much more powerful activation of cortical targets than does tonic firing, which has been shown empirically (Swadlow and Gusev, 2001; Swadlow *et al.*, 2002).

From the above observations, the following hypothesis has been developed (Sherman, 1996; Sherman, 2001; Sherman and Guillery, 2004; Sherman and Guillery, 2006). One important property of tonic firing is the relatively linear relay of information that is sent to cortex. If the cortex is to reconstruct faithfully the information relayed through thalamus, this linear relationship is a significant advantage and the sort of non-linear distortions associated with burst firing would be limiting. The advantage of burst firing is that it represents a better signal-to-noise ratio in its firing pattern and also activates the cortex much more strongly, so that the signal is detectable more readily by the cortex.

These advantages indicate that burst firing is more suited to a thalamocortical pathway representing information that is not being strongly attended to, such as occurs during either low overall attentive states or in situations in which other information streams are being selectively attended (e.g. visual information at the expense of auditory, or one part of the visual field at the expense of others). In such cases, the burst would represent a response to new information to be relayed (e.g. a novel visual stimulus for a geniculate relay cell) and would serve as a 'wake-up call' to the cortex that something has changed in the outside environment. The response mode of the thalamic relay cell could then be switched to tonic so that the new information is analyzed more faithfully.

We emphasize that the above idea is a hypothesis for which there is only indirect evidence. Generally, burst firing in alert animals is relatively rare, but it does increase as the animal becomes drowsy (Ramcharan *et al.*, 2000; Edeline, 2003; Massaux and Edeline, 2003; Bezdudnaya *et al.*, 2006), which is in agreement with the above hypothesis. Also, there is some evidence from the visual system that geniculate relay cells often respond to a repeating stimulus (such as a flashing spot) with a burst to the first cycle (the novel part of the stimulus) and then switches to tonic firing for the remaining stimulus cycles (Weyand *et al.*, 2001). There are also other hypotheses that suggest that burst firing is not a significant event during the waking state and is mainly associated with slow-wave sleep (Llinas and Steriade, 2006). Clearly, more research is needed concerning burst firing and the relay of information through the thalamus.

### CONTROL OF RING MODE BY THALAMIC CIRCUITRY

For the above hypothesis to make sense, there must exist efficient mechanisms to switch the firing mode of relay cells between burst and tonic. The functional circuitry outlined in Fig. 1 does just this. Recall that inactivation of $I_T$ produces tonic firing and de-inactivation produces burst firing. Also recall that to change the inactivation state of $I_T$ requires a sufficient hyperpolarization or depolarization that is sustained for $\geq$100 msec. We need to ask: which inputs to relay cells are likely to produce such sustained changes in membrane potential? The key here is the nature of postsynaptic receptors. Ionotropic receptors include AMPA glutamate receptors, nicotinic acetylcholine receptors and the $GABA_A$ receptor, whereas metabotropic receptors include various metabotropic glutamate receptors, various muscarinic acetylcholine receptors and the $GABA_B$ receptor. Ionotropic and metabotropic receptors differ in many ways (Nicoll *et al.*, 1990; Mott and Lewis, 1994; Recasens and Vignes, 1995; Pin and Duvoisin, 1995; Conn and Pin, 1997; Brown *et al.*, 1997), but a crucial one is the duration of their related postsynaptic potentials. Ionotropic postsynaptic potentials generally last 10 msec or a few 10 s of msec, whereas those related to metabotropic receptors last hundreds of msec to several sec. This means that a fast excitatory postsynaptic potential (i.e. from an ionotropic receptor) or an action potential, is too short in duration to inactivate $I_T$ sufficiently to switch firing from burst to tonic. Likewise, ionotropic inhibitory postsynaptic potentials are too brief to de-inactivate much $I_T$ and, thus, are not effective in switching firing from tonic to burst. Metabotropic receptors provide the answer: activation of either metabotropic glutamate receptors from cortical inputs or muscarinic receptors from brainstem inputs produces sustained, excitatory, postsynaptic potentials that effectively switch firing from burst to tonic, and activation of $GABA_B$ receptors by GABAergic inputs does the opposite (reviewed in Sherman and Guillery, 2004; Sherman and Guillery, 2006). Note that only the modulator (not the driver) inputs are associated with metabotropic receptors and, thus, the modulators have the main role in controlling the response mode of the relay cells.

