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CHAPTER 9

Thalamic relays and cortical functioning

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Abstract: Studies on the visual thalamic relays, the lateral geniculate nucleus and pulvinar, provide three key properties that have dramatically changed the view that the thalamus serves as a simple relay to get information from subcortical sites to cortex. First, the retinal input, although a small minority (7%) in terms of numbers of synapses onto geniculate relay cells, dominates receptive field properties of these relay cells and strongly drives them; 93% of input thus is nonretinal and modulates the relay in dynamic and important ways related to behavioral state, including attention. We call the retinal input the *driver* input and the nonretinal, *modulator* input, and their unique morphological and functional differences allow us to recognize driver and modulator input to many other thalamic relays. Second, much of the modulation is related to control of a voltage-gated, low threshold Ca^{2+} conductance that determines response properties of relay cells — *burst* or *tonic* — and this, among other things, affects the salience of information relayed. Third, the lateral geniculate nucleus and pulvinar (a massive but generally mysterious and ignored thalamic relay), are examples of two different types of relay: the LGN is a *first order* relay, transmitting information from a subcortical driver source (retina), while the pulvinar is mostly a *higher order* relay, transmitting information from a driver source emanating from layer 5 of one cortical area to another area. Higher order relays seem especially important to general corticocortical communication, and this view challenges the conventional dogma that such communication is based on direct corticocortical connections. In this sense, any new information reaching a cortical area, whether from a subcortical source or another cortical area, benefits from a thalamic relay. Other examples of first and higher order relays also exist, and generally higher order relays represent the majority of thalamus. A final property of interest emphasized in chapter 17 by Guillery (2005) is that most or all driver inputs to thalamus, whether from a subcortical source or from layer 5 of cortex, are axons that branch, with the extrathalamic branch innervating a motor or premotor region in the brainstem, or in some cases, spinal cord. This suggests that actual information relayed by thalamus to cortex is actually a copy of motor instructions (Guillery, 2005). Overall, these features of thalamic relays indicate that the thalamus not only provides a behaviorally relevant, dynamic control over the nature of information relayed, it also plays a key role in basic corticocortical communication.

Introduction

Virtually all information reaching cortex, and thus conscious perception, must first pass through thalamus. It thus follows that the thalamus sits in a strategically vital position for brain functioning. One would think this enough to ensure that the thalamus was constantly a major focus of neuroscience research, but that has not been so. Indeed, we have recently emerged from the dark ages of thinking about thalamus: the prevalent idea being that its main purpose during normal waking behavior was simply to relay information from the periphery to cortex, a relay function that was machine-like, unvarying, and rather boring. According to this view, the thalamus only behaved in an interesting fashion during sleep or certain pathological conditions, such as epilepsy (Steriade and Llinaás, 1988; Steriade et al., 1993;

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McCormick and Bal, 1997), but this aspect of thalamic functioning, while interesting and still viable, is beyond the scope of the present study. Rather, the focus here is on the more recent finding that the thalamus plays an interesting and dynamic role during normal, waking behavior of the animal, and there are three aspects to this. First, it is considered that the thalamus provides a changeable relay of information to cortex, the purpose of which is to adjust the nature of relayed information to varying behavioral demands. Second, the thalamus serves not only to relay peripheral information to cortex, but it continues to play a vital role in further cortical processing of this information by acting as a central link in various corticothalamocortical routes of information processing. Third, most or all inputs to thalamus that are relayed to cortex carry information about ongoing motor instructions, so that the main role of thalamic relays is to provide a copy to cortex of these instructions. This last point has enormous implications for cortical functioning, and has been discussed in detail in Chapter 17 of this book (Guillery, 2005).

The vast majority of detailed information we have about the cell and circuit properties of the thalamus comes from studies of the lateral geniculate nucleus, which is the thalamic relay of retinal input to cortex. Studies of the lateral geniculate nucleus derive mostly from carnivores, rodents, and primates. Fortunately, this nucleus has served as an excellent model for thalamus, and all of the major concepts learned from study of this relay that are described below apply widely to thalamus.

Relay functions of the thalamus

One question that remains relevant and profound is: Why does information destined for cortex need to pass through a thalamic relay? Why, for instance, does retinal information pass through the lateral geniculate nucleus instead of projecting directly to cortex? If one looks at information processing in the visual system, it is clear that as one progresses up the hierarchical ladder across the various synaptic zones in retina, the receptive fields of cells become richer and more complex, and this also occurs as one ascends the various hierarchical steps within visual cortex (reviewed in Dowling, 1970, 1987; Hubel and Wiesel, 1977; van Essen, 1979, 1985; van Essen and Maunsell, 1983; van Essen et al., 1992). These increasingly elaborate receptive fields represent the processing of visual information, and especially elaborate receptive fields in cortex are thought to underlie specific perceptual processes. For instance, the complex receptive fields in the middle temporal cortical area in monkeys are thought to be a key neural substrate for the processing of visual motion (Britten et al., 1993; O'Keefe and Movshon, 1998; Grunewald et al., 2002; Kohn and Movshon, 2003; Osborne et al., 2004).

The one synapse across which there is virtually no receptive field elaboration is the retinogeniculate synapse (Hubel and Wiesel, 1961; Sherman, 1985; Sherman and Guillery, 1996). A similar pattern holds for the other main sensory systems involving a thalamic relay[1]: somatosensory information involves little or no receptive field elaboration across the synapse from the medial lemniscus to the ventral posterior nucleus, and likewise there is essentially no such elaboration across the synapse from the inferior colliculus to the medial geniculate nucleus, although in both systems there is significant receptive field elaboration across synapses peripheral to thalamus and within the cortex (Purves et al., 1997; Kandel et al., 2000).

These observations used to be viewed as evidence that not much was happening in thalamus during normal information processing, leading to the above-mentioned "dark ages" for thalamic enquiry. In fact, this pattern is now interpreted to mean that the thalamus has an absolutely unique role to play in information processing. That is, while other subcortical and cortical stages involved have a function that is related to receptive field elaboration, the thalamus does something completely different. It controls the flow of information to cortex. Indeed, the complex cell and circuit properties controlling

[1]The olfactory system is unusual in that information passes from a subcortical to a cortical level without a thalamic relay, although the cortex in this case is paleocortex rather than neocortex. There is a higher level olfactory input to the medial dorsal nucleus of the thalamus which may be relayed to frontal neocortex, but it is not clear whether this is the only entry of olfactory information to cortex or whether a nonthalamic route from paleocortex to neocortex exists.

relay cell responses contradict the notion that the thalamus behaves as a simple relay.

Thalamic relay cell properties

Like all other brain neurons, thalamic relay cells possess many membrane conductances controlled by membrane voltage or specific ion concentrations, in addition to synaptic activity. This supplies the cell with a highly variable, dynamic range of responses that thereby varies the nature of information relayed to cortex. A detailed discussion of all these properties is beyond the scope of the present account and can be found elsewhere (McCormick and Huguenard, 1992; Sherman and Guillery, 1996, 2001). The focus here is a voltage gated Ca^{2+} conductance involving a T type Ca^{2+} channel found in the cell body and dendrites that, when activated, leads to an inward current, I_T.

Tonic and burst firing modes

Figure 1 shows the basic voltage dependence of I_T (Jahnsen and Llinaás, 1984a,b; McCormick and Huguenard, 1992; Sherman and Guillery, 1996, 2001; Smith et al., 1998; Zhan et al., 1999; Gutierrez et al., 2001). Anyone who understands the basic properties of the Na^+/K^+ action potential, will appreciate that the properties of IT are qualitatively identical to those of the Na^+ channel involved with the action potential, albeit with important quantitative differences. Like the Na^+ channel, the T type Ca^{2+} channel has two voltage sensitive gates, activation and inactivation gates, and both must be open for Ca^{2+} to flow into the cell. The sequence of events is shown in Fig. 1 starting at the lower left panel and moving clockwise:

(1) At a relatively hyperpolarized membrane potential (V_m), more than about 5 mV below rest, the inactivation gate is open, but the activation gate is closed, and there is no I_T. In this condition, I_T is said to have its inactivation removed, or it is ''deinactivated'', but because the activation gate is closed, it is also deactivated.

(2) Depolarization above threshold (roughly −65 mV to −60 mV) then rapidly opens the activation gate, and Ca^{2+} flows into the cell in the form of I_T. This creates a depolarizing, all-or-none Ca^{2+} spike that propagates through the dendritic tree and cell body, but not the axon, which lacks a sufficient concentration of these channels. I_T is thus activated.

(3) After a period of sustained depolarization lasting for ~100 ms[2], the inactivation gate closes, and thus I_T is now inactivated. A variety of slower, non-inactivating K^+ conductances also come into play, and this plus I_T inactivation serves to repolarize the cell.

