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Distinct functions for direct and transthalamic corticocortical connections

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Sherman SM, Guillery RW. Distinct functions for direct and transthalamic corticocortical connections. *J Neurophysiol* 106: 1068–1077, 2011. First published June 15, 2011; doi:10.1152/jn.00429.2011.—Essentially all cortical areas receive thalamic inputs and send outputs to lower motor centers. Cortical areas communicate with each other by means of direct corticocortical and corticothalamocortical pathways, often organized in parallel. We distinguish these functionally, stressing that the transthalamic pathways are class 1 (formerly known as "driver") pathways capable of transmitting information, whereas the direct pathways vary, being either class 2 (formerly known as "modulator") or class 1. The transthalamic pathways provide a thalamic gate that can be open or closed (and otherwise more subtly modulated), and these inputs to the thalamus are generally branches of axons with motor functions. Thus the transthalamic corticocortical pathways that can be gated carry information about the cortical processing in one cortical area and also about the motor instructions currently being issued from that area and copied to other cortical areas.

driver; first-order relay; higher order relay; modulator

THE GENERAL VIEW OF COMMUNICATION between cortical areas is based on two implicit assumptions: one is that the relevant glutamatergic pathways are functionally uniform, and the other, that the communication is effectively limited to pathways directly connecting cortical areas as feedforward or feedback projections (Felleman and Van Essen 1991; Hilgetag et al. 2000). In this article we argue that this view needs to be changed. First, there are distinct classes of glutamatergic pathways that vary substantially in their properties, more fundamentally than currently available observations suggest (Covic and Sherman 2011; Lee and Sherman 2008, 2009b, 2010; Petrof and Sherman 2009; Reichova and Sherman 2004; Viaene et al., 2011). To understand how any pathway relates to information processing, the synaptic properties of each must be known. Second, there is another player in corticocortical communication: a transthalamic, corticothalamocortical pathway. Anatomical evidence for this pathway has been available for some time (Guillery 1995), as has in vivo physiological evidence that certain thalamic nuclei are involved in corticocortical communication (Shumikhina and Molotchnikoff 1999; Soares et al. 2004). In addition, recent evidence in slice preparations shows that activity is robustly passed along this pathway from one cortical area to another and blocked by thalamic silencing (Theyel et al. 2010). Thus the transthalamic pathway must be treated as another functionally distinct entity, raising an important question about what this transthalamic corticocortical relay is for. An understanding of cortical functions can no longer ignore corticocortical links that depend on subcortical structures, particularly the thalamic link, which is the focus of this review.

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Drivers and Modulators: Class 1 and Class 2 Glutamatergic Pathways

In many current accounts, glutamatergic pathways are considered to be the basis for most information processing, and other pathways, including those using acetylcholine, norepinephrine, etc., and often also γ-aminobutyric acid (GABA), are considered modulatory in function. However, we have argued that within the family of glutamatergic pathways can be found both information-bearing and modulatory inputs, and thus identifying them as part of a functionally relevant classification is an important step in understanding complex brain circuits. This distinction was described first for thalamic circuitry.

Thalamic circuits. The concept that glutamatergic pathways are functionally distinct types emerged from studies of the thalamus, where, for example, the lateral geniculate nucleus shows two distinct glutamatergic pathways innervating relay cells: the retinal input and a feedback projection from layer 6 of visual cortex (Sherman and Guillery 1998, 2006). These two inputs have clearly different anatomical and functional properties, and we called them drivers or modulators, respectively (see Table 1 and Fig. 1). In the thalamus, these glutamatergic inputs are characterized by certain functional and anatomical properties (reviewed in Sherman and Guillery 2006):

1) Drivers produce larger initial excitatory postsynaptic potentials (EPSPs) that show paired-pulse depression, indicating a high probability of transmitter release, whereas modulators produce smaller initial EPSPs that show paired-pulse facilitation, indicating a low probability of transmitter release (Dobrunz and Stevens 1997).

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Table 1. *Properties of class 1 and class 2 pathways*

Class 1/Driver (e.g., Retinal)	Class 2/Modulator (e.g., Layer 6)
Large EPSPs	Small EPSPs
Synapses show paired-pulse depression	Synapses show paired-pulse facilitation
Less convergence onto target	More convergence onto target
Dense terminal arbors (type 2)	Sparse terminal arbors (type 1)
Thick axons	Thin axons
Large terminals	Small terminals
Contacts target cell proximally	Contacts target cell peripherally
Activates only iGluRs	Activates iGluRs and mGluRs

EPSPs, excitatory postsynaptic potentials; iGluRs, ionotropic glutamate receptors; mGluRs, metabotropic glutamate receptors.

2) The available counts of afferent synapses from anatomical studies combined with a comparison of the all-or-none activation of driver inputs with the graded activation of modulators indicate that although the driver synapses form a minority of the inputs to the target neurons, they dominate the action of the target neurons. For instance, corticogeniculate modulator inputs produce 5–10 times as many synapses as do retinal driver inputs to geniculate relay cells, and yet driver inputs are functionally dominant (reviewed in Sherman and Guillery 2006). Thus assessing the relative strength of inputs based solely on anatomical numbers can be very misleading.

3) Drivers have thicker axons with larger terminals that contact proximal dendrites and are distributed in denser, more tightly localized terminal arbors.

4) Drivers activate only ionotropic receptors, mainly α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid but some *N*-methyl-D-aspartate, whereas modulators in addition activate metabotropic receptors.

