THALAMIC RELAY FUNCTIONS

by

S. Murray Sherman

Department of Neurobiology

State University of New York

Stony Brook, NY 11794-5230

USA

S.M. Sherman
Department of Neurobiology
State University of New York
Stony Brook, NY 11794-5230
email: s.sherman@sunysb.edu
phone: (631) 632-8620
FAX: (631) 632-4198

Address from 1 Sept 2000 to 1 Sept 2001:

Department of Physiology
University of Oxford
Parks Road
Oxford OX1 3PT
U.K

ABSTRACT

The lateral geniculate nucleus is the best understood thalamic relay. Only 5-10% of the input to geniculate relay cells derive from retina, which is the driving input, the rest, being modulatory, derive from local inhibitory inputs, descending inputs from visual cortex, and ascending inputs from brainstem. The nonretinal, modulatory inputs, which form the vast majority, dynamically control the nature of the geniculate relay. Among other actions, these modulatory inputs regulate membrane properties of relay cells and thereby control their mode of response to retinal inputs, and this dramatically affects the nature of information relayed to cortex. Our studies of the lateral geniculate nucleus of the cat lead to the speculation that this dynamic control depends on the animal's behavioral state and represents the neuronal substrate for many forms of visual attention. The lateral geniculate nucleus is a first-order relay, because it relays subcortical (i.e., retinal) information to cortex for the first time. In contrast, the other main thalamic relay of visual information, the pulvinar (and lateral posterior nucleus in carnivores), is largely a higher-order relay, since much of it seems to relay information from one cortical area to another. Much more corticocortical processing may involve these “re-entry” routes than has been hitherto appreciated. If so, the thalamus sits at an indispensable position for corticocortical processing.

For a long time, the thalamus has had a bad press, particularly in studies of the visual system. The lateral geniculate nucleus, which is the thalamic relay for retinal information to visual cortex, has traditionally been seen as a passive and trivial relay (Hubel and Wiesel, 1977; Zeki, 1993). There is no significant receptive field transformation across the retinogeniculate synapse, making this relay different from all the others of the visual pathways, and in this regard, the only role it seems to play is in subtracting some retinal action potentials from information relayed. That is, it has been asserted that every action potential in a geniculate relay cell follows one in its retinal input(s) with a fixed synaptic delay, and that some retinal action potentials fail to evoke one in the relay cell (Cleland et al., 1971). Yet we know that the thalamus is an essential relay to neocortex, that it has complex patterns of synaptic interconnectivity, and its cells and circuitry display a rich array of receptors, channels, transmitters, and second messenger systems. If the machine-like relay with some reduction in efficacy were all that the thalamus does, one would have to wonder why we even have a thalamic relay at all. What purpose is served by the lateral geniculate nucleus specifically and thalamus more generally? Why, for instance, does the retina not project directly to visual cortex?

Recent research on thalamic function will be reviewed with focus on the lateral geniculate nucleus, because this offers some answers to these questions. It seems evident now that the complex cell and circuit properties seen in thalamus have some useful functions. As a result, we can replace the above questions with some relating to what these specific functions may be and how they are carried out. One that is emphasized below is the observation that all thalamic relay cells can transmit information to cortex in two very different response modes that depend on intrinsic properties, and these different modes emphasize different aspects of the input information that is relayed to cortex. Thus the nature of these properties and how they are controlled by thalamic circuitry is of great interest. Also, once this obvious function of thalamic relays is laid out, the idea is developed that transmission of information to cortex benefits from a thalamic relay whether the information emanates from a subcortical region, like retina or brainstem, or from another cortical area. This leads to the final hypothesis that thalamus might play a critical role in corticocortical communication.

The low threshold Ca^{2+} spike

Like virtually all other neurons in the brain, thalamic relay cells do not behave like passive cables but instead display many voltage dependent membrane conductances. A detailed review of these can be found elsewhere (McCormick and Huguenard, 1992; Sherman and Guillery, 1996). One of particular interest for thalamic function is a voltage dependent, low threshold, transient conductance involving T (for transient) type Ca^{2+} channels. These T channels are located in the cell bodies and dendrites of relay cells, apparently being more concentrated in the latter (Zhou et al., 1997; Destexhe et al., 1998; Zhan et al., 2000). The properties of the T channels provide relay cells with the two very different response modes indicated above (see Figure 1), and these channels are ubiquitous for relay cells: they are found for every relay cell of every thalamic nucleus of every species so far studied (reviewed in Sherman and Guillery, 1996). When these channels are open, Ca^{2+} flows into the cell, creating a current known as the *T current* or I_T, and this depolarizes the cell, producing an all-or-none Ca^{2+} spike known as the *low threshold spike* (Jahnsen and Llinás, 1984a,b; McCormick and Huguenard, 1992; Sherman and Guillery, 1996). Figure 1D shows the all-or-none nature of this spike (Zhan et al., 1999). This spike is typically 30-50 mV in amplitude and lasts for

50-100 msec. Thus the T channels, I_T, and low threshold spike are all terms related to the same membrane property.

Figure 1 about here

These T channels and I_T have 3 voltage-dependent states (see Figure 1A-C). 1) When the membrane is more depolarized than roughly -60 to -65 mV for 50-100 msec[1], I_T becomes *inactivated* (Figure 1A). 2) When the membrane is more hyperpolarized than about -65 to -70 mV, the inactivation of I_T is removed, and it thus becomes *de-inactivated*. 3) If I_T is de-inactivated and the membrane is then sufficiently depolarized, I_T is *activated*, leading to a low threshold spike (Figure 1C). Thus, depolarization from more depolarized levels, when I_T is inactivated, produces no I_T or low threshold spike, but depolarization from more hyperpolarized levels, when I_T is de-inactivated, evokes I_T and a low threshold spike. Notice that qualitatively these T channels have the same voltage dependency and states of activation, inactivation and de-inactivation as the Na^+ channels underlying the conventional action potential. The main differences are quantitative: the voltage range over which the Na^+ channels operate is more depolarized, and the time constant for inactivation and de-inactivation of the Na^+ channels is roughly two orders of magnitude faster than the 50-100 msec for T channels.

1. The degree of inactivation or de-inactivation is described by a complex function of membrane voltage and time.

The two response modes provided by the T channels are known as *tonic*[2] and *burst* (Figure 1A-C). Tonic mode is operative when I_T is inactivated. Under these conditions, a suprathreshold depolarization (e.g., from a large EPSP) will activate a stream of unitary action potentials as long as the membrane potential is held above threshold for their firing. Burst mode is operative when I_T is de-inactivated. In this mode, a suprathreshold EPSP will activate a low threshold spike that is itself usually large enough to activate a high frequency cluster of action potentials riding its crest. It is important to emphasize here that the T channels are not found in the axon, so the low threshold spike is not conducted to cortex; only action potentials are.

Another temporal feature of the T channels involves its activation. Activation once I_T is de-inactivated requires depolarization, and, as shown in Figure 2, the rate of depolarization, or *dV/dt*, is important. That is, dV/dt must exceed a rate of about 5-10 mV/sec to activate I_T and a low threshold spike (Gutierrez et al., 2000). A slower rate of depolarization will not activate I_T, because, before its activation level is reached, the slower rate of depolarization allows inactivation of I_T to build up to the point that a full blown low threshold spike cannot be activated. Interestingly, it is possible with a very slow depolarization (i.e., a dV/dt < 5-10 mV/sec) to start with a cell in burst mode with fully de-inactivated I_T and switch it to tonic mode with fully inactivated I_T without activating I_T. How this might be done under physiological conditions is considered below under *Control of response mode*.

Figure 2 about here

It had been thought that burst firing was a special case not seen during the normal waking state but was only evident during certain phases of sleep or in some pathological states, such as epilepsy (Steriade and Llinás, 1988; Steriade et al., 1993; McCormick and Bal, 1997). During these unconscious conditions, bursting is rhythmic, occurring at various rates, usually 1-10 Hz, and synchronized across large regions of thalamus. In this view, burst mode is not a true relay mode and instead represents a functional state during which the relay is disconnected. However, there is increasing evidence that, while rhythmic burst firing dominates responses during slow wave sleep, burst mode dependent on I_T is also sometimes present during alert wakefulness (Guido and Weyand, 1995; Nicolelis et al., 1995; Lenz et al., 1998; Radhakrishnan et al., 1999; Ramcharan et al., 2000), although in the awake animal, bursting is usually arrhythmic, occurring at seemingly random intervals. Furthermore, geniculate relay cells in the behaving animal do respond well to visual stimuli with occasional bursts mixed among tonic firing, indicating that both tonic and burst modes are

2. "Tonic" used in this sense refers to a response mode of a thalamic relay cell, and here it is paired with "burst". This use of "tonic" should not be confused with another use of "tonic" when paired with "phasic" to refer to a cell type in the lateral geniculate nucleus: "tonic" for X and "phasic" for Y cells. Throughout this chapter, the use of "tonic" refers only to response mode and not to cell type.

effective relay modes (Guido and Weyand, 1995; Ramcharan et al., 2000).