(4) Even though it is back at the starting membrane potential, I_T remains inactivated for ~100 ms. After this time, the inactivation of I_T is removed (i.e., it becomes deinactivated). The cycle is then reset as the initial starting conditions as in panel 1 are re-established.

There are several implications to the above. First, while activation of I_T is very fast, both inactivation and deinactivation take time, on the order of 100 ms. For inactivation, this means that a typical, fast excitatory post-synaptic potential (EPSP) or even an action potential will not much inactivate I_T. Likewise, for deinactivation, a fast inhibitory post-synaptic potential (IPSP) will not do. For either process, it is necessary to sustain a change in V_m. Second, the all-or-none Ca^{2+} spike created when I_T is activated propagates through the dendrites and soma, but not up the axon, because there are virtually no T channels there. Nonetheless, as shown in more detail below, this spike does affect the pattern of conventional action potentials generated and thus will affect the signal sent up the axon to cortex. This Ca^{2+} spike is commonly called the ''low threshold spike'', because its activation threshold is hyperpolarized with respect to that of the action potential. This means that, with some exceptions (Gutierrez et al., 2001), if I_T is deinactivated, a ensuing depolarization will activate I_T and the low threshold spike before activating a conventional action potential. Third, as noted, the T channel behaves qualitatively just like the Na^+ channel involved in the action potential — both

[2]Actually, inactivation and deinactivation are complex functions of voltage and time so that the more the cell is depolarized, the faster I_T inactivates, and the more the cell is hyperpolarized, the faster I_T deinactivates.

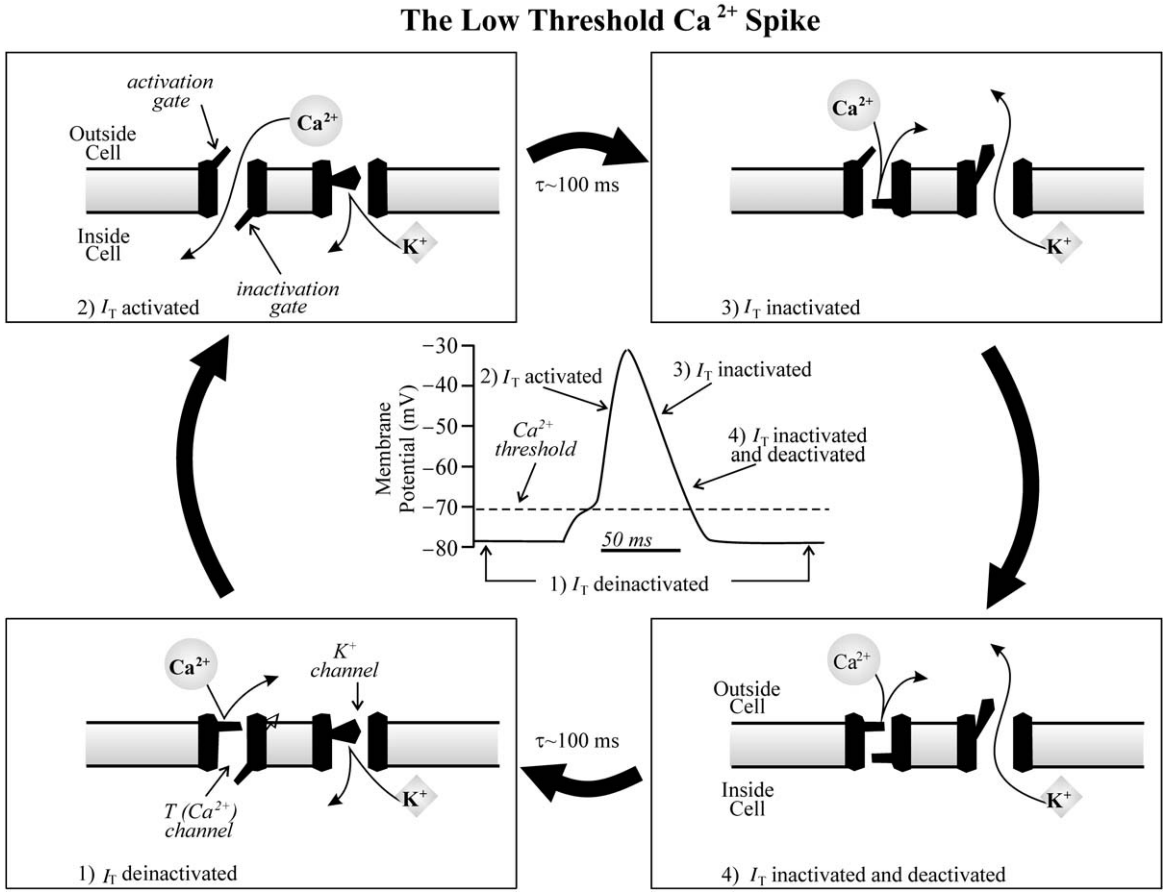

Fig. 1. Schematic view of actions of voltage dependent T (Ca^{2+}) and K^+ channels underlying low threshold Ca^{2+} spike. The 4 numbered panels show the sequence of channel events in a clockwise fashion, and the central graph shows the effects on membrane potential. The T channel has 2 voltage dependent gates: an *activation* gate that opens with depolarization and closes at hyperpolarized levels; and an *inactivation* gate that shows the opposite voltage dependency. Both of these gates must be open for Ca^{2+} to enter the cell, and this flow of Ca^{2+} is an inward current known as I_T. The K^+ channel shown is really a heterogenous conglomeration of different K^+ channels with only a single gate that opens during depolarization; thus, these channels do not inactivate. (1). At a relatively hyperpolarized resting membrane potential (~70 mV), the inactivation gate of the T channel is open, and so the T channel is deinactivated, but the activation gate is closed. The single gate for the K^+ channel is closed. (2) With sufficient depolarization to reach its threshold, the activation gate of the T channel opens, and Ca^{2+} flows into the cell, producing I_T. The T channel is now activated. This further depolarizes the cell, providing the rise of the low threshold spike, which is all-or-none. (3) The inactivation gate of the T channel closes after ~100 ms of depolarization, and so the channel is now inactivated. The K^+ channel also opens. These actions repolarize the cell. (4) Even though the initial resting potential is reached, the T channel remains inactivated, because it takes ~100 ms of hyperpolarization to deinactivate it. Eventually, the T channel deinactivates, and the conditions of panel 1 are restored. Note that the behavior of the T channel qualitatively matches that of the Na^+ channel involved with the action potential, but with several quantitative differences: the T channel is slower to inactivate and deinactivate, and it operates in a more hyperpolarized regime.

channels inactivate with a similar voltage dependency and the time required for deinactivation establishes a refractory period — but there are important quantitative differences. Thus the T channel has a much slower time course for inactivation and deinactivation, a longer duration spike, a more hyperpolarized regime (by about 10 mV), and little or no distribution in the axon.

Figure 2 shows some of the functional implications of I_T. When the cell has been sufficiently depolarized, I_T is inactivated and plays no role in the cell's response. Now, a suprathreshold excitatory input

