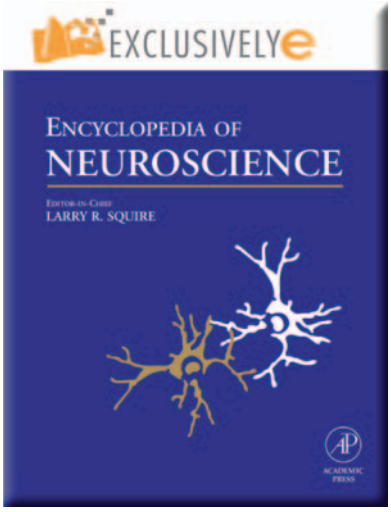

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Thalamic Mechanisms in Vision

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Introduction

The thalamus is a paired structure, roughly the size of a walnut, lying along the midline near the center of the brain. Thalamus proper can be divided into dorsal thalamus, which contains the relay nuclei that project to cortex, and ventral thalamus, the major part of which is the thalamic reticular nucleus (TRN). (Dorsal and ventral here represent embryonic relative locations that change during development. Unless otherwise specified, thalamus used by itself refers to the relay nuclei of the dorsal thalamus.) The TRN is a thin shell of neurons that lies generally lateral to the dorsal thalamus, like a shield, extending somewhat dorsally, ventrally, and anteriorly. A number of cytoarchitectonically distinctive zones of dorsal thalamus can be recognized, and these are the various thalamic relay nuclei. Each nucleus is reciprocally connected with cortex, and most do so with one or a small group of cortical areas. Although not divided into cytoarchitectonically clear zones, nonetheless the TRN can be functionally divided into zones, each of which is reciprocally connected with one or a small group of thalamic relay nuclei. Reticular cells target thalamic relay cells and are not known to project outside of thalamus.

An important fact to keep in mind is that effectively all information reaching cerebral cortex is relayed via thalamus. Thus, all information that reaches consciousness does so by being successfully relayed through thalamus, and if such a relay is blocked, the affected information is not consciously recognized or acted upon. An equally important fact is that, as far as we know, every cortical area receives a thalamic input. A number of thalamic nuclei innervate telencephalic targets other than cortex, examples of such targets being the basal ganglia and amygdala, but this will not be considered further here: only cerebral cortex will be regarded among thalamic targets.

The main thalamic relays of visual information are the lateral geniculate nucleus (LGN) and pulvinar. (Strictly speaking, this includes the lateral posterior nucleus and is often referred to as the lateral posterior/pulvinar complex, but for the sake of brevity, we shall refer to this simply as the pulvinar.) Until fairly recently, the LGN was viewed as a trivial, machine-like relay of retinal information to primary visual cortex, and the pulvinar was regarded as a rather mysterious entity that innervates extrastriate visual areas; one specific theory for its function is that it is somehow involved in attention. The purpose of the present account is twofold: to demonstrate that the complex cell and circuit functions of the thalamus, including the LGN, belie any simple relay functions, and instead affect the nature of information relayed in a manner that reflects behavioral state, including attention; and to suggest a relatively new hypothesis for the function of pulvinar as a central element in information transfer between cortical areas involving a cortico-thalamo-cortical route. Finally, the point shall be emphasized that all thalamic relays share most basic cell and circuit functions, but certain differences between the LGN and pulvinar identify them as members of two different kinds of relay found throughout thalamus.

The LGN

We know most about the cell and circuit properties of the LGN, particularly in the cat. The details learned from this nucleus seem broadly applicable to the rest of thalamus in all mammals. Certain differences are elaborated later. This section focuses on how retinal information to be passed on to cortex is modulated by the cell and circuit properties of geniculate relay cells.

Parallel Processing

Relay cells, at least in the LGN, are not homogeneous but can actually be divided into at least three functional classes. Each of these geniculate classes represents a thalamic link in separate streams of retino-geniculo-cortical processing; that is, there are equivalent distinct classes of retinal ganglion cells that project to the LGN, and each retinal class seems to innervate a single class of geniculate relay cell to maintain separate, parallel streams of information to cortex. In general, the receptive field properties that distinguish these cell types are similar for retina and the LGN, because geniculate receptive fields are essentially the same as their retinal inputs. These classes have been best studied in the cat, where they are called X, Y, and W cells, and in the monkey, where they are called magnocellular (M), parvocellular (P), and koniocellular (K).

The cat LGN

1. *X and Y cells.* X and Y cells are fairly homogeneous classes. Anatomically, in the retina, X cells are equivalent to the anatomical class known as 'beta,' and Y cells as 'alpha.' Compared to retinal Y cells,

X cells have smaller cell bodies with smaller dendritic arbors and thinner caliber axons. Similar relationships exist for geniculate X and Y cells, and Figure 1 summarizes some of these anatomical differences. The X cells have smaller cell bodies with thinner axons, and their dendritic arbors are elongated perpendicular to the geniculate laminar borders (see below for geniculate layers), whereas those of Y cells are organized into a roughly spherical shape. Also, X cells tend to have grape-like appendages near proximal dendritic branch points, whereas Y cell dendrites are generally smooth (see Figure 1). This is interesting, because these appendages on the X cells mark the postsynaptic target of the retinal inputs; on Y cells, retinal inputs terminate directly onto proximal dendritic shafts. The receptive fields of both cell types in retina and the LGN are organized into classic center/surround regions with roughly equal numbers of on and off center cells. However, X cells have smaller receptive fields and respond to higher spatial and lower temporal frequencies.

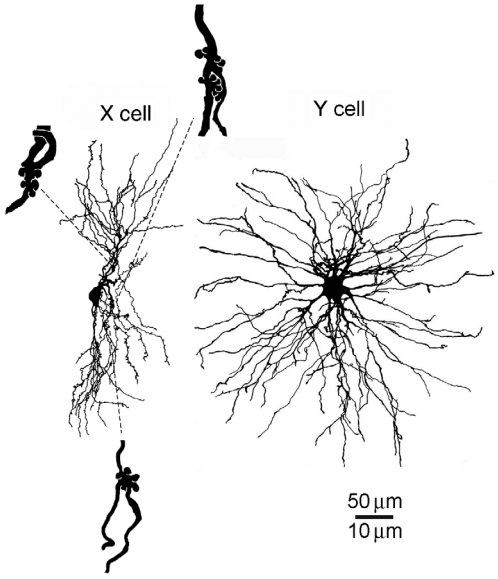

Figure 1 Tracings of an X and Y cell from the A layers of the LGN of the cat. The cells were first identified during *in vivo*, intracellular recording, and then horseradish peroxidase was iontophoresed from the recording pipette into the cells. After appropriate histological processing, the procedure provides a dense stain, allowing visualization of the morphology of the cell body and entire dendritic arbor. The dendritic arbor of the X cell is elongated and oriented perpendicular to laminar borders, while the Y cell dendrites show a stellate distribution with an approximately spherical arbor. The X cell also has prominent clusters of grape-like appendages near proximal dendritic branch points. These are hard to see in the cell reconstructions, so three examples are shown at greater magnification, with dashed lines indicating their dendritic locations (the scale is 50 μm for the cell reconstructions and 10 μm for the dendritic appendage examples). Adapted from Sherman SM and Guillery RW (2006) *Exploring the Thalamus and Its Role in Cortical Function*, 2nd edn. Cambridge, MA: MIT Press.

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

2. *W cells.* W cells are probably a heterogeneous group with several distinct classes, but for convenience and because the final classification and functional correlates of W cells remains to be done, they are treated together here. More details of these cells can be found elsewhere (see 'Further reading'). Retinal W cells generally have small- to medium-sized cell bodies with long, sparsely branched dendrites, but the morphological features of this group are so varied that any generality must be considered limited. W cells so far described in the LGN have medium-sized cell bodies and dendritic arbors oriented parallel to the layers. The receptive fields of these cells, both in retina and the LGN, are also quite varied but tend to be large and poorly responsive (some have named them 'sluggish'): some have center/surround configuration; others have poorly defined borders with on/off responses throughout, some have directional selectivity, and some have limited wavelength sensitivity. To date, there has not been much speculation regarding the function of the W pathway(s), which remains a mystery.

The monkey LGN Details of the organization of the parallel pathways in the monkey are less well understood than those in the cat, but the same general principles apply. At least three parallel pathways start in the retina and are relayed separately through the LGN. These have been called the P, M, and K pathways. Relationships of these pathways to those in the cat has been a source of confusion and controversy, but a consensus seems to be developing that the P, M, and K cells and pathways are homologous, respectively, to the cat's X, Y, and W. However, homology does not mean functional equivalence, only that a common ancestral form is shared, and, indeed, evolution works to create functional differences between homologous structures. An example is our fingers and the wings of bird: these are homologous structures that have evolved quite different functions. In contrast, the fins of a fish and whale are examples of nonhomologous structures that have evolved similar functions.

