Thalamic Relay Functions and Their Role in Corticocortical Communication: Generalizations from the Visual System

Review

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Summary

All neocortical areas receive thalamic inputs. Some thalamocortical pathways relay information from ascending pathways (first order thalamic relays) and others relay information from other cortical areas (higher order thalamic relays), thus serving a role in corticocortical communication. Most, possibly all, afferents reaching thalamus, ascending and cortical, are branches of axons that innervate lower (motor) centers, so that thalamocortical pathways can be viewed generally as monitors of ongoing motor instructions. In terms of numbers, the thalamic relay is dominated by synapses that modulate the relay functions. One of the roles of these modulatory pathways is to change the transfer of information through the thalamus, in accord with current attentional demands. Other roles remain to be explored. These modulatory functions can be expected to act on corticocortical communication in addition to their action on ascending pathways.

Introduction

Direct corticocortical connections are widely regarded as providing the functional properties of most cortical areas other than primary sensory areas (Felleman and Van Essen, 1991; Van Essen et al., 1992; Kandel et al., 2000). We propose that transthalamic corticocortical pathways play a crucial role. All areas of neocortex receive afferents from the thalamus. Where, as in the primary visual cortex (e.g., Hubel and Wiesel, 1977), cortical function has been most closely studied, the receptive field properties of cortical cells depend on this thalamic input, which can, therefore, be regarded as the "driver" input (Sherman and Guillery, 1998, 2001). That is, the basic information for the neural computations in these cortical areas is carried in the thalamic afferents. This is so even though these afferents represent only a small percentage of all of the synaptic inputs to the cortical cells[1] (Ahmed et al., 1994; Latawiec et al., 2000). The extent to which many other cortical areas receive key driver inputs from the thalamus is currently unexplored. Such inputs are likely to play a far more significant role in cortical function than is currently recognized.

Afferents that provide driver inputs to the thalamus are of two distinct types. One comes from ascending pathways, carrying information from the sensory periphery and from lower brain centers such as the mamillary

bodies or the cerebellum, and the other comes from the cells in layer 5 of cortical areas that, as noted above, are themselves in receipt of thalamic driver inputs (Sherman and Guillery, 2001). The former have been called "first order" afferents and relays because they represent the first relay of a specific kind of input to cortex, and the latter, "higher order" because they represent a second, third, or higher stage of processing through a thalamocortical pathway. Relays to primary sensory areas, to motor cortex and cingulate cortex, are largely or entirely first order, whereas relays to most other cortical areas will probably prove to be either higher order or a mixture of first and higher order.

The majority of afferents to the thalamus are not drivers, but are modulators. Thus only 5%–10% of synapses onto layer 4 cells in cortex are from geniculate afferents (Ahmed et al., 1994; Latawiec, 2000). The modulators can change the nature of the relay but do not significantly alter the receptive field properties. The majority come either from cortex or from the brain stem, and can act directly or through an inhibitory relay in the thalamic reticular nucleus or thalamic interneurons.

Most, possibly all, of the pathways that bring driving afferents to the thalamus, whether from subcortical sites or from layer 5 of cortex, carry information that is also sent, by branching axons, to lower motor centers. That is, the information that the thalamus sends to cortex, both first and higher order, represents a copy of instructions that are concurrently being sent to motor centers, so that thalamocortical pathways can be viewed as monitors of motor instructions, rather than simple relays in sensory systems.

This summary of the thalamus as a relay that keeps all of neocortex informed about ongoing motor instructions from subcortical and also from cortical centers says nothing about the functional nature of the thalamic relay itself. We here look at this problem in relation to the connectional organization of the visual relays in the thalamus. We first look more closely at the distinction between drivers and modulators, describing how each group is characterized in terms of its structure and synaptic connections in the thalamus. This provides the basis on which we can compare first and higher order relays, showing that the driver inputs to higher order relays come from the cortex. We then explore the functional organization of thalamic connections, focusing first on the lateral geniculate nucleus, which is the best studied first order relay in the thalamus, and then, using the same ground rules as far as possible, we consider the pulvinar, a higher order visual relay.

Drivers and Modulators

There is a common organizational pattern, in terms of cell types, axonal and dendritic arbors, and synaptic relationships, that is seen throughout the thalamus of all mammals, and in most thalamic nuclei (Jones, 1985; Sherman and Guillery, 2001), with only a few exceptions that are not relevant to this review. One of the keys to understanding the functioning of any thalamic relay is
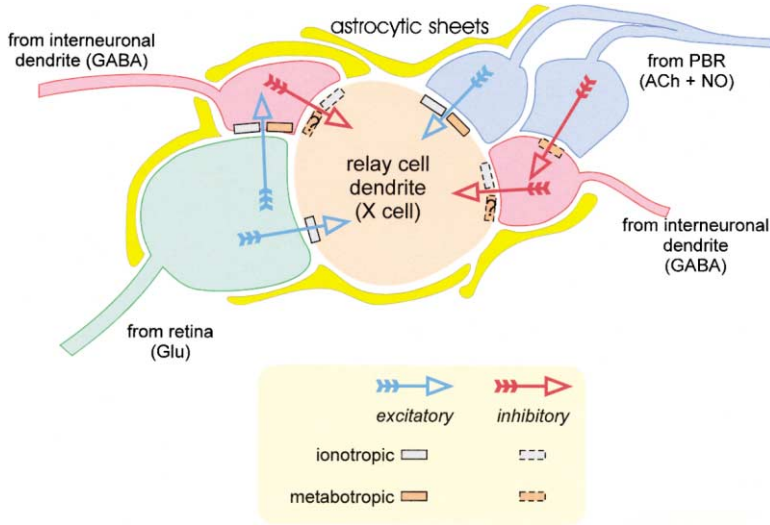
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Figure 1. Schematic View of Triadic Circuits in a Glomerulus of the Lateral Geniculate Nucleus in the Cat

The arrows indicate presynaptic to postsynaptic directions. The question marks postsynaptic to the dendritic terminals of interneurons indicate that it is not clear whether or not metabotropic (GABA$_B$) receptors exist there.

identifying which of its inputs are drivers and which are modulators (Sherman and Guillery, 1998). In first order thalamic relays, the driving afferents are readily recognized by their light and electron microscopic appearance.