The obvious question, then, is: What is the functional implication of these firing modes? They represent very different ways in which the relay cell responds to the same input, indicating that the same message is relayed to cortex in one of two different ways. Thus when messages arrive at the relay cell, the level of its membrane potential, which determines the inactivation state of I_T, can strongly influence the nature of the information that is transmitted to cortex. Receptive field analysis from relay cells of the cat's lateral geniculate nucleus indicates that both response modes convey comparable levels of information in the relay to cortex (Reinagel et al., 1999), although it is also clear that the nature of that information differs between modes (Sherman, 1996). There may be many differences related to these two modes, but two that have received considerable attention are linearity of the relay process and detectability of the message that is relayed to cortex.

Linearity. From the cellular properties described above and from Figure 1, it becomes clear that tonic mode provides a more linear relay than does burst mode. During tonic firing, an increase in amplitude of the input (e.g., EPSP size) evokes a higher rate of firing, and there is a range over which this relationship is linear (Figure 1E). However, because the action potentials during burst firing are not evoked directly from an EPSP but instead are evoked by an all-or-none low threshold spike, the firing rate or number of action potentials in a burst tends to be fairly fixed over a wide range of EPSP amplitudes. Thus the relationship between the amplitude of the input and the response in action potentials during burst firing resembles a step function, which is highly nonlinear (Figure 1E).

Figure 1 shows the two firing modes in an *in vitro* slice preparation. Both firing modes can also be readily seen during *in vivo* recording, both in lightly anesthetized and in fully awake animals (Guido et al., 1992, 1995; Lu et al., 1992; Mukherjee and Kaplan, 1995; Guido and Weyand, 1995; Sherman, 1996; Ramcharan et al., 2000). When the recording is intracellular *in vivo*, as is usual *in vitro*, it is possible to control the inactivation state of I_T, and thus the response mode, by injecting current into the cell to vary membrane potential. However, with extracellular recording, which is more commonly used *in vivo*, firing mode cannot be controlled directly. Nonetheless, relay cells then seem to switch more or less randomly between response modes every few seconds, apparently as a result of variations of synaptic input that produce fluctuations of membrane potential. It is nonetheless possible to recognize the two modes during extracellular recording because of their distinctive pattern of intervals between action potentials, and it is thus possible to divide response periods into burst or tonic modes (Lu et al., 1992; Guido and Sherman, 1998; Ramcharan et al., 2000).

One can also use more natural stimuli such as visual targets, rather than current injections, to activate the geniculate relay cells. When this is done, the same difference in linearity is seen: tonic mode reflects a higher degree of linear summation than does burst mode. Figure 3 shows the response of a geniculate relay cell to the same visual stimulus: a drifting, sinusoidally modulated, luminance grating. During tonic firing, the shape of response resembles a sine wave and thus it faithfully or linearly reflects the contrast modulation in the visual stimulus (Figure 3A, *lower*). During burst firing, the response no longer looks smoothly sinusoidal, because there is a nonlinear distortion between the visual input and response (Figure 3B, *lower*). This can be demonstrated formally by Fourier analyzing the response to sinusoidal gratings, and this is shown for a population

of geniculate neurons in Figure 4A (Sherman, 1996).

Figures 3 and 4 about here

There is an obvious benefit for maintaining a linear relay related to tonic firing, since the nonlinear distortions associated with the burst mode limit the ability of the cortex to faithfully reproduce the visual scene. What then is the purpose or advantage of burst mode? The answer to this question may be related to stimulus detection.

Detectability. The response profiles to a drifting sinusoidal grating shown in Figure 3 reveal another difference between firing modes besides that of linearity. Whereas the response to the grating in both modes is vigorous, the spontaneous activity (when the grating stimulus is not present) is much lower during burst firing (Figure 3A,B, *upper*)[3]. We may consider the response to the grating as the signal to be conveyed to cortex and the spontaneous activity as the noisy background against which this signal must be detected. From Figure 3, it seems that the ratio of signal (the response to the grating) to noise (the spontaneous activity) is higher during burst than tonic mode. A higher signal-to-noise ratio is usually associated with better detectability.

Signal detectability can be formally tested by using a method from signal detection theory known as *ROC* (for *R*eceiver *O*perating *C*haracteristic) analysis (Green and Swets, 1966; Macmillan and Creelman, 1991). When this is done for responses of a population of geniculate neurons to visual stimuli, the impression gained from Figure 3 is confirmed. As summarized in Figure 4B, all cells show better signal detectability during burst than tonic firing (Sherman, 1996).

It thus appears that each response mode has certain advantages. Tonic mode provides a more faithful, linear relay of visual information. Burst mode provides better stimulus detectability. Perhaps burst firing is preferred when stimuli must be detected or as a sort of "wake-up call" when the relevant portion of visual field is not attended to, ensuring that novel stimuli are detected. Once a novel stimulus is detected, the firing mode might be switched to tonic to enhance stimulus analysis by reducing nonlinear distortions in the relay (for details of this hypothesis, see Sherman, 1996; Sherman and Guillery, 2000). There may well be many other features, besides linearity and stimulus detectability, related to these different response modes, but they are presently unexplored and undefined. By focusing on the linearity and the detectability of signal transmission, a theoretical framework for the meaning of the two response modes can be entertained. If this is to make any sense, however, there must be means of effectively controlling response mode by various afferents to relay cells. To explore this requires a consideration of geniculate circuitry.

Geniculate circuitry

If the above description of cellular properties of relay neurons were not enough to convince the reader that the thalamic relay is dynamic and consequential, then a consideration of the complex

3. Interestingly, the higher spontaneous activity during tonic firing also helps preserve linearity by reducing nonlinearities associated with rectification.

circuitry of thalamus should certainly do so.

Survey of afferents. Figure 5 summarizes the major afferents contributing to the circuitry of the thalamus, using the lateral geniculate nucleus as an example; other thalamic nuclei have similar circuitry, although a number of details differ (Jones, 1985; Sherman and Guillery, 1996, 2000). The pattern of ionotropic and metabotropic receptors on relay cells is also shown, and the significance of this will be considered below. Relay cells receive a glutamatergic input from retina. They are also innervated by a variety of nonretinal sources. Most of the latter include GABAergic inputs from local, inhibitory cells (i.e., both intrinsic interneurons and cells of the nearby thalamic reticular nucleus), glutamatergic inputs from layer 6 of visual cortex, and cholinergic inputs from the parabrachial region of the brainstem. Synaptic terminals derived from this last input appear to contain nitric oxide as well as acetylcholine, and although the effects of nitric oxide are not well understood, several studies have suggested effects (Pape and Mager, 1992; Shaw and Salt, 1997; Cudeiro and Rivadulla, 1999).

Figure 5 about here

The numbers are illuminating: only 5-10% of the synaptic inputs derive from retina, whereas about a third each derives from the local GABAergic neurons, the corticogeniculate axons, and the cholinergic brainstem inputs (Guillery, 1969; EriÕir et al., 1997; Van Horn et al., 2000). There is a remaining small input (perhaps 5% or so) not shown in Figure 5 and not further considered here that includes noradrenergic and serotonergic inputs from the brainstem and histaminergic inputs from the tuberomamillary mamillary nucleus of the hypothalamus (for further details of other inputs, see (Sherman and Guillery, 1996, 2000). The fact that retinal input, generally regarded as providing the information to be relayed to cortex, represents such a small minority of input to relay cells, which, in turn, are embedded in such complex nonretinal circuitry, belies a simple, trivial relay function for this thalamic nucleus.

Figure 5 also shows other details of geniculate circuitry (Sherman and Guillery, 1996, 2000). Retinal input innervates interneurons as well as relay cells, but does not innervate cells of the thalamic reticular nucleus. Geniculocortical axons branch *en route* to cortex to innervate reticular cells, and corticogeniculate axons do likewise in the opposite direction. Reticular cells innervate relay cells almost exclusively, with very little input to interneurons (not shown in Figure 5). Both brainstem and corticogeniculate axons branch to innervate all of the thalamic cell types: relay cells, interneurons, and reticular cells.

The functional effects of the different inputs on relay cells are difficult to predict (see Figure 5). Even retinal input, which excites relay cells directly, indirectly inhibits them through interneurons, so the overall, sustained effect of this input is not obvious. Likewise, cortical inputs directly excite relay cells but indirectly inhibit them via the local GABAergic cells. Cholinergic inputs from the brainstem have a less complicated excitatory effect on relay cells, because they directly excite them and also disinhibit them by inhibiting local GABAergic cells (reviewed in (McCormick, 1992; Sherman and Guillery, 1996). However, Figure 5 shows global pathways, and individual axons may not be organized in the manner suggested. Take corticogeniculate axons for example (and this reasoning can be applied to most of the inputs). A single axon will branch to innervate reticular cells and relay cells, but if the target reticular cells do not innervate any of the target relay cells, there is no disynaptic inhibition of relay cells from cortex, as Figure 5 might be

misconstrued to suggest. To really interpret the functional significance of the thalamic circuitry as suggested by Figure 5 requires knowledge of circuits entered into by individual axons, knowledge that is presently lacking.