1. *P and M cells.* In the retina, P cells (called midget cells) are smaller than M cells (called parasol cells), and this size differential also holds in the LGN,

as the names (parvocellular and magnocellular) imply. In both structures, their receptive fields are organized into center/surround configurations, but P cells have smaller receptive fields. M cells are much more sensitive to luminance contrast and moving stimuli, but, while M cells show no wavelength sensitivity, P cells show sensitivity for green and red wavelengths. One exception to this is the owl monkey, which is crepuscular and thus not so reliant on color vision. For these animals, P cells show little wavelength sensitivity.

As is the case for the cat, there has been much speculation concerning the role of these cell types in the monkey. Common suggestions are that P cells are important for color discrimination, especially for red/green distinctions, and may also be involved in high-acuity vision, whereas M cells provide for better luminance contrast sensitivity and are also important for motion detection. Naturally, the role of P cells in monkeys without much color vision, such as the owl monkey, would be different. This would be another example of evolution working on homologous systems to create different functions.

2. *K cells*. Like W cells, K cells probably include many distinct cell classes but are grouped together here, because their complete classification remains to be done. As the name (koniocellular) implies, these are smaller than M or P cells in both the retina and the LGN. Not much is known of their receptive field properties, but some of these cells are thought to be responsible for yellow/blue-wavelength discrimination.

Laminar Relationships

Lateral geniculate nucleus The LGN in all mammals so far studied has distinct zones that in cats and monkeys have evolved to separate layers, and each of these layers receives an input from one or the other eye. Geniculate laminar patterns vary greatly among species, but this ocular division between sets of layers seems to be one constant.

In addition to ocular dominance, the various cell types are distributed with varying levels of laminar specificity. For instance, in the cat, X and Y cells commingle in the dorsal two layers (called the A layers), and the next ventral layer (layer C) has only Y cells, and the ventral few layers have only W cells. For the rhesus monkey, P and M cells are completely separated into four dorsal parvocellular layers and two ventral magnocellular layers. The K cells are found in all the interlaminar zones but also extend dorsally to commingle with P cells in the ventral portions of the parvocellular layers.

Figure 2 summarizes the laminar patterns for cats, monkeys, and some other species to illustrate the sort of bewildering variation in patterns present. Note that two closely relayed carnivore species like the cat versus the ferret or mink differ in that the cat has its on- and off-center cells mixed together in the layers, while the ferret and mink have further divided the dorsal two layers into four to separate on and off center cells. The bottom line here is that geniculate lamination does correlate with cell type, but the nature and extent of this correlation varies widely across species, and it is difficult to discern any special significance to these correlations.

Visual cortex There is also a laminar correlation regarding the target zones of the various cell types. In the cat, geniculate X cell axons innervate the ventral part of layer 4, while those of Y cells innervate the upper part. Most W cells innervate layer 3. A similar arrangement holds for the monkey: P cells innervate the ventral half of layer 4 (sometimes called layer 4Cβ), M cells innervate the dorsal half of layer 4

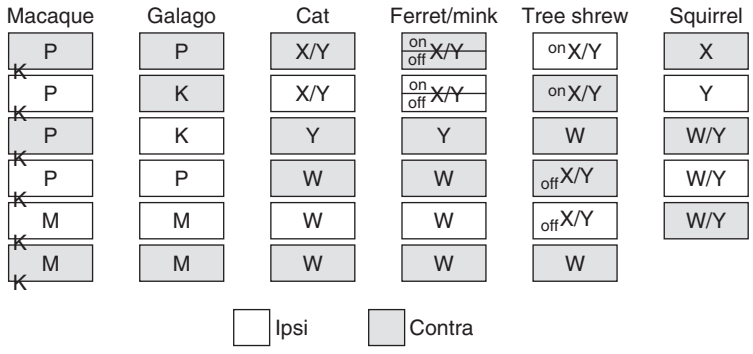

Figure 2 Schematic rendering of layers and distribution of cell types in the LGN of six different species. The shaded boxes show layers innervated by the contralateral eye (contra), and the unshaded boxes show the input from the ipsilateral eye (ipsi). The X, Y, and W pathways are shown for cat, ferret, mink, tree shrew, and squirrel, and the magnocellular (M), parvocellular (P), and koniocellular (K) pathways are shown for macaque and galago. Where there is a clear segregation of on- and off-center (on, off) cells, this is also indicated. Adapted from Sherman SM and Guillery RW (2006) *Exploring the Thalamus and Its Role in Cortical Function*, 2nd edn. Cambridge, MA: MIT Press.

(sometimes called 4Cα), and K cells mostly innervate layer 3. Thus, through the first stage of processing, the three parallel pathways are kept fairly independent through this first stage of cortical processing, although what happens further centrally with regard to these pathways is not at all clear.

Thalamic Cell Types

There are three basic thalamic cell types related to the LGN: relay cells (which in the LGN can be further divided into W, X, and Y; K, P, and M; etc.), interneurons, and cells of the TRN. Relay cells are glutamatergic, and the latter two cell types are GABAergic, providing a major inhibitory input to relay cells. Interneurons are located within the main geniculate layers, intermixed with relay cells, and the ratio of relay cells to interneurons is roughly 3:1. This ratio is similar throughout thalamus in all mammals with a peculiar exception. That is, outside of the LGN, the thalamus of rats and mice are essentially devoid of interneurons, but, curiously, the LGN in these animals does have a normal complement of interneurons. This is not a property of rodents, because hamsters, guinea pigs, squirrels, etc., have interneurons throughout thalamus. However, this point has been questioned recently by evidence that the lateral posterior nucleus of the rat has a substantial fraction of interneurons.

Cell Properties

All thalamic relay cells, like cells throughout the central nervous system, exhibit a number of voltage-gated ionic membrane conductances. Geniculate relay cells serve as a typical example. The best known of these ubiquitous conductances is the voltage-gated Na^+ conductance underlying the action potential. Other examples include various voltage-gated K^+ and Ca^{2+} conductances. A detailed listing of these is beyond the scope of this article. The presence of these conductances means that membrane voltage, which determines if and when each of these becomes activated, plays an important role in cell excitability and thus the gating of retinogeniculate information flow. Most of these conductances are garden-variety properties found in neurons everywhere, but one in particular, a voltage-gated Ca^{2+} conductance that operates via T-type Ca^{2+} channels, is worth further consideration.

When T-type Ca^{2+} channels are open, Ca^{2+} flows into the cell, depolarizing it via a current known as I_T. However, the T channel can only be opened by depolarization from a relatively hyperpolarized level. That is, depolarization initially activates the channel, but after about 100 ms or so, inactivates it. Once inactivated, it takes about 100 ms or so of subsequent hyperpolarization to remove the inactivation of (i.e., de-inactivate) IT, so that it can again be activated. Actually the opening or closing of the inactivation gate is a complex function of voltage and time so that the more depolarized (or hyperpolarized) the more quickly the gate closes (or opens), but the important point is that under normal conditions, roughly 100 ms is required for these activations.

Once activated, however, the depolarization initiated by I_T becomes an all-or-none Ca^{2+} spike, much like the conventional Na^+/K^+ action potential, and it propagates throughout the dendrites and soma. This is often known as the low-threshold spike, which is tens of millivolts in amplitude and thus large enough to evoke a cluster of action potentials that rides its crest; typically, there are 2–10 such action potentials with interspike intervals <4 ms or so. Such burst firing is ubiquitous for relay cells: every relay cell of every thalamic nucleus of every mammalian species so far tested shows this property. T channels, however, are found in neurons throughout the brain, but what makes thalamic relay cells relatively unique is the density of T channels they express: in relay cells, this density is high enough to support an all-or-none Ca^{2+} spike, while in most other neurons, T channel density is too low for this and can thus underlie only a graded depolarization.

From the above, the voltage-dependent properties of the T channel can be characterized by two gates, an activation gate and an inactivation gate. The activation gate opens with depolarization and closes with hyperpolarization, and it does so with very fast kinetics, typically requiring <1 ms for opening or closing. The inactivation gate has the opposite voltage relationships, since it opens with hyperpolarization and closes with depolarization; also, it operates much more slowly, taking about 100 ms for either action. This slow action is important to how the channel is controlled by thalamic circuitry, which is considered below.