The present terminology reflects the apparent function of each of these thalamic inputs. Drivers provide a powerful drive to thalamic relay cells. They also represent the main route for the information that is relayed to cortex. For instance, retinal input to the lateral geniculate nucleus represents the driver input there, providing the information that is transmitted to cortex. It is clear that the retinal input represents the main information to be relayed, because the relay cell's center/surround receptive field properties are clearly created by retinal inputs (Cleland et al. 1971; Usrey et al. 1999) and not by other inputs, such as the input from layer 6 of cortex (Briggs and Usrey 2009; Grieve and Sillito 1995), even though this pro-

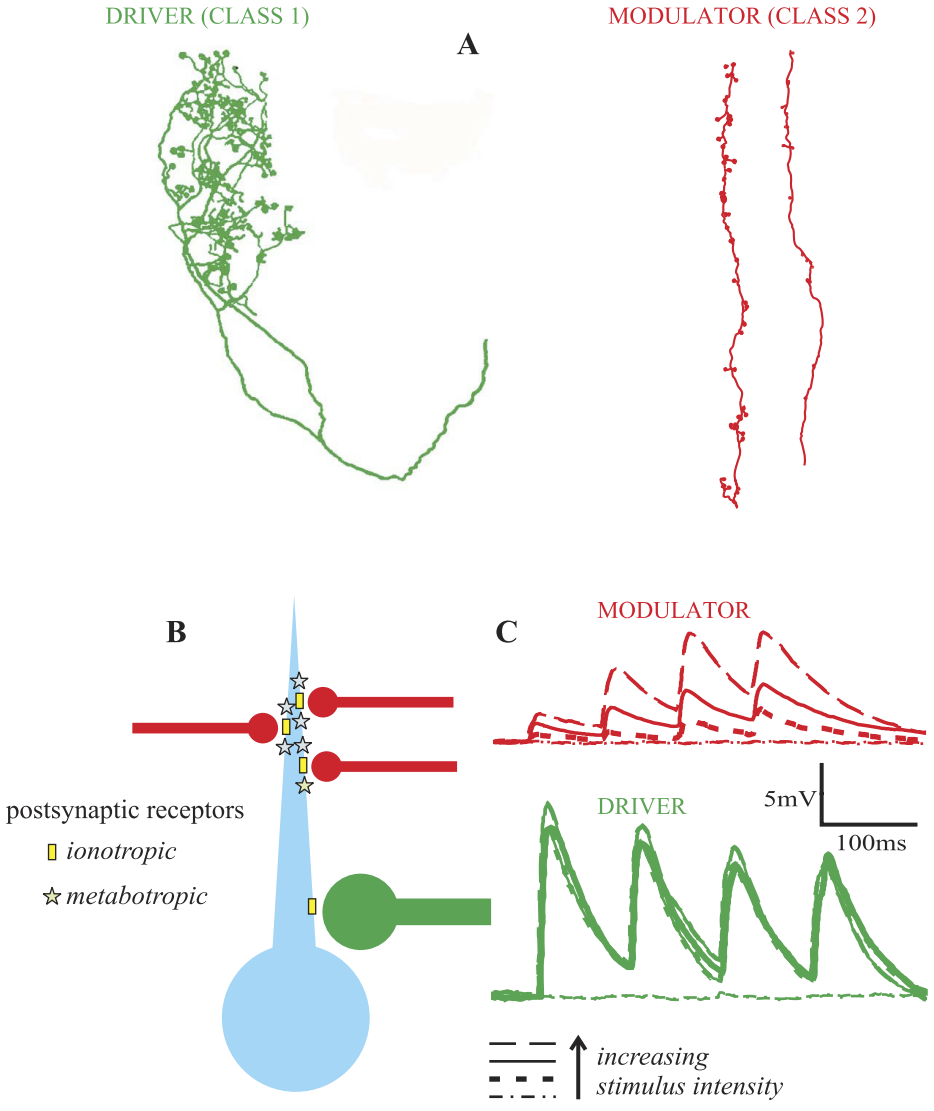

Fig. 1. Distinguishing driver (class 1) from modulator (class 2) inputs. *A*: light microscopic tracings of a driver (class 1) afferent (a retinogeniculate axon from the cat) and a modulator (class 2) afferent (a corticogeniculate axon from layer 6 of the cat). [Redrawn from Sherman and Guillery 2006.] *B*: modulators (red) shown contacting more peripheral dendrites than do drivers (green). Also, drivers activate only ionotropic glutamate receptors, whereas modulators also activate metabotropic glutamate receptors. *C*: effects of repetitive stimulation on excitatory postsynaptic potential (EPSP) amplitude: for modulators it produces paired-pulse facilitation (increasing EPSP amplitudes during the stimulus train), whereas for drivers it produces paired-pulse depression (decreasing EPSP amplitudes during the stimulus train). Also, increasing stimulus intensity for modulators (shown as different line styles) produces increasing EPSP amplitudes overall, whereas for drivers it does not; this indicates more convergence of modulator inputs compared with driver inputs.

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vides a rich innervation of geniculate cells. The same can be said of lemniscal input to the ventral posterior nucleus (e.g., Friedberg et al. 2004; Minnery et al. 2003) or inferior collicular input to the ventral part of the medial geniculate body (reviewed in Wenstrup 2005). Modulators were so named because they do not represent the main information to be relayed, but rather function as modulators of transmission through the thalamus.