Ionotropic and metabotropic receptors. A particularly important aspect of functional circuitry involves the nature of the postsynaptic receptors. These come in two basic flavors; *ionotropic* and *metabotropic* (see Figure 6; for details, see Nicoll et al., 1990; Mott and Lewis, 1994; Recasens and Vignes, 1995; Pin and Duvoisin, 1995; Pin and Bockaert, 1995; Isaac et al., 1997; Brown et al., 1997). Ionotropic receptors are directly linked to the ion channel they control, and indeed, the ion channel is typically part of the receptor itself (e.g., Figure 6, *top*). Presumably because of this direct linkage, the receptor responds to its transmitter to open its ion channel quickly and transiently, with a latency of <1 msec and a duration of a few 10s of msec. In contrast, metabotropic receptors (Figure 6, *bottom*) are linked to the affected ion channels rather indirectly. Most of these receptors are linked to a G-protein, and binding of the transmitter to the receptor releases the G-protein to initiate a cascade of biochemical reactions inside of the cell. One end result is the opening or closing of an ion channel, usually a K^+ channel in the case of thalamic neurons[4]. Presumably because of the many indirect links between receptor and ion channel, this is a slow process with a latency from transmitter binding to opening or closing of the ion channel of several msec or more and a duration of 100s of msec to several sec, or even longer.

Figure 6 about here

If we consider the nature of receptors activated by the afferents to relay cells, an interesting pattern emerges (see Figure 5). Retinal input activates *only* ionotropic glutamate receptors (mostly AMPA and NMDA; reviewed in (Sherman and Guillery, 1996, 2000). All other inputs activate a combination of ionotropic and metabotropic receptors. Thus cortical inputs activate the same receptor types as do retinal inputs but also activate metabotropic glutamate receptors. Cholinergic brainstem inputs activate nicotinic (ionotropic) and muscarinic (metabotropic) receptors. Other inputs using noradrenaline, histamine, or serotonin as neurotransmitters (not shown in Figure 5) seem to activate mostly only metabotropic receptors. GABAergic cells of the thalamic reticular nucleus activate $GABA_A$ (ionotropic) and $GABA_B$ (metabotropic) receptors; inputs to relay cells from interneurons activate $GABA_A$ receptors, and whether or not they also activate $GABA_B$ receptors is presently unknown What is not clear and obviously of some importance is whether

4. Other long-term effects of the second messenger cascade initiated by activation of a metabotropic receptor have been reported, included control of gene expression, so this can have quite extensive and long-lasting effects on the postsynaptic cell. In contrast, ionotropic receptor activation affects little other than the appropriate ion channels. However, such effects of metabotropic receptor activation beyond indirect control of ion channels have not yet been investigated in thalamic neurons.

individual axons of the various nonretinal inputs activate both ionotropic and metabotropic receptors or whether some activate only one or the other type.

The importance of the distinction between receptor types is further considered below in terms of the control of response mode and for faithfully conveying information in the relay through thalamus.

Control of response mode. As suggested above, the nature of the tonic or burst response mode of a relay cell is a key parameter of thalamic relay functioning, and thus control of response mode by thalamic circuitry is of obvious importance. Such control, as noted, involves sustaining a change of membrane potential long enough (>50-100 msec) to change the inactivation state of I_T.

Consider what would be necessary to switch response mode from tonic to burst, that is, to de-inactivate I_T after the membrane had been sustained at a relatively depolarized potential sufficient to inactivate I_T. De-inactivation would now require a hyperpolarization via IPSPs to be of sufficient amplitude *and* duration. The obvious candidates to produce an IPSP in a relay cell are the local GABAergic neurons. If they activate ionotropic ($GABA_A$) receptors in the relay cell, this will not likely serve to change response mode, because the resultant IPSP would be over in 20-40 msec or so, which is not long enough to de-inactivate I_T. Only if there were considerable temporal summation of $GABA_A$-mediated IPSPs due to sustained, high firing rates of the GABAergic inputs could the hyperpolarization be sustained long enough to switch response mode. However, if these inputs activated metabotropic ($GABA_B$) receptors, the resulting IPSP would be sustained for >100 msec, which is long enough. Thus the $GABA_B$ receptors seem a much better tool for controlling response mode than do the $GABA_A$ receptors. Another advantage for $GABA_B$ activation in this regard is that it depends on increasing a K^+ conductance with a reversal potential of roughly -100 to -110 mV, while $GABA_A$ activation increases a Cl^- conductance with a reversal potential of about -70 mV. Thus, activation of the metabotropic, $GABA_B$ receptor produces a stronger hyperpolarization, which would also more effectively de-inactivate I_T.

A similar logic can be applied in considering inactivation of I_T to switch the firing mode from burst to tonic. Here the task is to produce a sustained depolarization. A fast EPSP via ionotropic receptors, such as retinal activation of ionotropic glutamate receptors, will not last long enough to inactivate I_T effectively. Instead, if the EPSP is large enough, it is fast enough in terms of dV/dt to activate I_T and a low threshold spike, but once this finishes, the membrane will return to its previously hyperpolarized level, and the cell will remain in burst mode. Only with temporal summation would the retinal EPSPs likely be able to switch firing modes. In contrast, the slow EPSPs evoked via metabotropic receptors (e.g., metabotropic glutamate receptors via corticogeniculate activation or muscarinic receptors via activation of brainstem inputs) can sustain the depolarization long enough to inactivate I_T and switch the response mode.

There is another potentially significant advantage of metabotropic receptors in switching response mode from burst to tonic. As noted above, activating I_T requires a minimal rate of rise of a depolarizing input. This minimum dV/dt is exceeded by EPSPs via ionotropic receptors, such as retinal EPSPs. This means that if such EPSPs through summation manage to switch firing mode to tonic from burst, they must necessarily always first activate a burst, which would be spurious if the only result wanted was a switch in firing mode. This burst signal, then, always reaches cortex, and if the ideas of burst firing as a "wake-up call" are valid, then this serves its function before the

sustained retinal inputs are then relayed via tonic firing. In other words, the switching of response mode to tonic firing with ionotropic EPSPs is a more complex event than just a mode switch. However, the very slowly rising EPSPs activated via metabotropic receptors might perform the neat trick of a clean switch in response mode to tonic firing without ever activating a spurious burst. This scenario has not yet been experimentally verified by synaptically activating only metabotropic receptors in a thalamic relay cell in burst mode, but it is a verifiable hypothesis that lends further support to the importance of metabotropic receptors in controlling response mode of these neurons. It should be noted that the appearance of a fast retinal EPSP during any slow, metabotropic depolarization before I_T is inactivated will activate a low threshold spike, but because it is initiated by a retinal input, it will not result in a spurious signal to cortex.

With this in mind, the pattern of synaptic inputs outlined in Figure 5 can be considered further. Since retinal input activates only ionotropic receptors, it is a poor candidate to control response mode. All of the nonretinal inputs (including others not illustrated here) activate metabotropic inputs, and these could more efficiently control response mode. However, they also activate ionotropic receptors, suggesting perhaps that these inputs have functions other than controlling response mode. As noted above, what is not clear from Figure 5 is whether subsets of nonretinal inputs exclusively activate one or the other receptor type, which would clearly provide these pathways with more flexibility and diversity of function. If, for example, every cortical axon activated both ionotropic and metabotropic glutamate receptors, it is difficult to see how this pathway could switch response mode from burst to tonic without activating a burst. Nonetheless, with this proviso and the need to learn the pattern of postsynaptic receptors activated by individual afferents, one can suggest that one important function of nonretinal inputs to the lateral geniculate nucleus is to control response mode of the relay cells.

Drivers and modulators. The point has been made in detail elsewhere (Sherman and Guillery, 1998) that afferent inputs to thalamic relay cells are not all the same but can be divided into at least two functionally distinct groups: *drivers* and *modulators*. Drivers are the inputs that covey the basic information to be relayed to cortex. In the lateral geniculate nucleus, this is the retinal input, and in other sensory relays, drivers can also be clearly defined as the medial lemniscal afferents for the ventrobasal nuclei (or, the ventral posterolateral and ventral posteromedial nuclei, which are the somatosensory relays) and the lateral lemniscal afferents for the ventral part of the medial geniculate nucleus (i.e., the auditory relay). Drivers can also be clearly recognized for some other thalamic relays, but in some nuclei, the identity of the drivers is not yet obvious. By definition, any afferents that are not drivers are modulators. Their job is to provide modulation of the thalamic relay. An example of modulation is the control of response mode.

As is indicated in Figure 5, one distinction between the driver (retinal) and modulator (nonretinal) inputs is the nature of postsynaptic receptors they can activate: the drivers activate only ionotropic receptors, whereas the modulators can also activate metabotropic receptors. The fact that drivers such as retinal inputs activate only ionotropic receptors implies that the EPSPs they evoke are relatively fast in terms of latency and duration. The short latency is clearly important if the information is to be relayed to cortex in a timely fashion, and the long latencies associated with metabotropic receptors would be an obvious disadvantage. Also the short duration of the EPSP helps ensure that the pattern of two events, or action potentials, closely spaced in time will be relayed to

cortex. If the EPSPs were very long-lasting, as would happen with metabotropic receptors, action potentials occurring with short intervals in the input would no longer be resolved as individual signatures in the relay to cortex. Another way of stating this is that a postsynaptic potential via metabotropic receptor activation acts like a low pass temporal filter that results in a loss of high frequency information. This loss is minimized via ionotropic receptors. Thus there seems to be an obvious advantage to assigning only ionotropic receptors to driver inputs that carry the information to be relayed.