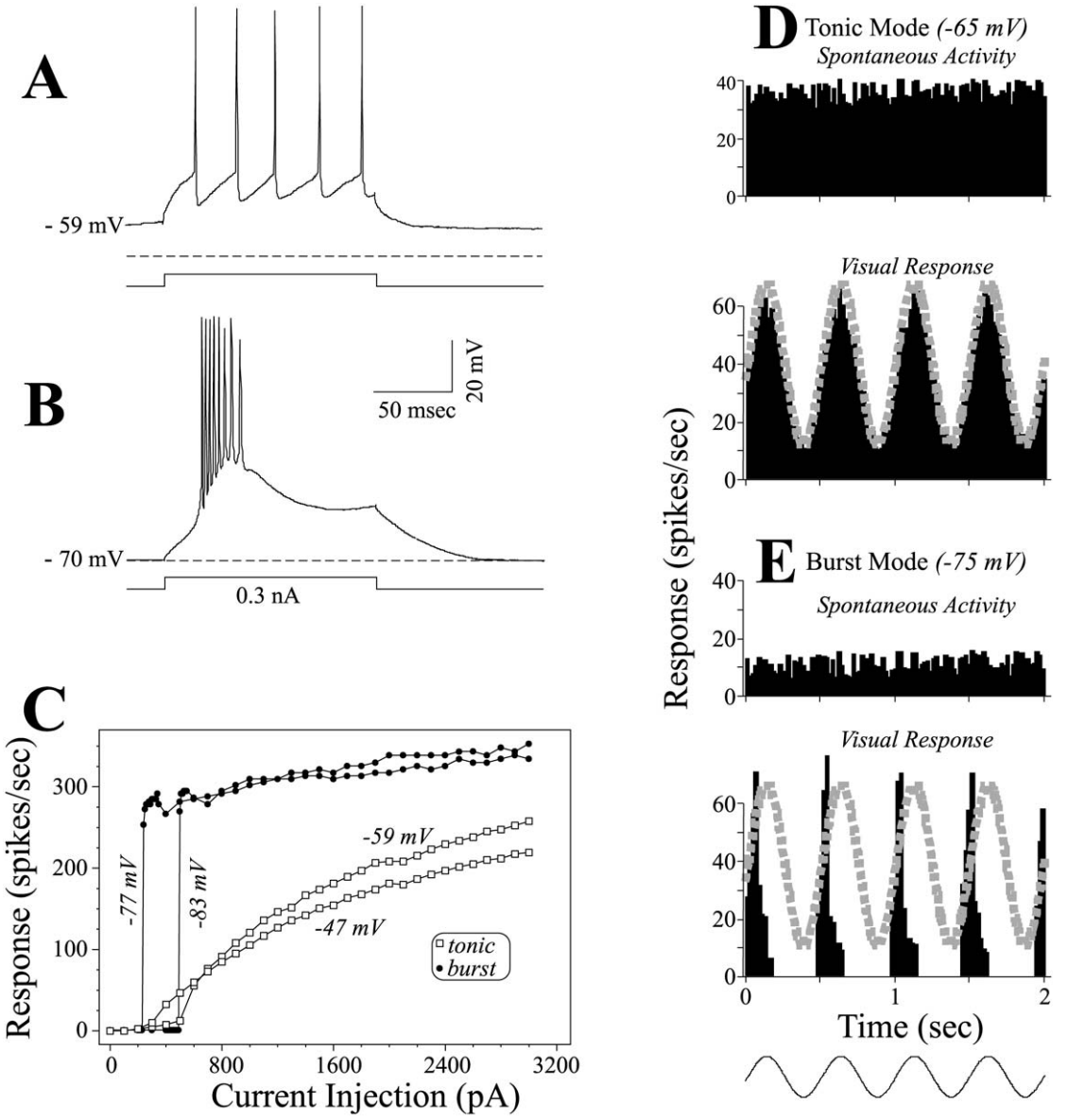

Fig. 2. Various properties of the low threshold Ca^{2+} spike. A, B: Intracellular recording of a relay cell from the lateral geniculate nucleus of a cat in vitro. At an initial V_m of −59 mV, I_T is inactivated and thus the cell responds in tonic mode (A). Thus, the response to a depolarizing 3 nA current injection is a steady stream of unitary action potentials. At an initial V_m of −70 mV, I_T is deinactivated and thus the cell responds in burst mode (B). Now, the very same current injection activates the low threshold Ca^{2+} spike, which in turn activates, in this case, a burst of 8 conventional action potentials. C: Initial response of cell in A, B to various levels of current injection from different initial V_ms. At levels that inactivate I_T and produce tonic firing (−47 mV and −59 mV), a fairly linear relationship ensues. At levels that deinactivate I_T and produce burst firing (−77 mV and −83 mV), a very nonlinear relationship in the form of a step function is seen. D,E: Effect of firing mode on response to drifting sinusoidal grating from a relay cell in the lateral geniculate nucleus of an anesthetized cat recorded intracellularly in vivo. The sinusoidal contrast changes in the visual stimulus are shown below the histograms and is also shown as a gray dashed line for the lower histograms of D,E. At an initial V_m (−65 mV) that promotes tonic firing (D), the spontaneous activity is relatively high, and the response to the grating has a sinusoidal profile. At an initial V_m (−75 mV) that promotes burst firing (E), the spontaneous activity is relatively low, and the response to the grating no longer has a sinusoidal profile.

(a current injection in this example, but think of it also as an EPSP) evokes a steady stream of unitary action potentials (Fig. 2A). This is called the *tonic mode* of firing. However, when the same cell is sufficiently hyperpolarized so that I_T is deinactivated, the exact same excitatory input produces a very different response (Fig. 2B): now I_T is activated, producing the all-or-none low threshold spike, which is large enough to elicit a high frequency volley of action potentials. This is called the *burst mode* of firing, and the burst typically includes 2–6 action potentials, although up to 10 or more may be involved. The important point is that the same excitatory input elicits two different messages relayed to cortex (i.e., the action potentials) depending on the recent voltage history of the cell, which in turn determines the state of I_T.

Both response modes, burst and tonic, are seen in thalamic relay cells during normal waking behavior. Thus burst firing has also been reported in awake, alert animals for lateral geniculate cells in response to visual stimuli (Guido and Weyand, 1995; Ramcharan et al., 2000; Weyand et al., 2001); for medial geniculate cells in response to auditory stimuli (Massaux et al., 2004); and for the ventral posterior medial cells during periods of active whisking (Nicolelis et al., 1995; Fanselow and Nicolelis, 1999; Swadlow and Gusev, 2001; Swadlow et al., 2002). Such burst firing has also been reported in various thalamic nuclei of humans during wakefulness (Lenz et al., 1998; Radhakrishnan et al., 1999). Generally, the more awake and alert the animal, the more tonic firing dominates (Ramcharan et al., 2000; Swadlow and Gusev, 2001; Massaux et al., 2004). This means that relay cells switch frequently between modes, reflecting a change in V_m sufficient to change the inactivation state of I_T. A major challenge is to define the conditions and mechanisms for this switching, and some preliminary insights into this are presented below. Another challenge is to understand the significance for information processing of the response mode, and part of this is introduced in Figs. 2C–E.

Implications of firing mode for thalamic relays

Note that, in the case of tonic firing (Fig. 2A), the action potentials are evoked directly from the depolarizing current injection. Thus one would expect that the larger the current injection, the greater the response. This is in fact the case, as shown in Fig. 2C for tonic firing for this cell (responses at initially depolarized V_m of −47 and −59 mV), where the input/output relationship is relatively linear. However, with burst firing (Fig. 2B), the action potentials are no longer directly caused by the current injection but instead result from the low threshold Ca^{2+} spike; because this is an all-or-none spike, a larger current injection would not evoke a larger low threshold Ca^{2+} spike, and thus a larger current injection would not evoke more action potentials. This relationship for burst firing is shown in Fig. 2C (responses at initially depolarized V_m of −77 and −83 mV), where the input/output relationship is a decidedly nonlinear step function. Thus tonic firing represents a much more linear relay than does burst firing.

Another way of determining the effect of firing mode on the thalamic relay is to see its effect on response properties of the relay cell as determined by receptive field analysis: this reflects how incoming information is relayed to the cortex. Figs 2D, E shows a prototypical example of this. The example is from a lateral geniculate relay cell recorded intracellularly in vivo in an anesthetized cat, and shown is the spontaneous activity plus the visual responses evoked by a sinusoidal grating (i.e., a visual stimulus of constant luminance along one axis and of sinusoidally modulated luminance along the perpendicular axis) drifting through the receptive field of the cell. By injecting constant current of different amplitudes, the cell was biased either toward a more depolarized initial V_m, producing tonic firing (Fig. 2D) or toward a more hyperpolarized initial V_m, producing burst firing (Fig. 2E). During tonic firing, the profile of the response to the visual stimulus looks sinusoidal (Fig. 2D, lower histogram), like the stimulus itself, and thus there is a close correlation between firing rate and stimulus contrast (compare the firing with the superimposed stimulus contrast represented by the dashed, gray curve). This is another way of saying that the response is very linear. The visual response to the same stimulus during burst firing is quite different, because it no longer is sinusoidal in shape (Fig. 2E, lower histogram). This nonlinearity during burst firing is predicted from the nonlinear input/output relationship of burst firing depicted in Fig. 2C.

The advantage of tonic firing and its more linear relay is self-evident, because the type of nonlinear distortion imposed on the relay by burst firing limits the extent to which visual cortex can faithfully reconstruct the visual scene. Any advantage of burst firing is harder to discern, but one such advantage is tied to spontaneous activity (i.e., background firing or responsiveness when there is no visual stimulus present). As shown in the upper histograms of Figs. 2D, E, this is considerably lower during burst firing. Because spontaneous activity represents responsiveness that, by definition, bears no relationship to a visual stimulus, it actually represents noise in the relay to cortex. The response to the visual stimulus (Figs. 2D, E, lower histograms) is the signal, which is quite large in both firing modes. What is of interest here is the signal-to-noise ratio, which, chiefly because of the lower noise during burst firing, is higher during burst firing. A higher signal-to-noise ratio is often associated with stimulus detectability. This suggestion of improved detectability during burst firing has been supported experimentally (Guido et al., 1995).

