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PERSPECTIVE

Thalamus plays a central role in ongoing cortical functioning

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Several challenges to current views of thalamocortical processing are offered here. Glutamatergic pathways in thalamus and cortex are divided into two distinct classes: driver and modulator. We suggest that driver inputs are the main conduits of information and that modulator inputs modify how driver inputs are processed. Different driver sources reveal two types of thalamic relays: first order relays receive subcortical driver input (for example, retinal input to the lateral geniculate nucleus), whereas higher order relays (for example, pulvinar) receive driver input from layer 5 of cortex and participate in cortico-thalamo-cortical (or transthalamic) circuits. These transthalamic circuits represent an unappreciated aspect of cortical functioning, which I discuss here. Direct corticocortical connections are often paralleled by transthalamic ones. Furthermore, driver inputs to thalamus, both first and higher order, typically arrive via branching axons, and the transthalamic branch often innervates subcortical motor centers, leading to the suggestion that these inputs to thalamus serve as efference copies.

This Perspective proposes an alternative to the textbook view of thalamocortical organization and cortical functioning with a focus on sensory processing. The textbook view can be summed up as follows: information first arrives at cortex via a simple, machine-like thalamic relay (think of retinal input relayed through the lateral geniculate nucleus to visual cortex); it is then processed through a hierarchical series of sensory, sensorimotor and finally motor areas until a top level is reached from which a message is sent from cortex to a brainstem or spinal motor region to change or initiate some behavior. This represents a sensorimotor loop involving a chain of glutamatergic neurons that defines a functional input–output circuit involved in the transmission and processing of information leading to a behavioral result.

This view is challenged here on several grounds. The main point is that new ways of looking at how neural circuits function, particularly the glutamatergic elements, has revealed complex relationships between thalamus and cortex in both directions. This, in turn, leads to the understanding that thalamus continues to contribute to the processing of information within cortical hierarchies and is not just limited to relaying information in the initial stage of processing. Interestingly, inputs reaching the thalamus often also contact subcortical motor centers via branched axons. This Perspective will also discuss the suggestion that these thalamic inputs are efference copies.

One important proviso about this Perspective is that the best evidence for the ideas that are discussed below comes from studies of rodents (mostly mice) and from studies of the main sensory pathways: visual, somatosensory and auditory. Evidence from other species, such as cats and primates, and from other than sensory systems, while supportive, is sparse. Thus, more evidence beyond these examples will be needed to test the generality of these hypotheses.

Two types of glutamatergic input: driver and modulator

The first challenge to the conventional view of thalamocortical functioning comes from an appreciation that the relevant glutamatergic pathways are not a homogeneous collection and thus should not be treated as acting in a sort of anatomical democracy. Different functions are attributable to the different types, and the classification of component parts is a requisite early step in analyzing complex systems such as neuronal circuits. It is thus important to appreciate the different classes of synaptic input in complex circuits.

Classification of glutamatergic inputs. Glutamatergic inputs in thalamus and cortex include at least two very different types, and a clear example is seen in the circuitry of the lateral geniculate nucleus. Geniculate relay cells receive two main glutamatergic inputs, one from retinal ganglion cells and the other from layer 6 of visual cortex (**Fig. 1**), but with very different afferent properties (**Table 1**). From knowledge of receptive field features (reviewed in refs. 1,2), the relative importance of the two inputs for information processing has been clear for decades. That is, the receptive field of a visual neuron provides a good measure of the information transmitted to its postsynaptic targets. The receptive field of a representative retinal input displays the classic center–surround organization and is monocularly driven, whereas that of the layer 6 input is more complex, typically with selectivity for orientation, shape, direction, etc., and is binocularly driven (**Fig. 1**). The receptive field of the relay cell closely matches that of its retinal input and looks nothing like that of its cortical input. It is thus clear that the main information relayed through the lateral geniculate nucleus is provided by retinal and not cortical input. Because retinal input provides the main information to geniculate relay cells and so strongly activates them, we have called this type of glutamatergic input "driver"[3,4].

What then does the cortical input provide for geniculate circuitry? Evidence from a number of sources suggests that it acts in a modulatory fashion in the sense that it affects, or modulates, retinogeniculate transmission in a variety of ways without changing the basic nature (such as receptive field center-surround organization) of the retinal

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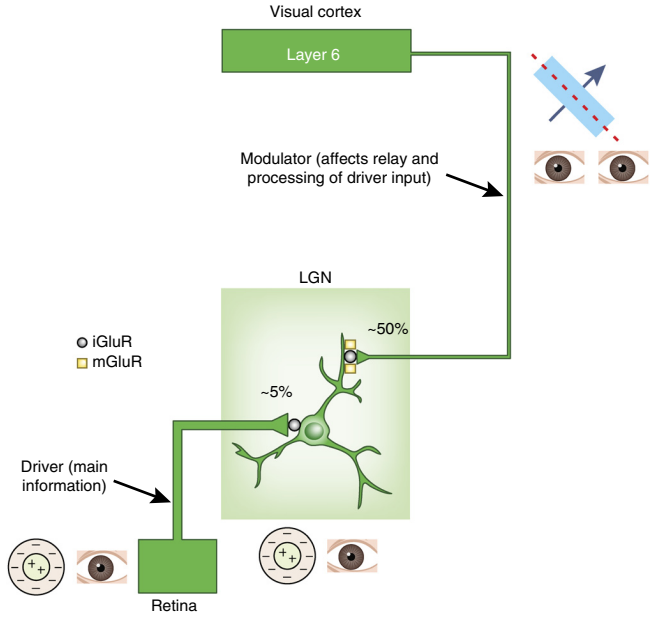