General Features of Drivers

Golgi preparations, injections into single axons of axonally transported markers, and electron microscopic studies have shown that the drivers in first order nuclei have relatively large synaptic terminals with a characteristic fine structural appearance, resembling the mossy axon terminals of the cerebellum. They make multiple complex contacts with dendrites of relay cells and interneurons, often forming a characteristic "triadic" junction described below (see Figure 1), and these are commonly in a zone that lacks astrocytic processes but is surrounded by sheets of astrocytic cytoplasm. Because of their resemblance to the glomeruli of the cerebellum, these zones have also been called "glomeruli," and they give thalamic nuclei a distinct appearance. We recognize these afferents as driving afferents because they come from the pathways that are known to be the primary driving afferents in sensory thalamic relays such as the visual, auditory, and somatosensory relays. Other such driving afferents for first order relays come from the cerebellum (Harding, 1973; Kultas-Ilinsky and Ilinsky, 1991) and the mamillary nuclei (Somogyi et al., 1978), and for higher order relays, axons with strictly comparable morphological characteristics come from layer 5 of cortex. The structure and synaptic relationships of these corticothalamic terminals have been demonstrated by electron microscopy for axons arising in somatosensory cortex (Hoogland et al., 1991), visual cortex (Mathers, 1972; Ogren and Hendrickson, 1979; Feig and Harting, 1998), auditory cortex (Bartlett et al., 2000), and frontal cortex (Schwartz et al., 1991); and light microscopic studies of individual axons have demonstrated their cortical origin from layer 5 and their characteristic terminal structure for axons from somatosensory (Bourassa et al., 1995), visual (Bourassa and Deschênes, 1995; Vidnyánszky et al., 1996), and auditory cortex (Rouiller and Welker, 1991; Ojima, 1994). Where the transmitter has

been identified, these driving inputs, whether to first or higher order thalamic relays, are glutamatergic (Sherman and Guillery, 2001). Most tellingly, for the view that these act as drivers in the thalamus, they not only share all of the major features of the ascending drivers but, as summarized below, where their action has been tested, they differ from modulators because when they are silenced, the receptive field properties of the higher order thalamic relays are lost (Bender 1981; Diamond et al., 1992).

Recent studies have shown a few corticothalamic axons from layer 5, having the appearance of drivers, going to nuclei that also receive ascending afferents, and this suggests that there are regions of the thalamus where first and higher order relays are likely to be intermingled (Rouiller et al., 1998; Darian-Smith et al., 1999; Kakei et al., 2001), and for this reason we refer to first and higher order "relays" rather than "nuclei." The tectal recipient zone of the pulvinar may prove to be another such mixed relay; reports concerning the fine structural appearance of the tectal afferents have varied (Mathers, 1971; Partlow et al., 1977; Robson and Hall, 1977).

Several recent reports, based on injections of single or small numbers of axons, have stressed that the axons from cortical layer 5 cells that innervate thalamic relays do so with branches of axons that descend to the midbrain or to lower centers (Casanova, 1993; Deschênes et al., 1994; Rouiller and Welker, 2000; Guillery et al., 2001). That is, they are sending to the thalamus (and through the thalamus to the cortex) copies of messages that are going to lower centers; generally these are centers concerned with motor control, although a precise analysis of the lower terminal distribution of these axons is usually not available. It may be important to recognize that a connectional and functional analysis of the terminal sites of these axons could provide critical clues for understanding the nature of the messages that the thalamic branch conveys to the higher order thalamocortical pathways.

At present it is too early to know whether this branching pattern of the corticothalamic drivers to higher order relays is characteristic of all higher order

relays, although it has been reported for several. However, it may well prove to be so since it is, like most of the other features that characterize the drivers, seen for both first and higher order relays. Examples of branched afferents to the thalamus include the retinofugal pathways, where most retinal axons that have terminals in the lateral geniculate nucleus also send branches to the midbrain (Dreher et al., 1985; Sur et al., 1987; Tamamaki et al., 1994; Tassinari et al., 1997). Other examples are cerebellar afferents to the ventral lateral thalamic nucleus that also send branches to the red nucleus and tegmental reticular nucleus (McCrea et al., 1978; Shinoda et al., 1988), and mamillothalamic axons are branches of mamillotegmental axons (Kölliker, 1896; Guillery, 1961). The medial lemniscus comes from nuclei that are innervated by axons having rich connections in the spinal cord (Cajal, 1911; Brown et al., 1977), and the inferior colliculus transmits auditory inputs to the thalamus and also has pathways to the superior colliculus (Harting and Lieshout, 2000) and rich descending connections (Shore et al., 1998; Vetter et al., 1993). These connections suggest that the thalamus should not be seen, as often it is, as a "screen" for sensory inputs that are passed to cortex where they can play a role in perceptual processes. Rather, it is a relay that is sending information to cortex about instructions that are currently being sent to lower motor centers.

General Features of Modulators

In addition to the driver inputs, all relay cells in the thalamus, first and higher order, receive a rich innervation from the brain stem, from the thalamic reticular nucleus, and, to a greater or lesser extent, from local interneurons; these can all be regarded as modulators (Sherman and Guillery, 2001). Further, all thalamic relays receive a layer 6 modulatory input from cortex (only the higher order relays receive a driver input from layer 5). Figure 2 shows the major modulatory pathways schematically and also shows the transmitters (and receptors) used: cortical inputs are glutamatergic; the thalamic reticular and interneuronal inputs are GABAergic; and the parabrachial brain stem inputs are cholinergic, although these inputs may use nitric oxide as well. Not shown for simplicity are small inputs from the brain stem that are noradrenergic and serotonergic, and from the hypothalamus that are histaminergic.

The cortical layer 6 afferents have a characteristic and quite distinct light and electron microscopic appearance, do not form triads, are rarely or never seen in glomeruli, and make simple axodendritic synaptic junctions. They contact peripheral dendritic segments of relay cells in contrast to the drivers, which contact proximal dendrites (Wilson et al., 1984; Vidnyánszky and Hámori, 1994; Eriṣir et al., 1997). In contrast to the layer 5 afferents to thalamus, these axons do not have extradiencephalic descending branches, but they characteristically have branches that terminate in the thalamic reticular nucleus, which the axons from cortical layer 5 lack. We regard these as modulators because in first order relays, which receive layer 6 but no layer 5 afferents, cortical inactivation produces no major changes in the receptive field properties of the thalamic relay cells (Kalil and Chase, 1970; Geisert et al., 1981; McClurkin and Marrocco, 1984; McClurkin et al., 1994), nor do the relay cells under normal conditions show any of the properties
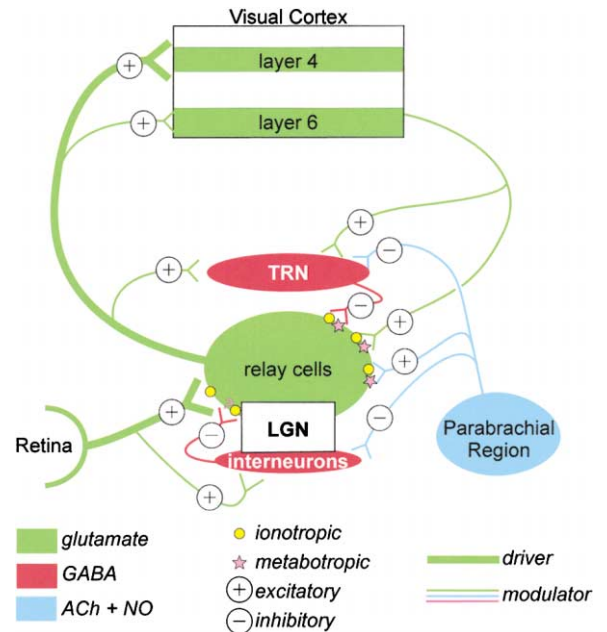