Note that driver properties are consistent with features expected of a main information source (see Table 1). The large EPSPs are important to ensure that the information is processed robustly; paired-pulse depression is usually associated with high probability of transmitter release (Dobrunz and Stevens 1997) and may serve to dynamically regulate neuronal sensitivity (Chuang et al. 2002). Furthermore, lack of a metabotropic glutamate receptor response ensures relatively brief EPSPs, allowing a more faithful relay of temporal information. The weaker and more convergent inputs of the modulators can combine in many different ways to provide a variety of modulatory functions. The prolonged response of the metabotropic glutamate receptors not only provides an effective control for various time- and voltage-dependent conductances with long time constants for inactivation kinetics (e.g., I_T, I_h, and I_A; reviewed in Sherman and Guillery 2006), but the response outlasts activity in the input, often by seconds (Govindaiah and Cox 2004), and this can be useful for modulation but distorts temporal information. Furthermore, activation of metabotropic glutamate receptors in a postsynaptic cell is implicated in the release of endocannabinoids that in turn modulate synaptic transmission to that cell (Brown et al. 2003; Zhang et al. 2009; Zhang and Alger 2010). Indeed, metabotropic glutamate receptor activation associated with modulators may prove to be a clear identifying characteristic of these inputs, although a lack of such a response does not necessarily indicate a main information input, because one can imagine many modulatory functions carried out exclusively by ionotropic glutamate receptor activation (Chance et al. 2002). We suggest that these glutamatergic modulator inputs operate like other classic modulatory inputs, such as cholinergic or serotonergic inputs, and it is important to note that these other modulatory inputs also typically involve metabotropic receptors. This is not to say that modulators convey zero information any more than we would make this claim for cholinergic or serotonergic inputs. The point is that whereas all of these inputs necessarily convey some information, a distinction should be made among glutamatergic inputs between those that are primarily information bearing and those that are primarily modulatory.

There are two other important issues that derive from this driver/modulator concept for the thalamus. One is that the identity of the driver input to a thalamic relay largely defines the function of that relay. Thus, as indicated above, we consider the main function of the lateral geniculate nucleus is to relay retinal information to cortex. Likewise, for any thalamic relay whose functions are currently unknown, such as for higher order relays that are discussed below and whose functions at present seem mysterious, identifying the driver input can help to expose their functions.

The other issue is that the concept of a driver input to the thalamus carries with it the implication that outputs from thalamic relay cells must be interpreted at the cortical level as if they were the result of driver inputs. For the lateral geniculate nucleus, for example, this means that every relay cell spike must be interpreted as if it has been evoked by retinal and not, for instance, by cortical input. Available evidence indeed suggests that this may be so, because paired recordings from retinal inputs and their geniculate relay cell targets indicate that whereas many retinal spikes may fail to generate a relay cell spike, only very rarely is a relay cell spike not generated by one from a retinal afferent (Cleland et al. 1971; Usrey et al. 1999). The above discussion relates to the general case of geniculate cells firing in tonic, or single-spike mode, but occasionally, they fire in bursts related to the activation of voltage-dependent T-type Ca^{2+} conductances (for details, see Jahnsen and Llinás 1984; Sherman 2001). These bursts involve 2–10 action potentials with very brief interspike intervals (generally <5 ms); each is typically activated by a single retinal action potential (Usrey et al. 1999). However, since a burst can be regarded as a singular event regardless of the number of associated action potentials, the above point is still valid but now extended to bursts. That is, the concept of a driver implies that cortex must interpret the firing of a geniculate cell, either a single action potential during tonic mode or a burst during burst mode, as due to a retinal action potential.

The distinction between drivers and modulators was introduced specifically for the thalamic relays. The extent to which this distinction can be usefully applied to other centers has so far not been explored, and an important part of ongoing studies of the cerebral cortex will be an exploration of the extent to which this classification can prove useful.

Glutamatergic pathways in cortex. Several studies have demonstrated the heterogeneity of glutamatergic circuits in cortex (Agmon and Connors 1992; Hull et al. 2009; Tan et al. 2008; Thomson and West 2003), but these have generally not been aimed at a detailed classification of the inputs. Given the more complex circuitry of cortex compared with thalamus, one might expect different or at least additional classes to the driver and modulators types seen in thalamic circuitry. Whereas it is appropriate in the thalamus to use the driver/modulator terminology, because these names clearly describe the different function of these inputs, cortical circuitry is more complex and less understood, and so we have adopted a more conservative and neutral terminology for the cortex. Inputs with the properties of drivers we have called class 1, and those with modulator properties, class 2 (Covic and Sherman 2011; Viaene et al. 2011). Somewhat surprisingly, more recent studies of a variety of cortical circuits (Covic and Sherman 2011; Lee and Sherman 2008, 2009a, 2009b; Viaene et al. 2011) have found basically the same two driver and modulator classes of glutamatergic input (see Fig. 2). Perhaps further classification of additional cortical circuits will reveal additional classes.

A three-dimensional scatter plot of three major parameters measured from many glutamatergic inputs recorded in thalamus and cortex is shown in Fig. 2, which illustrates two important points. First, the points cluster into two clear groups, class 1 (driver) and class 2 (modulator), further supporting the basis of this classification. Second, the examples within each class for both thalamic and cortical inputs completely overlap, meaning that there are no clear differences between these classes for the parameters that have so far been tested for the thalamic and cortical circuits (see legend to Fig. 2 for details).