Figure 1 Glutamatergic drivers and modulators in the lateral geniculate nucleus (LGN) showing inputs to geniculate relay cells. As indicated in **Table 1**, the driver (retinal) input has thicker axons, has larger terminals, innervates more proximal dendrites and activates only ionotropic glutamate receptors (iGluRs). The modulator (cortical) input also activates metabotropic glutamate receptors (mGluRs). Retinal inputs, which comprise ~5% of synapses on these cells, have center–surround, monocularly driven receptive fields that closely resemble those of the relay cells. Layer 6 cortical inputs, which comprise ~50% of the synapses, have complex, binocularly driven receptive fields that are quite different from those of the relay cells.

message to be relayed. For instance, it affects the scale and other properties of retinogeniculate transmission (for example, refs. 5–7; see "Layer 6 corticothalamic cells" below). Thus we refer to this type of glutamatergic input as "modulator." In recent publications we have referred to the driver input as class 1 and the modulator as class 2 to avoid terminology suggestive of function (reviewed in ref. 3), which is not entirely established. For simplicity and to reflect our current thinking, we shall use the driver and modulator terminology here.

Most of the differences shown in **Table 1** for the lateral geniculate nucleus apply to other thalamic nuclei and to cortical circuitry[3]. **Figure 2** displays accumulated population data from 639 neurons, studied in the author's laboratory, supporting the driver and modulator classification. Three of the criteria of **Table 1** (amplitude, synaptic paired-pulse dynamics and presence of a metabotropic component) are plotted in **Figure 2a**. Overall, **Figure 2** supports three conclusions: (i) the driver and modulator classification is robust for both thalamus and cortex; (ii) only two main classes exist in thalamus and cortex, at least as is known so far (but see ref. 8); and (iii) the driver or modulator synaptic properties in thalamus are quite similar to those in cortex. These data should be interpreted with the usual provisos associated with *in vitro* slice preparations. For instance, activity present in many circuits, including those involving classical modulatory circuits, is reduced or absent in brain slices, and thus important features of modulatory plasticity in synaptic function may be overlooked. One might also question whether a given input may change from one class to another under differing conditions, but certain of the distinguishing properties, such as the presence or absence of metabotropic glutamate receptors or terminal size, seem likely to be permanently associated with each class. Synaptic properties of these driver and modulator inputs therefore need to be determined in whole animals under various behavioral regimes to test the physiological relevance of this classification.

Driver inputs appear to be smaller in number than are modulator inputs (**Table 1** and **Fig. 1**). In the lateral geniculate nucleus, driver (retinal) synapses provide only about 5% of those onto relay cells, whereas modulator (layer 6) synapses are roughly 50% of the total[9]; preliminary evidence (for example, ref. 10) suggests that in cortex, too, modulator inputs are much more numerous than are driver inputs, but detailed quantitative data are generally lacking for cortex. Clearly the proportion of synapses does not adequately correlate with a glutamatergic input's significance: identifying driver versus modulator inputs (for example, by various criteria in **Table 1**) is a much better strategy.

Functional correlates of the driver and modulator classification. We have extrapolated our understanding of geniculate circuitry to hypothesize more generally that driver inputs represent the main information to be transmitted, whereas modulator inputs affect how driver inputs are processed (reviewed in refs. 3,4; examples in refs. 7,11–14). These glutamatergic modulators act synaptically much like classical modulators (such as acetylcholine and noradrenaline): for example, they all activate metabotropic receptors. Furthermore, classical modulators generally are diffusely organized and seem more relevant to overall behavioral state, whereas glutamatergic inputs, both driver and modulator, seem to be highly topographic, and topographic modulation is needed for such processes as spatial attention, adaptation, context and modality specificity, etc. Other examples that involve activation of metabotropic glutamate receptors, presumably via modulatory glutamatergic inputs, are reviewed elsewhere[15]. Thus, identifying driver versus modulator components is important for understanding the functional organization of circuits (for example, ref. 16).

It is important to note that each of the glutamatergic driver and modulator classes likely contains subclasses, indicating a further level of complexity in these circuits that needs to be explored. Evidence has already been provided for three subclasses so far of drivers in cortical circuitry[8], and modulator subclasses need to be identified. Finally, major classes beyond driver and modulator may be documented as more glutamatergic pathways are studied.

Layer 6 corticothalamic cells

Every thalamic nucleus so far studied receives a feedback projection from layer 6 of cortex, meaning that the layer 6 cells project to the same thalamic region that innervates the layer 6 cortical region (reviewed in ref. 3). This corticothalamic pathway is a prototypical modulatory input that provides powerful control over thalamocortical

Table 1 Types of glutamatergic input to lateral geniculate nucleus

Retinal (driver)	Cortical layer 6 (modulator)
Activates only ionotropic receptors	Activates metabotropic and ionotropic receptors
Synapses show paired-pulse depression (high *p*)[a]	Synapses show paired-pulse facilitation (low *p*)[a]
Large EPSPs	Small EPSPs
Minority of inputs	Majority of inputs
Little or no convergence onto target	Much convergence onto target
Thick axons	Thin axons
Large terminals on proximal dendrites	Small terminals on distal dendrites
Dense, well-localized terminal arbors	Delicate terminal arbors

[a]*p* is the probability of transmitter release.