The absence of metabotropic receptors associated with driver inputs is also important from another perspective. This is that, for fairly high firing rates in a driver afferent, each action potential evokes one excitatory postsynaptic potential, because the excitatory postsynaptic potentials associated with ionotropic receptors are brief. By contrast, with the longer responses associated with metabotropic receptors, the excitatory postsynaptic potentials would merge through temporal summation and the one-to-one relationship would be lost. Another way of putting this is that the long responses associated with metabotropic receptors act as low-pass temporal filters with the result that action-potential codes that are associated with higher frequency firing in the afferent would be compromised in the thalamic relay. So the fact that drivers seem to activate only ionotropic receptors means that more information is faithfully relayed to cortex.

## First and higher order thalamic relays

### THE CASE FOR FIRST AND HIGHER ORDER THALAMIC RELAYS

As noted above, one key to understanding the nature of the information that any one thalamic relay passes to cortex is to identify its driver input. That is, knowledge of the relevant pathways demonstrates that the lateral geniculate nucleus relays visual information to the cortex and that the medial geniculate nucleus transmits auditory information. We know the drivers come from the retina and the inferior colliculus. However, until recently, driver inputs were not known for much of the thalamus. By using Table 1 as a guide define driver inputs for some of those previously mysterious thalamic relays, it becomes clear that there are really two different types of thalamic relay. This is illustrated in Fig. 4. One type, called first order, receives its driving input

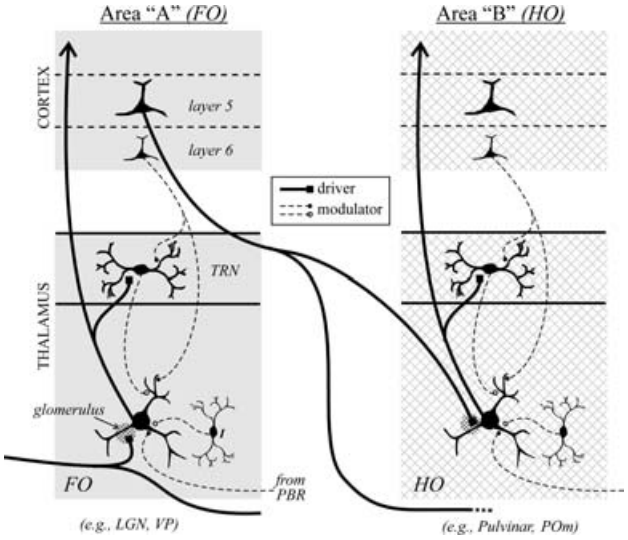


**Fig. 4. Schematic of the distinction between first order and higher order relays.** Left: a first order thalamic relay represents the first relay of subcortical information of a particular type (e.g. vision) to either a first order or primary cortical area. Right: a higher order relay relays information from layer 5 of one cortical area to another cortical area; this can be between a first order and higher order cortical area (as shown) or between two higher order cortical areas (not shown). The difference is the driver input, which is subcortical (left) for a first order relay and from layer 5 of cortex (right) for a higher order relay. Another feature of the driver inputs is a thick axon with a large terminal that innervates a proximal dendritic site, often in complex synaptic zones called glomeruli, and many or all of these driver axons branch to innervate extrathalamic, subcortical sites. See text for further details. Abbreviations: FO, first order; HO, higher order; I, interneuron; LGN, lateral geniculate nucleus; PBR, parabrachial region; POm, posterior medial nucleus; TRN, thalamic reticular nucleus; VP, ventral posterior nucleus. Adapted from (Sherman, 2005).

from a subcortical source (e.g. retinal for the lateral geniculate nucleus); the other, called higher order, receives its driving input from layer 5 of a cortical area. Note that modulatory inputs are organized in a generally similar fashion for both types of relay, although one of the main aims of this essay, addressed below, is to identify features that differ in first and higher order relays. Note also that this implies that all thalamic relays receive a layer 6 cortical input, which is modulatory and mostly feedback. In addition, the higher order relays receive a layer 5 cortical input that is not feedback and, we presume, is always feedforward, although the feedforward feature has been demonstrated in only a few examples (Bender, 1983; Diamond *et al.*, 1992; Van Horn and Sherman, 2004). That is, Fig. 4 shows that the higher order relays appear to relay information about the output of one cortical area to another, higher cortical area.