As noted above, class 1 properties are consistent with an input that operates as a main information source, whereas class

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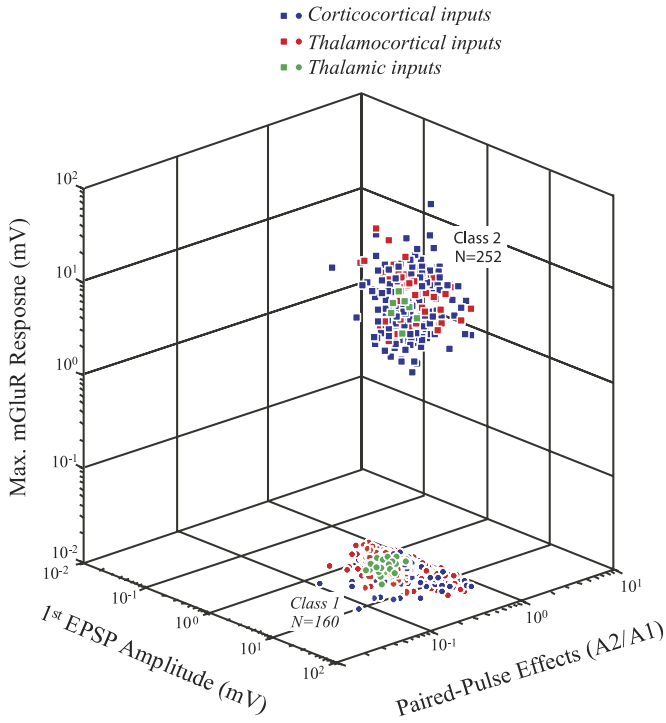

Fig. 2. Three-dimensional scatter plot showing clustering of selected properties for different class 1 and 2 inputs. Data are from in vitro slice experiments in mice (Covic and Sherman 2011; Lee and Sherman 2009a, 2009b, 2010; Petrof and Sherman 2009; Reichova and Sherman 2004; Viaene et al. 2011). The 3 parameters are *1*) the amplitude of the first EPSP elicited in a train at a stimulus current level just above threshold, *2*) a measure of paired-pulse effects (the amplitude of the second EPSP divided by the first) for stimulus trains of 10–20 Hz, and *3*) a measure of the response to metabotropic glutamate receptor (mGluR) activation, which is the maximum voltage deflection (i.e., depolarization or hyperpolarization) during the 300-ms period after high-frequency electrical stimulation and in the presence of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and *N*-methyl-D-aspartate blockers to isolate any mGluR activation. Pathways tested include various inputs to thalamus from cortex and subcortical sources, various thalamocortical pathways, and various intracortical pathways. Not only do the two classes of response separate into distinct clusters, documenting the present classification, but different pathways overlap extensively within each class, indicating basic similarity on these parameters for these classes in thalamic and cortical circuitry.

2 properties are more consistent with a modulatory function. For instance, we are reasonably confident that receptive fields of geniculate relay cells are derived from retinal and not cortical inputs, which identifies retinal input as the main information source for relay, but similar well-understood examples in cortex are rare. We nonetheless suggest as a starting hypothesis that these same two classes play the same role in cortical circuitry: namely, that class 1 pathways represent the main information routes, and class 2 pathways serve mainly to modulate processing of this information.

There is one possibly major difference between thalamic and cortical circuitry that is relevant. There is no evidence so far that there is much information processing in thalamus, and thus receptive fields of thalamic relay cells, such as those in the lateral geniculate nucleus, effectively match those of their driver inputs in terms of spatial arrangement, although geniculate cell and circuit properties can affect temporal properties of the receptive field (Mastronarde 1987a, 1987b; Rathbun et al. 2010; Sincich et al. 2009; Wang et al. 2010). This is likely related to the observation that the driver inputs to thalamus so far investigated show little or no convergence (e.g., Cleland et al. 1971; Rathbun et al. 2010; Sincich et al. 2007; Usrey et al. 1999; Wang et al. 2010). In this sense thalamus acts merely as a modulated relay. However, information processing and receptive field elaboration almost certainly occur in cortex, and so one would expect more convergence among class 1 inputs there; indeed, this has been observed (Covic and Sherman 2011). The point is that class 1 inputs may still be the main information bearing route in cortex, but various combinations of these inputs may drive a given cortical cell under different conditions, a situation different from thalamus, where in known cases, one or very few driver inputs activate a relay cell (Cleland et al. 1971; Usrey et al. 1999). These authors suggest that typically no more than one to six retinal axons converge to innervate each geniculate cell, and when there are multiple retinal inputs, they are generally of the same type (e.g., X or Y, on or off center) so that the same message is conveyed by the convergent driver inputs; also, this is consistent with limited anatomical data (Hamos et al. 1987). Compare this to the apparent convergence of class 2 inputs from cortical layer 6 to geniculate neurons. It is estimated that 30–100 layer 6 axons innervate the lateral geniculate nucleus for every relay cell there (Sherman and Koch 1986), and the spread of cortical arbors in the lateral geniculate nucleus makes it clear that each axon innervates multiple thalamic cells (Murphy and Sillito 1996). If each axon innervates 10 geniculate cells (and this seems a conservative estimate), then 300–1,000 axons must converge on each.