Figure 2. Schematic Representation of Synaptic Circuitry in the Lateral Geniculate Nucleus of the Cat

As in Figure 1, the question mark postsynaptic to interneuronal input to relay cells indicates uncertainty regarding the presence of GABA_B receptors. For simplicity, no distinction is made between dendritic and axonal outputs of interneurons onto relay cells, and triadic circuits are not shown.

that characterize the layer 6 cells (Gilbert, 1977; Gilbert and Wiesel, 1985; Sherman, 1985). This is in contrast to higher order relays that receive layer 5 afferents, where cortical inactivation produces a complete loss of receptive fields (Bender, 1983; Diamond et al., 1992), and where receptive field properties often resemble those in the cortical areas that give rise to the layer 5 afferents (Chalupa and Abramson, 1989; Casanova, 1993).

The axons that come from the brain stem resemble the layer 6 afferents, but contact more proximal parts of dendritic segments and, unlike the cortical afferents, often participate in triads (see below and Figure 1; Eriṣir et al., 1997). Inputs from interneurons are inhibitory and tend to contact proximal dendrites; they come from both axons and dendrites of the interneurons; the modulatory axons from the thalamic reticular nucleus are also inhibitory, and tend to contact more distal dendrites (Wang et al., 2001). Whereas the interneuronal, reticular, and cortical modulators show clear patterns of topographic order, with small parts of the visual field represented in small parts of the pathway, the brain stem modulators show little or no topographic order. That is, the former are likely to be able to influence small sectors of the visual field at any one time whereas the brain stem afferents are more likely to have a global action.

Comparing the Arrangement of Drivers for First and Higher Order Visual Relays

In the first order visual relay (lateral geniculate nucleus), retinal afferents innervate relay cells, which then project to visual cortex, primarily but not exclusively to area 17.

Single cell recordings have shown that retinal ganglion cells are arranged as a mosaic of functionally and morphologically distinct cell types. In the cat, these have been classified as W, X, and Y cells and in the primate, as koniocellular (K), magnocellular (M), and parvocellular (P) types (for details of these cell types, see Sherman, 1985; Irvin et al., 1993; Hendry and Calkins, 1998; Hendry and Reid, 2000; Xu et al., 2001). These can be further subdivided into on-center and off-center, and each functionally distinct cell type is relayed through the lateral geniculate nucleus with little or no interaction between any two types. That is, there are distinct, independent, parallel pathways relayed through the thalamus. The relays often go through separate geniculate laminae, but the degree to which any two types are separated varies from one species to another, and even from one part of the visual field to another. Where two types share a lamina, as do the X and Y pathways and the on-center and off-center pathways in the cat, there is no evidence for any significant interaction, so that the laminar separation is not required for a functional separation of pathways, and is in fact one of the interesting mysteries of geniculate organization (Sherman and Guillery, 2001). In so far as we understand the lateral geniculate relay, our knowledge depends on tracing specific pathways having specific functional properties from localized regions of the retina through localized regions of the thalamus to localized regions of cortex. The localization is represented in two orthogonal dimensions. Retinal position, and thus visual field position, is represented along two dimensions that correspond to the geniculate layers and, where the functionally distinct types (X, Y, W, konio, magno parvo) are separated, this occurs perpendicular to the layers, along the "lines of projection," which represent single points in the visual field.

It is reasonable to ask how far the same approach can guide us to an understanding of the higher order visual relay represented primarily by the lateralis posterior and pulvinar nuclei, which for the sake of simplicity we will refer to jointly as the "pulvinar region." That is, to what extent can comparable studies of the connections of cells in the pulvinar region provide a guide about the nature of the inputs that these cells are sending to higher cortical areas? The most detailed studies of visual field representations and corticothalamic pathways are those of Updyke in the cat (Updyke, 1983; Hutchins and Updyke, 1989), who used electrophysiological recordings of receptive field positions and autoradiographic tracing methods. Corresponding details are far more difficult to extract from studies of the monkey, which also indicate clearly that there are several functionally distinct subdivisions in the pulvinar region, but which do not allow us to relate these subdivisions as clearly to visual field maps or to maps of related cortical areas (e.g., Bender, 1981; Adams et al., 2000).

Since Updyke's studies used tritiated amino acids to trace corticothalamic pathways, they did not differentiate between layer 5 (driver) and layer 6 (modulator) afferents. Some evidence about the distribution of these afferents is now becoming available from experiments that allow us to distinguish the corticothalamic drivers from the corticothalamic modulators (Bourassa and Deschênes, 1995; Vidnyánszky et al., 1996; Guillery et al., 2001), and these show that the drivers have very well localized terminals whereas the modulators are more widespread, and in this, the relationship is like that in the lateral geniculate nucleus (Bowling and Michael, 1984; Sur et al., 1987; Murphy et al., 1999). However, in contrast to the lateral geniculate nucleus, there are examples in the cat of drivers and modulators, recognizable on the basis of their light microscopic appearance, that come from the same cortical column, and so presumably have comparable receptive fields, and these form reciprocal terminal zones in the pulvinar region (Guillery et al., 2001). That is, the small terminal focus of the drivers is essentially free of the modulators from the same cortical column, but is surrounded by them. Further, closely adjacent parts of the pulvinar region receive different patterns of drivers and modulators from distinct cortical areas. In the cat, areas 17, 18, and 19 send small driver foci to the same thalamic cell division (lateral posterior), which receives modulators primarily from area 19, but an adjacent region (pulvinar) receives drivers and modulators from area 19, not 17 or 18. That is, modulators from one cortical area can act on relay cells that receive drivers from another area.

In the cat, the pulvinar region receives afferents from other cortical areas as well, and a "line of projection," representing a small part of the visual field, goes through several zones that are distinguishable in terms of their cortical inputs (Updyke, 1981, 1983; Hutchins and Updyke, 1989). The drivers from cortical areas 17, 18, and 19 are focused around one part of such a line of projection and they can be regarded as providing some of several functionally distinct, parallel pathways that go to the pulvinar region from several functionally distinct cortical areas. That is, pulvinar cells, like geniculate cells, act as relays for a number of distinct parallel pathways, each likely to have distinct functional properties. However, understanding this mixture of functional properties will not be enough to understand the pulvinar relay.