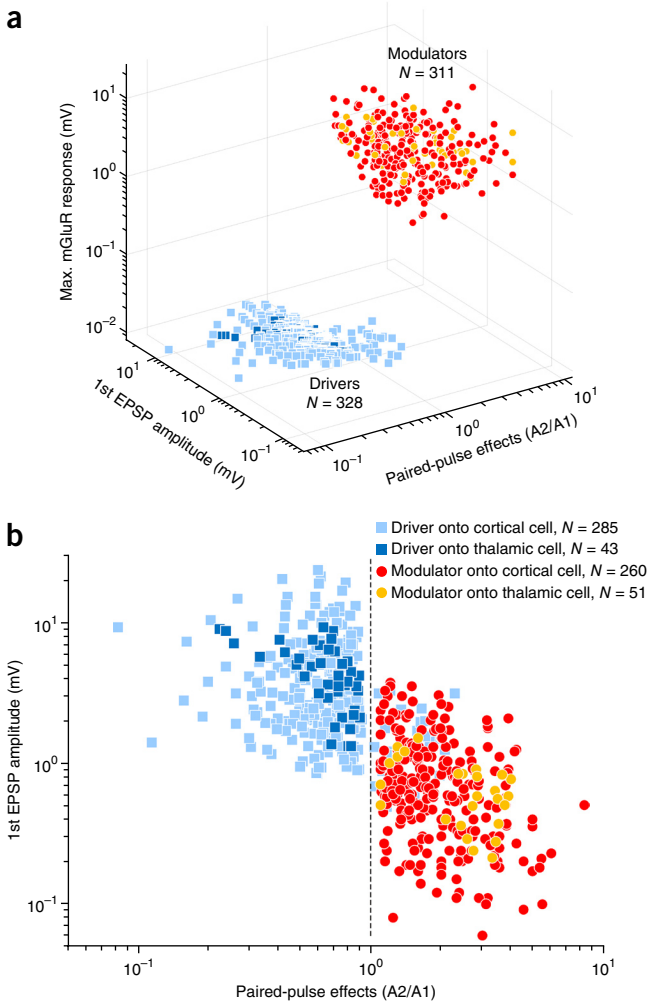

Figure 2 Population data showing distributions of various parameters for driver and modulator inputs to thalamic and cortical cells. (**a**) Three-dimensional scatter plot for inputs classified as driver or modulator to cells of thalamus and cortex. Each data point represents a cell for which a glutamatergic input was identified as driver or modulator (data from *in vitro* slice experiments in mice from the author's laboratory). The three parameters are (i) the amplitude of the first EPSP elicited in a train at a stimulus level just above threshold; (ii) a measure of paired-pulse effects, the amplitude of the second EPSP (A2) divided by the first (A1) for stimulus trains of 10–20 Hz; and (iii) a measure of the response to synaptic activation of metabotropic glutamate receptors, taken as the maximum voltage deflection (depolarization or hyperpolarization) during the 300-ms postsynaptic response period to tetanic stimulation in the presence of AMPA and NMDA blockers. Pathways tested here include various inputs to thalamus from cortex and subcortical sources, various thalamocortical pathways and various intracortical pathways. Of the cortical cells, 108 with driver inputs and 162 with modulator inputs reflect the activation of intracortical circuits, either between cortical areas or locally between laminae; the remainder of cortically recorded cells reflect thalamocortical inputs. It is noteworthy that the complex circuitry of cortex does not feature more variability in types of glutamatergic input. (**b**) Same data replotted as scatter diagram showing more clearly the *x* and *y* axes from **a**. Interestingly, the overlap for paired-pulse effects is due entirely to an unusual subset of thalamocortical driver inputs (referred to as class 1C)[8] that shows facilitation only for the first two evoked responses in a train: for following responses and overall, this synaptic property has been identified as one of depression[8], but for consistency with the remaining data, only data derived from the first two responses (specifically, A2/A1) are plotted here.

transmission. There are several features of this pathway that present challenges to elucidating its specific modulatory function(s). One is that the layer 6 cells of its origin are highly heterogeneous[17,18], so any attempt to find a single function for this feedback seems fruitless. For instance, parallel processing exists in the retino-geniculo-cortical pathway, leading to at least three separate streams known as W, X and Y in the cat and koniocellular (K), parvocellular (P) and magnocellular (M) in the monkey, each with its own geniculate relay cell type (reviewed in refs. 19,20); recent evidence suggests different classes of layer 6 cells innervate each of these relay cell types[21].

Another reason arises from the detailed circuitry of this layer 6 feedback illustrated in **Figure 3**, which depicts two configurations among other possibilities. **Figure 3a** represents a circuit that both directly excites relay cells and indirectly inhibits them via feedforward inhibitory circuits through reticular cells and (or) interneurons, so that the overall effect on cortical activation via this scheme is hard to evaluate. In cases where these excitatory and inhibitory inputs are approximately balanced, their conjoint activation might have little effect on a cell's membrane voltage, but this would reduce the cell's input resistance through activation of synaptic conductances, making the cell less responsive to other (for example, driver) inputs[22]. Thus the circuit of **Figure 3a** could control relay cell excitability. **Figure 3b** offers a different picture. Here activation of a cortical input excites some relay cells and inhibits others. Evidence for both circuits in **Figure 3** exists[23]. Note that, for either circuit shown in **Figure 3**, overall removal of the layer 6 projection would eliminate both direct excitation and indirect inhibition, and if these were approximately balanced, little overall effect would result; that is, the high degree of topography in this pathway suggests that its functional organization can be revealed only by approaches that are topographically specified, perhaps even to the single afferent axon level.

Figure 3b suggests that the layer 6 corticothalamic pathway could help regulate resting membrane potential in relay cells, and this could prove important to the control of voltage-gated ionic conductances that affect relay cell responses (reviewed in ref. 3). One of these conductances, based on T-type calcium channels, controls the firing mode, burst or tonic, of thalamic relay cells. Although the potential significance of these different firing modes remains debatable, they appear to be partly controlled by the layer 6 input (reviewed in ref. 3).

An important anatomical fact of the layer 6 corticothalamic cells is that their axons not only innervate thalamus, but they also branch to innervate layer 4 of cortex[24,25], and this suggests that they can affect thalamocortical transmission both at its thalamic source and at its main cortical target in layer 4. Evidence for this dual site of action exists, as the layer 6 cells affect both thalamocortical and retinogeniculate transmission as well as having direct effects on the postsynaptic thalamic relay cells and layer 4 target cells[7,14,23,26]. However, recent work on suppressing this pathway from visual cortex in mice using optogenetic techniques is not in full agreement: one study indicates that increasing layer 6 activity has an overall suppressive effect on visual responses in cortex[27], whereas another study suggests that this suppressive effect occurs when the layer 6 cells are firing at low rates, but when they are firing at high rates, activation of the pathway serves to increase visual responses in cortex[5].