The labels in Fig. 4 show the relationship between primary and secondary cortical areas (e.g. V1 to V2). However, it is important to recognize that higher order thalamic relays such as the pulvinar receive from many different cortical areas and can also serve to link the outputs of one higher order cortical area to another, even higher, cortical area.

The evidence for higher order thalamic relays being organized as shown in Fig. 4, is convincing for some parts of the thalamus but tentative for others. This is summarized in Table 1 (reviewed in Sherman and Guillery, 2006). Fig. 5 shows the division of the thalamus into first order and higher order relays. Comparing the volumes of tissue involved, it is clear that most of the thalamus serves as higher order relays. For example, the pulvinar, a higher order visual relay, is much larger than the lateral geniculate nucleus, the first order visual relay.

One complicating factor is that many, perhaps all, of the nuclei associated with higher order relays might also contain first order circuits. For example, the pulvinar seems mostly higher order, with layer 5 cortical inputs innervating much of it, but a part of the pulvinar receives inputs from the superior colliculus and pretectum. There is evidence from cats (Kelly *et al.*, 2003) that at least some of these inputs are drivers. Likewise, the posterior medial nucleus, which contains higher order circuits for somesthesis also receives spinothalamic input that, if driver in nature, would represent first order circuitry. This is why I prefer the term 'thalamic relay' to 'thalamic nucleus', because many of the nuclei associated with higher order relays might be mixed with first order circuitry. The primary sensory thalamic nuclei appear to be pure, first order relays. However, more information is needed about the possible mixture of first and higher order circuits in many other thalamic nuclei.

Nonetheless, the important conclusion is clear: higher order relays represent a cortico–thalamo–cortical route for information transfer.

### BRANCHING OF AXONS OF DRIVER INPUTS

Fig. 4 also illustrates an important feature of most driver inputs, which is that they innervate the thalamus via branching axons, with one branch heading past thalamus to innervate various other brainstem structures. Detailed evidence for this can be found elsewhere (reviewed in Guillery and Sherman, 2002; Guillery, 2003; Guillery, 2005; Sherman and Guillery, 2006). This is true for both first order and higher order driver inputs. For example, many, probably all, retinogeniculate axons branch to innervate midbrain targets and many, perhaps all, layer 5 axons that innervate higher order thalamic relays also innervate various brainstem and, sometimes, spinal cord targets.

What is particularly interesting about these extrathalamic branches is that they innervate motor nuclei. For example, retinogeniculate axons also innervate midbrain structures involved in oculomotor functions and pupillary control, and the layer 5 equivalents also innervate motor structures in the brainstem and spinal cord. Thus, the axons that serve as drivers for the thalamic relays send information to the cortex about instructions that are being passed to motor centers for ongoing motor actions.

The obvious question that arises is: if these higher order thalamic relays represent a cortico–thalamo–cortical information route, what of the rich, direct connectivity between cortical areas? There are at least two main possible answers, and more data are needed to know which is correct. First and the most extreme possibility, is that all direct corticocortical connections are modulatory, with the cortico–thalamo–cortical pathways representing the only transfer of information between cortical areas. If true, this means that any time new information reaches a cortical area, whether originating in a subcortical site or another cortical area, it must be relayed by thalamus. The second possibility is that both direct corticocortical and indirect cortico-thalamo-cortical routes are used for information transfer in parallel. If, as suggested above, the cortico–thalamo–cortical routes are used to notify a higher cortical area about a motor command, this makes sense in the