The two classes of input shown in Fig. 2 are clearly distinct both in the cortex and in the thalamus. It is thus important to identify the various participants in glutamatergic circuits to understand the role of each input and the overall function of any one circuit, an approach that is clearly different from the currently more usual method of treating all of these circuit elements as equal as if they participated in a form of anatomical and functional democracy. Furthermore, data from the inputs to the thalamus and to the cortex suggest that class 1 inputs are the minority (Ahmed et al. 1997; Van Horn et al. 2000). We cannot yet generalize this to intracortical circuitry, but class 1 pathways may prove to be a small but crucial part of all cortical circuitry, and this further emphasizes the point that treating all glutamatergic inputs as equal can mislead us in our understanding of information flow through cortical circuitry. Finally, further classifications may reveal additional types.

It is also worth noting some additional properties of class 2 pathways in cortex related to their ability to activate metabotropic glutamate receptors. Not only are group I metabotropic glutamate receptors activated, which depolarize cells by closing K^+ channels, but class 2 inputs can instead or additionally activate group II metabotropic glutamate receptors, which hyperpolarize, and thus inhibit cells by opening K^+ channels. Such actions of group II metabotropic glutamate receptors have been described for neurons of the thalamic reticular nucleus (Cox and Sherman 1999) but not for relay cells. However, this inhibitory action of many class 2 glutamatergic afferents is commonly seen for intracortical circuitry (Covic and Sherman 2011; Lee and Sherman 2009a). Inhibition has been long considered an important property of cortical circuitry in such processes as receptive field elaboration (Anderson et al. 2000; Ferster and Miller 2000; Hirsch and Martinez 2006; Monier et

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al. 2003), and such inhibition has always been considered strictly in terms of GABAergic circuitry. The action of class 2 inputs that activate group II metabotropic glutamate receptors offers the possibility that these glutamatergic pathways can also contribute to such functions. Finally, the time course of metabotropic glutamate receptor activation offers another possibility to consider for modulatory action. That is, as noted above, whereas actions of ionotropic receptors last tens of milliseconds, those of metabotropic receptors last hundreds of milliseconds to several seconds, and this suggests the possibility that metabotropic glutamate receptor activation by class 2 inputs could be involved in certain behavioral phenomena, such as adaptation effects, afterimages, etc., that have longer time courses (Anwyl 2009; Chuang et al. 2002; McCormick and Von Krosigk 1992). This has also been suggested for the activations of certain metabotropic glutamate receptors in the thalamus (Sherman 2004).

Corticothalamocortical Pathways

The class 1 input largely defines the function of a thalamic relay. For many primary sensory thalamic relays, the function is readily defined, and so we understand that a main function of the lateral geniculate nucleus (or ventral posterior nucleus) is to relay retinal (or lemniscal) input. However, other nuclei, such as parts of the pulvinar or medial dorsal nucleus, remained obscure because their class 1 inputs were unknown. A hypothesis was put forward that class 1 inputs to many of these thalamic relays come from layer 5 of cortex itself (Guillery 1995; Sherman and Guillery 1998, 2006). Recently, this hypothesis was confirmed by direct physiological evidence: cells in cortical layer 5 do, indeed, provide a strong class 1 input to higher order target thalamic relay cells in the lateral posterior nucleus (Li et al. 2003) and posterior medial nucleus (Reichova and Sherman 2004). That is, whereas all thalamic relays receive a class 2 input from cortical layer 6, which is organized in a largely feedback manner, some also receive a class 1 input from layer 5, which is organized in a feedforward manner (Llano and Sherman 2008; Reichova and Sherman 2004; Sherman and Guillery 2006; Theyel et al. 2011; Van Horn and Sherman 2004). Furthermore, this class 1 input from layer 5 to the targeted thalamic relays has the same physiological and morphological properties as the class 1 inputs from subcortical sources to their thalamic targets.

These cortical Class 1 inputs define a higher order thalamic relay. Whereas a first-order relay receives class 1 inputs from subcortical sources such as visual or auditory afferents and relays this information for the first time to cortex, a higher order relay serving as a corticocortical link receives class 1 input from layer 5 of one cortical area and relays this information to another cortical area, forming an important route for corticocortical communication (Guillery 1995; Sherman and Guillery 2006). The class 1 inputs, subcortical or cortical, define the crucial difference. As Fig. 3 shows, all thalamic relays receive a layer 6 class 2 input, but higher order relays also receive the layer 5 input that structurally and functionally matches the subcortical class 1 inputs to first-order relays.

Examples of first-order relays are the lateral geniculate nucleus for vision, the ventral posterior nucleus for somesthesis, and the ventral division of the medial geniculate body for hearing; their equivalent higher order counterparts are, respectively, the lateral posterior pulvinar complex, the posterior medial nucleus, and the dorsal division of the medial geniculate body. Other examples have been described elsewhere (Sherman and Guillery 2006). However, many relay nuclei, like the pulvinar, may be mostly higher order but may also contain some first-order circuits. Nonetheless, most of the thalamus by volume is higher order. Many thalamic nuclei previously hard to fathom can be seen to relay information between cortical areas, and since this relayed information is carried by corticothalamic class 1 afferents, it becomes a crucial issue for understanding thalamic as well as cortical functions to identify the nature of this relayed information.