Two types of thalamic relay: first and higher order

Transthalamic pathways. A key function of a thalamic relay is defined by its driver input. Thus the lateral geniculate nucleus serves to relay retinal input to cortex, the ventral posterior nucleus, medial lemniscal input, etc. These examples of primary sensory relays have long been

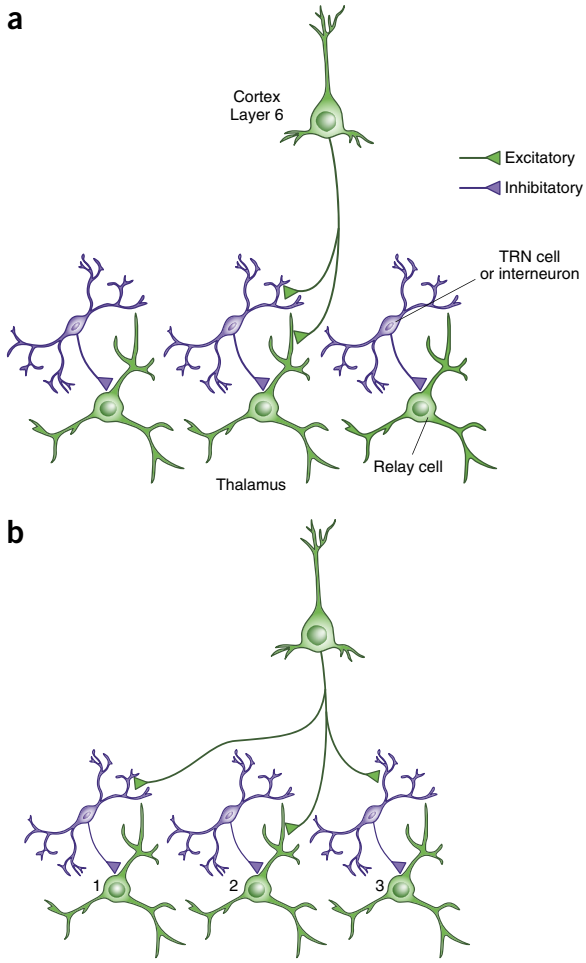

Figure 3 Different circuits for layer 6 corticothalamic inputs involving the layer 6 cells, thalamic relay cells and local GABAergic neurons, which include both cells of the thalamic reticular nucleus (TRN) as well as interneurons. (**a**) Circuit resulting in simple excitation and feedforward inhibition of relay cells. (**b**) More complex circuit in which activation of a cortical axon excites some relay cells directly (for example, cell 2) and inhibits others through activation of reticular cells or interneurons (for example, cells 1 and 3).

understood to relay subcortical information (for example, from retina, spinal cord or brainstem) to cortex.

More recently, driver inputs to many other thalamic nuclei were identified as originating in layer 5 of cortex, leading to the hypothesis that these nuclei were central components of transthalamic corticocortical circuits[3]. Thus, all thalamic relays have a layer 6 modulatory input organized largely in a feedback manner, and, in addition, some thalamic relays get a driver input from layer 5 of cortex that is organized in a feedforward manner[3]. On the basis of the source of driver input, we define those thalamic nuclei receiving a subcortical driver input as "first order" (for example, the lateral geniculate nucleus) and those receiving a cortical driver input as "higher order" (for example, the pulvinar). Higher order relays, which we estimate to be the majority of thalamus by volume, are involved in the transfer of information between cortical areas. It appears that often, and perhaps always, when cortical areas have a direct connection, they also have a parallel one through thalamus (see also below). One potential advantage of using a transthalamic pathway is that such information transferred by it can be modulated or gated by thalamic circuitry in ways unavailable to direct corticocortical pathways.

Examples of first and higher order nuclei for the main sensory pathways are, respectively, the lateral geniculate nucleus and pulvinar for vision, the ventral posterior and posterior medial nuclei for somatosensation, and the ventral and dorsal divisions of the medial geniculate nucleus for hearing[3]. The medial dorsal nucleus seems organized mainly as a higher order nucleus for prefrontal cortex[28], and the ventral anterior–ventral lateral nuclei seem organized as a mosaic for motor cortex, one part serving as a first order relay for cerebellar inputs and the other as a higher order relay[3,29–31].

The best evidence for these transthalamic pathways is a projection in the mouse from layer 5 of primary somatosensory cortex (S1) to the higher order posterior medial nucleus to the secondary somatosensory cortex (S2)[32–34]. Less complete evidence also exists for transthalamic feedforward pathways from primary visual and auditory cortices (V1 and A1, respectively) to higher areas[3]. For instance, the pulvinar in both cat and monkey has neurons with receptive field properties apparently inherited from cortical input, supporting their role as a link in transthalamic circuitry[35–37]. Also, suppression of somatosensory cortex, which eliminates layer 6 input to cells of the ventral posterior medial nucleus, has little effect on these cells; however, such suppression also eliminates layer 5 input to cells of the posterior medial nucleus, and this procedure does eliminate responsiveness of these cells[38].

Furthermore, evidence from the monkey indicates that the pulvinar plays a central role in the transfer of information between cortical areas[39]. Perhaps related to this, recent evidence using optogenetics and calcium imaging in mice indicates that activation of cortical layer 5 cells produces waves of activity in other cortical areas that depends largely on transthalamic pathways[40]. These observations support the idea that these transthalamic pathways provide the means whereby different cortical areas cooperate for various cognitive functions, including attention[41–43]. That is, this observed phenomenon of dynamic cooperation might rely heavily on the observation that the parallel direct and transthalamic pathways have been seen to converge onto individual postsynaptic cells (for example, in layer 4; refs. 44–46), and this could prove important both to information transfer between areas as well as to this dynamic cooperation among cortical areas.