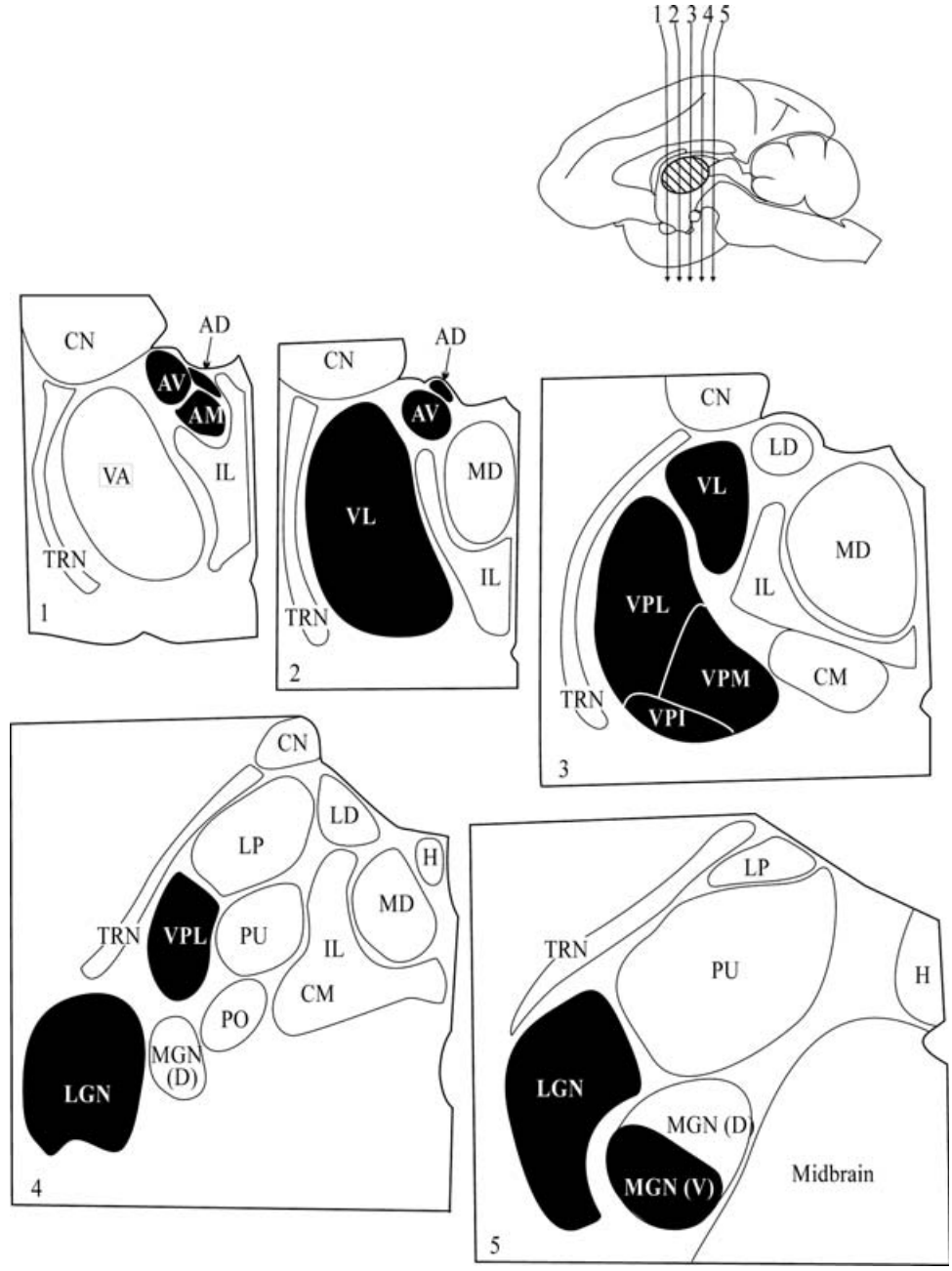


**Fig. 5. Major thalamic nuclei in primates.** First order nuclei are filled and higher order nuclei are open. Numbers in the bottom left of the coronal sections correspond to positions in the antero–posterior drawing (top). Abbreviations: AD, anterodorsal nucleus; AM, anteromedial nucleus, AV, anteroventral nucleus; CM, centermedian nucleus; CN, caudate nucleus (not a part of the thalamus); H, habenular nucleus; IL, intralaminar (and midline) nuclei; LD, lateral dorsal nucleus; LGN, lateral geniculate nucleus; LP, lateral posterior nucleus; MGN, medial geniculate nucleus; PO, posterior nucleus; PU pulvinar; TRN, thalamic reticular nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VPI, VPL, VPM, are the inferior, the lateral and the medial parts of the ventral posterior nucleus or nuclear group. Adapted from (Sherman and Guillery, 2006).

following way: direct corticocortical pathways are used for basic information transfer, whereas the cortico–thalamo–cortical route adds information about movements of key body parts. In vision, for example, this would offer a means by which cortex could track both environmental changes and eye movements so that the individual can distinguish between movements of visual targets and the eyes. Even if this second possibility proves correct, it does not mean that all corticocortical pathways are drivers: it is plausible that many or most are modulators. Therefore, to make sense out of the myriad corticocortical pathways, it is necessary to determine the function of each.