One further, outstanding question concerns the degree to which there is, or is not, any functional interaction between drivers from different cortical areas. Are these like the W, X, and Y pathways, maintaining more or less independent lines through the thalamus with virtually no interaction, or is there some significant integrative function for this part of the thalamus? We also need to know whether all of the drivers coming from any one cortical area share the same functional properties. The fact that injections from a small cortical area produce small foci of driver terminals in thalamic zones that are widely separated along a line of projection suggests that there may be several functionally distinct layer 5 cells sending driver afferents to the thalamus from any one small piece of cortex.

In addition to the above, of course, we need a clear knowledge of the pattern of projection of the thalamic relay cells to cortex. We know that these parts of the thalamus send axons to several higher visual cortical areas, but at present we are entirely unable to relate the pattern of the mingled corticothalamic driver inputs to the pattern of the thalamocortical outputs. Finally, we need to know the extent to which the corticothalamic axons that project from the pulvinar region to higher cortical areas serve these areas as primary drivers, and

A

-55 mV
I_T inactivated
tonic mode

B

-70 mV
I_T de-inactivated
burst mode

40 mV

80 msec

0.3 nA

C

Response (spikes/sec)

-77mV
-83mV
-59mV
-47mV

Current Injection (nA)

D: Tonic Mode *(-65 mV)*

Spontaneous Activity

Visual Response

E: Burst Mode *(-75 mV)*

Spontaneous Activity

Visual Response
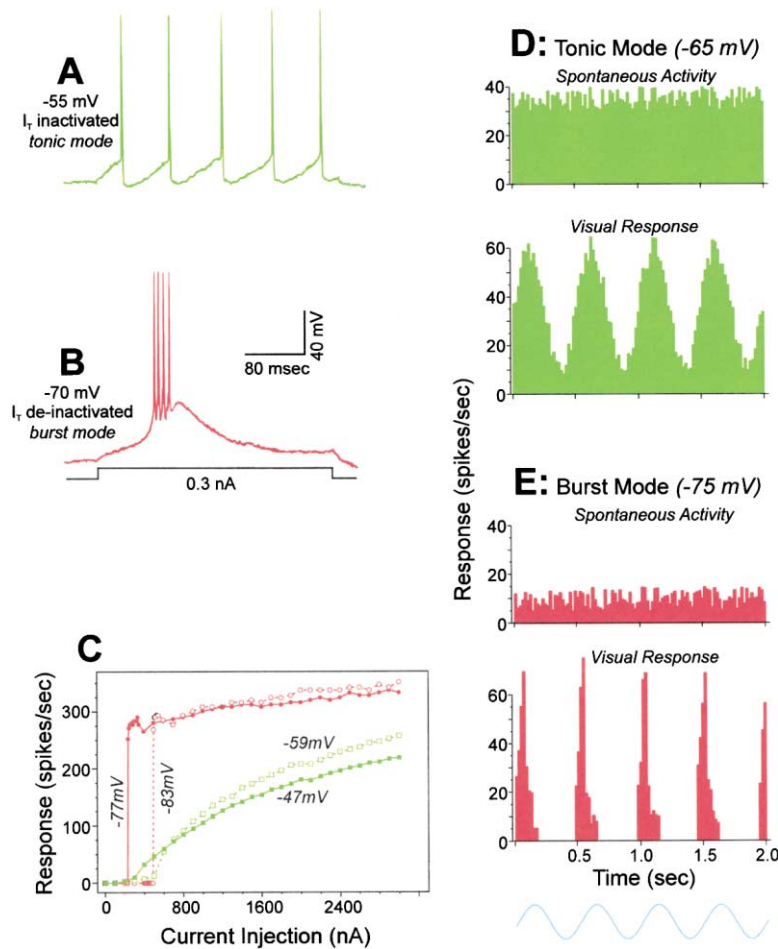
Response (spikes/sec)

Time (sec)

Figure 3. Properties of I_T and the Low Threshold Spike

These examples are from relay cells of the cat's lateral geniculate nucleus recorded intracellularly. (A) and (B) show voltage dependency of the low threshold spike during in vitro recording. Responses are shown to the same depolarizing current pulse delivered intracellularly but from two different initial holding potentials. When the cell is relatively depolarized (A), I_T is inactivated, and the cell responds with a stream of unitary action potentials as long as the stimulus is suprathreshold for firing. This is the *tonic mode* of firing. When the cell is relatively hyperpolarized (B), I_T is de-inactivated, and the current pulse activates a low threshold spike with four action potentials riding its crest. This is the *burst mode* of firing. (C) shows input-output relationship for another relay cell recorded in vitro. The input variable is the amplitude of the depolarizing current pulse, and the output is the firing frequency of the cell. To compare burst and tonic firing, the firing frequency was determined by the first six action potentials of the response, since this cell usually exhibited six action potentials per burst in this experiment. The initial holding potentials are shown. When in tonic mode, because the initial potentials were depolarizing (−47 and −59 mV), the input-output relationship is fairly linear. When in burst mode, because the initial potentials were hyperpolarizing (−77 and −83 mV), the input-output relationship is quite nonlinear and approximates a step function. (D) and (E) show some differences for geniculate neurons in the cat between tonic and burst modes during both spontaneous activity as well as responses to visual stimuli recorded in vivo. The visual stimulus was a drifting, sinewave grating, and the resultant contrast changes over the receptive field are shown below the histograms. Current injected through the intracellular recording electrode was used to bias membrane potential to more depolarized (−65 mV), producing tonic firing, or more hyperpolarized (−75 mV), producing burst firing. The responses are shown as average response histograms. The upper histograms show spontaneous activity when the grating stimulus was removed (or, more precisely, its contrast reduced to zero), and the lower histograms show the averaged response to four cycles of the grating drifted through the receptive field. During tonic firing (D), the spontaneous activity is relatively high, and the response to the grating has a distinctly sinusoidal profile. During burst firing (E), the spontaneous activity is relatively low, and the response to the grating no longer has a sinusoidal profile.

the extent to which they interact with the closely related corticocortical pathways.

For the lateral geniculate nucleus, we can understand some of the basic ground rules that govern the organization of the pathway from the retina to the cortex. For the corresponding higher order visual thalamic relays, we still have a long way to go before we can have a comparably clear understanding. However, for each of these thalamic relays, we also need to know what is happening in the thalamus. What is gained by having this relay, or better perhaps, what would be lost if, for instance, the eye were connected directly to the cortex? To answer this question, we need to look at the cell and circuit properties of the lateral geniculate nucleus.