First order versus higher order relays. Higher order thalamic nuclei employ more complex and heterogeneous circuitry than do first order nuclei. A number of subtle differences have been documented[3], but, in addition, three key ones stand out. (i) First order nuclei appear to be completely first order, meaning that all relay cells in such nuclei are innervated by subcortical drivers, but higher order nuclei often include first order circuits. Thus whereas most pulvinar, posterior medial or medial dorsal relay cells have layer 5 driver input, a subset have subcortical driver input: the superior colliculus for pulvinar and medial dorsal relay cells and the spinal trigeminal nucleus for posterior medial relay cells[47–50]. The functional unit of thalamus is the relay cell, and, since there is no evidence of connections or significant effects of one relay cell on another (but see ref. 51), each relay cell can be regarded as an independent relay link to cortex. Thus it may be more accurate to refer to relay cells as first order or higher order, and keep in mind that what we refer to as first order nuclei (for example, the lateral geniculate nucleus) contain only first order relay cells, whereas what we refer to as higher order nuclei (for example, the pulvinar) contain mostly higher order relay cells but probably also contain some first order ones. (ii) Almost by definition, first order relays innervate cortex in a feedforward manner, since they are the

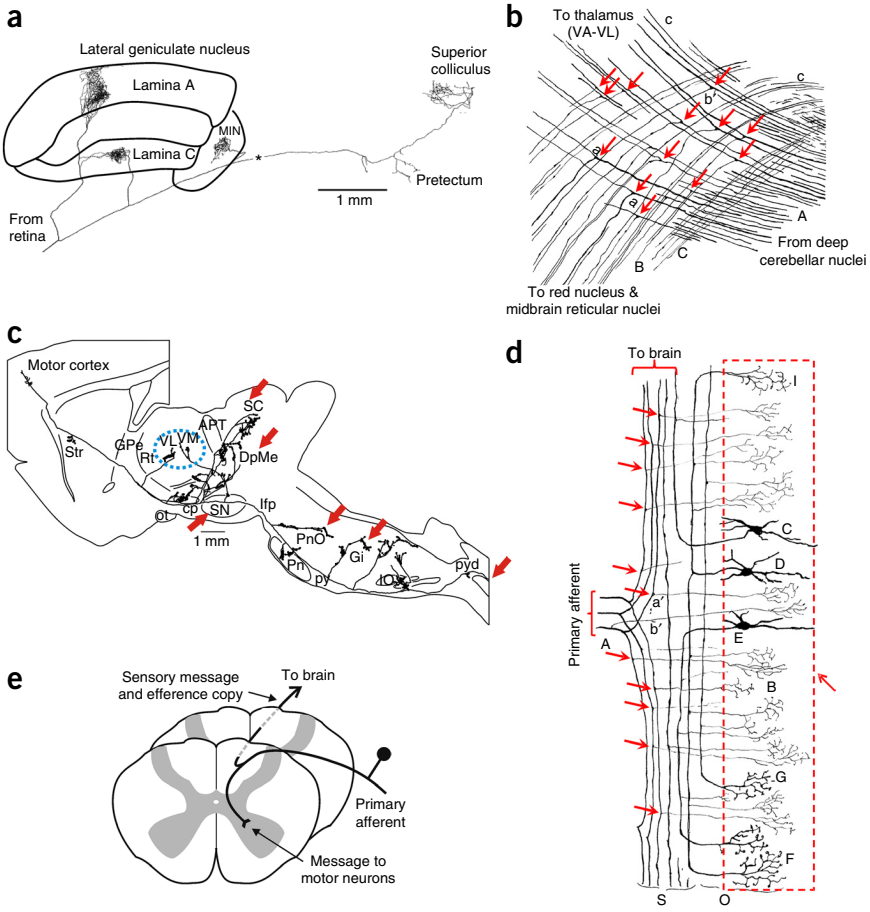

Figure 4 Examples of branching axons of driver inputs to thalamus. (**a**) Example from retinogeniculate axon of cat; adapted from ref. 58, *Journal of Comparative Neurology*. The asterisk indicates a gap in the axon not shown to keep the reconstruction from becoming unnecessarily wide. (**b**) Cajal illustration[65] showing innervation of the ventral anterior–ventral lateral (VA-VL) thalamic complex from cerebellum involves axons that branch (red arrows) to innervate other brainstem structures as well. (**c**) Example from layer 5 pyramidal tract cell of rat motor cortex; adapted from ref. 76 ("The subthalamic nucleus is one of multiple innervation sites for long-range corticofugal axons: a single-axon tracing study in the rat", T. Kita & H. Kita, 2012, in *Journal of Neuroscience*, 32 (17), 5990–5999). Branches innervating thalamus are indicated by the dashed blue circle, brainstem motor regions by red arrows. cp, cerebral peduncle; DpMe, deep mesencephalic nuclei; Gi, gigantocellular reticular nucleus; GPe, globus pallidus external segment; IO, inferior olive; MIN, medial interlaminar nucleus (part of the lateral geniculate nucleus); Pn, pontine nucleus; PnO, pontine reticular nucleus, oral part; py, medullary pyramid; pyd, pyramidal decussation; Rt, reticular thalamic nucleus; SC, superior colliculus; SN, substantia nigra; Str, striatum; VL, ventrolateral thalamic nucleus; VM, ventromedial thalamic nucleus. (**d**) Cajal illustration[65] of primary axons entering the spinal cord and branching to innervate the spinal gray matter and brain areas. The red arrows indicate branch points. (**e**) Schematic interpretation of **a**.