## DIFFERENCES BETWEEN FIRST AND HIGHER ORDER RELAYS

There is scattered evidence, based on observations from a limited subset of first and higher order thalamic relays, for consistent differences in functional organization between these relay types. To date, the evidence is too sparse

to establish such differences convincingly, but a pattern is indicated that justifies further studies of these putative differences.

*Relative Number of Driver Synapses*
In a quantitative electron microscopic study of the lateral geniculate nucleus (a first order relay) and pulvinar (a higher order relay) in the cat, Wang *et al.* (Wang *et al.*, 2002) showed that the ratio of driver to modulator synapses was much higher in the first order relay. This has now been extended to the first and higher order thalamic relays of the somatosensory and auditory systems (Van Horn and Sherman, 2007). It remains to be seen if this is true of all first and higher order relays. If it it, it indicates that higher order relays are under relatively more modulatory control. A key question concerns the relative number of driver synapses because, even with limited data, it is not clear if this reflects more modulatory synapses and/or fewer driver synapses onto higher order relay cells.

*Brainstem Modulatory Inputs*
As noted above, thalamic relay cells are under the modulatory influence of various brainstem inputs. The specific inputs vary somewhat among thalamic nuclei, but there is growing evidence that certain types of brainstem sources preferentially target higher order relays. For example, evidence from rats indicates that GABAergic inputs from the zona incerta and anterior pretectal nucleus target higher order relays with little or no innervation of first order relays (Barthó *et al.*, 2002; Frère *et al.*, 2004). Likewise, a recent study in monkeys indicates that dopaminergic axons, from a presently unknown source, relatively selectively target higher order relays (Sanchez-Gonzalez *et al.*, 2005). More data are needed to determine if these isolated examples from two species represent a general pattern in mammals. Nonetheless, it might be that these extra sources of modulatory input to higher order relays are related to the observation that the ratio of driver to modulator synapses is lower in these relays.

A further curious difference involves the effect of cholinergic modulators on relay cells based on data from rodents and carnivores. Effectively, all relay cells in first order relays and most in higher order relays are depolarized by acetylcholine acting chiefly via muscarinic M1 receptors. However, a significant subset (~25–33%) of relay cells in higher order relays are hyperpolarized by acetylcholine acting, perhaps, via M2 receptors (Mooney *et al.*, 2004; Varela and Sherman, 2004). Again, this is very preliminary, but it raises the possibility that transmitter actions other than those associated with acetylcholine differ between first and higher order relays.

*Firing Mode*
From the above, it appears that higher order relays cells are more likely to be relatively hyperpolarized, both because they receive GABAergic inputs that are not destined for first order relays, and because many higher order relays cells are hyperpolarized by cholinergic inputs. More hyperpolarization means more de-inactivated $I_T$ and, thus, more burst firing. A recent study of behaving monkeys supports this, namely, during spontaneous activity, there is considerably more burst firing among higher order than first order relay cells, although only several examples of each type of relay were studied (Ramcharan *et al.*, 2004).

The significance of this is unclear and, as is the case with other perceived differences between first and higher order relays, more data are needed to confirm this point. More thalamic relays in more species must be studied, and it will be interesting to determine if the extra higher order bursting is seen generally for most cells, perhaps reflecting extra GABAergic inputs, or if it is seen mainly in the subset of these cells that are hyperpolarized by cholinergic input. Nonetheless, this does raise some interesting, if speculative, points. If, as suggested, bursting represents a sort of wake-up call to signal that a new stream of information is being relayed, this indicates that such signaling is more important to higher order relays and, thus, to communication between cortical areas via that thalamus.

One reason for the extra bursting in higher order relays is the possibility that higher order cortical areas receive inputs from multiple higher order thalamic relays, whereas this is not the case for typical first order relays. Thus, a first order cortical area, like primary visual cortex, receives effectively all of its thalamic information via a single thalamic relay, the lateral geniculate nucleus. A major issue for the information stream is whether a geniculate relay cell is responding to visual stimuli. We know little about the detailed organization of higher order relays, but if these involve inputs to one cortical area from multiple thalamic relays, then it might be particularly important to signal when a particular thalamic relay begins to send a stream of new information, and this might be the explanation for the extra bursting. Indeed, this might be accomplished by a subset of relay cells that are always in burst mode because of hyperpolarizing cholinergic input.