Functional Properties of the Lateral Geniculate Nucleus
Relay Cell Properties

The response of relay cells to their driver inputs depends significantly on the intrinsic membrane properties of these cells. These are varied and consist mainly of cable properties, various "leak" conductances, and dynamic ionic channels, mostly gated by membrane voltage. Most are common to neurons in many other parts of the brain and will not be considered here (for details, see Sherman and Guillery, 2001). However, one that is particularly important for understanding thalamic relay cells and is found in all of them is I_T, which results from a voltage-gated Ca^{2+} conductance involving T (for transient) type Ca^{2+} channels distributed in the dendrites and somata. For details of the properties of I_T, see Jahnsen and Llinás (1984), Sherman and Guillery (1996, 2001), Hughes et al. (1999), and Sherman (2001); they will be briefly summarized here. Relative membrane depolarization, say above about −65 to −60 mV, inactivates I_T, preventing it from playing any role in cell responses. With I_T inactivated, the cell responds in *tonic mode* (Figure 3A). However, if the relay cell is hyperpolarized from rest by about 5 mV or more, I_T is de-inactivated and thus primed for action, being activated by the next suprathreshold depolarization or excitatory postsynaptic potential (EPSP). This activation produces an all-or-none

Ca^{2+} spike that propagates through the dendrites and soma, and this is known as the low threshold Ca^{2+} spike. It is typically large enough to activate a burst of several action potentials that ride its crest, and this produces the *burst mode* of firing (Figure 3B).

Switching between the tonic and the burst firing modes requires a change in membrane potential: depolarization switches the cell from burst to tonic mode by inactivating I$_T$, and hyperpolarization does the opposite by de-inactivating I$_T$. However, the switch is a complex function of voltage and time since the inactivation and de-inactivation requires that the change in membrane polarization last ≥50–100 ms. Both firing modes occur during wakefulness, and these modes have important implications for relay functions (Sherman, 2001). It is to be noted parenthetically that burst firing during certain phases of sleep and pathological conditions are rhythmic and synchronized across large regions of thalamus, and in these conditions, relay cells are relatively unresponsive to driver inputs. We do not consider this rhythmic bursting further here (for details, see Steriade and Llinás, 1988; Steriade et al., 1990, 1993). In contrast to this rhythmic bursting, the bursting during wakefulness is arrhythmic, and relay cells in the arrhythmic burst mode are quite responsive to driver inputs.

Circuit Properties

One interesting feature shown in Figure 2 is the nature of postsynaptic receptors related to the various afferents. These come in two basic types: ionotropic and metabotropic (Nicoll et al., 1990; Mott and Lewis, 1994; Recasens and Vignes, 1995; Pin and Duvoisin, 1995; Pin and Bockaert, 1995; Conn and Pin, 1997; Brown et al., 1997). Ionotropic receptors include AMPA for glutamate, GABA$_A$, and nicotinic receptors for acetylcholine; examples of metabotropic receptors are various metabotropic glutamate receptors, GABA$_B$, and muscarinic receptors for acetylcholine. Among many other differences, the ionotropic receptors operate with a more direct route between ligand binding and evoked postsynaptic potentials (PSPs), resulting in PSPs with relatively brief latencies (≤1 ms) and durations (typically mostly finished within 10–20 ms), whereas the metabotropic receptors work via second messenger pathways producing PSPs with longer latencies (∼10 ms or more) and durations (hundreds of ms or longer). Retinogeniculate synapses activate only ionotropic glutamate receptors, whereas each of the modulatory input pathways activates metabotropic receptors, and most also activate ionotropic ones (McCormick and Von Krosigk, 1992; Godwin et al., 1996a; Sherman and Guillery, 2001). It is not known whether any individual modulatory axons activate both receptor types. Another difference between ionotropic and metabotropic receptors is that, generally, ionotropic receptors are activated at lower rates of presynaptic firing than are metabotropic ones.

Because retinal inputs activate only ionotropic receptors, they produce relatively fast EPSPs, resulting in relatively fast transmission of signals to cortex. This also means that the relay cells can faithfully transmit stimuli at relatively high frequencies. If the EPSPs were very long, as would happen with metabotropic glutamate receptor activation, temporal summation would occur at much lower firing frequencies so that information in input signals having higher frequencies would be smeared and lost. Thus, the fact that retinal inputs activate only ionotropic receptors helps to preserve information, and it may be a hallmark of driver inputs that they activate only ionotropic receptors (Sherman and Guillery, 1998).

Conversely, because modulator inputs can activate metabotropic receptors, they can produce sustained (i.e., >100 ms) changes in membrane potential, leading to sustained changes in excitability of relay cells. Furthermore, changes in membrane potential must be sustained for >50–100 ms to change the inactivation state of I$_T$ and thus change the relay cell's firing mode between burst and tonic, and metabotropic receptor activation seems ideally suited for this. Indeed, there is evidence that activation of brain stem or cortical inputs to relay cells produces a sustained depolarization that inactivates I$_T$ and effectively switches the firing mode from burst to tonic (McCormick and Von Krosigk, 1992; Lu et al., 1993; Godwin et al., 1996b). It seems likely that the opposite—sustained hyperpolarization to de-inactivate I$_T$ and switch firing from tonic to burst—can be achieved by activating GABA$_B$ receptors via GABAergic inputs, particularly from the thalamic reticular nucleus. These cells, as seen in Figure 2, are themselves controlled from cortex and brain stem so that these extrathalamic inputs can effectively control firing mode via direct and indirect innervation of relay cells.

An important difference between the cortical and brain stem inputs, both direct and indirect, is topography. The corticogeniculate pathway is precisely mapped, so that cortex can control small, precisely localized relay cell populations, perhaps selectively controlling different cell classes or visuotopic representations. Brain stem inputs, in contrast, are poorly mapped, if at all, and thus activation of this pathway is likely to affect relay cells more globally.

Other voltage-gated currents also, like I$_T$, have fairly slow kinetics (e.g., I$_A$ and I$_h$), so it is likely that modulatory inputs operating via metabotropic receptors effectively control these as well. Thus we can see that the modulatory inputs can dramatically affect how relay cells respond to retinal inputs. An additional complication arises because most modulatory inputs also activate ionotropic receptors. It is not clear what the functional significance of this may be, but one suggestion is that activation of ionotropic receptors can begin a membrane voltage change earlier, and by the time these PSPs fade, the metabotropic receptors become activated: this could help to reduce the delay expected if only metabotropic receptors were involved in control of voltage-gated currents.

The Synaptic Triad

An unusual synaptic arrangement found throughout thalamus is the synaptic triad, which is schematically shown in Figure 1. This takes two slightly different forms, each involving as a central element the dendritic terminal of an interneuron, a terminal that is both pre- and postsynaptic, and indeed is the only postsynaptic, vesicle-containing terminal found in thalamus. The thalamic interneurons are the only thalamic cells so far described with extensive dendritic synaptic outputs. In addition, many, possibly all, possess a conventional axonal output. (For further details and discussion of the significance of this separate pattern of dendritic and axonal

outputs, see Sherman and Guillery, 2001.) In one form of the triad, which we call the retinal triad, a retinal terminal contacts both the interneuron terminal and a relay cell dendrite, with the interneuron terminal contacting the same dendrite. In the other, the brain stem triad, a single parabrachial axon innervates the interneuron terminal and relay cell dendrite with separate terminals, and again the interneuron terminal innervates the same relay cell dendrite. Retinal and brain stem triads generally, wherever they have been separately identified, involve different interneuronal terminals. The complex circuitry of Figure 1 is found in the glomeruli described above. Not all relay cells have their retinal inputs involved in such triads and glomeruli since in the cat's lateral geniculate nucleus, only X cells show this pattern, whereas Y cells have simple synaptic arrangements without significant numbers of triads or glomeruli (Wilson et al., 1984; Hamos et al., 1987).