Figure 3 illustrates and summarizes many of these features of the T channels. Activation of T channels requires that they be first de-inactivated, which in turn requires hyperpolarization. The more hyperpolarization that occurs, the more T channels are de-inactivated and can thus participate in the subsequently evoked low-threshold spike, and the larger the evoked low-threshold spike. This is shown in Figure 3(a) for two relay cells. Thus, the size of the low-threshold spike can vary depending on the history of the cell's membrane voltage, and, as might be predicted, the number of conventional action potentials evoked from such a low-threshold spike is correlated with its amplitude (Figure 3(a)). However, for any given level of T channel de-inactivation, the low-threshold spike is all-or-none (Figure 3(b)).

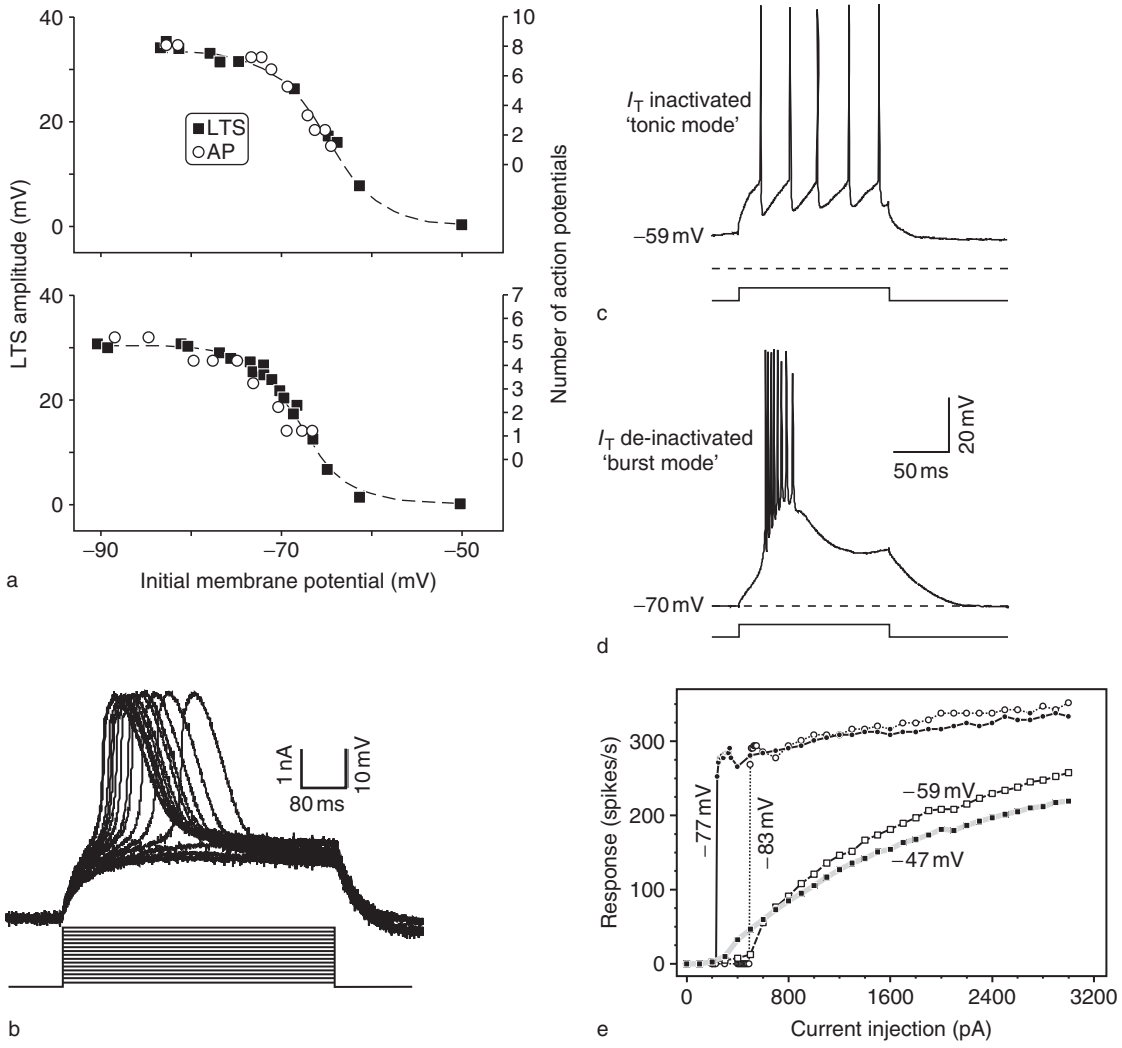

Figure 3 Properties of I_T and the low-threshold Ca^{2+} spike (LTS). All examples are from relay cells of the cat's LGN recorded intracellularly in an *in vitro* slice preparation. (a) Voltage dependency of amplitude of LTS and extent of burst response. Examples for two cells are shown. The more hyperpolarized the cell before being activated (initial membrane potential), the larger the LTS (filled squares and dashed curve) and the more action potentials (APs) in the burst (open circles). The number of APs were first measured, and then tetrodotoxin (TTX) was applied to isolate the LTS for measurement. (b) All-or-none nature of the LTS measured in the presence of TTX in another geniculate cell. The cell is initially hyperpolarized, and current pulses were injected starting at 200 pA amplitude and incremented in 10 pA steps. Smaller (subthreshold) pulses led to pure resistive–capacitative responses, but all larger (suprathreshold) pulses led to an LTS. Much like conventional APs, the LTSs are all the same amplitude regardless of how far the depolarizing pulse exceeded activation threshold, although there is latency variability for smaller suprathreshold pulses. (c, d) Voltage dependency of the LTS. Responses are shown to the same depolarizing current pulse delivered intracellularly but from two different initial holding potentials (–59 and –70 mV). When the cell is relatively depolarized (c), I_T is inactivated, and the cell responds with a stream of unitary action potentials as long as the stimulus is suprathreshold for firing. This is the tonic mode of firing. When the cell is relatively hyperpolarized (d), I_T is de-inactivated, and the current pulse activates an LTS with eight action potentials riding its crest. This is the burst mode of firing. (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 APs of the response, since this cell usually exhibited six APs per burst in this experiment. The initial holding potentials are shown, and –47 and –59 mV reflect tonic mode, whereas –77 and –83 mV reflect burst mode. (a) Redrawn from Zhan XJ, Cox CL, and Sherman SM (2000) Dendritic depolarization efficiently attenuates low threshold calcium spikes in thalamic relay cells. *The Journal of Neuroscience* 20: 3909–3914. (e) Redrawn from Zhan XJ, Cox CL, Rinzel J, and Sherman SM (1999) Current clamp and modeling studies of low threshold calcium spikes in cells of the cat's lateral geniculate nucleus. *The Journal of Neurophysiology* 81: 2360–2373.

Properties of burst and tonic firing T channel activity determines two very different response modes, tonic or burst, for the relay cell. This has important implications for relay of information for a number of reasons. Note that the only signal relayed to cortex is via conventional action potentials. However, the same retinal excitatory postsynaptic potential will evoke a very different response in the relay cell dependent

on the cell's response mode (see Figures 3(c) and 3(d)). During tonic firing mode, the action potentials rise directly from the excitatory postsynaptic potential, and thus a larger excitatory postsynaptic potential evokes a higher rate of firing. However, the action potentials during burst firing mode arise indirectly from the excitatory postsynaptic potential. Here, the excitatory postsynaptic potential evokes the low-threshold spike, which is all-or-none, and thus a larger excitatory postsynaptic potential will not evoke a larger low-threshold spike, meaning that the size of the burst is not linearly related to the size of the retinal excitatory postsynaptic potential. What this all means is that there is a fairly linear input/output relationship during tonic firing, but this relationship is very nonlinear during burst firing (Figure 3(e)).

The advantage for tonic firing is pretty clear: if cortex is to reproduce faithfully the visual scene, the sort of nonlinear distortion seen during burst firing would hamper this process. What, then, is the advantage for burst firing? There are at least two of them. First, burst firing is associated with low spontaneous activity but the burst itself represents a high rate of firing; together, this means that burst firing is associated with a higher signal-to-noise ratio and thus better stimulus detectability. Second, the combination of the nature of the thalamocortical synapse and the different pattern of action potentials between firing modes leads to a much greater postsynaptic response in cortex for burst firing. Two related observations support this second point. First, there is evidence that the first action potential in a burst evokes a much greater response in cortex than does a tonic action potential. Second, many cortical cells operate in an 'up' or 'down' state in which up state is relatively depolarized and responsive to thalamic input, whereas the more hyperpolarized down state is much less responsive to thalamic input; recent evidence indicates that tonic firing is relatively ineffective in switching a cortical cell from the down to the up state, but burst firing brings about this switch quite readily. The overall implication is that while tonic firing is better for stimulus reconstruction, burst firing is better for the detection of novel stimuli, and associated with this improved detectability is a much stronger cortical response.

