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My prolonged collaboration with Ray Guillery

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Abstract

My active collaboration with Ray Guillery started in 1968, when he was a Full Professor at the University of Wisconsin and I was a graduate student at the University of Pennsylvania. The collaboration lasted almost 50 years with virtually no breaks. Among the ideas we proposed are that glutamatergic pathways in thalamus and cortex can be classified into drivers and modulators; that many thalamic nuclei could be classified as higher order, meaning that they receive driving input from layer 5 of cortex and participate in cortico-thalamocortical circuits; and that much of the information relayed by thalamus serves as an efference copy for motor commands initiated by cortex.

Introduction

Rainer (Ray) Guillery and I first met in 1968, when I was a graduate student at the University of Pennsylvania and Ray was a Professor of Anatomy at the University of Wisconsin. We hit it off immediately and collaborated in the 1970s for a series of research papers that provided further evidence for binocular competition in the development of central visual pathways. However, after I spent a sabbatical with Ray in Oxford from August of 1985 until September of 1986, we moved our collaboration onto a more theoretical plane and started to develop ideas about thalamocortical relationships that challenged conventional views.

This began with many discussions during the sabbatical, after which time we realized that it might be useful to put our thoughts down on paper. The result, starting in 1986, has been 10 reviews and book chapters (Sherman & Guillery, 1996, 1998, 2002, 2004a, b, 2011, 2014; Guillery & Sherman, 2002a,b, 2011) plus three monographs (Sherman & Guillery, 2001, 2006, 2013). What follows is a somewhat informal summary of our ideas without the usual bookish citation for each; readers can easily obtain further details from the citations in this paragraph.

We developed three main ideas that are summarized below. The first is that glutamatergic pathways, which are typically viewed as the main conduits for information transfer in the brain, are not homogeneous but, at least in thalamus and cortex, are instead divided into *drivers* and *modulators*. This classification has important implications for parsing neuronal circuitry. The second is that thalamic nuclei can mainly be divided into *first* and *higher order* components, the latter being involved in cortico-thalamocortical circuitry. Finally, the third idea, which is the most speculative of the lot, is that much of the information relayed to cortex by thalamus serves as an efference copy for cortical motor commands.

Drivers and modulators

The idea that glutamatergic pathways are not homogeneous came to us from an understanding of circuitry of the lateral geniculate nucleus. Geniculate relay cells receive two distinct glutamatergic inputs: one from retina and the other from layer 6 of visual cortex. Actually, it had been clear from receptive field studies for decades that the retinal input represents the main information for geniculate relay cells to transfer to cortex and that the cortical input must be involved in very different functions.

If we want to understand what sort of information a visual neuron might pass on to its postsynaptic targets, the receptive field is a good place to start, because how such a cell responds to visual stimuli reflects the sort of messages it can convey to its targets. Figure 1 shows the receptive field properties of the two main glutamatergic inputs, retinal and cortical layer 6, to geniculate relay cells. For the most part, retinal input has the classic centre/surround receptive field configuration and is monocular, meaning that activation can be achieved by visual stimulation of one eye but not the other. The cortical input has receptive fields that are quite different and more complex: they typically show orientation and often direction selectivity, and they tend to be binocularly driven, meaning that stimulation of either eye can evoke responses. Which input provides the main information to be passed on to cortex by relay cells? The relay cell receptive field closely matches that of its retinal input and looks nothing like the cortical input, clearly indicating that the retina provides the main information to be transmitted by geniculate relay cells.

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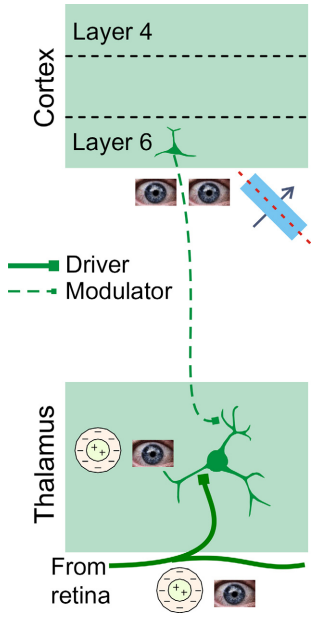

FIG. 1. Receptive fields of geniculate relay cells and their glutamatergic inputs. Retinal inputs have classic centre/surround receptive field organization with monocular activation, and the cortical inputs have binocular receptive fields with various forms of selectivity, such as for orientation, direction of movement, etc. Geniculate relay cell receptive fields closely match those of their retinal inputs.