However, not only does burst firing improve stimulus detectability, it also provides for a more powerful activation of cortex. To understand the reason for this, it helps to look at the special pattern of firing seen in burst mode, a pattern revealed by plotting a two-dimensional interspike interval distribution on logarithmic axes (Fig. 3). This plot shows that groups of action potentials are clustered and not spread evenly in time. In particular, the cluster at the lower right (in the shaded area) represents the first action potentials of bursts due to low threshold Ca^{2+} spikes. The second to penultimate action potentials in a burst are indicated by the cluster at the lower left of each histogram, and the last action potentials in a burst are found at the left side of each histogram. All other action potentials are during tonic firing. The criteria developed for the first action potentials in a burst are represented by the shaded area: the action potential must follow a silent period of $\geq$100 ms and be followed by the next action potential within 2ms (Lu et al., 1992), and minor variants of these criteria exist (e.g., Lenz et al., 1998; Zirh et al., 1998). The reason for this is as follows. In order for a burst to occur, I_T must be activated to produce the underlying low threshold spike. For this to happen, I_T must first be deinactivated, and that requires $\geq$100 ms or so of sustained hyperpolarization. The sustained hyperpolarization means that, by definition, there can be no evoked action potentials, and so this requirement to deinactivate I_T leads to a silent period of $\geq$100 ms before the first spike in a burst. In contrast to the clusters related to burst firing, the action potentials evoked during tonic firing tend to occupy one cloud of points with interspike intervals relatively evenly distributed, mostly between 5 and 30 ms.

One significance of this distribution of action potentials during the two firing modes has to do with properties of the thalamocortical synapse, which shows paired-pulse depression (Stratford et al., 1996;

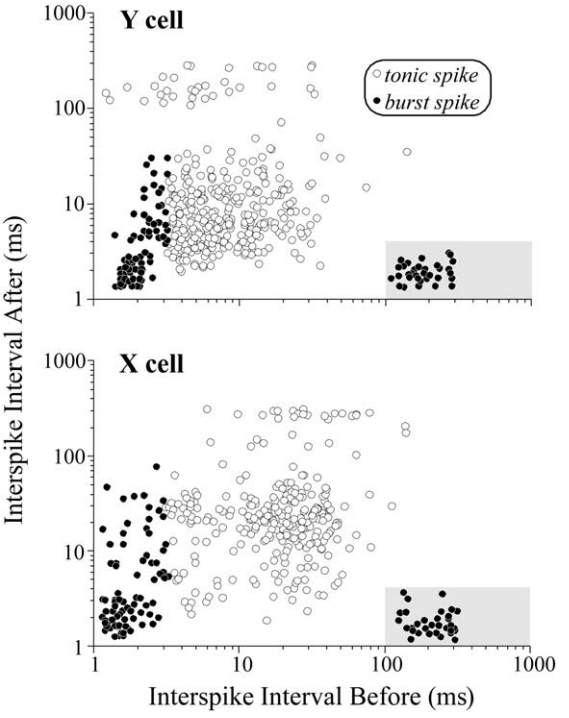

Fig. 3. Two-dimensional interspike interval plots for two representative relay cells in the lateral geniculate nucleus of an anesthetized cat recorded extracellularly in vivo. For each action potential recorded during a given period of time, the interval to the previous spike is shown on the abscissa, and the interval to the next spike is shown on the ordinate. Tonic and burst spikes are shown separately. Note the cluster of burst spikes on the lower right of each histogram. These follow a silent period of $\geq$100 ms and are followed by another spike within $\sim$2 ms. These are known to be the first spike in a burst (Lu et al., 1992). For further details see text.

Beierlein and Connors, 2002; Castro-Alamancos and Oldford, 2002; Chung et al., 2002; Nicolelis, 2002). This means that for a period of time following an evoked EPSP from this synapse, EPSP amplitudes will be substantially depressed. However, for most of these synapses, a silent period of $\geq$100 ms as occurs before the first action potential in a burst would relieve the depression and lead to a maximum EPSP. In contrast, tonic firing has interspike intervals that are generally too brief to permit much relief of the depression, so the synapse will be considerably depressed throughout tonic firing. Recent work studying efficacy of the thalamocortical synapse in the somatosensory system of the awake rabbit has shown that, on average, the first action potential in a burst is much more effective at driving cortical circuitry than is a tonic action potential (Swadlow and Gusev, 2001; Swadlow et al., 2002, 2005). This does not even take into account that the following action potentials in a burst will produce extra EPSPs, that, while depressed, would temporally sum and enhance the response. The result is that a burst punches through to cortex very effectively compared to tonic action potentials.[3]

These different features related to firing mode — a more linear relay for tonic firing versus better stimulus detectability and cortical activation for burst firing — have suggested what remains a working hypothesis for further research (Sherman, 1996, 2001; Sherman and Guillery, 2002, 2004). That is, burst firing acts as a "wake-up call" for periods during which the relevant relay cells are relatively suppressed, as may happen during periods of general inattention or drowsiness or when an alert animal directs its attention elsewhere. Under these conditions, the idea is that any change in the afferent input, such as a new visual stimulus for a lateral geniculate relay cell, evokes a burst that "wakes up" cortex with a signal that something has changed out there. This could then lead to a switch in the relay to tonic firing so that information about the changed environment can be relayed more linearly and thus more faithfully.

There is some very limited, indirect evidence consistent with this view (for details, see Sherman, 1996, 2001; Sherman and Guillery, 2002, 2004). One is that, as noted above, thalamic relay cells in a variety of nuclei and species (including rats, rabbits, cats, monkeys, and humans) show both tonic and burst firing during the animal's waking behavior, although in the alert animal bursting occurs much less frequently than does tonic firing (Guido and Weyand, 1995; Nicolelis et al., 1995; Lenz et al., 1998; Fanselow and Nicolelis, 1999; Radhakrishnan et al., 1999; Ramcharan et al., 2000; Swadlow and Gusev, 2001; Weyand et al., 2001; Swadlow et al., 2002; Massaux et al., 2004). Also, the amount of bursting increases as the animal becomes drowsy or inattentive, which is consistent with the hypothesis that bursting serves as suggested as a "wake-up call" (Ramcharan et al., 2000; Swadlow and Gusev, 2001; Massaux et al., 2004). It follows that such "wake-up calls" are especially important when the animal is drowsy or otherwise inattentive for the information being relayed through thalamus. Finally, recordings from lateral geniculate relay cells in the awake cat suggest a tendency for bursting to the first presentation of a novel stimulus with a switch to tonic firing as the stimulus remains (Guido and Weyand, 1995), and this, too, is consistent with the hypothesis.

For this to make sense, there must be thalamic circuitry available to control response mode efficiently, and this indeed is the case.

Thalamic circuit properties

Pattern of inputs to relay cells

Figure 4A schematically shows the various afferents that synapse onto relay cells; again the lateral geniculate nucleus is the example, but with relatively minor variations in the equivalent of the nonretinal afferents, the circuitry is similar for other thalamic relays, with the major change being the nature of the

[3]This scenario assumes that thalamocortical synapses show paired-pulse depression. However, the beauty of burst firing is that one would expect bursts to activate cortex more powerfully than tonic firing even if the thalamocortical synapse shows paired-pulse facilitation. This is because facilitation works well for short interspike intervals, and the short interspike intervals in a burst ensure considerable facilitation. Just as the interspike intervals during tonic firing are too short to relieve a depressed synapse, they are generally too long to produce facilitation for a facilitating synapse.