There is also a potential advantage to the slow time course of metabotropic receptor activation for modulators. Generally, the long, sustained postsynaptic potentials will lead to overall excitability changes in relay cells, which is one obvious task for modulator input. More specifically, thalamic relay cells have many voltage- and time-dependent ionic conductances in addition to those underlying action potentials and I_T: these include other K^+, Na^+, and Ca^{2+} conductances (for details, see McCormick and Huguenard, 1992; Sherman and Guillery, 1996), all of which are voltage- and time-dependent, meaning that, like I_T, they are activated by a change in membrane potential that must be sustained usually for 10s of msec or longer. These conductances together play important roles in how a relay cell responds to its driver input. As with I_T, activation of ionotropic receptors is poorly matched temporally to control these conductances, but activation of metabotropic receptors suits admirably. It thus makes as much sense for modulators to activate metabotropic receptors as for drivers not to do so.

Furthermore, note that, in the lateral geniculate nucleus, the driver (retinal) input represents a small minority of synaptic input to relay cells (5-10%). Limited evidence from other sensory thalamic relays also indicates that the driver inputs provide a small minority of synapses onto the relay cells. It has been argued elsewhere (Sherman and Guillery, 1998, 2000) that this makes sense, because bringing the basic information to a thalamic nucleus does not require as many synaptic inputs as would be required for fine modulation of the relay. This idea of driver inputs to an area is probably not limited to thalamus. For example, it now seems clear that the main information is brought to layer 4 cells in visual cortex by geniculocortical axons (Reid and Alonso, 1995, 1996; Ferster et al., 1996; Chung and Ferster, 1998), yet these provide only about 5-10% of the synaptic inputs to these cells (Ahmed et al., 1994; Latawiec et al., 2000). Also, an analysis of synaptic counts on spinal motoneurons indicates that Ia afferents, which constitute a major driver input, provides <5% of the synaptic terminals to these cells (reviewed on p. 462 of Henneman and Mendell, 1981). It will be interesting to see how general beyond the sensory thalamic relays this finding is that driver inputs constitute a small minority of synapses.

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

How, then, do we distinguish between driver and modulator inputs? If we use the lateral geniculate nucleus as a template, we can begin to enumerate some of the differences between drivers and modulators that may be generalized to other thalamic nuclei (see Figures 5 and 7 for some of

these differences and Sherman and Guillery, 1996, 1998, 2000) for others):

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

Figure 7 about here

In the following section, many of these criteria are used to help identify drivers to many thalamic nuclei and in the process demonstrate that two very different sorts of thalamic relays can be defined.

First and higher order relays

Layer 6 versus layer 5 corticothalamic inputs. It appears that a layer 6 modulatory input is a general property for all thalamic nuclei, and if the sensory relays are typical, this layer 6 corticothalamic pathway is roughly reciprocal in that it derives mostly, but not exclusively, from cortical areas to which the thalamic nucleus in question projects. It has been known for some time that some thalamic nuclei, in addition, receive a layer 5 input from some cortical areas (Guillery, 1995). Examples of nuclei that receive layer 5 afferents are the pulvinar[5], the posterior medial nucleus, the magnocellular division of the medial geniculate nucleus (as opposed to the ventral division, which receives lateral lemniscal input), the medial dorsal nucleus, and others (for details, see Guillery, 1995; Sherman and Guillery, 1996, 2000). It is not clear if the layer 5 innervation supplies the entirety of each of these nuclei or only certain as yet undefined segments. Also, there may be sparse layer 5 input to certain nuclei, like the ventrobasal complex. Knowledge of this layer 5 innervation was filed away for decades as a thalamic curiosity until Guillery (1995) pointed out the possible functional significance of certain differences between layer 5 and layer 6 afferents to thalamus. Figure 7 summarizes some of the evidence accumulated so far, from which it is clear that the layer 5 afferents are quite unlike layer 6 afferents but bear a striking anatomical resemblance to driver afferents as described for the main sensory relays (compare with the driver/modulator bulleted list above; for details, see (Sherman and Guillery, 1996, 1998; Vidnyánszky et al., 1996):

5. For simplicity, the term “pulvinar” includes the lateral posterior nucleus in carnivores.

- They innervate dorsal thalamic nuclei but fail to innervate the thalamic reticular nucleus with collateral branches even though they pass through this region *en route* to their dorsal thalamic target
- Where studied, layer 5 inputs activate only ionotropic receptors on relay cells, whereas layer 6 inputs activate metabotropic receptors as well
- Their axons are thick, with type II morphology and terminal fields
- Their synaptic terminals are quite large and seem to innervate proximal dendrites, often in glomeruli and having triadic arrangements with terminals from interneurons
- Many, if not all, branch to innervate extrathalamic targets

Indeed the above list matches point-for-point the earlier list that distinguishes drivers from modulators. It thus seems reasonable to regard these layer 5 afferents as drivers in the same sense that we consider retinal afferents as the driver for the lateral geniculate nucleus. This is of further interest, because, for the most part, there is no obvious subcortical driver input to most thalamic regions receiving layer 5 innervation.[6]

First and higher order thalamic relays. To extend this idea, it appears that some thalamic nuclei receive their main driver input from subcortical sources, like the retina, brainstem, etc., and relay this information to cortex, whereas others receive their main driver input from cortex itself and relay this information to another cortical area. We can consider the former type of relay as *first order*, because it represents a first pass of the relevant information into cortex, and the latter as *higher order*, because it represents a relay of information that has already reached cortex but from one cortical area to another (see Figure 7 and Guillery, 1995). Because some thalamic nuceli may get driver input from both subcortical and layer 5 sources, it may be more appropriate to consider first order versus higher order circuitry for thalamic relays rather than for entire thalamic nuclei.

6. There is a projection from the midbrain to parts of the pulvinar that is often treated implicitly as a driver. Perhaps it is, but it is also possible that it is a modulatory input. Also, it may be that the pulvinar can be divided into one sector that receives driver input from midbrain and another that receives its driver input from layer 5 of cortex.

It is interesting that, when thought of this way, each of the main sensory systems has both types of relay for vision, the lateral geniculate nucleus is the first order relay, and most of the pulvinar is the higher order relay; for somatosensation, the ventrobasal nuclei are the first order relay, and the medial portion of the posterior complex[7] is the higher order relay; and for audition, the ventral part of the medial geniculate nucleus is the first order relay, and the magnocellular part of this nucleus is the higher order relay. (Olfactory information reaches cortex in an unusual way that makes it difficult to fit into this duality) Whether there is such a neat duality for other types of information relayed through thalamus remains to be determined.

Implications for corticocortical communication. Cortex is comprised of many distinct areas that obviously communicate prolifically amongst themselves. Just how this is done is one of the major problems facing neuroscientists. A consideration of the many areas of visual cortex help to frame the problem and a different approach to it that is suggested here.

We know from many anatomical and electrophysiological studies over the past 4 decades that the visual world in carnivores and primates is analyzed by many different areas (more than 30 in monkeys) in the occipital, parietal, and temporal lobes (for reviews, see Van Essen, 1985; Felleman and Van Essen, 1991; Van Essen et al., 1992). Attempts to make sense of how these areas cooperate and communicate with one another in visual analysis has focused largely on direct corticocortical connections. Figure 2 of Van Essen et al. (1992), which is a much copied schema, shows the rich and often reciprocal connectivity among these areas. Strategies have been offered to distinguish feedforward from feedback pathways among these connections (Felleman and Van Essen, 1991). The basic notion in this scheme, a notion challenged below, remains constant: visual information enters striate cortex from the lateral geniculate nucleus, and in a more or less hierarchical set of feedforward connections, the information is passed from striate cortex to higher and higher areas, with many feedback connections present as well. Note that, according to this view, once the information reaches cortex from the lateral geniculate nucleus, it stays within cortex, being routed effectively only amongst cortical areas. Among other drawbacks, this view of visual processing has little regard for the pulvinar, which is a much larger thalamic structure than is the lateral geniculate nucleus.

One of the reasons this view is so widely held is the very massive nature of direct corticocortical connections. Any cortical area receives the vast majority of its extrinsic afferents from other cortical areas and rather little from subcortical structures, like the thalamus. But this linking of functional importance of a pathway with its size is the very thinking that, as suggested above,

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

would lead one to conclude that retinal input to the lateral geniculate nucleus is functionally of little consequence.

To frame our alternative view versus the traditional one for corticocortical communication, it is helpful to consider the extreme alternative first. For cortical afferents, just as in those of the thalamus, it may be that drivers and modulators exist. The drivers carry the main information, and identifying them among afferents to a cortical area becomes supremely important. If, as in thalamus, the driver inputs are a small minority, then concentrating on large pathways, such as most of the direct corticocortical connections, may be misleading. Perhaps only a small minority of these direct pathways are drivers, with the rest being modulators.

The most extreme view, offered for clarity, is that *none* of the direct corticocortical projections are drivers, and instead they are all modulators. The drivers, then, are limited to thalamocortical afferents. By this extreme version of our hypothesis, the information route for corticocortical communication travels from layer 5 of one area down to a higher order thalamic relay (i.e., pulvinar for visual cortical communication) and then back up to the target cortical area (see Figure 8). Another way of thinking about this is to consider the benefits of relaying retinal information through the lateral geniculate nucleus to cortex instead of having a direct retino-cortical pathway: it may be that *any* new information coming into a cortical area, whether originating subcortically or in a another cortical area, benefits from a thalamic relay.

Figure 8 about here

A less extreme hypothesis would maintain that one important route for corticocortical communication involves a relay through higher order thalamic nuclei, but that another route involves a minority of corticocortical connections, the rest being modulatory. However, even here it is possible to point out an important difference between corticocortical drivers and those involving cortico-thalamo-cortical routes. Information carried by the former stays strictly within cortex, but that carried by the latter pathway also informs other regions of the neuroaxis.