We thus called the retinal input the *driver* input, partly because it strongly drives relay cells. This leaves open the question: just what is the function of the cortical input? Data from a number of laboratories have indicated that the function of this input is modulatory and serves mainly to affect subtle features of retinogeniculate communication, such as gain of the transmission, temporal properties of relay cells firing, especially with regards to whether or not the responses are in tonic or burst mode, etc. (Godwin *et al.*, 1996; Govindaiah *et al.*, 2012; Olsen *et al.*, 2012; Andolina *et al.*, 2013; Lam & Sherman, 2013; Mease *et al.*, 2014; Crandall *et al.*, 2015; Wang *et al.*, 2016).

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 Sherman & Guillery, 2013), which is not entirely established. For simplicity and to reflect our current thinking, we shall use the driver and modulator terminology here.

We then set out to identify the synaptic parameters that distinguish glutamatergic drivers from modulators, that is, to attempt a classification of glutamatergic circuits. Table 1 summarizes a number of defining features of this classification for thalamic circuitry. The classification of drivers versus modulators for glutamatergic inputs has been extended from thalamic circuitry to cortical circuitry. Figure 2, which shows a scatter plot of the top three quantifiable parameters from Table 1, makes three points. First, the classification is quite robust. Second, so far only two classes of glutamatergic input have been identified. This despite the fact that the many parameters listed in Table 1 could be combined to create thousands of distinct classes. Perhaps more will be discovered as other glutamatergic pathways are studied. Third, with minor provisos, the properties of driver synapses in thalamus are quite like those in cortex, and the same holds for modulator synapses, as if there are basically two types of such glutamatergic synapses shared by thalamic and cortical circuitry.

TABLE 1. Types of glutamatergic input to LGN

Retinal (Driver)	Cortical layer 6 (Modulator)
Activates only ionotropic receptors	Activates metabotropic receptors
Synapses show paired-pulse depression (high *P*)*	Synapses show paired-pulse facilitation (low *P*)*
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 arbours	Delicate, sparse terminal arbours

**P* refers to the probability of transmitter release.

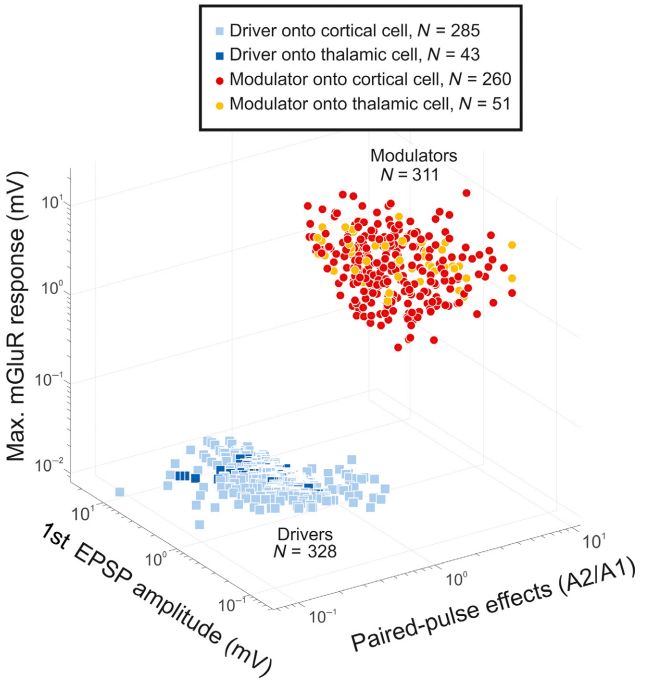

FIG. 2. Three-dimensional scatterplot for inputs classified as driver or modulator to thalamic and cortical cells. The data derive from experiments carried out in the author's laboratory on brain slices taken from mice. The three plotted parameters are as follows: (1) the amplitude of the first evoked EPSP at an electrical stimulation level just above threshold; (2) paired-pulse effects seen as the amplitude of the second EPSP divided by the first for stimulus trains of 10–20 Hz; and (3) a measure of the contribution of metabotropic glutamate receptors to the response to synaptic activation, taken as the maximum voltage deflection (i.e., depolarization or hyperpolarization) during the 300-msec 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. Redrawn from Sherman (2016).