Hypothesis for burst and tonic firing This difference between burst and tonic firing has led to the following hypothesis. Because burst firing is better for stimulus detection, it could be the mode more often seen when the receptive field of the geniculate neuron covers an unattended part of the visual field, unattended because the subject is drowsy, is attending to another sensory modality or part of the visual field, etc.; under these conditions, the burst evoked by a novel stimulus would more likely get through to cortex and be recognized as a signal than if the cell were firing tonically. In this sense, the burst is a sort of 'wake-up call' that something has changed, and that something should be attended to so that its importance can be evaluated. The idea here is not necessarily that bursting provides a stronger overall signal to cortex than does tonic firing, but rather that bursting overcomes any disadvantage regarding stimulus detectability or cortical activation imposed by inattention. Once the burst activates cortical circuits, the relay cell would then switch to tonic firing so that the novel stimulus can be properly evaluated.

Consistent with this hypothesis are several observations. Both tonic and burst firing are seen in behaving animals and humans, with switching occurring between modes. Bursting is seen relatively rarely in the alert animals and more commonly in drowsy animals. Studies of behaving cats show that a relatively common pattern of response of geniculate cells to a repeating stimulus (e.g., a flashing spot) would be to respond to the first cycle of stimulation, then switch to tonic firing in response to subsequent cycles. Finally, recent receptive field studies show that the type of visual stimulus most likely to evoke a burst is one that switches from an inhibitory one to an excitatory one, such as a dark region covering the receptive field of an on-center cell that is then switched to a bright spot; this indicates that the burst signals a significant change in the form of a novel stimulus just appearing. However, these observations, while supporting the hypothesis, do not constitute proof of its validity. Much more research will be needed to accept or reject the hypothesis.

Other cellular properties of relay cells While much is known about T channels and their significance for thalamic relays, many other voltage-sensitive ionic currents exist that affect these relays. These include a variety of voltage-gated K^+, Na^+, and other Ca^{2+} channels and also a hyperpolarization-activated cation channel known as I_h. While we understand much of the voltage-sensitive properties of each of these, much more work needs to be done to appreciate how these interact among themselves and also with I_T.

Circuit Properties

Figure 4 schematically shows the main inputs to geniculate relay cells. This circuitry is generally repeated, with some variations, throughout thalamus.

Anatomical features An important point shown in Figure 4 is that retinal input is one of the several inputs to relay cells. Other prominent input derives

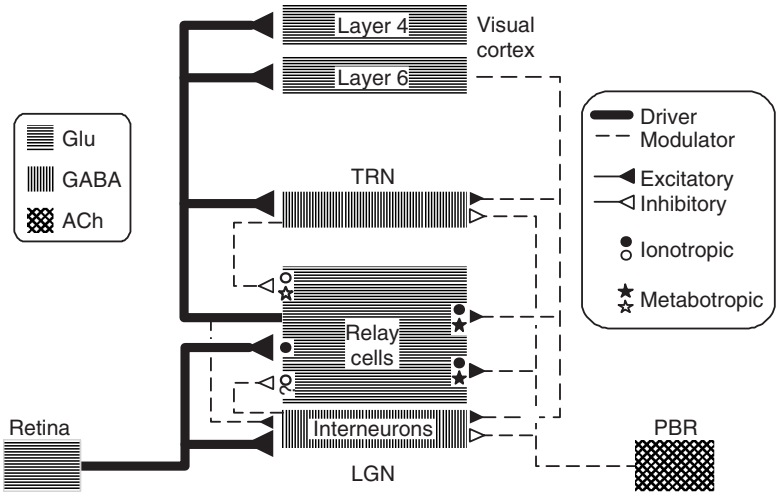

Figure 4 Circuitry of the LGN with related receptors present on relay cells. Other thalamic nuclei seem to be organized along the same pattern. The key to the left indicates the major transmitter systems involved. The retinal input activates only ionotropic receptors (circles), whereas all nonretinal inputs activate metabotropic receptors (stars) and often ionotropic receptors as well. The question mark related to input from interneurons indicates uncertainty whether metabotropic receptors are involved. Thick solid and thin dashed lines indicate driver and modulator inputs, respectively. Filled and open icons for synaptic terminals indicate excitatory and inhibitory inputs, respectively. ACh, acetylcholine; GABA, γ-aminobutyric acid; Glu, glutamate; LGN, lateral geniculate nucleus; PBR, parabrachial region of the brain stem; TRN, thalamic reticular nucleus. Adapted from Sherman SM and Guillery RW (1998) On the actions that one nerve cell can have on another: Distinguishing 'drivers' from 'modulators'. *Proceedings of the National Academy of Sciences of the United States of America* 95: 7121–7126 and Sherman SM and Guillery RW (2001) *Exploring the Thalamus*. San Diego: Academic Press.

from local GABAergic sources (interneurons and reticular cells), layer 6 of cortex, which provides a feedback, glutamatergic input, and ascending input from the brain stem, mostly from cholinergic cells in a midbrain area known as the parabrachial region. (Another term often applied to this area is 'pedunculopontine tegmental nucleus.' We prefer 'parabrachial region,' because the cells that innervate thalamus from this area do not have a clear nuclear boundary, and they are found scattered around the brachium conjunctivum.) Not shown for simplicity are other small inputs also seen widely throughout thalamus, such as serotonergic input from the dorsal raphé nucleus of the brain stem, noradrenergic inputs from the parabrachial region, and histaminergic inputs from the tuberomamillary nucleus of the hypothalamus. However, we focus here on the inputs shown in Figure 4, because these are the best understood.

Thus, the main extrinsic, nonretinal inputs to geniculate relay cells derive from cortex and brain stem. There are also local, GABAergic inputs, but these are also innervated by the same cortical and brain stem sources that innervate relay cells. Thus, these extrinsic inputs can affect relay cells directly or indirectly via local GABAergic circuitry.

Functional features

1. *Ionotropic and metabotropic receptors*. Figure 4 also shows the neurotransmitters used by various afferents to relay cells as well as the postsynaptic receptors involved. These receptors are critical in understanding how this circuit works, because the inputs to relay cells operate via conventional chemical synapses, meaning that they release transmitters that affect the relay cell via postsynaptic receptors. The receptors, which determine the final postsynaptic response of the relay cell, come in two main flavors: ionotropic and metabotropic. Examples of the relevant ionotropic receptors are α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) for glutamate, nicotinic for acetylcholine, and the $GABA_A$ receptor (GABA, γ-aminobutyric acid). For metabotropic receptors, examples are various metabotropic glutamate receptors, various muscarinic receptors for acetylcholine, and the $GABA_B$ receptor.

Differences between ionotropic and metabotropic receptors are many, and only certain ones are considered below. Ionotropic receptors are simpler in construction and function, and the receptor itself usually contains the ion channel it controls. Generally, the binding of the transmitter to the receptor changes the shape of the receptor, exposing and thus opening the ion channel. Opening the channel allows ions to flow into or out of the cell, leading to an excitatory or inhibitory postsynaptic potential. Typically, the postsynaptic potential occurs with a brief latency (<1 ms) and duration (mostly over in 10 ms or a few tens of milliseconds). The story with metabotropic receptors is more complicated.

Here, the receptor is only indirectly linked to the relevant ion channel. Typically, binding of the transmitter to the receptor causes release of a G-protein that interacts with an effector protein, setting off a cascade of biochemical reactions with many effects on the cell, one of which ultimately is on the ion channel. For thalamic relay cells, these are typically K^+ channels. Thus when the channel opens, K^+ flows out of the cell, leading to an inhibitory postsynaptic potential; when the channel closes, leakage of K^+ is stopped, leading to an excitatory postsynaptic potential. However, these postsynaptic potentials with metabotropic receptors typically have a long latency (~10 ms or so) and duration (hundreds of milliseconds to several seconds).

Given these differences between receptor types, particularly with regard to duration of the resultant postsynaptic potential, it is particularly interesting to note the pattern of postsynaptic receptors as they relate to various inputs onto relay cells (Figure 4). What is striking is that retinal inputs activate only ionotropic (mostly AMPA but also NMDA) receptors, whereas all nonretinal inputs activate metabotropic as well as ionotropic receptors. One obvious conclusion is that the nonretinal inputs, by activating metabotropic receptors, can achieve sustained changes in membrane potential and thus relay cell excitability, thereby modulating the gain of retinogeniculate transmission.

There is a further, more interesting implication of this pattern that involves control of the T channels. Recall that to inactivate the T channel (i.e., to close the inactivation gate) requires 100 ms or so of sustained depolarization; similarly, to de-inactivate it (i.e., to open the inactivation gate) requires 100 ms or so of sustained hyperpolarization. This means that the fast excitatory or inhibitory postsynaptic potentials seen with ionotropic receptors are ill suited to affect the inactivation gate; even action potentials, despite their amplitude, are terminated too quickly to effectively inactivate the T channel. In contrast, the sustained postsynaptic potentials of metabotropic receptors are ideally suited to inactivate or de-inactivate T channels. It thus follows that retinal input by itself, with its fast excitatory postsynaptic potentials, is less likely to directly affect T channels. This seems appropriate in the sense that burst or tonic firing is thought to be dependent on behavioral state.