Even if our hypothesis proves wrong, it does draw attention to the need to avoid treating all connections among cortical areas as functionally equivalent. Just knowing, for instance, which corticocortical afferents activate ionotropic and/or metabotropic receptors would be a useful step in functionally classifying these pathways.

Conclusions

The complex cell and circuit properties of thalamic nuclei leave little doubt that the relay of information to cortex is an active and mutable process. The question should no longer be why we have thalamic relays but rather how these relays affect the nature of information arriving in cortex and how their different relay properties are controlled. Some specific suggestions have been made here about how circuit properties control a voltage-dependent conductance, I_T, in relay cells to control responsiveness, and how this could affect the nature of information relayed to cortex. However, it should be appreciated that this property related to tonic and burst response modes may be one of many mechanisms by which thalamic relays can control the flow of information to cortex.

Nonetheless, once we appreciate that the insertion of a thalamic relay in the information pathway to cortex has great functional significance, we can also re-investigate the role of thalamus in corticocortical communication. The discovery that many thalamic regions seem to receive their

driving input from layer 5 of cortex itself leads to the suggestion that much of corticocortical communication involves a route through thalamus, with the same advantages of having a thalamic relay for this route as exists for relaying, say, retinal information to cortex. The alternate route for corticocortical communication—direct connections among areas—needs to be reconsidered with regards to the nature of these pathways and the possibility that many, and perhaps all, are modulatory in nature. Thus the full impact of thalamus may be much more than simply controlling flow of information to cortex: it may remain an active partner in all cortical computations.

ACKNOWLEDGMENT

The author's laboratory during the preparation of this manuscript was supported by USPHS Grants EY03038 and EY11409.

FIGURE LEGENDS

Figure 1

Properties of I_T and the low threshold spike. All examples are from relay cells of the cat's lateral geniculate nucleus recorded intracellularly in an *in vitro* slice preparation. ***A***-***C***: Voltage dependency of the low threshold spike. Responses are shown to the same depolarizing current pulse delivered intracellularly but from three 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 slightly more hyperpolarized (***B***), I_T remains mostly inactivated, but the current pulse no longer depolarizes the cell to above threshold. Thus a simple, resistive-capacitative response is seen. When the cell is further hyperpolarized (***C***), I_T is de-inactivated, and the current pulse activates a low threshold spike with 4 action potentials riding its crest. This is the *burst mode* of firing. ***D***: All-or-none nature of low threshold spikes. Here, TTX is added to block conventional action potentials and reveal the low threshold spikes more clearly. The cell is held at a hyperpolarized potential to completely inactivate I_T, and current pulses were injected starting at 200 pA amplitude and incremented in 10 pA steps. Smaller (subthreshold) pulses led to pure resistive-capacitative responses, but all larger (suprathreshold) pulses led to a low threshold spike. Much like conventional action potentials, the low threshold spikes are all the same amplitude regardless of how far the depolarizing pulse exceeded activation threshold, although there is some latency variability seen for smaller suprathreshold pulses. ***E***: Input-output relationship for one cell. The input variable is the amplitude of the depolarizing current pulse, and the output is the firing frequency of the cell. To compare burst and tonic firing, the firing frequency was determined by the first 6 action potentials of the response, since this cell usually exhibited 6 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 -83mV), the input-output relationship is quite nonlinear and approximates a step function.

Figure 2

Failure of slow ramps to activate low threshold spike in geniculate relay cell recorded intracellularly *in vitro*. ***A***-***E***: Responses to ramps producing decreasing *dV/dt*. low threshold spikes are activated by the faster ramps (***A***,***B***) but not in the slower ones (***C***-***E***), although a small, partial low threshold spike may be present in ***C***. Note that, with a sufficiently slow *dV/dt*, the cell can be switched from burst to tonic without ever activating a low threshold spike and burst. Data from (Guiterrez et al., 2000).

Figure 3

Tonic and burst responses of relay cell from the cat's lateral geniculate nucleus to sinewave grating. The cell was recorded intracellularly *in vivo*, and current injected through the 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 4 cycles of the grating drifted through the receptive field. The contrast changes resulting from the drifting grating are shown below the histograms. ***A***: Tonic mode. The spontaneous activity is relatively high, and the response to the grating has a distinctly sinusoidal profile. ***B***: Burst mode. The spontaneous activity is relatively low, and the response to the grating no longer has a sinusoidal profile.

Figure 4

Response linearity and signal detectability during tonic and burst firing. Each point in the scatter plots reflects data from one relay cell of the cat's lateral geniculate nucleus recorded *in vivo* during visual stimulation, and the plots compare the response during tonic firing on the abscissa versus burst firing on the ordinate. The dashed line of slope 1 is also shown in each plot. ***A***: Linearity. To obtain a measure of linearity, responses to sinewave gratings as in Figure 3 were Fourier analyzed and a linearity index was computed by dividing the linear F1 component by the sum of the higher-order nonlinear components (i.e., F2, F3, etc.). The larger this index, the more linear the response. Note that every single cell shows more linearity during tonic firing. ***B***: Detectability. The d' values were determined from ROC analysis (for details, see Green and Swets, 1966; Swets, 1973).

Figure 5

Circuitry of the lateral geniculate nucleus. Shown are the various inputs to relay cells. The retinal (driver) input is distinguished from the nonretinal (modulator) inputs. Note that only about 5-10% of the synaptic inputs to relay cells derive from retinogeniculate axons, and likewise, only about 5-10% of the inputs to layer 4 cells in visual cortex derive from geniculocortical axons. Also shown are the postsynaptic receptors on relay cells associated with each of the inputs illustrated. The retinal input activates only ionotropic receptors, whereas all nonretinal inputs activate metabotropic receptors and often ionotropic receptors as well. Abbreviations: *ACh*, acetylcholine; *GABA*, γ-aminobutyric acid; *Glu*, glutamate; *LGN*, lateral geniculate nucleus; *NO*, nitric oxide; *PBR*, parabrachial region of the brainstem; *TRN*, thalamic reticular nucleus. See text for further details.

Figure 6

Schema of ionotropic and metabotropic receptor. ***Upper***: Ionotropic receptor. The receptor is linked directly to an ion channel, which is usually part of the receptor molecule. Binding of the receptor to the neurotransmitter quickly causes a conformational change leading to opening of the ion channel. Ions flow through the channel, creating a postsynaptic potential. This happens with a relatively short latency and duration. ***Lower***: Metabotropic receptor. The receptor is not linked directly to an ion channel. Instead, binding of the neurotransmitter to the receptor releases a G-protein, and this produces a cascade of biochemical reactions. Occasionally the G-protein can affect the ion channel directly (not shown), but more commonly, the G-protein acts through an effector protein to eventually open or close an ion channel. Other properties of the cell can also be affected by the biochemical reactions. The end result is a slow postsynaptic potential with a relatively long

latency and duration.

Figure 7

Comparison of corticothalamic axons from layer 6 versus layer 5. First-order (*FO*) thalamic regions receive driver inputs from subcortical sources, whereas higher-order (*HO*) thalamic regions receive driver inputs from cortical layer 5. See text for details.

Figure 8

Schema of hypothesis that corticocortical information flow involves a relay through a higher-order thalamic region. The first-order (FO) relay (e.g., lateral geniculate nucleus) relays a driver (e.g., retinal) input to primary cortex (e.g., V1). From here, information is relayed among cortical areas via cortico-thalamo-cortical paths involving different regions of a higher-order (HO) thalamic nucleus (e.g., the pulvinar). routes Thick, dark pathways represent the drivers, and thin, lighter pathways with solid lines represent the modulators. The nature of direct corticocortical projections (dashed lines) is ambiguous as to identity as driver or modulator.