Based on what we know about the function of various inputs to thalamic relay cells, such as retinal or medial lemniscal input versus layer 6 input, we suggested the hypothesis that driver inputs carry the main information, and modulatory inputs modulate, which is not to say that they do not convey information, but rather that this is used in a modulatory fashion rather than used as a basic component in information processing. It should be emphasized that the classification of glutamatergic inputs into drivers and modulators is an empirical fact, but the notion that one represents a main information

conduit and the other performs a modulatory function remains nothing more than a hypothesis that requires further testing. What follows is our reasoning behind this hypothesis.

For the driver inputs, several of the features seem more suitable for information transfer. In particular, the high probability of transmitter release, large initial evoked EPSPs and proximal dendritic location of synaptic terminals would all serve to enhance fast, secure synaptic transmission of information. Lack of activation of metabotropic receptors, which exhibit relatively long latencies and durations, also serves to preserve temporal components of the message to be relayed, especially for higher frequency components. Furthermore, the paired-pulse depression associated with the high probability of transmitter release would serve to enhance the linear range for information transfer (Abbott *et al.*, 1997). Finally, the relatively little convergence means that few driver inputs need fire synchronously to activate their postsynaptic targets and thereby transmit the message, and sometimes the driver input, such as the retinogeniculate synapse, involves a single axon (Cleland *et al.*, 1971; Usrey *et al.*, 1999).

For the glutamatergic modulator inputs, the above parameters would seem to be less than ideal for information transfer. This includes the smaller initial EPSPs and low probability of transmitter release. Also, the resultant paired-pulse facilitation means that large EPSPs are evoked only after a train of input action potentials. Thus, for example, not perhaps until the 10th EPSP evoked at 20 Hz is the postsynaptic EPSP large enough to fire the target neuron; this means a delay in message transfer of 500 ms, which is clearly a poor way to transmit information in neuronal circuits. Another factor is the larger convergence of modulator inputs compared to drivers; for instance, it is estimated that layer 6 corticogeniculate axonal afferents to relay cells outnumber retinal inputs by a ratio of 30–100 (Sherman & Koch, 1986). From this, it follows that each individual modulator input produces a very small initial EPSP, and so to evoke an effectively large modulator EPSP would require an implausible synchronous firing of many such inputs. It thus seems clear that these glutamatergic inputs evolved for functions other than primary information transfer.

Activation of metabotropic receptors by glutamatergic inputs provides some insight into their function. It is interesting in this context that the classical modulator inputs (e.g., cholinergic, noradrenergic, serotonergic, etc.) all typically activate metabotropic receptors, which is key to their modulatory function. For example, thalamic relay cells, like neurons throughout the central nervous system, have a number of voltage and time dependent ionic conductances. As an example, consider the T-type Ca^{2+} channels that are ubiquitous to thalamic relay cells (McCormick & Huguenard, 1992; Sherman & Guillery, 2013). These channels are inactivated at depolarized levels (e.g., more depolarized than about −60 mV), and such inactivation is removed, or, the channels are de-inactivated, when the cell is sufficiently hyperpolarized (e.g., beyond about -70 mV). During de-inactivation, these channels can be activated (i.e., opened) by an appropriate depolarization, such as a sufficiently large EPSP; this leads to a large depolarization as Ca^{2+} flows into the cell that, in turn, produces a high frequency burst of action potentials. This is the burst mode of firing. A similar EPSP when these channels are inactivated, if large enough, produces a prolonged sequence of action potentials at a lower rate, and this is the tonic firing mode. Thus, depending on whether the recent history of a relay cells is slightly depolarized or hyperpolarized can be an important factor in how an incoming signal is relayed to cortex (Sherman, 2001; Sherman & Guillery, 2013). The important point here is that the crucial shift in firing mode from burst to tonic, or the reverse, requires a change in membrane potential that has an important time dependency: such a depolarization or hyperpolarization must be sustained for about 100 ms or so for the Ca^{2+} channels in question to shift between inactivated and de-inactivated. In this context, the depolarization affected by typical activation of ionotropic receptors, such as AMPA or even NMDA, is too brief to inactivate these Ca^{2+} channels, and, likewise, activation of the ionotropic $GABA_A$ receptors produces too short an IPSP to de-inactivate the channels. This is where metabotropic receptors play such a crucial role: by producing prolonged EPSPs or IPSPs that last 100 msec to several sec (Sherman & Guillery, 2013; Viaene *et al.*, 2013), they are well designed to control these Ca^{2+} channels. The example here regarding the temporal requirements of controlling T-type Ca^{2+} channels applies to most other voltage gated channels and demonstrates the importance of metabotropic receptors in the modulation of postsynaptic responses of neurons to driving inputs. In the case of metabotropic glutamate receptors, these come in several flavours that can produce not only prolonged EPSPs (e.g., group I metabotropic glutamate receptors) but also prolonged IPSPs (e.g., group II metabotropic glutamate receptors).