Branching Class 1 Axons to Thalamus

The role of higher order thalamic relays as a central element in transthalamic corticocortical circuitry raises the possibility that all cortical areas having direct connections may also have parallel transthalamic connections. This raises the obvious question: what is different between the direct and transthalamic circuits? One difference is shown by Fig. 3: class 1 inputs to both first-order and higher order thalamic relays arrive via branching axons, with one or more extrathalamic branches that

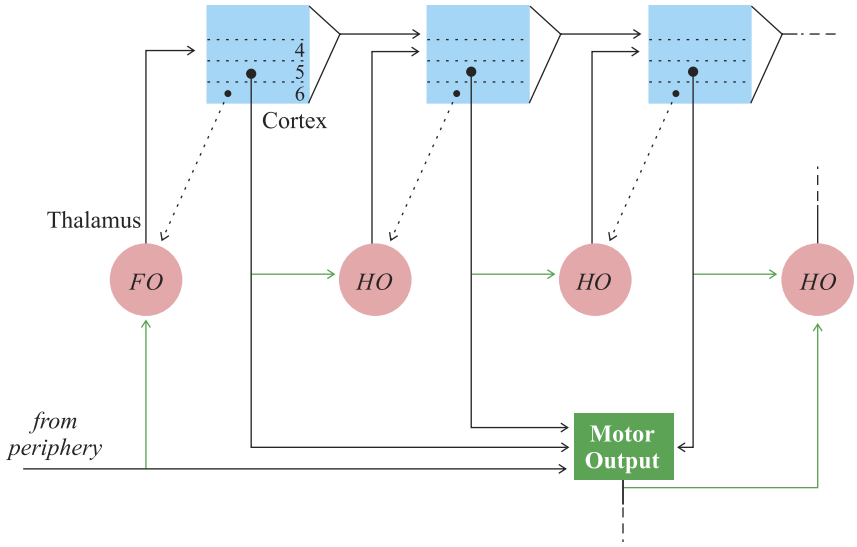

Fig. 3. Direct and transthalamic corticocortical pathways. Information relayed to cortex through thalamus is brought to thalamus via class 1 axons, most or all of which branch, with the extrathalamic branch innervating brain stem or spinal cord motor centers. This applies to inputs to both first-order (FO) and higher order (HO) thalamic relays. Thus the branches innervating thalamus (green) can be regarded as efference copies. The schematic diagram also shows the layer 6 class 2 feedback from each cortical area to thalamus, and this is contrasted with the layer 5 feedforward corticothalamic pathways. Note that this shows cortical areas connected by 2 parallel paths: a direct one and a transthalamic one.

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innervate brain stem or spinal motor centers. Most, if not all, of the class 1 inputs to thalamic relays, both first-order and higher order, are formed by branches in this way (Guillery and Sherman 2011). Thus most or all retinal axons that innervate the lateral geniculate nucleus branch to innervate midbrain regions involved in head and eye movements,[1] pupillary control, etc., and layer 5 corticothalamic axons also branch to innervate brain stem motor regions or the spinal cord (Bourassa et al. 1995; Bourassa and Deschênes 1995; Guillery et al. 2001).

This branching pattern has suggested a novel and unexpected function for class 1 afferents to thalamus (Guillery and Sherman 2011). The extrathalamic branches send instructions to motor centers, and the thalamic branches, which necessarily carry the same message, are, therefore, carrying a copy of these motor instructions to the thalamus and cortex. That is, they are all bringing efference copies to the thalamus, although the extent to which these efference copies serve to stabilize a sensory map in the sense used classically (Sommer and Wurtz 2004; Sperry 1950; von Holst and Mittelstaedt 1950) or serve some other purpose, such as simply bringing information about ongoing motor instructions to cortex rapidly, remains to be explored. The "forward receptive fields" described for several cortical areas (Duhamel et al. 1992; Sommer and Wurtz 2006; Umeno and Goldberg 1997) that represent an anticipation of a saccade may well depend on such inputs. In this way, the transthalamic corticocortical pathways may differ crucially from the direct ones by serving to monitor and perhaps anticipate a motor action.

To the extent that data are available, every cortical area so far studied, including the classical primary sensory areas, has a layer 5 projection to subcortical motor centers, and many of these have branched axons that also innervate thalamus (reviewed in Guillery 2003; Sherman and Guillery 2006). These branched layer 5 outputs show that the transthalamic corticocortical pathways communicate at each stage with the motor centers, and copies of this motor communication form an intrinsic part of the message passed up the cortical hierarchy (Fig. 3). One important outcome is that at every level of sensory processing, perception is inextricably linked to ongoing instructions for action, prior to the action itself. The extent to which a sense of the intention to move precedes the actual movement may depend on the many copies of motor instructions that are a part of the messages traveling in the corticothalamocortical circuitry, messages that are not so directly present in the corticocortical circuitry. Although this functional sensorimotor link has long been recognized (Merleau-Ponty 2002; O'Regan and Noe 2001; Pfeifer and Bongard 2007), no anatomical basis has previously been defined.

[1] Details of experimental evidence for these branching patterns can be found elsewhere (Guillery 2003; Guillery and Sherman 2002, 2011). For the visual pathways of rodents and rabbits, the evidence is clear that all retinal ganglion cells have axons that go to the midbrain and send branches to the lateral geniculate nucleus. For the cat, there is good evidence that Y and W cells all have axons that go to the midbrain and send branches to the lateral geniculate nucleus, and for the monkey, the magno- and koniocellular components also have such a branching pattern. For both cat and monkey, some of the remaining cells (X for cat, parvocellular for monkey) have been shown to have the same branching pattern, and given that the methods that have been used are very likely to generate a false negative, it is not unreasonable to conclude that all retinal ganglion cells are likely to branch like this, while stressing the need for further evidence, especially for the monkey.

Note also that there is no strict division between sensory and motor cortex (Fig. 3); information enters cortex and leaves as motor instructions at each cortical level, and copies of these instructions are present at each level of input to cortex. In this scheme, such differences between what is commonly known as sensory and motor cortex are quantitative (e.g., stronger motor outputs via layer 5 projections for "motor" areas) rather than qualitative. All cortical areas appear to function as sensorimotor regions.