One would expect that to be mainly the function of inputs to relay cells that do not carry the main information to be relayed. However, the fast retinal excitatory postsynaptic potentials means that each can represent a specific retinal action potential up to high rates of firing, thus preserving temporal information. Put another way, if retinal inputs activated metabotropic glutamate receptors, the resultant long excitatory postsynaptic potentials would act like low-pass temporal filters, and higher-frequency temporal information would fail in the relay. From this reasoning, it falls to the nonretinal inputs via activation of metabotropic receptors to provide the main control of T channels and determine whether the response to retinal input is in tonic or burst firing mode.

In addition, there is clear evidence that visual stimuli can also affect firing mode: for instance, a visual stimulus that inhibits a geniculate cell for a sufficient time (e.g., a dark stimulus falling on the center of an on-center cell) can de-inactivate the T channels, and when this stimulus is replaced by an excitatory one (e.g., a bright spot), a burst is evoked. Note that this is likely due to inhibitory circuits involving interneurons or reticular cells, or both, and perhaps also involving $GABA_B$ receptors and is not likely to represent retinal inputs alone.

Indeed, evidence exists that metabotropic glutamate receptors activated from layer 6 of cortex and muscarinic receptors activated from the parabrachial region produce long, slow excitatory postsynaptic potentials that inactivate the T channels and switch relay cells from burst to tonic firing mode. Similarly, activation of $GABA_B$ receptors from reticular inputs does the opposite: it produces a sustained inhibitory postsynaptic potential that switches firing modes from tonic to burst. Interneurons may also participate in this, but as indicated by the question mark in Figure 4, it is not yet known whether or not these inputs activate $GABA_B$ receptors on relay cells.

2. *Role of parabrachial and cortical inputs*. Further inspection of Figure 4 shows that, as parabrachial inputs become more active, relay cells become more depolarized and responsive. This is because the main effect of parabrachial input onto relay cells is depolarizing, via activation of nicotinic and M1 muscarinic receptors (activations of M1 receptors closes K^+ channels), and its main effect onto the local GABAergic cells is hyperpolarizing, via activation of another (M2?) muscarinic receptor that opens K^+ channels. Thus, parabrachial input directly depolarizes relay cells and also disinhibits them. Not only does parabrachial input excite relay cells, but the resultant depolarization also inactivates T channels, biasing relay cell responses to tonic mode. Consistent with this scenario is the further observation that parabrachial neurons become more active and relay cells become less bursty with increasing vigilance, from slow-wave sleep through drowsiness to full attention.

Understanding the consequence of the layer 6 cortical input is much more difficult. Figure 4 suggests that this input directly excites relay cells while it indirectly inhibits them, but, in fact, the actual effect of this input depends on details of the circuit that are generally unknown. This is illustrated in Figure 5,

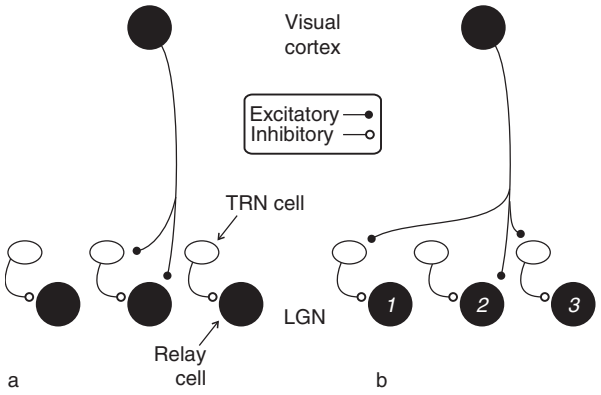

Figure 5 Two patterns among others possible for corticothalamic projection from layer 6 to cells of the TRN and geniculate relay cells. (a) Pattern of simple excitation and feedforward inhibition. (b) More complicated pattern in which activation of a cortical axon can excite some relay cells directly and inhibit others through activation of reticular cells. For further details, see text. LGN, lateral geniculate nucleus; TRN, thalamic reticular nucleus.

which shows two variants of the many possible for the relevant circuit. (The example of Figure 5 includes just reticular cells, but one can easily imagine a similar circuit involving interneurons.) In Figure 5(a), individual corticogeniculate axons innervate a reticular cell and relay cell, with the reticular cell innervating the same relay cell. The consequence of increased corticogeniculate activity might be of little or no effect on the relay cell's membrane voltage (and T channel inactivation or de-inactivation) if the excitatory and inhibitory inputs are balanced. However, while this may not affect membrane voltage, the increased synaptic conductance among other factors will reduce relay cell excitability to other (i.e., retinal) inputs, and thus reduce the gain of retinogeniculate transmission. Thus, the more active the corticogeniculate inputs in the circuit of Figure 5(a), the lower the gain of retinogeniculate transmission.

The circuit of Figure 5(b) has very different consequences. Here, activation of the corticogeniculate axon purely excites one or a few relay cells (e.g., cell 2) and purely inhibits others (e.g., cells 1 and 3). Also, note that the final effect on relay cell membrane voltage is such that activation of the corticogeniculate axon would promote tonic firing in cell 2 and burst firing in cells 1 and 3. This means that layer 6 corticogeniculate can have very different and localized effects. Figure 5 illustrates the importance of a much better understanding of these functional circuits at the single-cell level than we have at present.

Drivers and Modulators

Figure 4 also partly demonstrates a fundamental observation, namely, that all inputs to geniculate relay cells are not equal. That is, the retinal input alone represents the main information actually relayed to cortex. Among other factors, a consideration of receptive field properties demonstrates this fact, because the responses of the relay cell to visual stimulation does, in fact, identify the information relayed. In this regard, the receptive fields of geniculate relay cells are remarkably like those of their retinal afferents, having the same center/surround configuration and with only minor, subtle differences. If we consider the other extrathalamic inputs, receptive fields of corticogeniculate afferents, which show selectivities for orientation and often direction typical of cortical cells, are utterly unlike geniculate receptive fields, and parabrachial inputs are not plausible sources of such clear center/surround properties. If it is the retinal input that provides the information to be relayed, then the nonretinal inputs must have another function. This, plus a number of morphological, pharmacological, and physiological differences that distinguish retinal and nonretinal afferents to relay cells, has led to the idea that these can be functionally divided: the retinal inputs are the drivers (so called because one of its properties is the very strong postsynaptic drive of their target relay cells; see Table 1), while all the nonretinal inputs are the modulators, the idea being that the driver input is the information-bearing input, while the modulators serve to modulate retinogeniculate transmission. Modulation can take many forms, including, for example, the above-mentioned consequences of metabotropic receptor activation that lead to overall changes in relay cell excitability and that serve to control the tonic/burst transition; also, as indicated above, the circuit suggested by Figure 5(a) can operate to control the gain of retinogeniculate transmission.

There is actually an extensive list of properties that distinguish drivers from modulators in thalamus, and this list will likely increase in size as we learn more about this issue. Table 1 summarizes the most important features but is not meant to be exhaustive. Layer 5 drivers (the second column in Table 1) are considered below. The 13 criteria in Table 1, in a roughly decreasing order of importance, are as follows:

1. As already noted, drivers determine the main receptive field properties of the relay cell; modulator input does not.
2. Also as already noted, drivers activate only ionotropic receptors; modulators activate metabotropic as well as ionotropic receptors.
3. Drivers evoke very large excitatory postsynaptic potentials; modulators generally evoke much smaller excitatory or inhibitory postsynaptic potentials.