Evidence indeed exists that activation of modulatory glutamatergic inputs can affect the gain of driver inputs to neurons and also affect firing mode of thalamic relay cells (Godwin *et al.*, 1996; DePasquale & Sherman, 2012; Lam & Sherman, 2013; Liu *et al.*, 2014, 2015). As noted above, other evidence indicates that the layer 6 corticothalamic pathway controls the gain of thalamocortical responsiveness (Lee & Sherman, 2009, 2012; DePasquale & Sherman, 2013). These observations, while still scattered, are consistent with the hypothesis that these inputs provide a modulatory function. One might ask: Why, given the plethora of classical modulatory systems (cholinergic, noradrenergic, etc.), are glutamatergic modulators needed? A plausible answer involves topography: classical modulatory systems are diffusely organized, more or less globally affecting processing in large parts of the neuraxis, and thus best organized for affecting overall behavioural states such as drowsiness and overall alertness. In contrast, glutamatergic modulatory pathways are the only ones known to be highly topographic, and topographic modulation is needed for such behavioural processes as spatial or feature-based attention, adaptation.

One final note about these glutamatergic inputs relates to their relative numbers. In the lateral geniculate nucleus, where quantification of anatomical circuits is best known, modulators far outnumber drivers in terms of inputs to relay cells. As noted above, layer 6 axons outnumber retinal axons by up to two orders of magnitude, and, in terms of actual synaptic counts, corticogeniculate synapses, at roughly 50% of all synapses, provide about an order of magnitude more synapses than do retinogeniculate inputs, which account for roughly 5% of the total synaptic count, the remaining synapses divided nearly equally among local GABAergic sources and brainstem modulatory (e.g., cholinergic) ones (Erisir *et al.*, 1997; Van Horn *et al.*, 2000). Thus, treating all glutamatergic inputs equally as if they operate in a sort of anatomical democracy can be quite misleading: in the case of the lateral geniculate nucleus, one might be led by the numbers into concluding that the layer 6 cortical inputs is the dominant input for relay to cortex, whereas the retinal input represents a small, rather insignificant contributor.

First and higher order thalamic relays

Key to understanding the role of a thalamic nucleus is the identification of its driver input(s). Thus, we can say that a main function of the lateral geniculate nucleus is to relay retinal input and of the

ventral posterior nucleus, to relay medial lemniscal input. However, until relatively recently, the function in this sense of most thalamus nuclei, such as the pulvinar, remained an enigma, because their driver inputs remained undefined. A major breakthrough occurred with a paper by Ray Guillery proposing that a driver input for many thalamic nuclei emanates from layer 5 of cortex (Guillery, 1995). Ray and I then developed this idea to suggest that many cortical areas were connected via cortico-thalamo-cortical, or transthalamic, circuits instead of or in addition to direct connections.

Figure 3 schematically illustrates this. As indicated, all thalamic relay cells receive a layer 6 glutamatergic input that is modulatory and is organized chiefly in a feedback manner. The driver input to first order relay cells emanates from a subcortical source, such as the retinal input to the lateral geniculate nucleus. However, higher order relay cells, such as those in pulvinar, in addition, receive a second cortical input from layer 5 that serves the purpose of a driver input, just like retinal input to the lateral geniculate nucleus, and this input is organized in a feedforward pattern. We refer to the lateral geniculate nucleus as an exemplar of a *first order* relay, meaning that it relays information from a subcortical source (retina in this example), whereas the pulvinar is mostly an exemplar of a *higher order* relay, meaning that its driver input derives from layer 5 of cortex.