*Development*
There is some evidence that higher order thalamocortical pathways develop later and are more plastic than are first order pathways (Feig, 2004; Feig, 2005; Sherman and Guillery, 2006). There are two lines of evidence to support this. First, evidence from humans indicates that myelin formation occurs later in higher order cortical areas (Flechsig, 1920; Paus *et al.*, 2001; Gogtay *et al.*, 2002; Gogtay *et al.*, 2004) Second, GAP-43, which is associated with growth and neuronal plasticity, is more prominent in higher order circuits (Feig, 2004; Feig, 2005).

## CONCLUSIONS

Several conclusions can be made about the functioning of the thalamus during normal waking behavior.

### Dynamic nature of thalamic relays

The importance of the thalamus is manifest because of its position as the final bottleneck for all information reaching cortex. In this context, the thalamus is no longer considered a passive relay. Instead, the amount and the nature of the information relayed varies with several factors related to behavioral state. For instance, the burst/tonic transition might be related to attention and overall vigilance, with burst firing associated more with less vigilant states. Like so much of new ideas about thalamic functioning, this one about the firing mode is a hypothesis, which exemplifies the need for more experimental evidence.

## Drivers and modulators

Inputs to relay cells are varied and include a mixture of cortical, subcortical and local GABAergic sources. Nonetheless, where functional information is available, only one of these inputs (the driver) reflects the main information to be relayed to cortex, with the other inputs (modulators) serving to modify the extent and/or nature of the information relayed. Also, where sufficient information is available, it is clear that driver input to relay cells, although functionally powerful, anatomically represents a small minority of synapses (5–10%). An important point is that, without functional information about the large EPSPs evoked by drivers and their dominance of relay cell response properties (e.g. retinal input dominates receptive field properties of geniculate relay cells), one might be tempted to suggest that parabrachial input, at ~30% of synapses, is relayed by the lateral geniculate nucleus, with retinal input, at 5–10%, acting in some vague, limited manner. The point is that anatomical data alone can be misleading, which underscores the importance of the distinction between driver and modulator.

A curious point about many driver inputs, to both first and higher order relays, is that they involve axons that branch, with the extrathalamic branch apparently innervating subcortical motor centers. One interpretation of this anatomical fact is that thalamus relays to the cortex information about impending motor commands. This is considered more fully elsewhere (Guillery, 2003; Guillery, 2005; Sherman and Guillery, 2006), but it does seem to be a relevant observation regarding the nature of peripheral information upon which the cortex acts and upon which perception is built.

## First and higher order relays

The division of thalamus into first and higher order relays that is documented above follows from a consideration of drivers and modulators. That is, defining the driver input to a thalamic relay characterizes what the relay transmits to cortex, and recent evidence has uncovered that much of thalamus, namely the higher order relays, receives driver input from layer 5 of one cortical area and sends it on to another cortical area. As noted above, there is evidence of fundamental differences between first and higher order relays. It is important to realize that the evidence is largely circumstantial, but the data do identify the sorts of experiments that might elucidate more clearly any differences between these types of thalamic relay.

For now, we can only speculate on these presumptive differences, which indicate that higher order relays are under more modulatory control, often leading to more hyperpolarization and, thus, more bursting of relay cells than first order relays. What follows, then, is the hypothesis that these higher order circuits, which relay information between two cortical areas, require more control of relay functions than do first order relays. There are many difference one can imagine between the needs of first order relays (i.e. to get subcortical information to cortex) and those of higher order relays (i.e. to communicate between cortical areas) and it seems fruitless to consider these here except to illustrate the point with one speculative example. That is, one plausible reason for the difference is given above: namely, that first order cortical areas receive from a single first order thalamic relay (e.g., the lateral geniculate nucleus is effectively the only thalamic input to primary visual cortex), whereas higher order cortical areas might receive inputs from multiple, higher order thalamic relays, and the extra bursting and modulation of these thalamic relays is used to switch effectively between different thalamic inputs.

Thus, the thalamus is an interesting structure that provides a dynamic relay of all information reaching cortex. It also is important for continued cortical functioning via higher order relays that subserve much corticocortical communication. However, our understanding of these processes is in the early stages and much of this essay is speculative. Clearly, more research is needed, and I hope that the ideas developed here will help in the design of some experiments that will prove useful to our further understanding of the thalamus.

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