Why Are There Two Parallel Pathways for Corticocortical Communication?

Figure 3 shows two parallel corticocortical pathways, one direct and one transthalamic, connecting cortical areas. Available anatomical data indicate that most or all of the cells giving rise to the direct pathways do not have subcortical branches and that few if any of the layer 5 axons going to thalamus send branches to other cortical areas (Hübener et al. 1990; Hübener and Bolz 1988; Llano and Sherman 2009; Weber et al. 1983). Figure 3 shows that whereas the direct pathway processes intracortical information only, with no reference to motor instructions on the way to the lower motor centers until the final motor stage has been reached, the transthalamic pathway serves also to inform the (higher) target cortical area about motor instructions currently being issued by the lower area. That is, the two pathways appear to be functionally distinct. In addition to this, on the transthalamic corticocortical pathway, the thalamic relay can be modulated, via thalamic circuitry, as the message passes from one cortical area to another in a way that is not possible on the direct corticocortical pathway.

Selective thalamic modulation. The transthalamic relay in Fig. 3 allows for the message to be blocked or modulated in ways not present in the direct pathway. As indicated above, this message carries information from one cortical area to another, not only about ongoing activity in the first cortical area but also about concurrent motor instructions. Different forms of thalamic modulation exist that can affect the gain of transmission of the class 1 input and thus affect transmission of the corticothalamocortical pathway (details in Jones 2007; Sherman and Guillery 2006). For example, thalamic circuitry can act as a gate. Relay cells receive inhibitory, GABAergic inputs from local sources (interneurons and cells of the thalamic reticular nucleus) and from extrinsic sources (reviewed in Jones 2007; Sherman and Guillery 2006): if these inputs are highly active, relay cells are so inhibited that the gate is shut; if these inputs are silent, relay cells are disinhibited, and the gate is open; if these inputs are moderately active, the gate is partly open.

The external innervation of relay cells, from brain stem sources, from the layer 6 feedback, and from local, thalamic inhibitory neurons, is critical to this gating function (reviewed in Sherman and Guillery 2006). If the gate is shut, the information in the corticothalamocortical pathway will not reach the next cortical area, even though the layer 5 branch innervating lower motor structures will still convey its message. This gating opportunity would be lost if the layer 5 axons, instead of innervating thalamus, innervated the higher cortical area directly. The obvious question is: what purpose is served by controlling whether or not the motor instruction, which is not gated, is copied to the next cortical area? Two different answers that are not mutually exclusive may be considered.

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ANSWER 1: EMPHASIZING UNEXPECTED MOTOR INSTRUCTIONS. The hypothesis suggested in this case is that a motor instruction that deviates significantly from the expected or represents the initiation of a novel set of movements is passed through the transthalamic pathway to higher areas as an alert. This idea involves a property of thalamic relay cells that is under modulatory control, namely, their ability to switch their firing pattern between burst and tonic modes (for details, see Sherman 2001; Sherman and Guillery 2006). These different modes depend on a voltage-gated T-type Ca^{2+} conductance. When relay cells are relatively depolarized, as during periods when the thalamic gate and thus the transthalamic pathway is mostly open, this Ca^{2+} conductance is inactivated and the cell responds to class 1 input in tonic mode, representing a linear, faithful, relay mode. However, when relay cells are relatively hyperpolarized, as would be expected during periods when the thalamic gate and transthalamic pathway are mostly closed, inactivation of the Ca^{2+} conductance is relieved, and the next sufficiently strong EPSP from the class 1 input activates the Ca^{2+} conductance, producing a large depolarization on which rides a burst of 2–10 action potentials. This opens the thalamic gate, at least temporarily.

Because this class 1 input activating the burst arrives after a period with no throughput of the corticothalamocortical pathway, it may be seen in the target cortical area as a new, perhaps unexpected, motor instruction. Unlike tonic firing, burst firing is highly nonlinear and thus is not a faithful relay mode; however, it does activate cortex more strongly than does tonic firing (Sherman 2001; Swadlow and Gusev 2000). For this reason, burst firing may represent a "wake-up call" to the target cortical area that something new or unexpected is being relayed through thalamus, and the strong activation of cortex may affect its layer 6 corticothalamic feedback to alter the gating and switch the firing of relay cells to the more linear tonic mode by depolarizing these cells, thereby inactivating their T-type Ca^{2+} conductances (Sherman 2001). The unexpected event may arise in a sensory pathway to a first-order relay or from a cortical area to a higher order thalamic relay.

An interesting speculative example of this scenario involves the zona incerta, a GABAergic brain stem structure. Connectional studies indicate that the zona incerta innervates thalamus widely, but projections to higher order relays appear to be greater than those to first-order relays (Barthó et al. 2002; Power et al. 1999). Innervation of zona incerta derives from wide areas of cortex, always from layer 5 (Mitrofanis and Mikuletic 1999). Studies of the relationship of motor cortex, the zona incerta, and the posterior medial nucleus, which is a higher order transthalamic relay between the first and second sensorimotor areas (Theyel et al. 2010), offer some possible insight into how this circuit functions. It appears that under most conditions during which the animal is not alert or not actively whisking, the posterior medial nucleus is tonically shut down by powerful GABAergic input from the zona incerta (Barthó et al. 2002; Bokor et al. 2005; Lavallée et al. 2005; Masri et al. 2006; Trageser et al. 2006; Trageser and Keller 2004), indicating that the relay cells there are hyperpolarized and in burst mode. Furthermore, increased activity in the motor cortex region that controls whisking strongly inhibits the zona incerta, thereby disinhibiting the posterior medial nucleus and opening the gate for the transthalamic relay of appropriate messages to the higher cortical areas innervated by the posterior medial nucleus (Barthó et al. 2007; Urbain and Deschênes 2007).