Table 1 Drivers and modulators in LGN plus layer 5 drivers

Criteria	*Retinal (driver)*	*Layer 5 to HO (driver)*	*Modulator: layer 6*	*Modulator: PBR*	*Modulator: TRN & Int*
Criterion 1	Determines relay cell receptive field	[a]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
Criterion 2	Activates only ionotropic receptors	Activates only ionotropic receptors	Activates metabotropic receptors	Activates metabotropic receptors	TRN: Activates metabotropic receptors; Int:[b]
Criterion 3	Large EPSPs	Large EPSPs	Small EPSPs	[b]	TRN: small IPSPs; Int:[b]
Criterion 4	Large terminals on proximal dendrites	Large terminals on proximal dendrites	Small terminals on distal dendrites	Small terminals on proximal dendrites	Small terminals; TRN: distal; Int: proximal
Criterion 5	Each terminal forms multiple contacts	Each terminal forms multiple contacts	Each terminal forms single contact	Each terminal forms single contact	Each terminal forms single contact
Criterion 6	Little convergence onto target	[a]Little convergence onto target	Much convergence onto target	[b]	[b]
Criterion 7	Very few synapses onto relay cells (~5%)	Very few synapses onto relay cells (~5%)	Many synapses onto relay cells (~30%)	Many synapses onto relay cells (~30%)	Many synapses onto relay cells (~30%)
Criterion 8	Often thick axons	Often thick axons	Thin axons	Thin axons	Thin axons
Criterion 9	Glutamatergic	Glutamatergic	Glutamatergic	Cholinergic	GABAergic
Criterion 10	Synapses show paired-pulse depression (high *p*)	[a]Synapses show paired-pulse depression (high *p*)	Synapses show paired-pulse facilitation (low *p*)	[b]	[b]
Criterion 11	Well localized, dense terminal arbors	Well localized, dense terminal arbors	Well localized, dense terminal arbors	Sparse terminal arbors	Well localized, dense terminal arbors
Criterion 12	Branches innervate subtelencephalic targets	Branches innervate subtelencephalic targets	Subcortically known to innervate thalamus only	[b]	Subcortically known to innervate thalamus only
Criterion 13	Innervates dorsal thalamus but not TRN	Innervates dorsal thalamus but not TRN	Innervates dorsal thalamus and TRN	Innervates dorsal thalamus and TRN	TRN: both; Int: dorsal thalamus only

[a]Very limited data to data.
[b]No relevant data available.

4. Drivers form very large terminals on proximal dendrites; modulators usually form small terminals, and these can be on proximal or distal dendrites.
5. Each driver terminal forms multiple large synapses; each modulator terminal usually forms a single, small synapse.
6. Driver inputs show little convergence, meaning, for example, that one or a small number of retinal axons converge to innervate each geniculate relay cell; where evidence is available, modulator inputs show considerable convergence.
7. Driver inputs produce a small minority (~5%) of the synapses onto relay cells; many modulator inputs produce larger synaptic numbers (e.g., the cortical and parabrachial modulator inputs in Figure 4 each produces about 30% of the synapses).
8. Drivers have thick axons; modulators have thin axons.
9. Drivers are glutamatergic; modulators can use a variety of neurotransmitters.
10. Driver synapses show high release probability and paired-pulse depression, meaning that a given action potential is likely to result in transmitter release, and that, with the initiation of a train of action potentials, there is a period after each evoked postsynaptic potential lasting for tens of milliseconds that the next one will be smaller (depressed); modulator synapses that have been tested so far show the opposite properties of low release probability and paired-pulse facilitation.
11. Driver terminal arbors are well localized with a dense array of terminals; modulator terminal arbors can be either well localized and dense or relatively poorly localized and sparse.
12. Branches of driver axons tend to innervate extrathalamic targets as well as thalamus (e.g., many or all retinogeniculate axons branch and also

innervate midbrain targets); those modulator inputs so far tested innervate thalamus only.

13. Driver inputs innervate relay cells and interneurons in dorsal thalamus but do not innervate the TRN; modulator inputs innervate relay cells, interneurons, and reticular cells.

This driver/modulator distinction is clear not just in the LGN but also in other thalamic relays for which sufficient information is available, such as the ventral portion of the medial geniculate nucleus (the primary auditory thalamic relay) and the ventral posterior nucleus (the primary somatosensory thalamic relay). The main point, again, is that not all anatomical pathways are functionally equivalent, acting in some sort of anatomical democracy, and if one is to understand the functional organization of the thalamus and what it is that is being relayed, one must identify and characterize the driver input. This may also apply outside of thalamus.

This point can be underscored with a consideration of criterion (7) above. It may seem surprising at first that driver input, which provides the main information to be relayed, is responsible for such a small percentage of the synapses onto relay cells, but there are two factors to be considered. First, despite the small number of inputs numerically, these are especially powerful and do manage to drive the relay cells effectively. Second, it may only take a relatively small number of synapses to get the basic information to the relay cell, provided these are powerful synapses, but to provide a wide range of subtle modulatory effects, it also makes sense to have many more, individually weaker synapses that can be combined in myriad ways.

One last point should be made regarding the driver/modulator distinction with regard to the LGN. If one had only anatomical information, such as numbers of synapses from subcortical sites, the number from the parabrachial region (~30%) is considerably greater than that from retina (5–10%). Such anatomical data in isolation would suggest the conclusion that the parabrachial input is the more important and thus represents the information being relayed, while the retinal input, being so small, performs some vague, lesser function that might not even merit inclusion in some schematic illustrations of geniculate circuitry. The key lesson here is that anatomical data, on their own, can be very misleading when trying to unravel functional circuits. With regard to information processing through thalamus, the most important issue is to identify what is being relayed, and to do so, it is potentially misleading to treat all pathways as equal: one must instead separately identify drivers from modulators.

Usually, one is likely to find examples of schematically illustrated circuits that are based on anatomy alone, as if all inputs were drivers in the sense the term has been used here. If the concept of drivers and modulators has validity beyond thalamus, many of these suggested circuits need to be reconsidered.

First- and Higher-Order Relays: The LGN and Pulvinar

There are two ways to think about the function of the thalamus. One is to consider the properties of thalamic circuitry as they affect relay functions; that is, how do the modulators affect relay cell responses to their driver input? The other is to consider what it is that the thalamic nucleus is actually relaying. Put another way, we can define the function of LGN or the ventral posterior nucleus as relaying retinal or medial lemniscal information, respectively. It is this latter aspect of thalamic functioning that chiefly concerns us in this section.

Layer 5 Corticothalamic Inputs as Drivers

Since, as defined above, the driver input is what is relayed by thalamus, we can define the function of thalamic relays by identifying the source and nature of their drivers. This may seem obvious and trivial for well-studied relays like the LGN, but there are many other less well understood relays with unknown functions because, until recently, their driver inputs remained undefined. Examples are the pulvinar and medial dorsal nucleus. We now know that a major source of driver input to thalamic relays like the pulvinar and medial dorsal nucleus is layer 5 of cortex. This is illustrated in Figure 6.

Figure 6(a) illustrates several key points of this arrangement. All thalamic relays receive a feedback corticothalamic projection from layer 6, and they also have inputs from the TRN; not shown for simplicity are inputs to relay cells from interneurons and the parabrachial region (see Figure 4). However, while some thalamic nuclei relay subcortical driver inputs to cortex (Figure 6(a)), others instead relay driver input that arises from cortical layer 5, and this appears to be feed-forward (Figure 6(b)). Because of this arrangement, we refer to the type of thalamic relay of Figure 6(a) as first order, because this is the first relay of a particular type of information to cortex, and that of Figure 6(b) as higher order, because this represents a relay of information already in cortex but from one cortical area to another. Examples of first-order relays are the LGN for vision, the ventral posterior nucleus for somesthesis, and the ventral (or lemniscal) portion of the medial geniculate