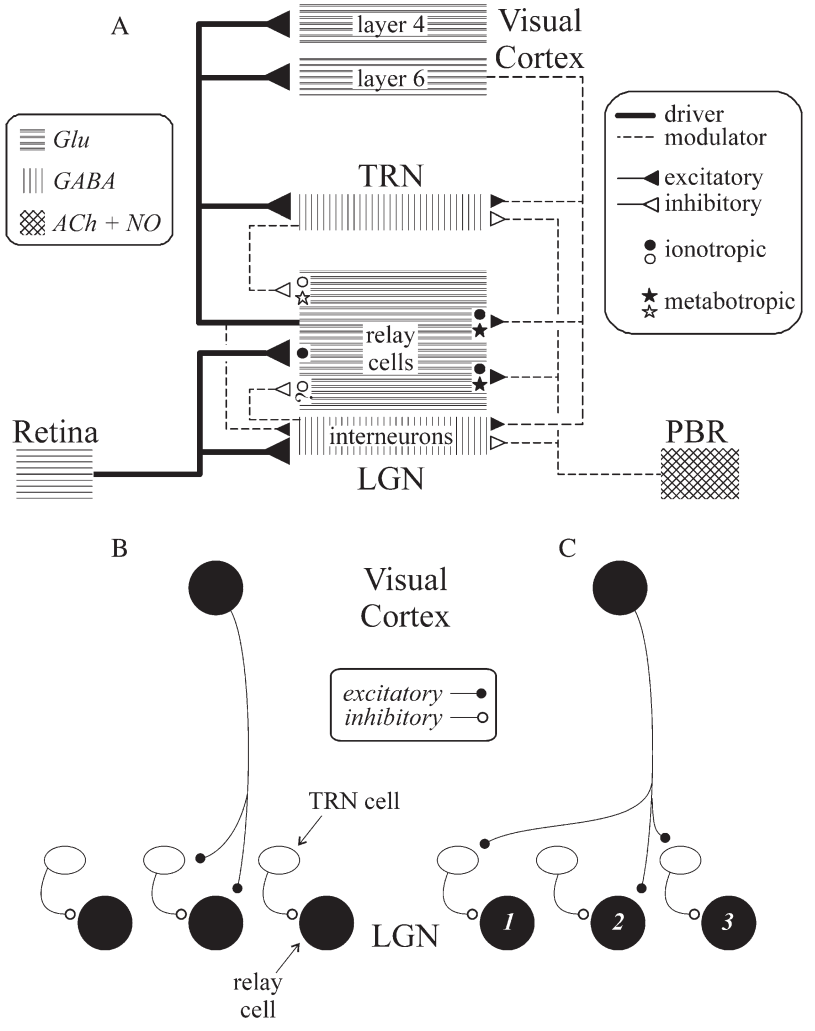

Fig. 4. Innervation patterns for the lateral geniculate nucleus. A: Inputs to relay cells, showing transmitters and post-synaptic receptors (ionotropic and metabotropic) involved. B, C: Two patterns among others possible for corticothalamic projection from layer 6 to reticular and relay cells. Simple excitation and feedforward inhibition is shown in B, and C shows a more complicated pattern in which activation of a cortical axon can excite some relay cells directly and inhibit others through activation of reticular cells. (*ACh*, acetylcholine; *GABA*, γ-aminobutyric acid; *Glu*, glutamate; *LGN*, lateral geniculate nucleus; *NO*, nitric oxide; *PBR*, parabrachial region; *TRN*, thalamic reticular nucleus.) For further details see text.

input to be relayed (e.g., instead of retinal input for the lateral geniculate nucleus, there would be medial lemniscal or inferior collicular input for the ventral posterior nucleus or medial geniculate nucleus, respectively, or, as noted below, cortical input from layer 5 for higher order relays).

Figure 4A, in addition to showing the inputs, also indicates the transmitters and post-synaptic receptors involved. There are two general classes of receptor: ionotropic and metabotropic. Ionotropic receptors relevant to Fig. 4A include AMPA and NMDA receptors (AMPARs and NMDARs) for glutamate, nicotinic receptors (nAChRs) for acetylcholine, and $GABA_A$ receptors ($GABA_A$Rs); metabotropic receptors include various metabotropic glutamate receptors (mGluRs), various muscarinic

receptors (mAChRs) for acetylcholine, and $GABA_B$ receptors ($GABA_BRs$). Detailed differences between these receptor classes can be found elsewhere (Nicoll et al., 1990; Mott and Lewis, 1994; Pin and Bockaert, 1995; Pin and Duvoisin, 1995; Recasens and Vignes, 1995; Conn and Pin, 1997; Conn, 2003; Huettner, 2003), but for the purposes here, only several differences are considered: ionotropic receptors are simpler, usually with an ion channel directly linked to the receptor complex so that when the receptor binds to a transmitter, rapid opening of the channel ensues. Post-synaptic potentials (PSPs) from activation of ionotropic receptors tend to have a short latency ($\sim$1 ms) and duration (mostly over in 10–20 ms). In contrast, metabotropic receptors are more complicated: each is linked to a G-protein, and transmitter binding to the receptor releases the G-protein and sets off a chain of biochemical reactions (also known as second messenger actions) that create many intracellular changes. Among them is the opening or closing of ion channels, which in the case of the receptors shown in Fig. 4A are usually K^+ channels. Opening the K^+ channel allows more positive (K^+) ions to leave the cell, leading to an IPSP, and closing the channel does the opposite, producing an EPSP.

What is more important in the present context is that the PSPs evoked via metabotropic receptors in the relay cells are slow, with a latency of 10 ms or so and a duration of hundreds of ms to several seconds. Recall that a change in V_m for $\geq$100 ms or so is needed for inactivation or deinactivation of I_T, and thus the fast PSPs related to ionotropic receptors are ill-suited for this (and so are action potentials, which are over in a ms or so). In contrast, the sustained PSPs of the metabotropic receptors are ideal for control of I_T. That is, the sustained EPSP related to the mGluR or the mAChR serves well to inactivate I_T and convert burst firing to tonic; similarly, the sustained IPSP of the $GABA_BR$ will deinactivate I_T and convert tonic firing to burst. These actions of metabotropic receptors are not limited to control of I_T: the sustained PSPs will also serve to control other slower voltage gated conductances that exist, such as I_h and I_A (for details of these other conductances, see McCormick and Huguenard, 1992; Sherman and Guillery, 1996, 2001), and the sustained alterations in V_m will also affect the overall excitability of the relay cell.

Thalamic circuitry and control of I_T

Figure 4A shows that the retinal input activates only ionotropic receptors, mainly AMPARs[4], and this has two consequences. First, the brief EPSP means that up to relatively high rates of firing in the retinal afferent(s), individual action potentials presynaptically can be converted to discrete EPSPs. Put another way, a sustained EPSP (e.g., from activation of an mGluR) would act like a low-pass temporal filter in relaying the retinal input, so that temporal information would be lost in the relay at higher input firing frequencies. Thus the fact that the retinal input activates only ionotropic receptors maximizes the relay of temporal information. The second implication of this pattern of receptors is that retinally evoked EPSPs, being relatively brief, would have relatively little effect on I_T. Only at rates of retinal firing sufficiently high to produce temporal summation of EPSPs would this input serve to inactivate I_T. The implication here is that a cell in burst mode could be switched to tonic mode by high rates of retinal firing, but otherwise, response mode of the relay cell is better controlled by inputs that activate metabotropic receptors.

Indeed, activation in the relay cell of either mGluRs or mAChRs from cortex or the parabrachial region, respectively, produces a sustained EPSP that inactivates I_T and serves to switch firing mode from burst to tonic. Activation of $GABA_BRs$ from the thalamic reticular nucleus (and possibly from interneurons, but the nature of receptors post-synaptic to interneuron inputs remains largely unexplored) does the opposite by producing a sustained EPSP that deinactivates I_T and switches firing mode from tonic to burst. Thus the two major extrathalamic, nonretinal inputs to the lateral geniculate nucleus — from cortex and the parabrachial region — control firing mode fairly effectively: the direct inputs to relay cells from both can promote tonic firing, and indirect

[4]Any role of NMDARs here is complicated by their voltage dependency, so that they will not contribute to an EPSP unless the cell is already fairly depolarized (Mayer and Westbrook, 1987; Nakanishi et al., 1998; Ozawa et al., 1998; Qian and Johnson, 2002). The role of NMDARs in control of I_T remains unclear.

inputs involving the thalamic reticular nucleus (and, perhaps, interneurons) can promote burst firing.

However, there are important differences in these inputs. As noted in Fig. 4A, parabrachial axons branch to innervate relay cells and both types of local GABAergic inhibitory cell (reticular cells and interneurons). The main effect on relay cells is excitatory while the simultaneous effect on the local inhibitory cells is inhibitory. This neat trick is effected by different post-synaptic receptors: mainly nAChRs and the M1 type of mAChR on relay cells to produce EPSPs and the M2 type of mAChRs on the GABAergic cells to produce IPSPs. This means that activity in these inputs has a straightforward depolarizing effect on relay cells due to direct excitation and indirect disinibition (i.e., inhibition of the GABAergic inputs), and this in turn implies that the more active these inputs, the more likely the relay cells fire in tonic mode.

The effect of cortical inputs is less obvious, because, according to Fig. 4A, it can produce direct excitation and indirect inhibition. Here, much depends on the details of circuitry, details of which are very little known, and this point is illustrated in Figs. 4B, C. If the corticothalamic circuitry is organized in a simple feedforward inhibitory circuit (Fig. 4B), then the net result of cortical activation will be relatively balanced increases in EPSPs and IPSPs. This would likely have little overall effect on V_m and thus on I_T. However, recent evidence (Chance et al., 2002; Abbott, 2005) suggests that such a balanced increase in EPSPs and IPSPs, while slightly affecting V_m, will increase synaptic conductance; this in turn reduces neuronal input resistance, making the relay cell less responsive to other (e.g., retinal) inputs. In this way, the circuitry of Fig. 4B can serve as a gain control mechanism. Fig. 4C shows another possible arrangement, and here the result of corticothalamic activation is quite different. For any specific cortical axon (or, perhaps, a small related group), activation will directly depolarize some relay cells (represented by *cell* 2), inactivating I_T to promote tonic firing, and indirectly hyperpolarize others (represented by *cells* 1 and 3), deinactivating I_T to promote burst firing. While there is some evidence for the arrangement shown in Fig. 4C (Tsumoto et al., 1978), it is plausible that heterogeneity exists in the corticothalamic circuits, so that those shown in Fig. 4B,C, as well as others not shown, exist.