As noted, widespread innervation of zona incerta derives from layer 5 of cortex, raising the possibility that axons innervating the zona incerta branch to innervate higher order relays. Thus, when the primary sensory cortex is quiescent and no layer 5 output messages are being generated from that cortical region, the higher order relay it innervates (e.g., the posterior medial nucleus) is inhibited by the zona incerta, placing the thalamic relay cells there in burst mode. A sufficiently strong, new signal sent out over these layer 5 axons leads to a burst in the posterior medial nucleus relay cells, and this also inhibits the zona incerta (Barthó et al. 2007; Urbain and Deschênes 2007), thereby disinhibiting posterior medial nucleus cells and allowing them to switch to tonic firing for the subsequent relay of messages from the layer 5 axons.

ANSWER 2: BLOCKING INCORRECT EFFERENCE COPIES. Consider a situation in which lower cortical areas along parallel streams (e.g., visual and auditory) generate different and conflicting motor instructions via their layer 5 projections, branches of which also initiate transthalamic corticocortical circuits. This conflict could then be resolved, first by a final single motor command issued from higher areas that takes precedence, and second by modulator pathways that innervate the relevant transthalamic relays, blocking transthalamic messages that run counter to this prioritized command. We recognize the speculative nature of this scenario but include it to stress the importance of defining the available direct and transthalamic corticocortical pathways that relate to particular behavioral or cognitive functions.

Dynamic coupling of cortical areas. Several studies have recently focused on situations where different cortical areas become functionally linked during particular cognitive tasks, and although the details of the relationship between cognitive needs and the corticocortical linking remain undefined, ideas about the underlying circuitry have focused on direct connections between cortical areas and have largely ignored thalamus as playing a role in this linking (Andersen and Cui, 2009 Fries, 2009; Gregoriou et al. 2009; Pesaran et al. 2008; Reynolds et al. 1999; Womelsdorf et al. 2006). However, for any group of functionally related areas, there are likely to be both direct and transthalamic corticocortical links. This may provide a basis for a form of coincidence detection. That is, coactivation of both pathways (i.e., the transthalamic gate is open) could lead to strong activation of the target area, activation that ultimately leads to linking of the two cortical areas; conversely, if the thalamic gate is closed, the response in the target area is too weak to support such linking. Thus the thalamus may play an important role in this cortical process, although details concerning controls of the thalamic gate and how coactivation of both the direct and transthalamic pathways leads to linking remain to be determined.

Conclusions

To understand how cortical areas or groups of areas interact with each other and with the body, it will be necessary to identify the nature of the information received by each area directly from the thalamus, recognizing that for most cortical areas this comes from cortex itself through the thalamic gate. For the inputs that come directly from other cortical areas, it

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will be necessary to distinguish class 1 from class 2 inputs. The relationships established in the cortex between these two input sources, cortical and thalamic, will need to be defined in terms of the ways in which they can interact to reinforce or cancel one another. Comparably, for each cortical area, or for several areas where these are clearly sharing in a particular behavioral or cognitive function, it will be necessary to understand how their layer 5 outputs relate to lower motor circuits, defining the major motor changes that these can produce and comparing them with the outputs of the direct corticocortical connections that emerge from the motor cortex.

One important point about these functional connections is the extent to which they raise questions about how cortical areas interact with each other and how these interactions relate to lower motor centers. We need to learn more about the transthalamic corticocortical pathways, the higher order thalamic nuclei involved, and about gating and other modulatory (class 2) influences on these thalamic links. Equally important will be information about the lower motor connections established by any one group of layer 5 cells. This needs to include the sites of the terminations as well as their actions at each site. Where the outputs relate to centers that feed back directly or indirectly to cortex (e.g., cortical projections to the posterior column nuclei, to the superior colliculus, the striatum or the pons), these pathways will also relate to the functional organization of corticocortical interactions. We have focused on the transthalamic pathways because they involve essentially all cortical areas and provide a functional link that can be modulated by mechanisms that are beginning to be understood. The importance of the higher order thalamic relays for understanding corticocortical interaction is the main focus of our argument. We need to learn a great deal more about how they are organized and what role they play in cortical integration and in the control of lower motor mechanisms.

We have stressed the general pattern of branching that characterizes the class 1 inputs to thalamus, from lower centers, and those from cortex itself. Essentially all of the messages entering cortex, and all those leaving cortex, have a sensorimotor motor content. The commonly held view that sensory and motor computations in cortex are separate and hierarchical in organization needs to be reconsidered and interpreted in relation to the fact that all sensory pathways also carry copies of motor instructions so that sensorimotor processing is unified throughout all levels of thalamocortical function.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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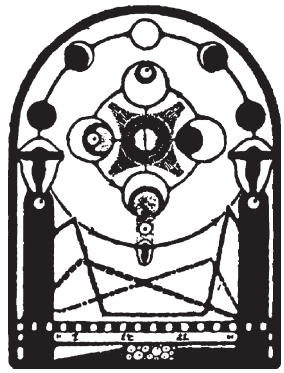

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