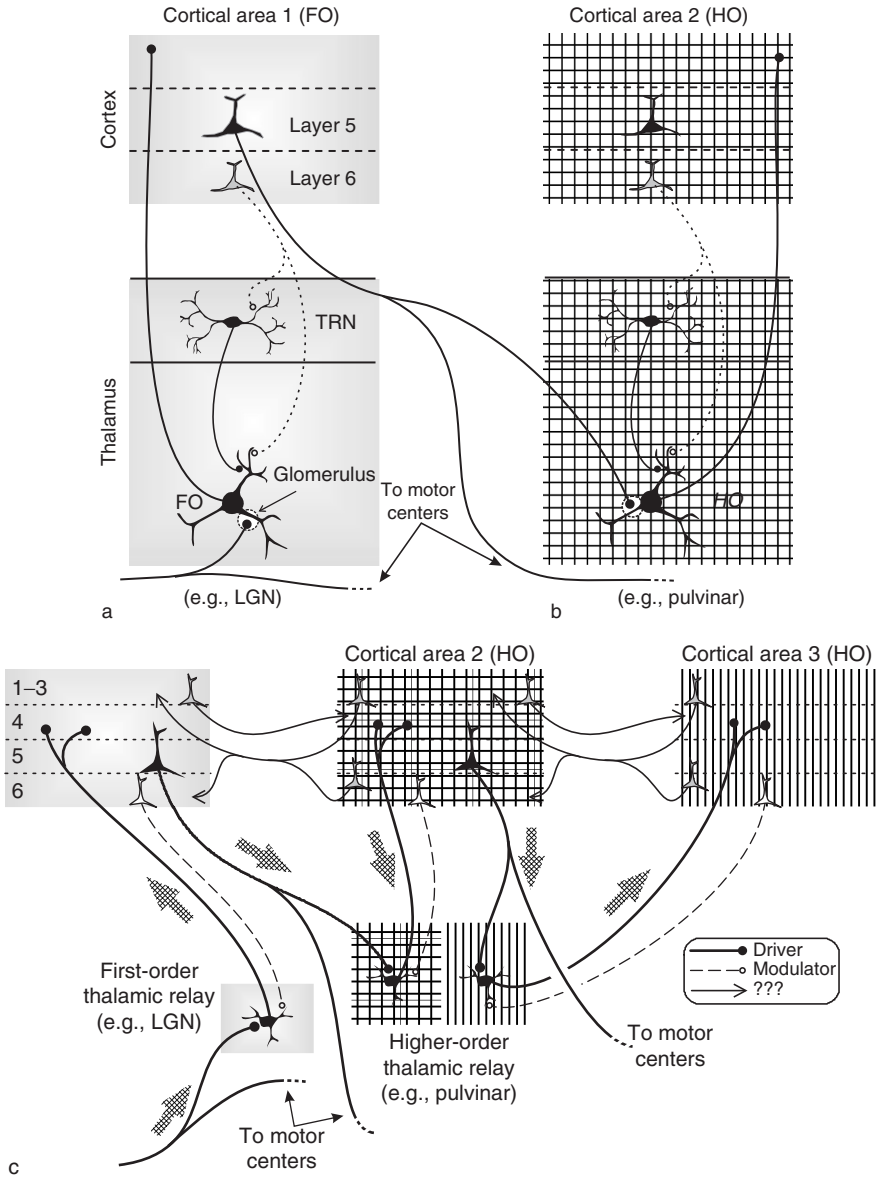

Figure 6 Schematic diagrams showing organizational features of first- and higher-order thalamic nuclei. (a, b) Distinction between first-order and higher-order thalamic nuclei. A first-order nucleus (a) represents the first relay of a particular type of subcortical information to a first-order or primary cortical area. A higher-order nucleus (b) relays information from layer 5 of one cortical area to another cortical area. This relay can be between first- and higher-order cortical areas as shown or between two higher-order cortical areas. The important difference between them is the driver input, which is subcortical (a) for a first-order thalamic nucleus and from layer 5 of cortex (b) for a higher-order one. Note that all thalamic nuclei receive an input from layer 6 of cortex, which is mostly feedback, but higher-order nuclei in addition receive a layer 5 input from cortex, which is feed-forward. (c) Role of higher-order thalamic nuclei in corticocortical communication. This involves a projection from layer 5 of cortex to a higher-order thalamic relay to another cortical area. As indicated, the role of the direct corticocortical projections, driver or modulator, is unclear. Note that in all drawings the driver inputs, both subcortical and from layer 5, are typically from branching axons, the significance of which is elaborated in the text. FO, first order; HO, higher order; LGN, lateral geniculate nucleus; TRN, thalamic reticular nucleus. Reprinted from Sherman SM (2005) Thalamic relays and cortical functioning. *Progress in Brain Research* 149: 107–126.

nucleus for sounds; examples of higher-order relays for these same sensory modalities, respectively, are most of the pulvinar, most of the posterior medial nucleus, and most of the medial and dorsal (or nonlemniscal) portion of the medial geniculate nucleus. We say 'most' here, because as defined by cytoarchitectonic boundaries, a minor part of these higher-order nuclei may relay subcortical driver inputs. Thus, there are small retinorecipient and tectorecipient zones of the pulvinar, a spinothalamic zone of the posterior medial nucleus, and an inferior collicular input to the nonlemniscal part of the medial geniculate nucleus that may be first-order relays. This has to be clarified, and it will not be considered

further here, but it does point up a potential shortcoming of classically defined, cytoarchitectonic boundaries for functional thalamic relays. The key to this division of thalamic relays into first and higher order is the observation that the layer 5 inputs to relay cells have the same properties as do the subcortical drivers (e.g., retinal input to the LGN and medial lemniscal input to the ventral posterior nucleus). Support for this can be found in Table 1: note from the first two columns of Table 1 that the layer 5 input to higher-order relays matches retinogeniculate input on all criteria; in contrast, the second and third columns show that the corticothalamic inputs from layers 5 and 6 differ on all criteria.

Branching of Driver Afferents to Thalamus

Another feature shown in Figures 6(a) and 6(b) is that the driver inputs to both first- and higher-order relays are borne mostly or wholly via axons that branch, with one branch innervating thalamic relay cells and the other innervating extrathalamic targets in the brain stem and spinal cord. For instance, most or all retinogeniculate axons branch to innervate the pretectum and/or superior colliculus, and, similarly, most or all layer 5 corticothalamic axons branch to innervate targets in the pons, midbrain, medulla, and sometimes even spinal cord. Limited data are consistent with a similar arrangement for relays of somatosensory and auditory information. RW Guillery has described this feature of driver afferents and suggested what its functional significance might be; this is briefly outlined below. This branching of afferent drivers to thalamus appears to be a general feature of thalamic relays and is not limited to the LGN and pulvinar.

The main extrathalamic targets of these branches seem to what can generally be described as motor centers. Thus, retinogeniculate axons branch to innervate pretectal and superior collicular targets implicated in eye movements, pupillary control, etc. Similarly, the layer 5 corticothalamic axons branch to innervate targets in brain stem and sometimes spinal cord that also appear to have motor functions. One interpretation of this pattern is that the information actually relayed by thalamus relates to motor commands, starting with first-order relays as perhaps quite crude commands that are constantly upgraded with further cortical processing and effected via higher-order layer 5 outputs from cortex. This notion implies that even first-order sensory processing, for instance, via the LGN, involves processing of motor commands, a notion that stands conventional views of early visual processing on its head. That is, conventionally, primary visual cortex (V1) is generally viewed as a purely sensory structure, and this view seems at odds with the idea that V1 is processing motor information. Furthermore, as already noted, V1 (and, indeed all cortical areas so far studied) has a layer 5 projection that branches to innervate pulvinar and extrathalamic motor targets, so that even the corticofugal outputs of V1 have a motor tag according to this perspective. Indeed, the whole notion that V1 or any other visual, auditory, or somatosensory area is purely 'sensory' is challenged by the observation that all of these areas have a motor output.

Role of Higher-Order Thalamic Relays in Corticocortical Processing

Figure 6(c) illustrates the suggested role played by higher-order thalamic relays. Information first reaches cortex via first-order relays, such as the LGN. Further processing of information as it is passed on to higher extrastriate visual cortical areas is relayed through higher-order thalamic nuclei. This can involve a number of hierarchical levels of both cortical and thalamic processing. The obvious question raised here is: if the cortico-thalamo-cortical pathways involving higher-order thalamic nuclei represent a significant information route, what of the direct corticocortical projections? The answer, simply, is not yet available, but to help to clarify the issue here, it is helpful to consider the three obvious hypotheses that follow.

Hypothesis 1: All information is relayed via higher-order thalamic nuclei One possibility is that all of the direct corticocortical pathways are modulators, in which case all information between cortical areas is relayed via the thalamus. One conclusion that could be drawn here is that all new information that reaches cortex, whether originating from a subcortical source such as the retina or from another cortical area, benefits from a thalamic relay. That is, for the same reason that retinal information is relayed by the LGN and does not project to visual cortex directly, information from one cortical area to another is relayed through thalamus. Benefits could include gating properties of the thalamus, the burst/tonic transition, etc.

A key challenge to this concept is whether or not higher-order relays such as the pulvinar have enough neurons to relay all of the requisite information needed for cortical processing. The pulvinar is indeed the largest thalamic nucleus and dwarfs the LGN. However, pulvinar neurons are orders of magnitude fewer than those in any cortical area, which poses a severe bottleneck on information transfer. Nonetheless, a very small percentage of visual cortical neurons are represented by the layer 5 efferents that could provide the afferent link in the cortico-thalamo-cortical pathway, and these numbers do not seem to pose a limitation on the role of the pulvinar as a central relay structure between cortical areas. We can thus ask

whether the limited number of layer 5 efferents to pulvinar is sufficient to project all of the information processed by a cortical area, such as V1. Unfortunately, we as yet have no answer to this question, because we simply do not know the nature of neural coding of this information that is passed on, and our ignorance here is such that we cannot rule out the possibility that the small number of layer 5 efferent cells is sufficient for this task. It is also possible that the full extent of information processed in a cortical area requires an additional, corticocortical route, the case to which we now turn.