Role of thalamus in corticocortical communication

The discussion in the previous section offers some functions for the thalamus to perform in relaying information to cortex, and other functions will doubtless be added as we learn more about this topic. This section examines the case that thalamus does more than just relay peripheral information to cortex; instead, it continues to play a role in how cortex processes such information. The logic underlying these arguments begins with a consideration of inputs to thalamic relay cells.

Drivers and modulators

Functional differences

A glance back at Fig. 4A shows that there are multiple inputs to lateral geniculate relay cells, yet only one of these, the retinal input, represents the information actually relayed. What are all the nonretinal inputs doing? A consideration of numbers only adds to the mystery, because the presumably dominant retinal input contributes only 7% of the synaptic inputs to relay cells; the rest are contributed roughly equally, about 30% each, from local GABAergic sources, from layer 6 of cortex, and from the parabrachial region (van Horn et al., 2000). Small numbers of serotonergic, noradrenergic, and histaminergic inputs are also present (reviewed in Sherman and Guillery, 1996, 2001) but are not considered further here. The point is that not all physical inputs are equal, as if they participate in some sort of anatomical and functional democracy. Indeed, the retinal inputs, despite the number, produce disproportionately large EPSPs in relay cells.

In terms of the lateral geniculate nucleus, there are a number of criteria that distinguish the retinal input from the nonretinal (Sherman and Guillery, 1996, 1998, 2001):

- Retinal inputs to relay cells provide the main receptive field properties and are necessary for the existence of the receptive fields, whereas nonretinal inputs produce only subtle changes in receptive field properties.

- Retinal inputs end in very large terminals, indeed by far the largest in the thalamus, and contribute up to 10 or more distinct synaptic contact zones. The smaller nonretinal terminals rarely have more than one synaptic contact zone each.
- Retinal terminals are limited to proximal dendrites, often in complex synaptic arrangements known as triads found within elaborate synaptic glomeruli, whereas modulator terminals can be found anywhere on the dendritic arbor.
- As noted, despite the small number of synapses, retinal EPSPs are large, suggesting powerful synapses, whereas individual nonretinal inputs are weak.
- Again as noted, retinal inputs activate only ionotropic glutamate receptors, whereas nonretinal inputs typically activate metabotropic receptors as well.
- There is relatively little convergence of retinal inputs onto relay cells, whereas many or most nonretinal inputs show considerable convergence.
- Retinal inputs do not innervate the thalamic reticular nucleus, whereas nonretinal inputs do.
- Retinal synapses show paired-pulse depression (following an evoked retinal EPSP, further EPSPs from retina are reduced in amplitude for 50–100 ms or so), whereas corticogeniculate synapses, the only nonretinal input so far tested for this effect, show paired-pulse facilitation (the opposite of depression, so that evoked EPSPs for 50–100 ms or so are enhanced in amplitude).

These systematic differences between retinal and nonretinal inputs led to the concept that these thalamic afferents could be divided into *drivers* and *modulators*, the former being the retinal inputs, so named because they strongly drive relay cells and transmit the message that is processed by cortex, and the latter being all other inputs, so named because their role is to modulate retinogeniculate transmission. One example of this modulation, among many others, is the abovementioned control of I_T by cortical and parabrachial input, both designated as modulators here. This division of afferents to relay cells into drivers and modulators works well in other thalamic relays for which sufficient information exists: for instance the driver inputs to the ventral portion of the medial geniculate nucleus or to the ventral posterior nucleus are, respectively, from the inferior colliculus or the medial lemniscus. As with the retinal input to the lateral geniculate nucleus, these other drivers bring the information to be relayed and thus confer the basic receptive field properties onto their target relay cells.

This concept that not all anatomical pathways are the same, and that some are important to the transmission of basic information (e.g., retinal inputs), while others play a subtler role in modulating how that information is transformed or relayed (e.g., nonretinal inputs), has a number of other implications considered below. A particularly interesting possibility is that this distinction between drivers and modulators can be extended beyond thalamus, for instance, into cortex. There are reasons for thinking this: there is now considerable evidence that the input that confers the basic receptive field properties onto layer 4 cells of primary visual cortex are the corticogeniculate axons (Hubel and Wiesel, 1962, 1977; Ferster et al., 1996; Ferster and Miller, 2000; Usrey et al., 2000; Alonso et al., 2001; Kara et al., 2002; Ferster, 2004); these synapses have many of the features of a driver from the bulleted list above, including large EPSPs with paired-pulse depression (Stratford et al., 1996), large terminals on proximal dendrites; and these contribute only about 6% of the synapses onto these layer 4 cells (Ahmed et al., 1994, 1997). As noted above, only 7% of input to geniculate relay cells derives from retina, and thus the 6% contribution made by geniculocortical inputs is remarkably close to this value, suggesting either an extraordinary coincidence or a common functional feature of driver inputs. Below, we consider further the possibility that other pathways in cortex can also be divided into drivers and modulators.

Drivers and the labeled line

Given that retinal input to geniculate relay cells is the defined driver and yet represents a minority of inputs, we can ask: What is the consequence in cortex of a change in geniculate firing produced by a modulator input? This could happen, for instance, if a highly

active period of corticogeniculate input were to elevate geniculate firing, although evidence cited below suggests this happens only rarely. The suggested answer follows from the concept that a driver input represents a ''labeled line''. This means that altered firing of the geniculate relay cell must always be interpreted by its cortical targets as due to altered firing of the retinal inputs. This concept is very much like the concept of labeled lines in sensory pathways. For instance, if one applies pressure to the side of the eyeball, the perception is of spots appearing in the visual field. That is, the resultant increased intraocular pressure changes retinal firing, and this is perceived not as a pressure change in the eye but rather as a visual signal.

The same principle is suggested to apply to the drivers throughout thalamus. If large numbers of relay cell action potentials were due to modulator inputs rather than drivers, this could create difficulties in information processing. However, evidence from the lateral geniculate nucleus suggests that this is rare: that is, simultaneous recording from a geniculate relay cell and its retinal input indicates that nearly every action potential in a relay cell result from one in its retinal afferent (Cleland et al., 1971; Usrey et al., 1999), but the caution here is that these data derive from anesthetized preparations.

Modulation via ionotropic receptors

The point made above is that an important feature of modulator inputs to relay cells is that, as a group, they activate metabotropic receptors, and the long PSPs that result are key to controlling the state of many slow acting, voltage-dependent conductances, such as that involving I_T. However, as shown in Fig. 4A, most pathways activate ionotropic receptors as well, and it is not clear if certain pathways, such as the corticothalamic, reticulothalamic, or those from the brainstem, include single axons that activate purely one or the other type of receptor.

As noted in the context of Fig. 4B, Abbot and colleagues have provided a clear modulatory role for inputs that activate ionotropic receptors, whether or not metabotropic receptors might also be involved (Chance et al., 2002; Abbott, 2005). That is, combined input from modulatory inhibitory and excitatory sources balanced to have little net effect on V_m can nonetheless affect neuronal input resistance and thus affect the gain of any driver input. A different modulatory role can also be imagined if the combined input is unbalanced, leading to a change in V_m. This would then lead to a change in spontaneous activity, another key modulatory function that affects how driver inputs will be processed. For instance, higher spontaneous activity could subserve more linear processing (i.e., reducing rectification in the processed signal), a lower signal-to-noise ratio, and could also have effects on the state of the synaptic efficacy of the post-synaptic cell as regards its status as a depressing or facilitating synapse.

One further point is important to consider in the case that a group of excitatory inputs becomes relatively more (or less) active, resulting in increased firing in the target cell. One possible interpretation is that the enhanced input that was once a modulator now becomes a driver, implying a dynamic shifting in the function of inputs between driver and modulator. While this cannot be ruled out, it would require more complex processing if the above idea of a labeled line is valid, because this would also require dynamic shifting in how targets of the cell in question preform computations on these messages. It seems more parsimonious to regard such changes in relative strength of excitatory versus inhibitory inputs as a means to control spontaneous activity, a purely modulatory function.