It is not at all clear how the triads function, but identification of postsynaptic receptors involved (Figure 1) offers some clues. Cox and Sherman (2000) showed that the retinal innervation of the inhibitory interneuron terminal involves a metabotropic glutamate receptor (type 5), activation of which *increases* GABA release from the interneuronal terminal. In contrast, in the brain stem triad, the parabrachial innervation involves a muscarinic (M2) receptor, activation of which *decreases* GABA release. Three consequences are suggested here, although many more can be imagined, and none has yet been empirically tested. First, for the retinal triad, the innervation and receptor patterns suggest that retinal activation will produce monosynaptic EPSPs followed by disynaptic IPSPs in the relay cell. However, given the requirement noted above for higher afferent firing rates to activate metabotropic receptors, one can imagine that the disynaptic inhibition grows relatively stronger with increasing retinal activation. Since increasing stimulus contrast will increase retinal firing rates, this suggests that the effect of increasing contrast is to reduce contrast sensitivity, which suggests a form of contrast gain control, a process heretofore thought to be strictly cortical in origin (e.g., Ohzawa et al., 1982; Määttänen and Koenderink, 1991; Allison et al., 1993; Truchard et al., 2000), although it has not yet been much explored at the thalamic level (but see Felisberti and Derrington, 1999; Przybyszewski et al., 2000). Second, the timing of these effects for the retinal triad might also be interesting, because of the long-lasting PSPs via metabotropic receptors. For instance, one would predict that, after a period of strong retinal activation, the disynaptic IPSP would continue to be present hundreds of ms after the monosynaptic EPSPs faded away, and this could have significant effects on control of response mode. That is, after cessation of a strong retinal input, the persistent inhibition kept active by the triad could hyperpolarize the relay cell, switching it to burst mode, so that it will burst in response to the next retinal input. Third, the parabrachial triad seems to work differently in that relatively high firing rates in the parabrachial afferent will reduce any background GABA release from the interneuron terminal, resulting in a form of disinhibition for the relay cell.

There are some interesting possibilities for differential thalamic processing for X and Y cells that would also apply to other relay cells in other parts of thalamus depending on whether or not they are associated with triadic circuitry. As suggested above, the triadic circuitry associated with X cells provides a means for retinal and parabrachial inputs to affect relay cell properties in ways that are not available to Y cells and their counterparts in other parts of thalamus. However, since Y cells do have inputs from interneuronal axons, and since the interneurons of origin receive retinal and parabrachial afferents that affect the firing of their axonal outputs, circuits are available for retinal and parabrachial inputs via interneurons to affect Y cell activity, but probably not in the same way that the triadic circuits permit these inputs to affect X cells. For instance, the retinal input to interneurons that increases interneuronal firing rate and thus the axonal output activates only ionotropic glutamate receptors, and not metabotropic ones (McCormick and Von Krosigk, 1992), which, as Figure 1 shows, are activated by the retinal input to the dendritic output of interneurons. Thus, the suggestion above that increasing retinal activity would lead to relatively increased inhibition through the triad should not apply via the axonal outputs of interneurons.

Proposed Role of the Thalamus
Significance of a Thalamic Relay
A key question about thalamocortical relationships is: why does retinal input not project directly to cortex, or, why do we have thalamic relays at all? While we cannot yet completely answer this question, a consideration of the complex cell and circuit properties in the lateral geniculate nucleus points to some important relay functions. As already noted, the facts that relay cells can respond in two modes, burst and tonic, and that these modes have important implications for the nature of information relayed indicate at least one important role for the geniculate relay and for the modulatory input that controls response mode.

However, this is probably just the tip of the iceberg, and it seems likely that, as we learn more about functional cell and circuit properties, we shall appreciate more functions of the geniculate relay. For instance, there are many voltage-gated membrane currents other than I_T that exist in thalamic relay cells as in other neurons (e.g., I_A, I_h, and many others; for further details, see McCormick and Huguenard, 1992; Sherman and Guillery, 1996, 2001). These are likely to be as important as I_T in determining how information is relayed to cortex. These other currents, like I_T, tend to have relatively slow time constants for their voltage control, which suggests that the modulatory inputs and their activation of metabotropic receptors might prove key to their action, as seems to be the case with I_T. Also, in addition to control of voltage-gated conductances, active thalamic circuits represent the summing of excitatory and inhibitory inputs to relay cells, and the balance of these will affect the overall excitability of these cells to their driver inputs.

We are far from understanding the full range of relay properties affected by the cell and circuit properties of the lateral geniculate nucleus. Although we need to learn much more, one thing is clear: the lateral geniculate nucleus does not simply perform a trivial, machine-like passing on of retinal inputs and it is reasonable to extend

this to all thalamic relays. The role of modulatory afferents to thalamus in the control of messages that reach cortex needs exploration not just for first order relays, where we can understand that the thalamic relay influences the sensory messages that reach cortex at any one time, but also for higher order relays, where we must regard the thalamic relay as acting on the messages that pass from one cortical area to another. The nature of this action in the higher order relays is likely to represent a critical difference between the direct and the transthalamic corticocortical pathways in the way that information is passed from one cortical area to another.

First and Higher Order Thalamic Relays

Observations of the two distinct types of corticothalamic afferent lead to two conclusions basic for understanding the functional nature of corticocortical pathways. One, introduced above, is that information passed from the thalamus to any one cortical area is subject both in first and in higher order relays to modulatory influences. Some come from that same cortical area, and others (not shown in Figure 2) come from other cortical areas, from the brain stem, the thalamic reticular nucleus, and from interneurons. The other conclusion, and the more important one from the point of view of this review, is that there are thalamic relays that serve to transmit information from one cortical area to another, and that this is commonly, perhaps always, a copy of information that is sent to lower brain centers. That is, the driver inputs that reach the higher order cortical areas are about the executive decisions that the lower order cortical areas are issuing to lower centers in the central nervous system. Here it is necessary to stress that there are large areas of cortex that receive no known inputs from first order thalamic relays, and whose major thalamic input is coming from higher order relays.