Hypothesis 2: All information is relayed via direct corticocortical pathways The idea that the cortico-thalamo-cortical pathways involving higher-order thalamic nuclei serve as an information conduit implies that the relevant corticothalamic and thalamocortical projections are drivers. There is some evidence that the layer 5 inputs to higher-order thalamic relay cells act as drivers, but there is no direct evidence that the companion thalamocortical projections are drivers. Evidence from thalamocortical projections from first-order relays indicate that they behave essentially like drivers, so it seems plausible that this would extend to thalamocortical projections more generally. However, one idea for pulvinar projections to cortex is that these serve to regulate attentional responses, which, in turn implies that these projections could act as modulators. We need empirical evidence on the nature of thalamocortical projections from higher-order thalamic nuclei. If such evidence indicates that these higher-order thalamocortical inputs are drivers, then at least much information passed between cortical areas involves higher-order thalamic relays in a cortico-thalamo-cortical route. If, instead, the evidence is that these inputs are modulators, then we would conclude that virtually all corticocortical processing is based on direct corticocortical projections.

Hypothesis 3: Information is relayed in parallel by both pathways Perhaps the most likely notion is that the higher-order cortico-thalamo-cortical and direct corticocortical pathways represent two parallel, largely independent, and complementary routes of information flow. One example of this would be that the very large corticocortical projection handles all of the details of information that must be analyzed about the environment, and the cortico-thalamo-cortical projections inform the target cortical area about motor commands initiated by the source area. This is a more limited form of information but is essential, because higher-order cortical areas must maintain a real-time appreciation of how motor commands affect sensory processing. For example, higher visual cortical areas need to be able to factor in eye movements that cause the visual world to move on the retina and not view these as movement in the environment. This example of the limited sort of information carried by the cortico-thalamo-cortical pathways is consistent with the motor branches of the layer 5 axons described above.

Two further points need to be emphasized here. First, even if both pathways are involved in information flow, there is an important distinction to be made. Whatever information is carried by direct corticocortical connections, this remains in cortex and is thus different in kind from information carried by the layer 5 outputs to higher-order thalamic nuclei, because, as just noted, these layer 5 axons branch to carry the same information to various extrathalamic, subcortical targets. Second, this assumes the possibility that the driver/modulator distinction makes sense for intracortical pathways, but even if some corticocortical projections carry information, the massive potential problem remains to determine which pathways are modulators and which are drivers. Identifying the subset of drivers among these, and the subset may well be small, along with a full appreciation of the cortico-thalamo-cortical pathways, would allow the creation of a more complete and accurate hierarchical scheme for cortical processing.

Overview Figure 7 summarizes some of the key differences between the conventional view of corticocortical processing and the alternative view offered here. In the conventional view, information is relayed by thalamus to sensory cortex and passes within cortex to sensorimotor and then motor cortex before an output is generated to motor centers (**Figure 7(a)**). One problem with this is that it provides no specific role for most of thalamus, which we have defined as higher order, although there are suggestions that some of these thalamic nuclei could play a modulatory role in cortex related to attention. The alternative view (**Figure 7(b)**) differs from the beginning, since initial information to be relayed via a first-order thalamic nucleus reflects information sent to motor structures, perhaps reflecting an early motor command. From primary cortex, information can be relayed to other cortical areas via higher-order thalamic nuclei, and this can continue through several hierarchical stages. Also, each of these further thalamo-cortico-thalamic projections involves a layer 5 corticothalamic axon that branches to innervate extrathalamic motor structures as well as thalamus. The role of direct corticocortical pathways remains unclear in this view, but it is plausible that there are two information routes operating independently and in parallel, one the direct corticocortical route and the other, the cortico-thalamo-cortical route.

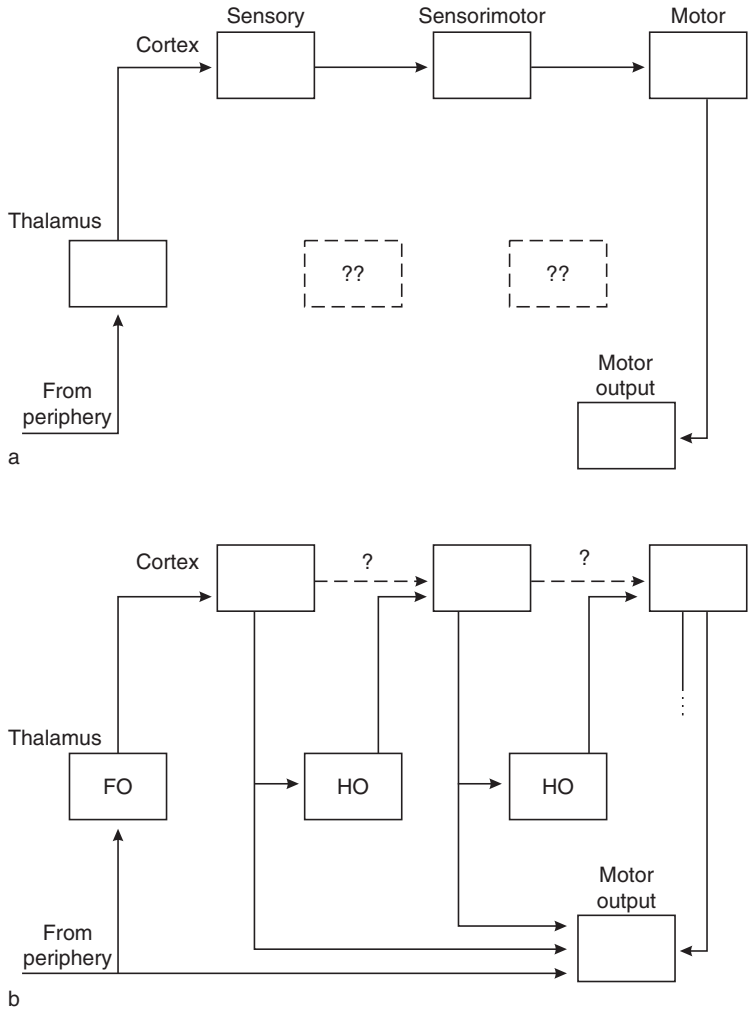

Figure 7 Comparison of conventional view (a) with the alternative view proposed here (b). The role of the direct corticocortical connections in (b) (dashed lines) is questioned (see text for details). FO, first order; HO, higher order. Reproduced from Sherman SM (2005) Thalamic relays and cortical functioning.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

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

Conclusions

We have come a long way from the bad old days when the thalamus was seen as a dull, machinelike relay, acting up in an interesting fashion only during epilepsy or slow-wave sleep. To a large extent, this misconception grew out of the success of the receptive field approach to the study of sensory systems, particularly vision. Studies of the retina showed that receptive fields become increasingly complicated as one ascends synaptic hierarchies, leading ultimately to the classic center/surround receptive field of ganglion cells projecting to the LGN. This process continues across synaptic hierarchies in cortex, providing receptive fields there with exquisite sensitivity to orientation, direction of movement, spatial frequency, stereoscopic depth, etc. We believe that this receptive field elaboration in retina and cortex is ultimately used to encode all features of the sensory environment. The one synapse in the visual system across which no significant receptive field elaboration occurs is the retinogeniculate synapse, since the same basic center/surround organization is seen in retinal afferents and their target geniculate

relay cells. Because of the prevalent receptive field chauvinism dictating how one determined functional organization, this led to the notion that the LGN specifically and thalamus more generally represented an uninteresting, simple relay.

We can now turn that view on its head. Indeed, while the rest of the visual and other sensory systems are engaged in receptive field elaboration, the thalamus has a completely unique role to play in information processing. Recent appreciation of the complex cell and circuit properties of thalamus make it clear that it is anything but simple and uninteresting in its functioning. These properties serve to regulate the flow of information to cortex through mechanisms such as gain control of the retinogeniculate synapse (or equivalent for other nuclei), the burst/tonic transition, etc., and here we are probably just seeing the tip of the iceberg, given the preponderance of modulatory pathways and voltage-gated conductances in addition to the T channels than can be manipulated. There is also the point that thalamus is not there just to get information to cortex but continues to play a significant role in corticocortical communication.

The challenge for students of the visual system is at least twofold. One is to gain a better appreciation of how and under what conditions information is affected before being relayed by the LGN or pulvinar to cortex. The other is to address questions about the pulvinar. One of the great problems here is that we have no complete map of pulvinar that includes a full demarcation of what regions of pulvinar innervate which regions of cortex and which are innervated by each cortical area, with a separate mapping of layer 5 and layer 6 inputs. Given these variables and the presence of more than 30 visual cortical areas with which the pulvinar is involved in rhesus monkeys and humans, it may be that more than a hundred separate pulvinar regions remain to be discovered. This is a daunting task and should be seen as one of the major challenges for future studies of the visual system.

See also: Thalamus and Oculomotor Control; Thalamus: Evolution in Vertebrates; Visual Cortex in Humans.

Further Reading

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