First and higher order relays are not limited to vision: in somatosensory processing, the ventral posterior (medial and lateral) nucleus is first order, and the posterior medial nucleus, higher order; in auditory processing, the ventral portion of the medial geniculate nucleus is first order, and the dorsal portion, higher order; also other nuclei, such as the medial dorsal nucleus and parts of the ventral anterior/ventral medial nuclear complex, among others, appear to be higher order due to the observation that they receive cortical layer 5 innervation. Overall, although many details must still be filled in, this analysis suggests that most of thalamus by volume is higher order. This, in turn, offers a simple hypothesis for much of thalamus that heretofore was rather mysterious with regards to function: these serve as a central node in transthalamic, corticocortical processing.

First and higher order thalamic nuclei differ in a number of subtle ways, and details of these differences can be found elsewhere (Sherman, 2017). However, one difference is worth emphasizing here. First order nuclei appear to be completely first order, meaning that the only driver inputs to these nuclei arise from subcortical sources. However, there is evidence that nuclei designated as higher order may also contain first order circuits. For instance, some relay cells in pulvinar appear to receive driver inputs from the superior colliculus (Kelly *et al.*, 2003), and some in the posterior medial nucleus are driven by inputs from the spinal nucleus of the fifth nerve (Mo *et al.*, 2017). In these cases, it still appears that most relay cells of these nuclei are higher order in terms of their driving inputs, but this proviso must be clear, and for this reason, we often refer to higher order thalamic "relays" (which relates to relay cells) rather than higher order thalamic "nuclei."

Although examples are few and mostly limited to the mouse, a suggested pattern for communication between cortical areas is that each direct pathway is paralleled by a transthalamic one (see Fig. 3). Specifically, this pattern in the mouse has been established for the main sensory systems (reviewed in Sherman & Guillery, 2013): primary visual cortex to secondary, both directly and via the pulvinar; primary somatosensory cortex to secondary, both directly and via the posterior medial nucleus; and primary auditory cortex to secondary, both directly and via the dorsal portion of the medial geniculate nucleus. We have just extended this to a sensorimotor example: primary somatosensory cortex to primary motor cortex, both directly and via the posterior medial nucleus (Mo & Sherman, 2017). These observations raise a series of questions:

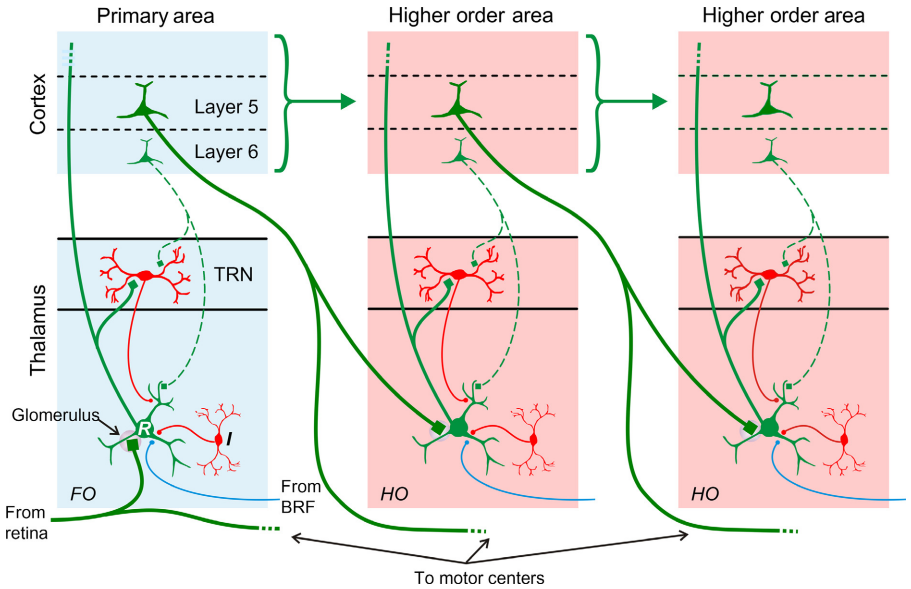

FIG. 3. Schematic diagrams showing organizational features of first and higher order thalamic relays. A first order nucleus (*left*) represents the first relay of a particular type of subcortical information to a first order or primary cortical area. Higher order nuclei (*centre* and *right*) relay information from layer 5 of one cortical area up the hierarchy to another cortical area. This relay can be from a primary area to a higher one (*centre*) or between two higher order cortical areas (*right*). The important difference between first and higher order nuclei is the driver input, which is subcortical for a first order relay and from layer 5 of cortex for a higher order relay. Note that all thalamic nuclei receive an input from layer 6 of cortex, which is mostly organized in a reciprocal feedback manner, but higher order nuclei in addition receive a layer 5 input from cortex, which is feedforward. Note that the driver inputs, both subcortical and from layer 5, are typically from branching axons, with some extrathalamic targets being subcortical motor centres, and the significance this is elaborated in the text. BRF, brainstem reticular formation; FO, first order; HO, higher order; TRN, thalamic reticular nucleus. Redrawn from Sherman (2007).