The idea that higher order relays can play a key role in corticocortical communication needs to become a focus of future experimental studies. Currently there has been a general, implicit assumption that the many distinct cortical areas serving any one modality, as well as those that relate to more than one modality (Felleman and Van Essen, 1991; Van Essen et al., 1992; Kaas, 1995), communicate primarily, or only, by direct corticocortical connections (see Figure 4). One schema of corticocortical communications of visual areas (Figure 2 of Van Essen et al., 1992) shows visual information entering striate cortex from the thalamus, and then, in a roughly hierarchical, complex set of feedforward connections, passing from striate cortex to higher and higher areas, with many feedback connections as well. The pulvinar plays a trivial and unexplored role in this and other such schemas. Generally, where experimental results indicate communication from one cortical area to another, the connections that are postulated are direct corticocortical pathways, not transthalamic ones. On the basis of currently favored views, once information reaches cortex, it stays within cortex and sensory information is processed by a chain of corticocortical connections that eventually passes to areas of cortex concerned with motor outputs. Corticofugal pathways to lower centers from intermediate levels of cortical processing play no role in the proposed connections.

This is a crucial point. The cortical processing suggested by Figure 4 would proceed with no reference to
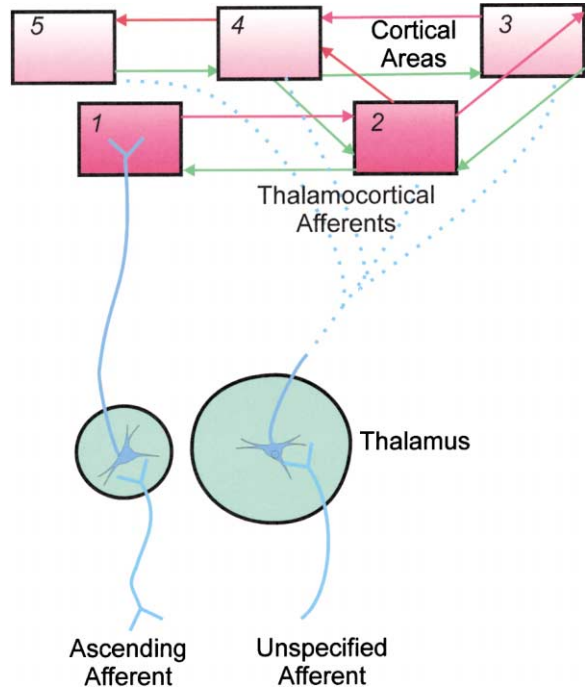

Figure 4. Schema to Show a Widely Accepted View of Pathways to Higher Cortical Areas

On the left is an example of a first order thalamic nucleus (FO) receiving its (blue) driving afferents from ascending pathways that come from (for example) the medial lemniscus, the optic tract, the inferior colliculus, the cerebellum, or the mamillary nuclei. These first order thalamic nuclei send their axons to primary receiving areas of cortex, represented by the (red) cortical area labeled 1 in the figure, and each of these cortical areas in turn sends a complex set of feedforward pathways, shown in red, to other cortical areas, represented here by cortical areas 2–5. Corticocortical feedback pathways are shown in green. Higher order thalamic nuclei (HO), such as the pulvinar, the lateral posterior, the mediodorsal, or the lateral dorsal nuclei, are represented by the larger circle on the right in the lower part of the figure. These receive afferents that are largely unspecified, and send widespread thalamocortical axons to higher cortical areas (2–5). These thalamocortical pathways are shown here as dotted lines because knowledge about the information that they carry to cortex plays little or no role in our current understanding of the functional organization of these cortical areas.

any of the ongoing outputs to lower centers from any of the participating cortical areas. However, such outputs arise at even the very first stages of cortical processing, from the layer 5 cells in primary cortical receiving areas such as V1, S1, or A1, and they are introduced into the processing functions of higher cortical areas through their thalamic branches. The roles in cortical functions of these higher order thalamic relays, for example, the pulvinar region for the visual pathways, the magnocellular division of the medial geniculate nucleus for the auditory pathways, the posterior nucleus for the somatosensory pathways, or the mediodorsal nucleus for the frontal lobes, most or all of which receive branches of layer 5 outputs, are essentially ignored in the current literature. We propose an alternative or modified schema for corticocortical communication, and this is shown in Figure 5. Here, the emphasis for information transfer is not on the direct corticocortical pathways, but
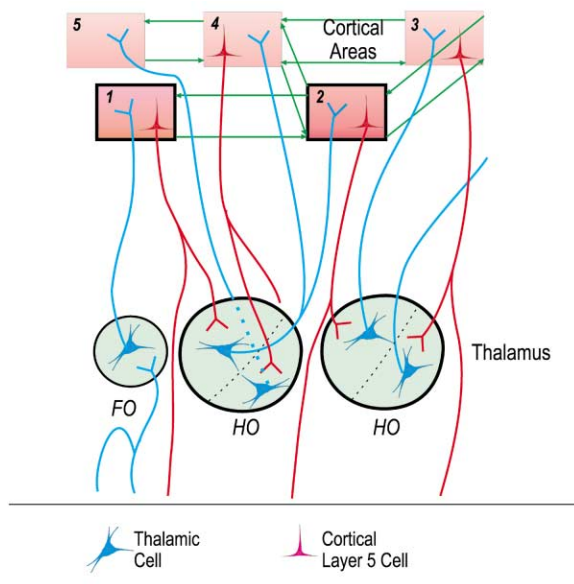
Figure 5. Schema to Show Thalamocortical Interconnections Proposed on the Basis of the Evidence Presented Here

The first order thalamic relay (FO) receives afferents as in Figure 4, but these afferents are now shown as branches of axons that innervate lower, motor centers. The first order relay sends thalamocortical axons to cortical area 1 and this, again, has feedforward and feedback connections with cortical areas 2–5. However, these cortical areas also receive transthalamic, that is, cortico-thalamo-cortical, connections from cortical area 1 and from other cortical areas through one or the other of the higher order (HO) thalamic relays shown on the right. Notice that the corticothalamic axons coming from the cortical layer 5 pyramids are also branches of long-descending axons going to motor centers.

rather on cortico-thalamo-cortical pathways involving higher order thalamic relays, which would appear to play an important role in providing one cortical area with information about the current outputs of another area.

The higher order relays in primates are significantly larger than the first order relays, and within the visual system, the pulvinar region sends afferents to many and probably all of the higher visual cortical areas. This component of corticocortical processing involving the transthalamic route must have functional consequences. Whatever the nature of the messages that the pulvinar region sends to cortex, they must play some role in defining the function of the recipient cortical areas. These messages can bring information about current outputs via long, descending pathways that other cortical areas are sending to the brain stem, and this is in contrast to the known direct corticocortical pathways, which would appear to be communicating some stages of ongoing cortical processing that stays strictly within cortex. It has to be stressed that, for the cortical areas that are most clearly understood in terms of their functional properties, such as V1 or S1, the information processing that has so far been most successfully analyzed has been shown to depend entirely on the thalamic inputs. There is no a priori reason, nor do we know of any experimental evidence, to suggest that other cortical areas are less dependent on their thalamic inputs.