first relay of a particular kind of information to cortex and predominantly innervate primary cortical areas. However, some relay cells of the pulvinar, posterior medial nucleus and dorsal division of the medial geniculate nucleus innervate primary sensory cortex (V1, S1 and A1, respectively), as well as higher areas, raising the possibility that some higher order inputs to cortex are organized in a feedback manner. (iii) First order relay cells generally transfer information from one or a few driver inputs conveying similar information (for example, refs. 52,53), leading to little or no significant convergence of information (but see ref. 54), whereas there is evidence that such convergence and elaboration exist for higher order relays, where single neurons in the posterior medial nucleus or pulvinar are innervated both by layer 5 and subcortical driver inputs[47]. This last point is quite important and needs to be unequivocally established because evidence, mostly from first order relays, indicates that thalamus acts as a gated relay and, unlike cortex, does not elaborate information processing via driver inputs that converge from different sources. An example of such convergence is that of geniculocortical driver inputs to create orientation selectivity[55,56], a novel receptive field property seen in cortex, and this stands in contrast to the lack of such convergence and receptive field elaboration in retinogeniculate inputs. If such convergence exists in some higher order thalamic relay cells, this would mark a significant new function for thalamus.

Thalamic driver inputs as branched axons

Branched axons are ubiquitous in the CNS. The two methods commonly used to identify axonal branching are double labeling of neurons from retrograde markers placed into different axonal target zones and orthograde tracing of axons by Golgi staining or intracellular dye filling, which allows identification of axonal branch points. These two methods have provided evidence that branching is common among driver afferents to thalamus. In particular, orthograde tracing of axons, while infrequently applied, has so far always revealed such branching. Examples follow.

Branched inputs to first order relays. Most or all retinogeniculate axons studied to date branch to also innervate the superior colliculus and pretectal regions of the midbrain (**Fig. 4a**)[57–60]. In the somatosensory pathways, some presumed driver axons innervating the ventral posterior lateral nucleus branch to innervate other brainstem structures[61]. Furthermore, trigeminothalamic axons branch to innervate the superior colliculus, prerubral field, pretectum and zona incerta[62]. In the auditory pathways, relevant data on branching afferents to thalamus are scarce, but there is some evidence that branching axons innervate the medial geniculate nucleus from the inferior colliculus, and these are the likely driving inputs[63].

Outside the sensory pathways, there also exists evidence of branching subcortical driving axons that innervate the thalamus. Cerebellar afferents to the ventral anterior–ventral lateral complex have anatomical driver features (for example, large terminals often engaged in triadic relationships) (reviewed in ref. 3), and these branch to also innervate the red nucleus and tegmental reticular nucleus[64,65] (**Fig. 4b**). Mammillary inputs to the anterodorsal nucleus are drivers[66], and these branch to innervate the dorsal and deep tegmental nuclei[65,67]. Vestibulothalamic axons branch to innervate the interstitial nucleus of Cajal, central gray substance and spinal cord[68,69]. Thus, wherever it has been appropriately tested, the subcortical driver inputs to thalamus branch to innervate extrathalamic brainstem targets as well.

Branched inputs to higher order relays. All inputs studied so far from layer 5 of cortex to higher order thalamic relays, all of which appear to be driver inputs[3], are also branched axons. Examples include thalamic projections in the rat from motor, somatosensory or visual cortex that branch to innervate various midbrain and pontine areas[70–73], visual cortical projections to the pulvinar in the cat that branch to innervate the midbrain[74] and projections in monkeys from primary visual cortex and the middle temporal area that innervate pulvinar and branch to innervate the midbrain[75]. In a particularly impressive example, pyramidal tract neurons from motor cortex branch extensively to innervate the ventrolateral and ventromedial thalamic nuclei, as well as numerous sites in the brainstem and undefined targets in the spinal cord (**Fig. 4c**)[76]. Many of these layer 5 subcortical targets are motor in nature, including bulbospinal control regions (for example, tectospinal and reticulospinal; reviewed in ref. 3). It is important in this context to recognize the universality of layer 5 projections to motor centers: every cortical area so far studied in this regard, including primary sensory areas, sends branching projections to subcortical targets, some of which are motor centers. In this regard, differences between sensory, motor and other cortical areas are more quantitative than qualitative.

This pattern of branching provides a possibly key difference between the direct and transthalamic pathways connecting cortical areas (see also below) because it means that the information sent through the transthalamic circuit is shared by other parts of the subcortical neuraxis, which is not the case for the direct corticocortical pathways. That is, the direct pathways rarely if ever involve axons with subcortical branches, meaning that the information carried by direct corticocortical axons is information that stays strictly within cortex. In contrast, the transthalamic pathways involve information that is shared with multiple subcortical parts of the neuraxis. Furthermore, whereas corticocortical axons seem not to have subcortical targets, corticofugal axons from one area of cortex do not branch to innervate other cortical areas, suggesting a degree of independence in the direct and transthalamic cortical circuits[77].

Are driver inputs to thalamus efference copies?

Efference copies (also known as corollary discharges) are messages sent from motor areas of the brain back into appropriate sensory processing streams to anticipate impending self-generated behaviors. This is an absolute requirement to allow the organism to disambiguate self-generated movements from external events. For instance, when we move our eyes, the image of the visual world on our retinas moves in the opposite direction, but we do not normally experience movement in our visual world because we anticipate the eye movement and account for it. Similarly, when we palpate an object with our hands and fingers, we can discern features of that object by separating tactile experiences we induce by our actions from those that movement of the object might evoke, and efference copies are needed for this. Note that this process requires a prediction, or 'forward model', of what will occur as a result of the impending action and that any sensory feedback that can indicate the position of the eyes or finger joints would occur after the movement and be too late for this purpose[50].

Indeed, the importance of the concept of the efference copy is such that its existence was predicted in the nineteenth century[78]. It was first demonstrated 66 years ago in flies and fishes[79,80], suggesting that it is part of our early evolutionary heritage (see also below) and must occur widely in the animal kingdom. Coordinated behavior of any reasonably complex animal without efference copies is improbable. Excellent recent reviews are available[50,81], so details of the subject are omitted here in to concentrate on the possible function of efference copies in thalamocortical processing.