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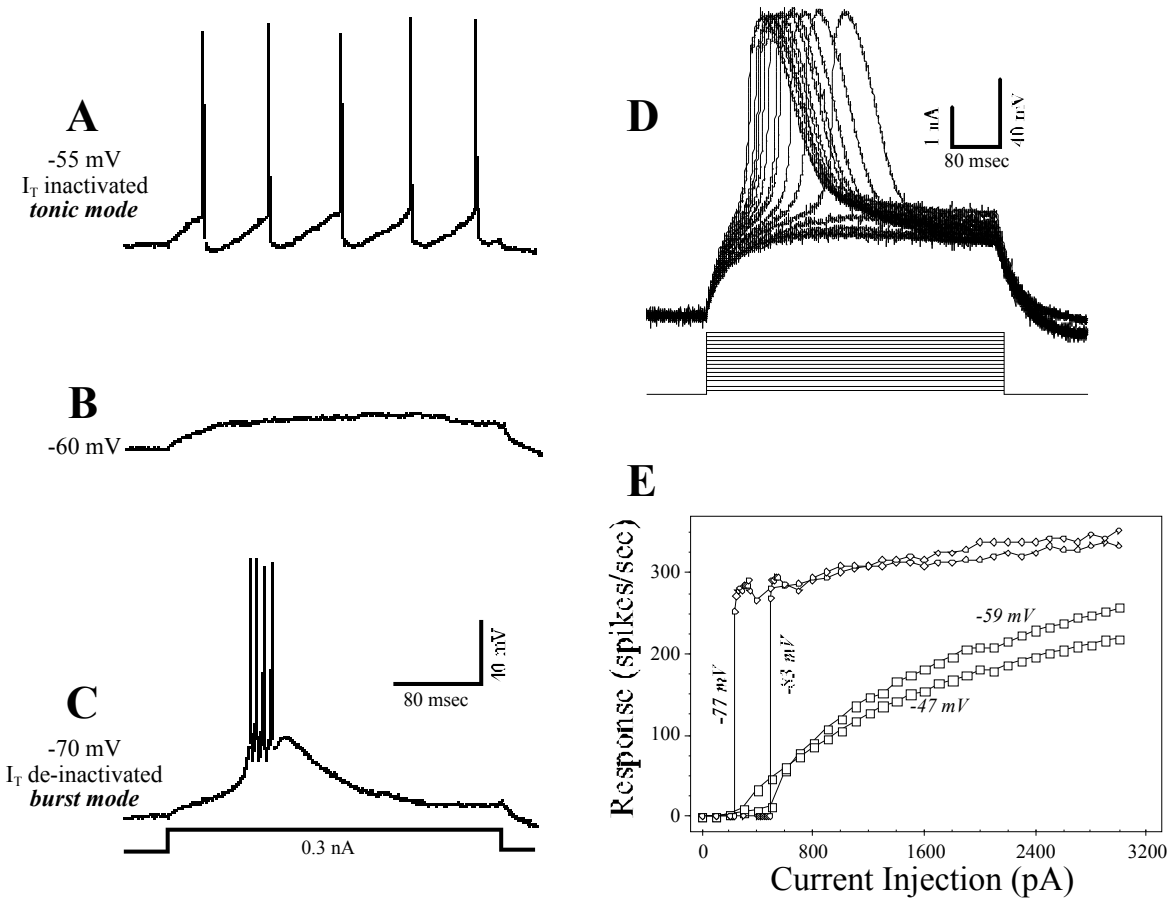
Fig. 1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tonic mode
B
-60 mV
C
-70 mV
I_T de-inactivated
burst mode
40 mV
80 msec
0.3 nA
D
1 nA
40 mV
80 msec
E
Response (spikes/sec)
300
200
100
0
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-53 mV
-59 mV
-47 mV
0
800
1600
2400
3200
Current Injection (pA)

Fig. 2

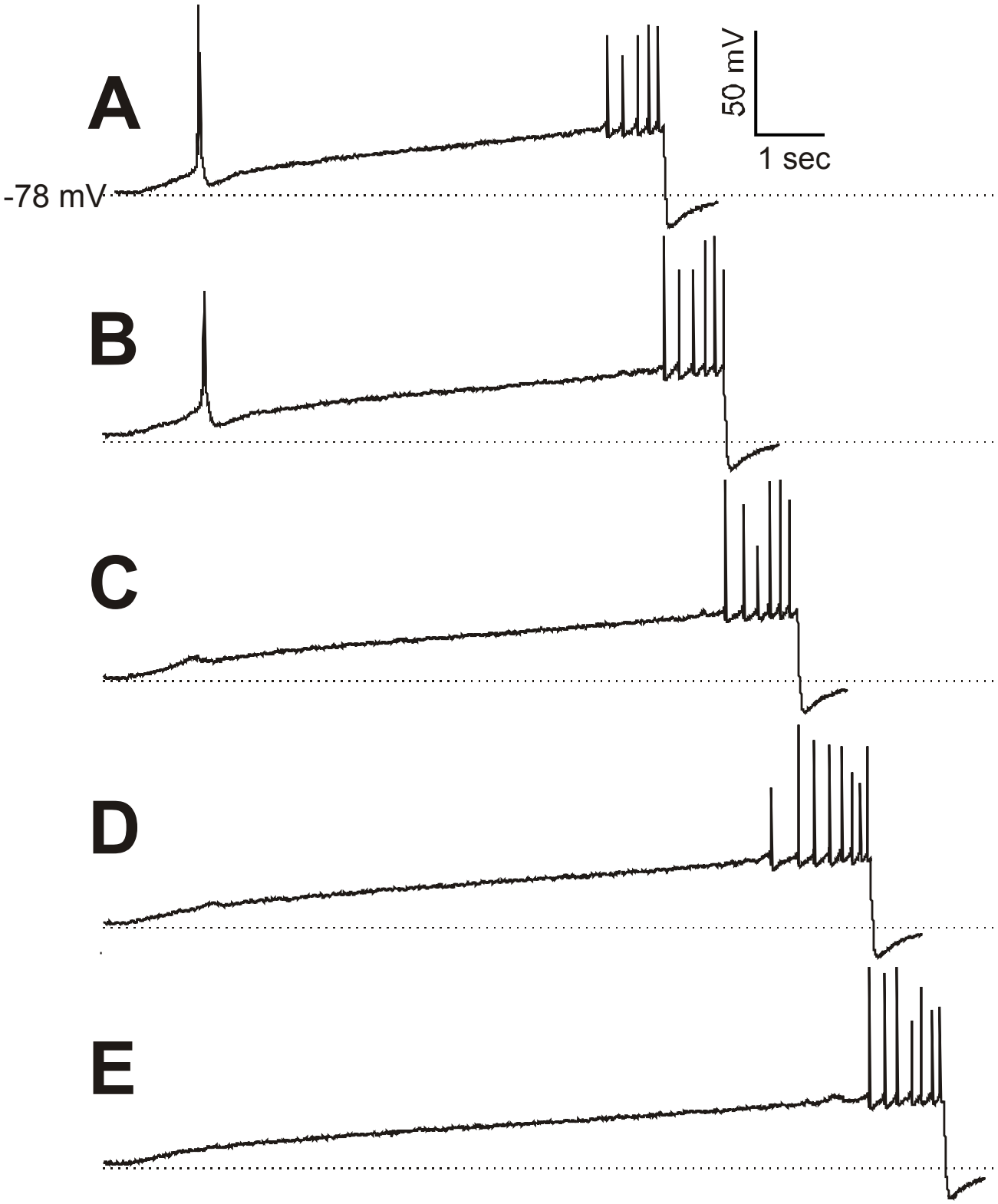


Fig. 3

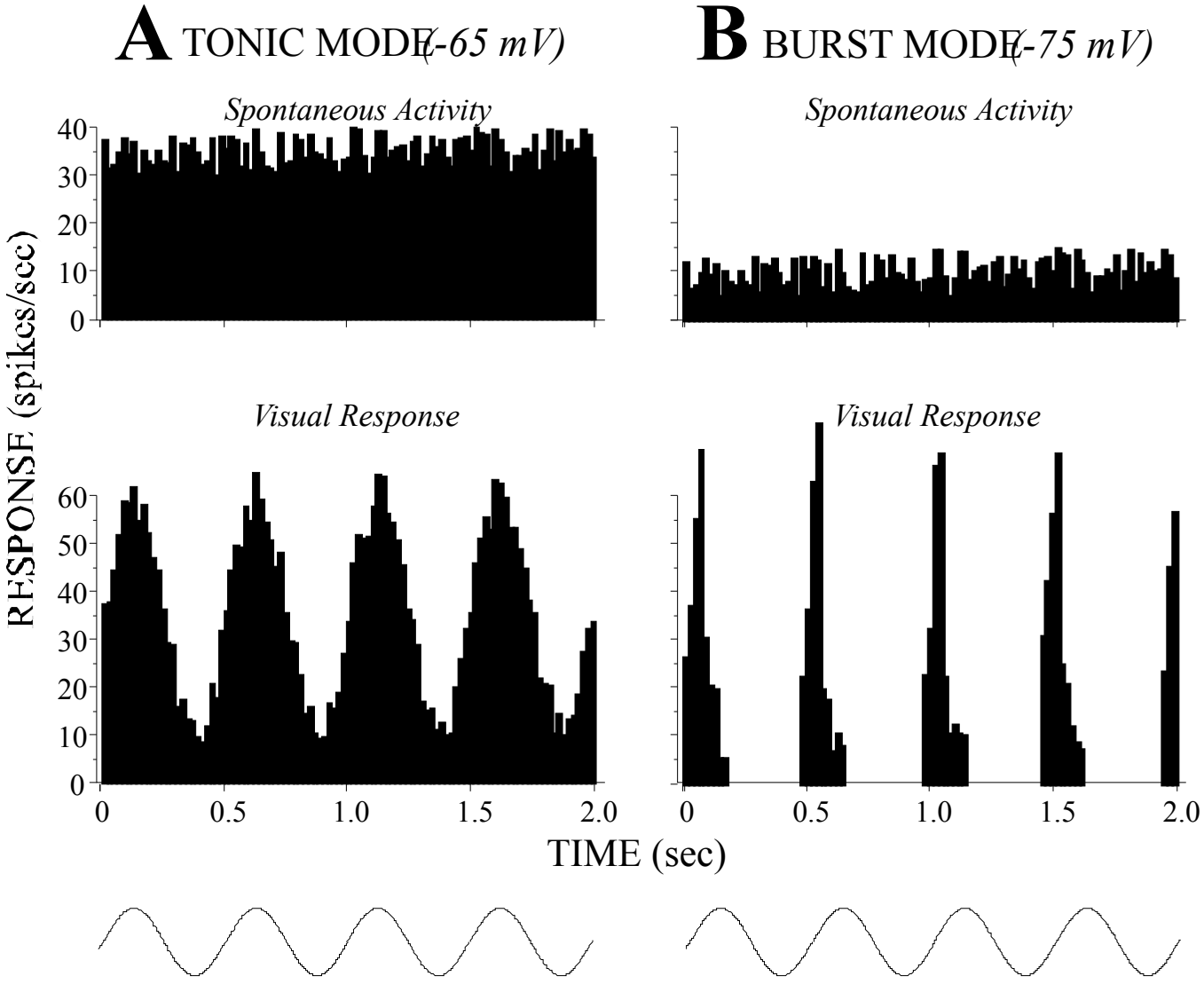

A TONIC MODE (-65 mV)
B BURST MODE (-75 mV)
Spontaneous Activity
Spontaneous Activity
Visual Response
Visual Response
RESPONSE (spikes/sec)
TIME (sec)
0
10
20
30
40
50
60
0.5
1.0
1.5
2.0