The relative importance of the two pathways, the di-

rect corticocortical and transthalamic, is undefined at present. If the transthalamic pathway can be regarded as a significant input to higher cortical areas, then knowledge about the functional properties of the layer 5 cortical cells that provide driver input will prove crucial for understanding the functions of the higher cortical areas that receive this information through the thalamus. Since these layer 5 cells also provide the pathway for the executive output (to lower centers) of the prethalamic cortical area, one should expect to find a clear functional link between the instructions that a cortical area is sending to brain stem centers and the messages that are passed through the thalamus to higher cortical areas for further processing. Understanding the roles of the direct and the transthalamic corticocortical pathways will depend on two types of information, neither of which is available at present. One is the extent to which either serves as a driver or modulator. The other is the nature of the cortical activity represented by the cortical cells that give rise to one or the other of these two pathways. We know of no evidence that establishes whether the corticocortical axons are drivers or modulators.

One reason why the past focus has been on direct corticocortical pathways rather than on transthalamic pathways is because these latter pathways are not numerically impressive. We have seen that numerical superiority does not identify drivers. Afferents to any cortical area can probably be classified as drivers or modulators, like those of the thalamus. Drivers carry the main information but may represent a small minority, as for retinal input to relay cells of the lateral geniculate nucleus, or geniculate input to layer 4 cells of striate cortex. It is important to allow for the possibility that the great majority of inputs to cortex, as to thalamic relay nuclei, are modulators. Were one to consider large numbers of afferents as critical for defining drivers, one would not treat the lateral geniculate nucleus as a visual relay, the ventral posterior nucleus as a somatosensory relay, or the medial geniculate nucleus as an auditory relay: for instance, based on numbers, one might conclude that the lateral geniculate nucleus relayed information to cortex from parabrachial inputs in the brainstem. With this in mind, we suggest that the pattern of information flow among visual cortical areas needs to be reconsidered, allowing a much larger role for higher order thalamic relays than in current interpretations. The hypothesis that the transthalamic route is a major, possibly even the only, *driver* route for corticocortical communication is useful because it points to the need for an identification of drivers and modulators in cortical circuitry. It also focuses on the possibility that the thalamic gate, controlled by a complex population of modulatory pathways, may play a crucial role in controlling the messages that pass from one cortical area to another.

To put the role of the transthalamic pathways into the clearest possible relief, it is worth looking at the extreme (but perhaps unlikely) possibility that *all* direct corticocortical pathways are modulatory. Such a view would force a focus on the function of the higher order transthalamic pathways and may well reveal that these pathways can establish all of the information needed for corticocortical communication. Part of the logic of this idea is that it implies that all major driving inputs entering a cortical area must be relayed by thalamus, with all of

the advantages implied above for having thalamic relays in the first place.

It is also worth noting that, even if many of the direct corticocortical pathways prove to be drivers, there are two important differences between this route of information flow and the transthalamic one. First, as just noted, the direct corticocortical route has no thalamic "screening" imposed. The transthalamic pathways are subject to the many modulatory afferents that supply the thalamus. The modulatory role of the thalamic relay is important in "gating" information through first order relays and is likely to play a significant role in modulating the inputs that any area of cortex receives (Sherman and Guillery, 1998, 2001). Second, any messages involving the direct corticocortical routes are confined to cortex, whereas those passing via higher order thalamic relays are also sent, via branching axons from the layer 5 neurons, to lower brain centers concerned chiefly with motor control. That is, they are transmitting information about the outputs that cortex is currently sending to lower centers.

Conclusions and Some Outstanding Questions

We have described driver and modulator afferents to the thalamus on the basis of their structure, synaptic relationships, and, where known, their actions. The drivers, which carry the information that is transmitted to cortex, establish only a small proportion of all thalamic synapses; the great majority of thalamic synapses are made by modulators, which change the nature of thalamic transmission, without significantly affecting the nature of the information that is being transmitted. We have shown that the modulators can change the relay mode of thalamic cells between burst and tonic, and have argued that there are likely to be other actions by means of which the modulators can modify the way in which information is transferred through the thalamic relay. These remain to be experimentally defined.

There are two important observations of the thalamic afferents that can, for reasons we have outlined, reasonably be regarded as drivers. First, in addition to the classically recognized ascending afferents carrying sensory information to cortex, there are many drivers that come from the cerebral cortex and thus serve as a transthalamic route for corticocortical communication; and second, many, possibly all, of the thalamic afferents that are drivers are branches of axons (or come from cells innervated by branches of axons) that are going to motor centers. These observations lead us to conclude that for many cortical areas, there are important driver inputs that travel over a transthalamic corticocortical route that differ from the more widely recognized and more closely studied direct corticocortical pathways to higher cortical areas. We also conclude that most of the information that passes through the thalamus to the cortex represents messages that are also being sent to motor centers. That is, one can regard the thalamocortical relays, the first order relays going to the classical primary cortical areas, as well as the higher order pathways that go to higher order cortical areas, as monitoring ongoing motor instructions arising from cortical and subcortical centers, and this can lead to new questions about the functional significance of neuronal activity in these pathways.

These observations raise a number of questions about the thalamocortical pathways that merit experimental attention:

- What are the varieties of modulatory action that can act on thalamic relays, and how do they change the nature of thalamic transmission?
- What is the relationship between the direct corticocortical pathways and the transthalamic corticocortical pathways? Are both acting as drivers of cortical cells, or does only one have this action? What is the nature of the interaction of these two pathways in the cortex? Which of the direct corticocortical pathways represent driver inputs, and which modulator inputs?
- For the drivers that innervate the thalamus, what is the nature of the termination, synaptic relationships, and actions of the branches innervating motor centers? How does this information relate to the nature of the messages that are passing through the transthalamic pathways to higher cortical areas?
- Where two parallel driver afferents, either cortical or subcortical, innervate the same local region of the thalamus, is there significant functional interaction of these two pathways? That is, are there thalamic relay cells that have integrative, not just relay, functions in information transfer to cortex?
- What are the rules (if any) that govern the way in which modulatory corticothalamic axons from layer 6 of a cortical column relate to corticothalamic drivers coming from layer 5 of the same column?
- Do all cortical areas have a layer 5 thalamic driver output? Do all have a layer 6 thalamic modulator output?
- How is the pulvinar region, or any other higher thalamic relay, mapped: (1) with respect to cortical areas to which it projects; and (2) relative to the cortical regions from which it receives a layer 5 input?
- If a large part of the thalamus can be viewed as providing links in communications among higher cortical areas, should clinical signs of thalamic dysfunction be analyzed in terms of cortical functions, and not of thalamic functions per se?

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