First and higher order thalamic relays

One of the problems in understanding the functional role of a thalamic relay is to identify the information it relays to cortex, and essentially this boils down to identifying the driver input. This is fairly straightforward for the primary visual, somatosensory, and auditory relays. However, in this regard, much of thalamus has, until recently, remained *terra incognita*. As a road map exploring thalamus more generally, one can start with the bulleted list above, identifying which inputs to such relays as the pulvinar, medial dorsal, or intralaminar nuclei are likely to be drivers. Doing so leads to the conclusion that thalamic relays can be divided into two groups — *first* and *higher order* — depending on the origin of the driver input

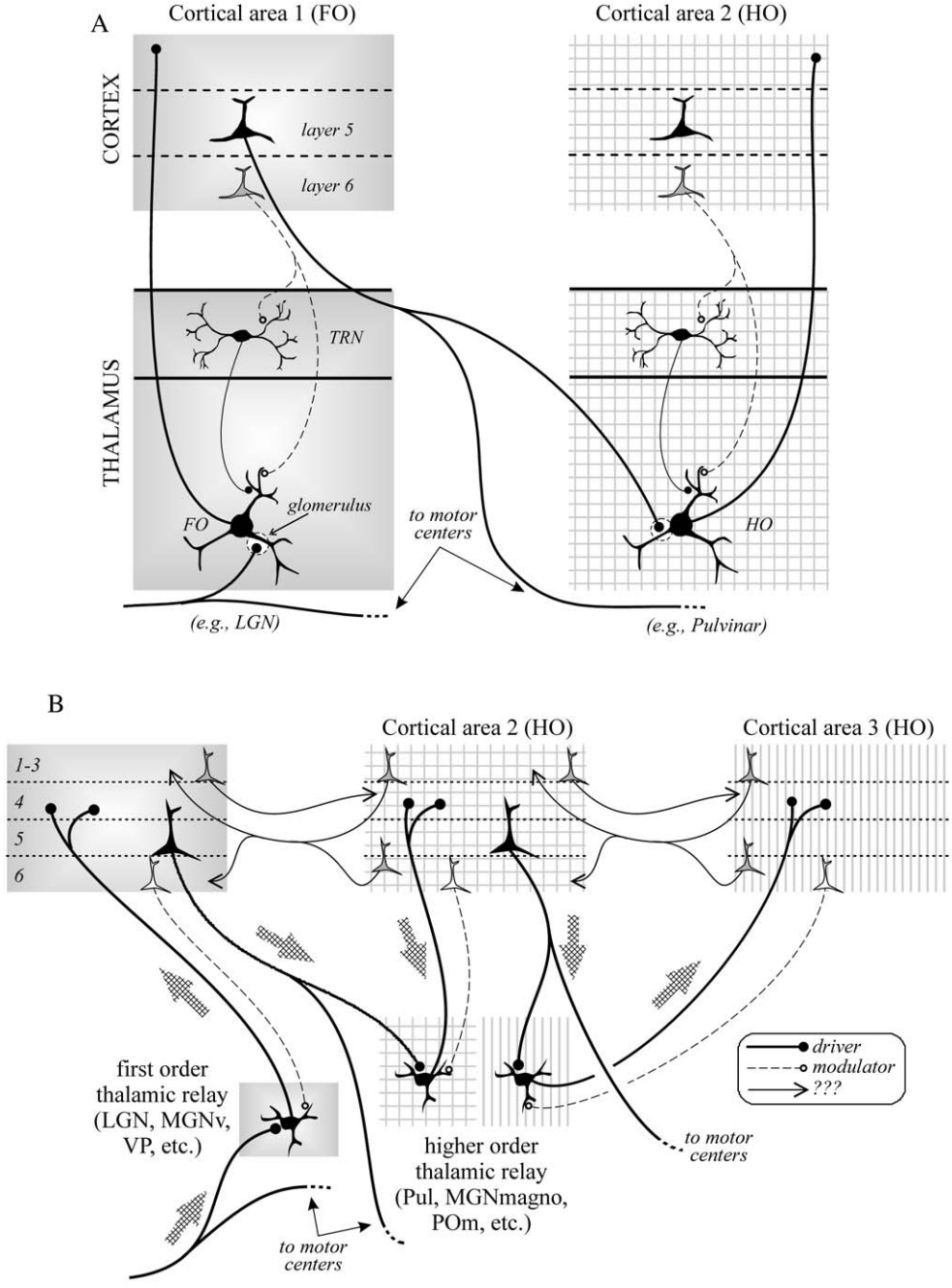

Fig. 5. Schematic diagrams showing first order and higher order relays. A: Distinction between first order and higher order relays. A first order thalamic relay (*left*) represents the first relay of peripheral or subcortical information of a particular type to a first order or primary cortical area. A higher order relay (*right*) relays information from layer 5 of one cortical area to another cortical area; this can be between first order and higher order cortical area (as shown) or between two higher order cortical areas (not shown). The difference is the driver input, which is subcortical (*left*) for a first order relay and from layer 5 of cortex (*right*) for a higher order relay. A feature of driver inputs to thalamus is a thick axon with a large terminal innervating a proximal dendritic site, often in complex synaptic zones known as glomeruli. Other distinguishing features are described in the text. Thus all thalamic relays receive an input from layer 6 of

(Guillery, 1995; Sherman and Guillery, 1996, 2001, 2002; Guillery and Sherman, 2002a). This is summarized in Fig. 5A.

First order relays receive their driver input from a subcortical site and relay that information for the first time to cortex. Examples of drivers and first order relays are retinal input to the lateral geniculate nucleus, medial lemniscal input to the ventral posterior nucleus, inferior collicular input to the ventral portion of the medial geniculate nucleus, and cerebellar input to the ventral anterior and lateral nuclei. Higher order relays, in contrast, receive their driver input from layer 5 of a cortical area and relay this input to another cortical area. Examples of higher order relays are most or all of pulvinar and of the medial dorsal nucleus. Overall, there appears to be considerably more thalamus devoted to higher order than to first order relays (Sherman and Guillery, 2001).

An implication that immediately springs from the appreciation of higher order thalamic relays is illustrated in Fig. 5B. That is, these relays serve as a critical link in a corticothalamocortical route for information transfer. Thus a great deal of corticocortical communication involves these routes with higher order thalamic relays.

An important challenge to this concept derives from a consideration of neuron numbers. Van Essen (2005) points out that numbers of neurons in pulvinar are orders of magnitude fewer than those in any cortical area, and that even for area V1 outputs to other cortical areas, this poses a severe bottleneck on information transfer. Nonetheless, given that a very small percentage of V1 neurons are represented by the layer 5 efferents that could provide the afferent link in the corticothalamocortical pathway (Callaway and Wiser, 1996), these numbers do not seem to pose a limitation on the role of the pulvinar as a central relay structure for these layer 5 inputs. Thus a related question raised is whether or not the limited number of layer 5 efferents is sufficient to project all of the information processed by a cortical area, such as V1. The answer is the nature of this information that is passed on is not known, and the ignorance here is such that the possibility that the small subset of layer 5 efferent cells is up to the task cannot be ruled out. Nonetheless, it is also possible that the full range of information processed in a cortical region requires an additional route, presumably involving direct corticocortical pathways.

What, then, of these direct corticocortical projections, of which there are many? The answer to this question may depend on the nature of these connections. For instance, if these, like thalamic inputs, can be divided into drivers and modulators, then the answer will depend on the subset of these direct pathways that are drivers, and thus it becomes important to characterize these connections functionally; to date virtually all have been defined strictly on light microscopic connectional bases with emphasis on their laminar origin and termination, and these criteria are insufficient to characterize their function. One should not be dazzled by sheer numbers here. That is, the fact that there are many more direct corticocortical inputs to a cortical area than there are thalamocortical does not mean that these are functionally dominant. Recall that only 7% of inputs to lateral geniculate relay cells are retinal while nearly a third derive from the brainstem parabrachial region: if this logic of numbers dictating function were applied to the lateral geniculate nucleus, one would be misled to the conclusion that this nucleus relays parabrachial information, with the small retinal input playing some minor, ethereal role.

Even if these direct corticocortical connections contain many drivers and thus subserve corticocortical communication, there is at least one important difference between this information route and that involving higher order thalamic relays. This has to do with the nature of driver afferents to thalamus.

cortex, which is mostly feedback, but higher order relays in addition receive a layer 5 input from cortex, which is feedforward. B: Role of higher order thalamic relays in corticocortical communication. The suggested route of much of this communication involves a projection from layer 5 of cortex to a higher order thalamic relay to another cortical area. In question is the function, driver or modulator, of the direct corticocortical projections. Note in both A and B that 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; *MGNmagno*, magnocellular portion of the medial geniculate nucleus; *MGNv*, ventral portion of the medial geniculate nucleus; *POm*, posterior medial nucleus; *Pul*, pulvinar; *TRN*, thalamic reticular nucleus; *VP*, ventral posterior nucleus.)