Fig. 4

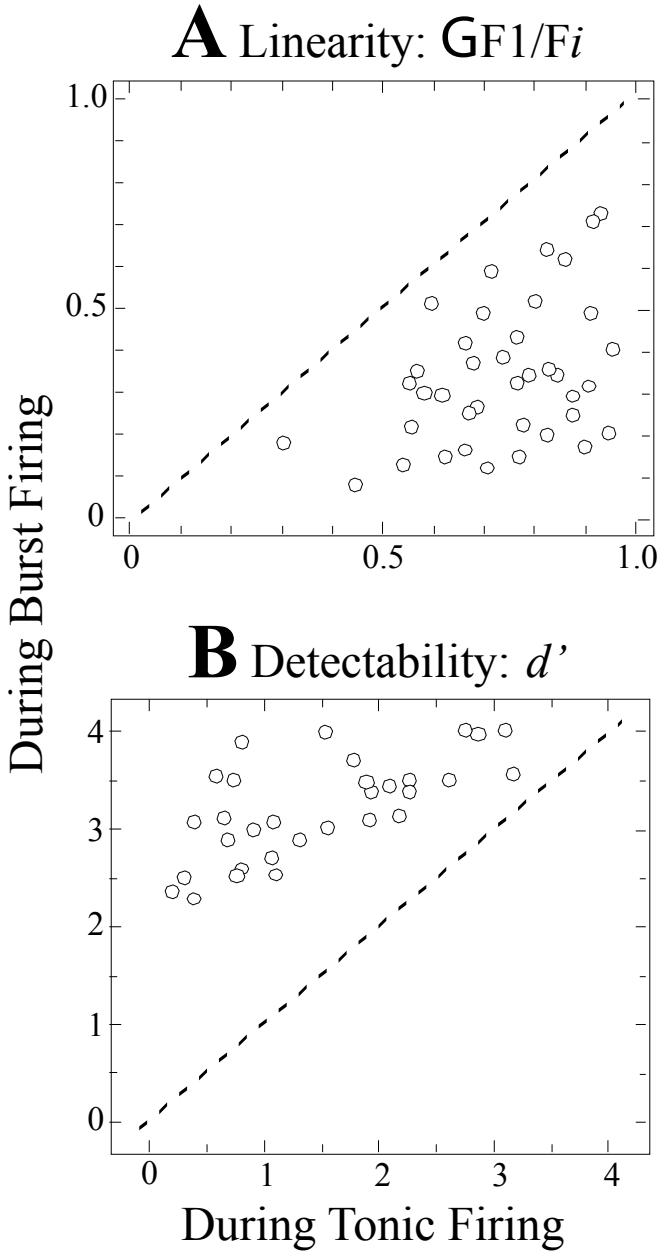

A Linearity: GF1/Fi
1.0
0.5
0
0
0.5
1.0
B Detectability: d'
4
3
2
1
0
0
1
2
3
4
During Burst Firing
During Tonic Firing

Fig. 5

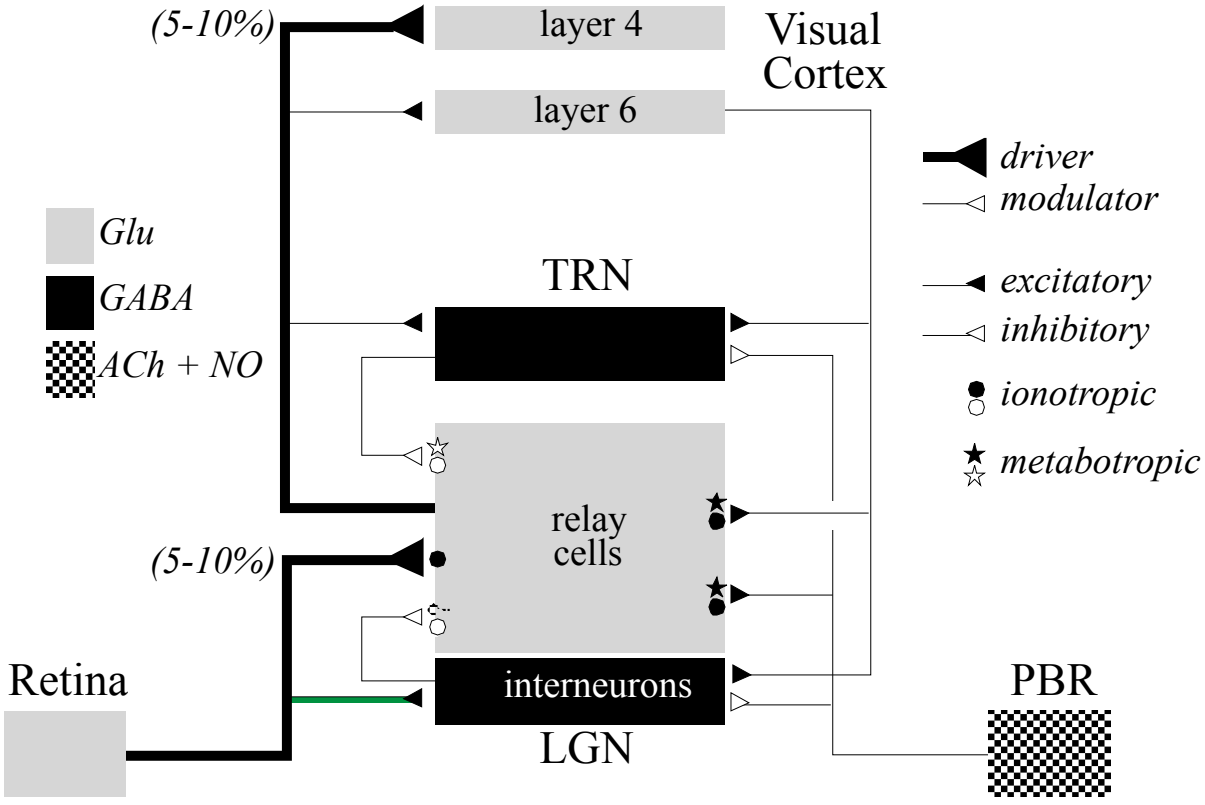

(5-10%)
layer 4
Visual Cortex
layer 6
driver
modulator
Glu
GABA
ACh + NO
TRN
excitatory
inhibitory
ionotropic
metabotropic
relay cells
(5-10%)
Retina
interneurons
PBR
LGN