- How common is this parallel arrangement, or, how often are cortical areas connected only by direct or transthalamic pathways?
- What is different in the nature of the information carried by the direct versus the transthalamic routes?
- Why is one of the connecting pathways relayed via thalamus?

Nature of driver inputs to thalamus: possible relation to efference copies

Before developing our idea that driver inputs to thalamus are related to efference copies, it seems appropriate to first introduce the topic itself of efference copies. A number of excellent reviews exist on this subject (Wurtz & Sommer, 2004; Sommer & Wurtz, 2008; Wolpert & Flanagan, 2010), so it will be only briefly outlined here. Note that "efference copy" and "corollary discharge" are terms that are used interchangeably; for consistency, the former term will be used throughout this paper.

Brief description of efference copies

Simply put, efference copies are necessary to allow an organism to distinguish between changes in the environment independent of the organism and those caused directly by that organism. For instance, when we move our eyes, and we make roughly three saccades per second as we scan a scene, the image of the world rotates across the retina in the opposite direction. However, we do not normally experience a spinning world during eye movements: instead, the visual world seems stable. This is because a copy of the motor message sent to the oculomotor muscles for an eye movement is fed back into the visual processing stream (Fig. 4A), which allows visual processing to nullify the visual stimulation created by the eye movement. This copy of the motor message is the efference copy.

Note that, in order for visual processing to be free of this spurious visual stimulation, the visual signals must be intercepted by the efference copy at an early stage, because the further processing of a spinning world ascends the sensory hierarchy the more difficult it becomes to negate. For this reason, any sensory feedback from the moving eyes would occur too late for such a useful interception to take place. What is needed instead is a predicted model of the expected visual world that would occur without the eye movements, a model against which the visual system can compare actual visual input, and it is this comparison that allows one to disambiguate real environmental events from those created by one's own movements. The efference copy must occur early enough for the forward model to be created.

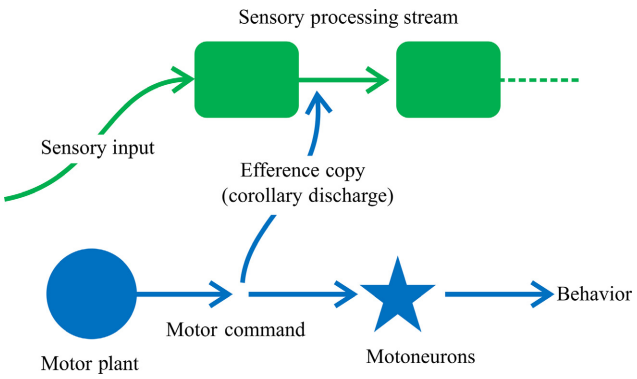

FIG. 4. Conventional view of circuitry for efference copies. A copy of a motor command, generated somewhere between the site of initiation of the command and its target motoneurons, is fed back into the early stages of sensory processing so that sensory signals directly related to the upcoming movement can be accounted for.

Such efference copies are a *sine qua non* for any organism with reasonably complex behaviour. The need for such a neuronal capacity was theoretically evident at least as early as the nineteenth century (e.g., Helmholtz, 1866). However, it was not until 1950 that efference copies were experimentally demonstrated independently in flies (von Holst & Mittelstaedt, 1950) and fishes (Sperry, 1950). Not only does this support the notion that efference copies must be ubiquitous in behaving organisms, but it also suggests that this feature evolved quite early in the natural history of life on earth.

Branching axons as bases for efference copies

Branching axons are pervasive in the central nervous system. One feature this would seem to provide is the ability to distribute the exact same message in the form of the same pattern of action potentials to numerous postsynaptic targets (Goldfinger, 2000; Huguenard, 2000; Zhou & Chiu, 2001). This does not mean that the postsynaptic responses are identical in all the target neurons, because synaptic properties vary widely, but it does suggest that branching axons are a particularly efficient and error-free means to produce multiple, exact copies of a message to multiple targets.