Branching axons and efference copies. As the term implies, effective efference copy requires an accurate copy of a motor message to be directed back into the appropriate sensory processing stream. In this context, axonal branching enables a single neuron to send the identical message to all of its target neurons[82,83]. This does not mean that the message has the same effect at all of its targets, because different synaptic properties at different targets likely exist and lead to postsynaptic variation in responses. Nonetheless, a branching axon is the most efficient way to share a single message with multiple targets. This suggests a plausible role for branching axons in efference copy circuits.

As an example, Cajal noted that most or all primary afferents entering the spinal cord branch, with one branch entering the spinal gray, often the ventral horn to affect motor neurons, and the other ascending the cord to the brain (**Fig. 4d**)[65]. Because of the branching pattern, the message to the brain is an exact duplicate of the one to the spinal gray matter. Since we can consider the branch innervating the gray matter likely to cause an action by affecting motor neurons and thus to carry a motor message, then the branch ascending to the brain is an exact copy of that motor message. This is the definition of an efference copy. In this view, the ascending branch carries a message that has two meanings: a sensory message (for example, about a joint movement or skin indentation) as well as an efference copy about an impending motor action related to the sensory message.

Driver inputs to thalamus and efference copies. In this context, we revisit the anatomical fact that many, most or all driver inputs to thalamus involve branched axons. The extrathalamic targets of these branched axons frequently include regions associated with motor control. Examples include retinogeniculate axons that branch to innervate midbrain structures associated with eye movements, pupillary control and so on (**Fig. 4a**)[58]. Many other examples exist of extrathalamic branches innervating brainstem sites of supraspinal control, such as the superior colliculus (tectospinal), red nucleus (rubrospinal) and reticular formation (reticulospinal) (**Fig. 4a–c**). In the case of pyramidal tract neurons, examples have been seen of axons innervating thalamus that branch to innervate both various brainstem sites involved in supraspinal control and the spinal cord itself (**Fig. 4c**)[76].

Regarding the notion that many corticofugal projections can be seen as carrying motor messages, note that all the corticocortical projections and intracortical processing in the world would be meaningless without projections to subcortical sites that can influence behavior. There are two types of corticofugal projection to consider. One is from layer 6, but these only innervate thalamus and thus are limited to affecting thalamocortical processing rather than more directly affecting behavior. The relevant cortical outputs emanate from layer 5, and these seem to provide cortex with the requisite motor outputs. This is a main reason that we should consider at least some layer 5 outputs to be carrying important motor messages to targets such as the superior colliculus and various other sites of supraspinal control.

To the extent that many and possibly all messages sent to thalamus for relay to cortex are copies of messages sent to motor centers, then these thalamic inputs may be regarded as efference copies (see ref. 3 for further elaboration of this idea). Furthermore, just as the ascending axon branch in **Figure 4e** contains related information about a sensory event and possible impending motor action, so do these driver inputs to thalamus carry a double message: information about the environment as well as an efference copy. Recall that the textbook view of thalamocortical processing (**Fig. 5a**) has no role for either higher order thalamic nuclei or efference copies within these circuits. The new idea here is that, as a cortical hierarchy is ascended,

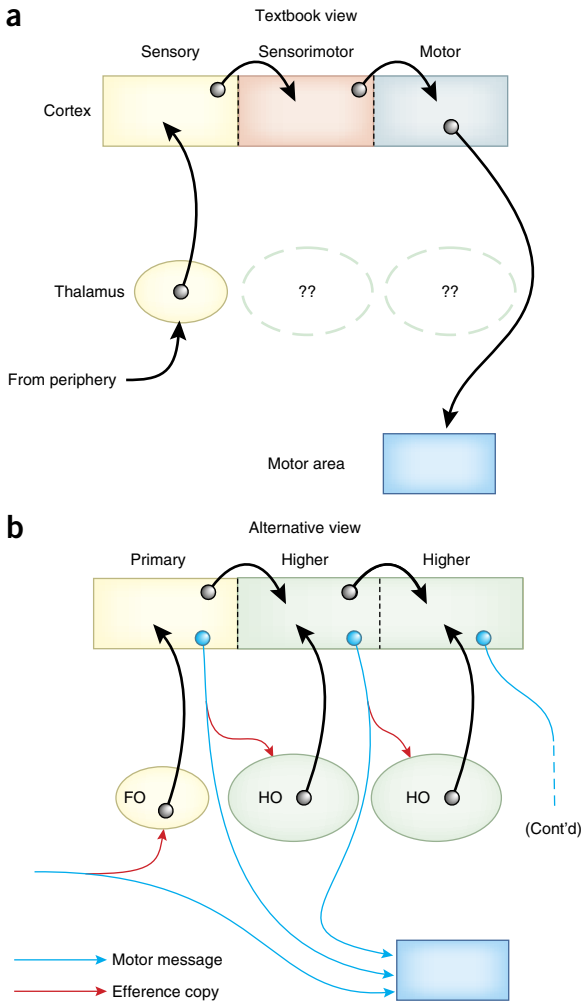

Figure 5 Two views of thalamocortical processing. (**a**) Textbook view. Here sensory information reaches the thalamus from the periphery, is relayed to sensory cortex and is then processed through various hierarchical levels of sensory and sensorimotor cortical areas until it reaches motor areas from which motor commands are sent to subcortical motor areas. There is no role here for what has been recognized as higher order thalamic relays (??). (**b**) Alternative view. Here higher order relays (HO; FO is first order) serve as a transthalamic link in corticocortical communication, and the inputs relayed by thalamus (red arrows) serve as efference copies as well as representing new information for cortical processing. Here all cortical areas have a motor output (blue arrows) that emanates from layer 5.

each level is kept informed about possible motor commands initiated by lower levels via the transthalamic pathways (**Fig. 5b**). This would provide a specific role for these pathways: for instance, the direct corticocortical pathways may be involved in basic analysis of the environment (for example, the visual world) while the transthalamic pathways may inform higher cortical levels of possible motor actions for which to correct in further information processing. However, this speculation should be seen as one possibility among others cited above: for instance, evidence that transthalamic pathways are important in the modulation of information transfer between cortical areas rather than representing that information directly[39], evidence that activation of these transthalamic pathways leads to general activity waves through multiple cortical areas[40], and the notion that transthalamic and direct pathways could act together as a sort of coincidence detector to support coordination between areas. These ideas are not incompatible, meaning that one or more may actually occur.