Fig. 6

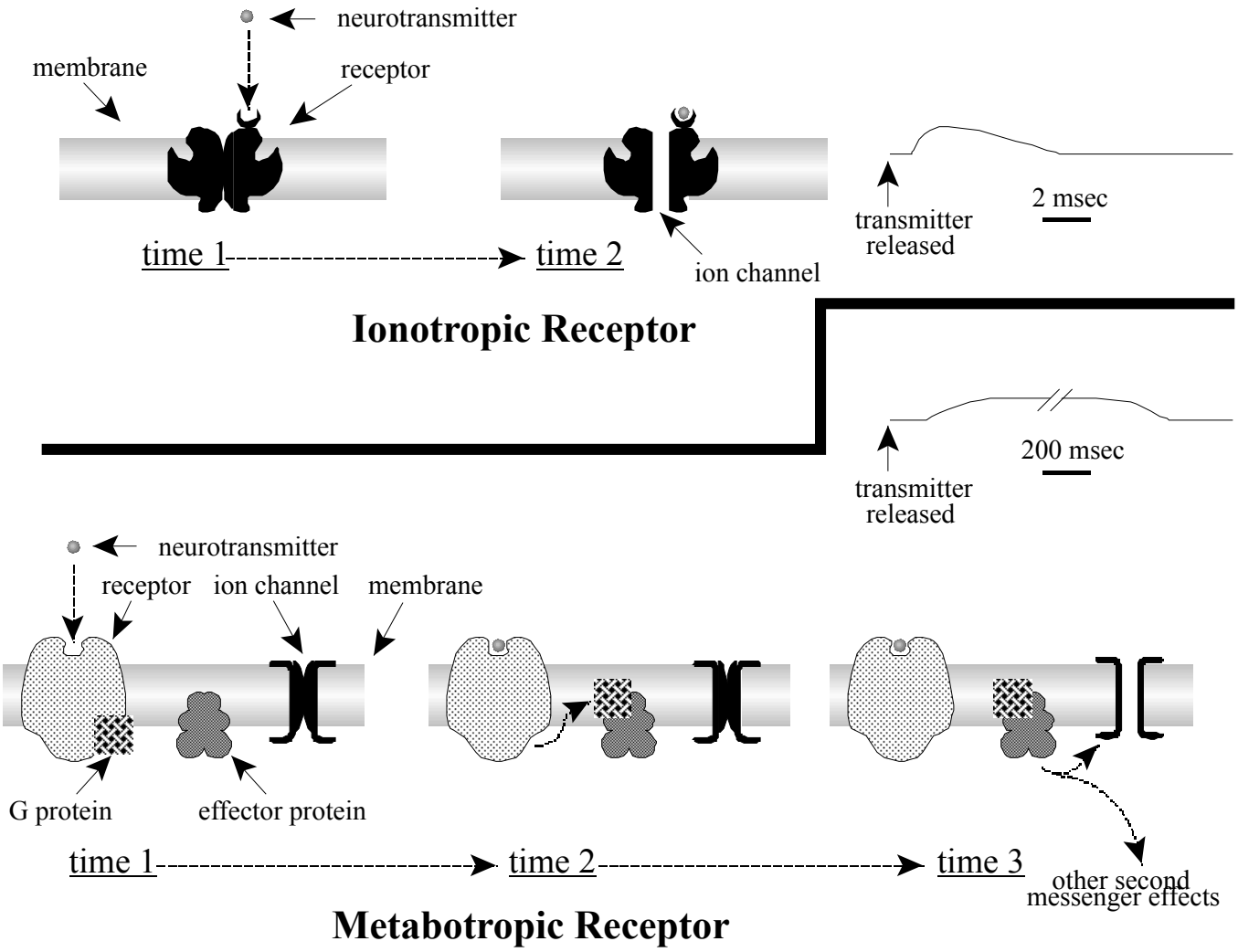

neurotransmitter
membrane
receptor
time 1
time 2
ion channel
transmitter released
2 msec
Ionotropic Receptor
transmitter released
200 msec
neurotransmitter
receptor
ion channel
membrane
G protein
effector protein
time 1
time 2
time 3
other second messenger effects
Metabotropic Receptor

Fig. 7

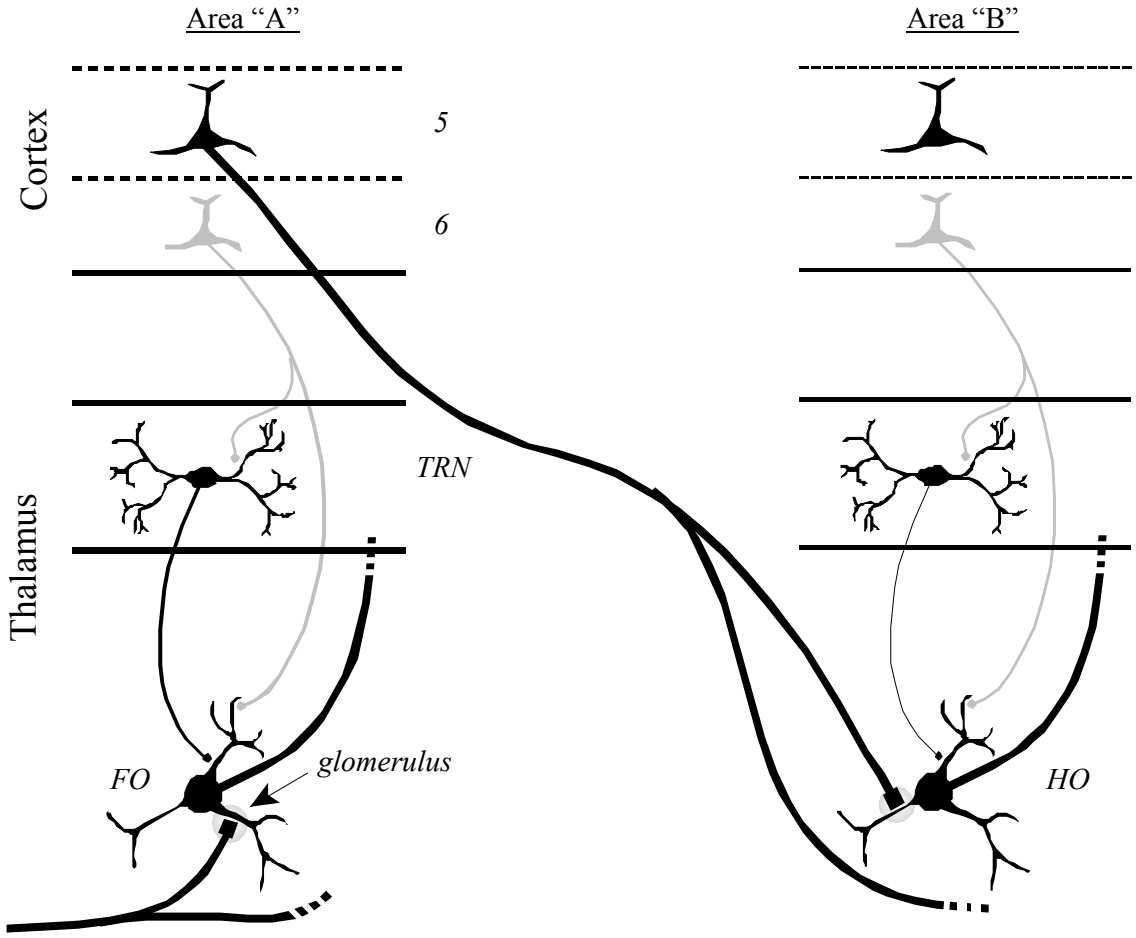
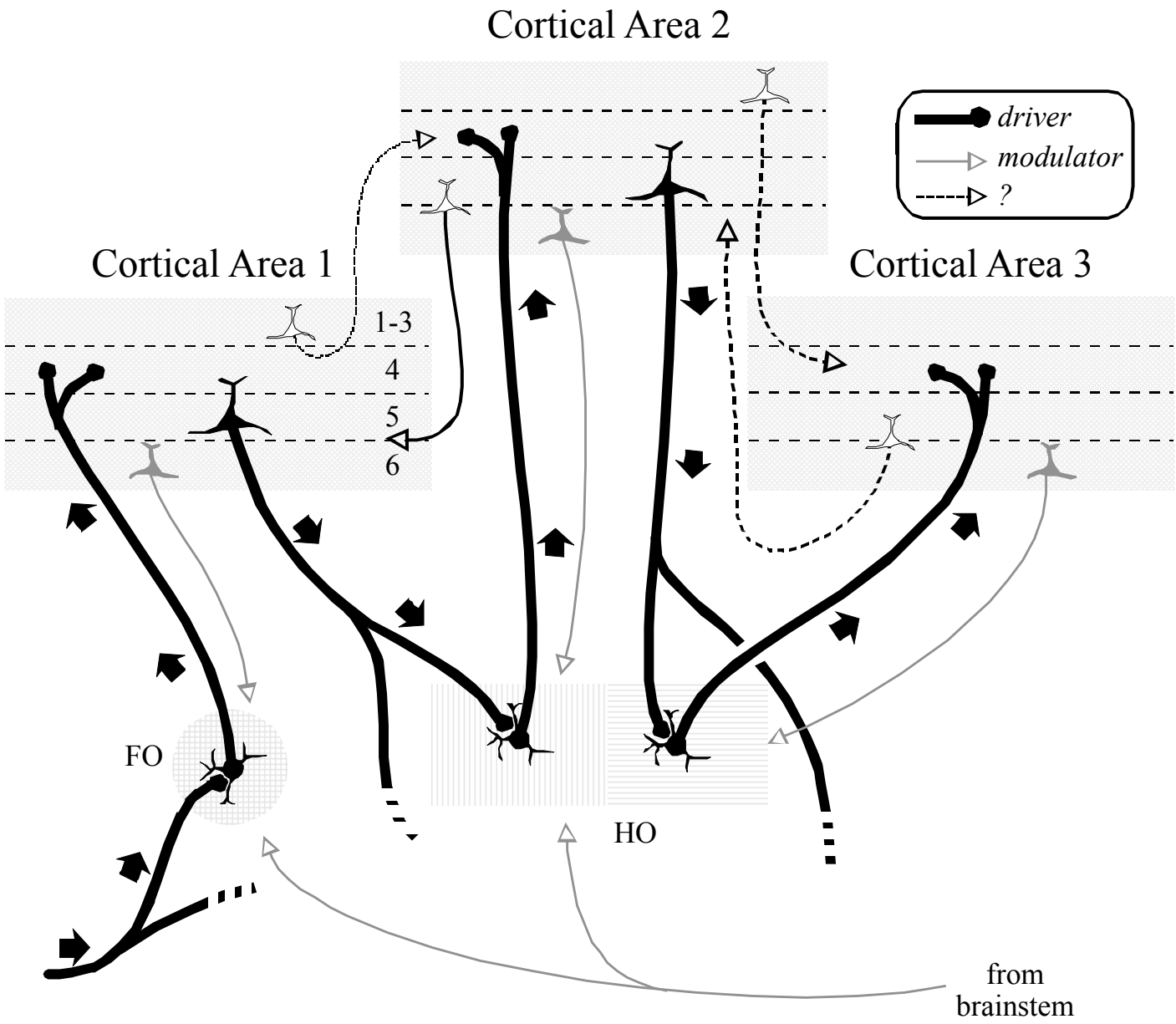


Fig. 8


Cortical Area 2
driver
modulator
?
Cortical Area 1
Cortical Area 3
1-3
4
5
6
FO
HO
from
brainstem