For both first order and higher order relays (Figs. 5A, B), most and perhaps all of these afferents are axons that branch, with one branch innervating thalamus and other(s) innervating apparent motor subcortical centers (Guillery and Sherman, 2002b; Guillery, 2003, 2005). As examples, most or all retinal axons innervating the lateral geniculate nucleus branch to innervate the midbrain as well, and these midbrain structures are involved in various oculomotor tasks; likewise, most or all layer 5 axons innervating pulvinar branch to innervate other subcortical structures, such as the pons and midbrain, that are involved in motor control. This pattern has led to the notion that the actual information being relayed to cortex via both first order and higher order relays are actually copies of motor commands. This notion and its implications for cognitive processing have been explored elsewhere (Guillery and Sherman, 2002b; Guillery, 2003) and are more fully developed by Guillery in Chapter 17. The main issue here, however, is that any messages sent by way of direct corticocortical drivers are messages that stay within cortex, whereas those sent by way of higher order thalamic relays are shared with various subcortical structures, implying that the very nature of the messages is likely to be quite different.

There is another point made by Fig. 5B, which is that most or all information reaching a cortical area, whether originating in the periphery or another cortical area, benefits from a thalamic relay. That is, just as retinal information passes through thalamus and does not directly innervate cortex, so does most or all information directed from one cortical area to another. The same benefits conferred to the relay of retinal information through the lateral geniculate nucleus — whatever they may be — apply as well to corticocortical information flow when a higher order thalamic relay is involved. As just one example, consider burst and tonic firing of thalamic relay cells. It has been suggested that the burst mode may be present in the lateral geniculate nucleus when attention is either reduced during drowsiness or directed elsewhere, so that the relay cells are generally inactive and presumably hyperpolarized. This results in a burst response to a novel visual stimulus, a response that is better detected and more strongly activates cortex, producing a sort of "wake up call"; tonic mode is then initiated to ensure a more faithful relay of information about the new stimulus. This same process may occur for inputs carried by cortical layer 5 axons to higher order thalamic relays. Thus if such a layer 5 cell has been inactive for a time due to drowsiness or other factors related to inattention, the target thalamic relay cells may be in burst mode, and now new activity from the layer 5 cell will activate a burst in the thalamic relay cell that "wakes up" the transthalamic cortical target area; tonic firing then commences for continued information processing along this route. Firing mode in the higher order thalamic relays would be controlled as in the first order relays like the lateral geniculate nucleus, with modulatory brainstem and layer 6 cortical inputs and their influence on the thalamic reticular nucleus providing this control.

Conclusions

It should now be clear that the thalamus actually plays a central and dynamic role in cortical functioning. Thalamus controls the flow of virtually all information to cortex, and does so in interesting ways that we are just beginning to resolve; it not only relays peripheral information to cortex in the first place but also plays a continuing role in further corticocortical processing; and the nature of the information relayed to cortex in many and perhaps all cases seems to be a copy of motor commands, allowing the target cortical areas to be updated about these commands. The complex cell and circuit properties of thalamus belie any sort of trivial, machine-like relay that was thought to be its only function until recently. One dynamic relay function that we are just beginning to understand is the control of response mode — burst or tonic — although we are clearly still far from a complete understanding of its control and behavioral significance. Yet this is probably just the tip of the iceberg: there are undoubtedly many more dynamic relay functions that remain to be identified.

The other two features of thalamic functioning — a continued role in corticocortical communication and the information relayed being motor commands — are summarized schematically in Fig. 6. This places the ideas presented here (Fig. 6B) in bold relief by comparing them to the conventional view of thalamic functioning (Fig. 6A). In the conventional view

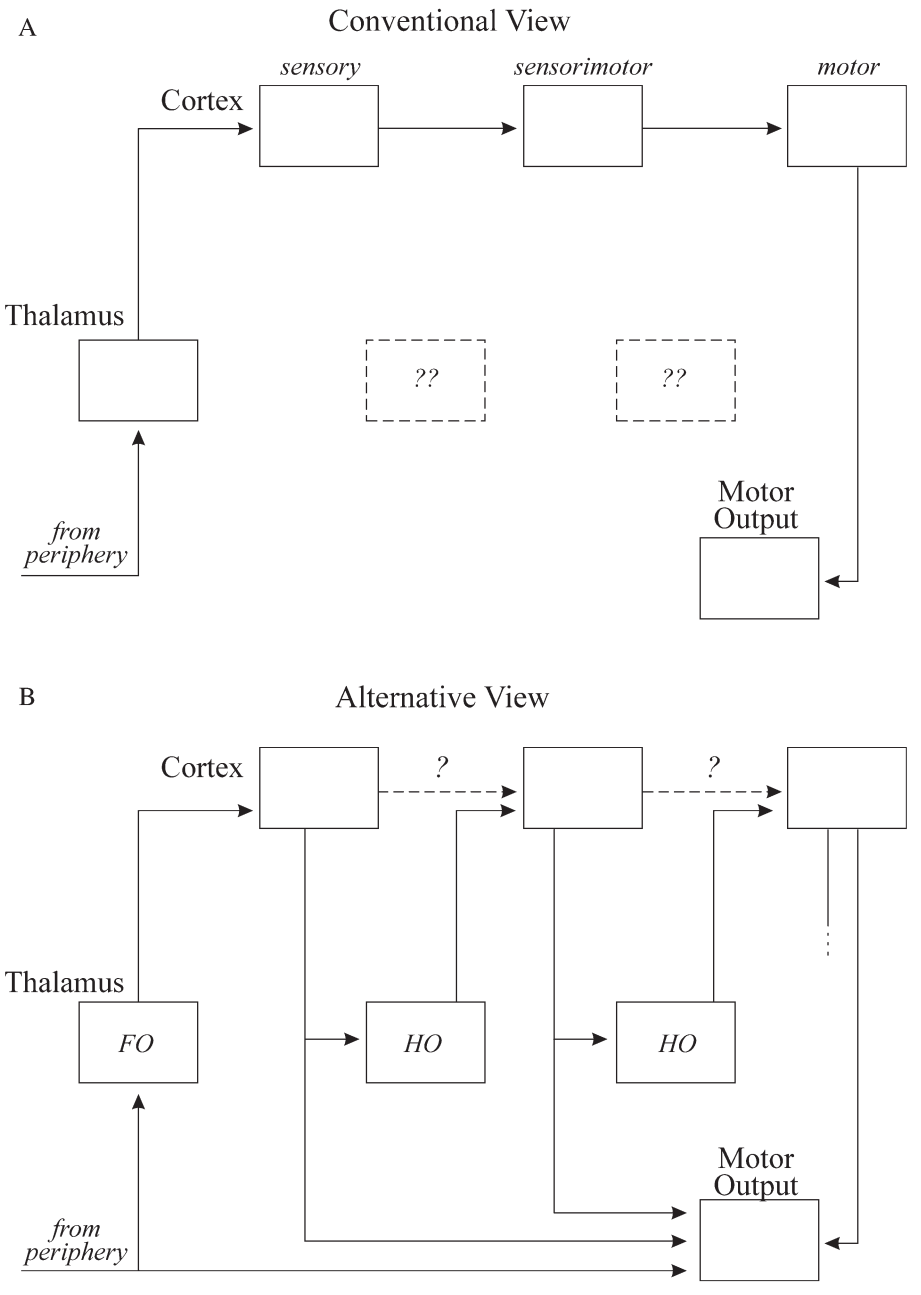

Fig. 6. Comparison of conventional view (A) with the alternative view proposed here (B). The role of the direct corticocortical connections in B (*dashed lines*) is questioned (see text for details). (*FO*, first order; *HO*, higher order.)

(Felleman and Van Essen, 1991; van Essen et al., 1992; Purves et al., 1997; Kandel et al., 2000), peripheral information, which is largely sensory, is relayed through appropriate thalamic relays to primary sensory cortex. This information then stays entirely within cortex, passing through sensorimotor and motor hierarchical levels, and finally a motor command is computed to be transmitted to subcortical

motor centers. All corticocortical communication is handled by direct connections wholly within cortex. One problem with this view is that it provides no role for the majority of thalamic relays, which we have designated as higher order.

The view presented here (Alternative View, Fig. 6B) clearly places the higher order relays in the thick of things by having them serve as essential links in a corticothalamocortical route for cortical processing. This view also shows that most or all of the information actually passed on to thalamus for relay, both through first order and higher order relays, is carried by branching axons that also innervate motor centers. In this view, cortical processing can be thought of as a continuing elaboration and fine tuning of these motor commands. One final point stands out: if the scheme shown in Fig. 6B has any truth to it, it is obvious that one can no longer think about cortical functioning without considering thalamus.

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