Efference copies are often discussed in very abstract form with no clear anatomical basis, but there have been several studies demonstrating clear evidence and specific neural substrates. Most are related to eye movements. For instance, Sommer and Wurtz[50] demonstrated that an efference copy signaling a saccadic eye movement is sent from the superior colliculus to the medial dorsal nucleus of the thalamus for relay to the frontal eye field in cortex. Thus the colliculothalamic input is a copy of a signal sent by the colliculus to oculomotor centers. The authors do not comment on how the copy is achieved, but it is plausible that the axons innervating thalamus are branches of those innervating oculomotor targets, which would fit the scheme of **Figure 5b**. Colby and colleagues[84–86] have demonstrated neurons in various areas of cortex that shift receptive fields before a saccade in exactly the manner predicted by development of a forward model.

Box 1 Questions arising

The challenge to traditional views of thalamocortical processing suggested here raise a number of new questions, and identifying these may be regarded as a key part of this Perspective:

- How common is the pattern of parallel direct and transthalamic corticocortical pathways? Are direct pathways always associated with parallel transthalamic ones, or are one or the other commonly found alone?
- Why is one of these pathways relayed through thalamus? Thalamus does offer the possibility, lacking in direct pathways, of gating or otherwise modulating the information represented.
- What is the significance of the convergence of direct and transthalamic pathways? The possibility that nonlinear summation exists and acts in functional linking of cortical areas has been raised, but many other possibilities can be imagined.
- What is different in the information carried by each route? We have speculated that the direct pathways participate in basic processing of information and transthalamic pathways update higher areas with efference copies. Note that this idea and the idea noted above regarding convergence of direct and transthalamic pathways are not mutually exclusive.
- What is the significance of the branching driver input to thalamus? The idea that this may be related to efference copy mechanisms is an attempt to make sense of the anatomical observation that the information relayed by thalamus commonly involves branching axons that also project to motor centers.
- Given the ubiquitous nature of efference copies in all behaving animals and the conserved nature of evolution, how does the brain handle a hierarchical multitude of efference copies for any movement? Evolution is like a pack rat: old neural circuits tend to remain and function even as newer ones emerge, and each of these circuits—spinal, brainstem and thalamocortical—likely evolved with its own set of efference copies.
- Is there significant convergence of driver inputs to thalamic relays cells, perhaps in higher order circuits? Limited evidence for this needs to be confirmed.
- How do driver inputs interact in cortex? Unlike the situation in thalamus, driver inputs commonly converge from different sources onto single neurons in cortex, and these potentially can be activated in a variety of combinations, perhaps under differential modulatory control. We are thus very far from understanding how such inputs function under various behavioral conditions.
- Given evidence that patients with schizophrenia seem to have anatomical and functional anomalies in higher order thalamic nuclei[87–89] and also show deficits in efference copy[90–92], might the ideas presented here regarding these thalamic nuclei, particularly with respect to their role in cortical functioning and representing efference copies, offer insights into the neural substrates of the disease?

Such neurons are found throughout the visual hierarchy and, although rare in V1, they are found there, and they increase in representation with hierarchical level[85]. Although the scheme in **Figure 5b** is hypothetical, there are not obvious alternative pathways for efference copy information to reach early visual areas.

Conclusions

Three basic ideas have been put forward here: (i) that glutamatergic pathways in cortex and thalamus are divided between driver and modulator pathways, and identifying driver pathways is an important early step in parsing circuits and in understanding the function of any thalamic nucleus; (ii) that this analysis leads to the appreciation that much of thalamus, which we call higher order, is involved in transthalamic corticocortical communication; and (iii) that driver inputs to thalamus commonly involve branched axons that also innervate subcortical sites identified as motor centers, which leads to speculation that these driver inputs may act as efference copies for information relayed to cortex. One way to summarize these ideas is to compare the traditional (textbook) framework with the alternative one created here (**Fig. 5**) along three issues:

- In the textbook view, the only explicit role for thalamus is to relay the initial information to cortex: once it reaches cortex, this information is processed completely within the cortical hierarchy until the output stage is reached. This leaves no specific function for higher order thalamic relays. We argue that these relays continue to play a critical role in cortical processing via transthalamic corticocortical pathways.
- Also, **Figure 5a** shows a single entry and exit point for cortical processing (the thalamocortical input and motor cortex output). As indicated above, it appears that every cortical area projects motor messages subcortically, and so every area has an input and output (**Fig. 5b**). Indeed, the notion that sensorimotor processing could involve so many steps (and so much time) as suggested by **Figure 5a** before a behavioral response is formed seems to go against our understanding of how these systems evolved: when a new sensory receptor is acquired in the course of evolution, it will have no survival value if it lacks a fairly immediate motor output. In this regard, **Figure 5b** seems more plausible.
- Finally, given that cortex issues motor commands via layer 5 outputs, it seems obvious that these should be correlated to efference copies. Their anatomical identity must remain speculative, but these are ignored in **Figure 5a** and suggested in **Figure 5b**.

As noted above, the alternative view proposed here is hypothetical, with important provisos, and it leads to new questions (**Box 1**). The hope is that this will encourage new research efforts to critically appraise this view.

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