Figure 5 illustrates how branching axons are a plausible neuronal substrate for efference copies. Cajal (1911) demonstrated over a century ago that all afferent axons entering the spinal cord branch, with one branch innervating the spinal grey matter, and the other, heading upstream to the brain (Fig. 5A). Figure 5B shows how a modern textbook might illustrate this. The branch targeting the spinal grey matter can be regarded as sending a message to motoneurons, or, in other words, providing a motor command. The branch heading towards the brain is conventionally viewed as carrying sensory information, such as a change in joint position or skin indentation. However, because of the branching, the message heading towards the brain is an exact copy of that headed for motoneurons. This means that it is an exact copy of a motor message, and this is a nice definition of an efference copy.

This interpretation of Fig. 5B indicates that the message carried upstream by the axon branch headed to the brain does double duty, serving as both a sensory message and an efference copy. One way to think about it is this: the branch headed to the brain branches further and innervates several cell groups, one involved in processing the sensory message, and another, the efference copy.

Axon branching and thalamic driver inputs

It is interesting in the context of Fig. 5 that many and perhaps all of the driving inputs to thalamus, both first order and higher order, arrive via branching axons (see Fig. 3). An important proviso to this statement is that, whereas the documented examples of driving afferents to thalamus are indeed carried by branching axons, there are still relatively few such examples. The obvious reason for so few examples is the technical difficulty in clearly documenting branching axons from source to target.

Three main approaches have been used to identify such branching, and each has serious limitations. The first approach is to apply antidromic activation from multiple sites while recording from a single neuron. This approach is rarely applied to test for branched axons, mostly because of the likelihood of false negatives: failure to find multiple sites for antidromic activation could be simply because of failure to stimulate the correct target zone(s). The second is an

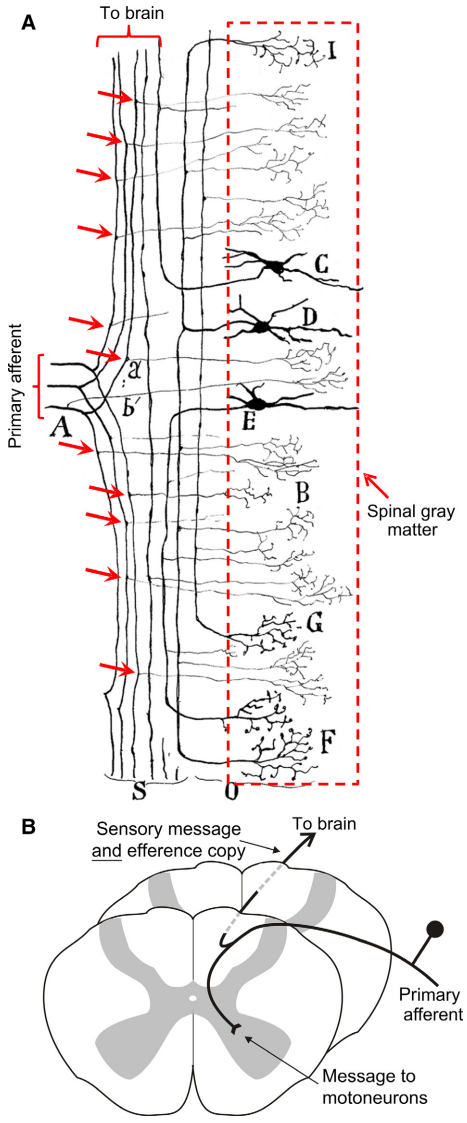

FIG. 5. Branching axons. A: Classic illustration from Cajal (1911) showing primary axons entering the spinal cord and branching to innervate the spinal grey matter and brain areas. The red arrows indicate branch points. Thanks to Javier deFelipe for providing this image. B: Schematic interpretation of A. Redrawn from Sherman (2017).

analogous anatomical approach, which is to label a neuron from different retrograde tracers placed in several sites, but this, too, suffers from false negatives due to failure to label the correct target zone(s). The third technique is orthograde tracing of single labelled axons, but there are serious flaws here as well. One such approach is to apply Golgi staining, but this is notoriously unreliable, and one cannot count on complete labelling of processes or cell types of interest. The most reliable approach does involve tracing single axons, but only after intracellular labelling of single cells *in vivo*, but the degree of difficulty to achieve this is so great that it is rarely used. For these reasons, orthograde labelling has not been systematically applied to detect branching within thalamic and cortical circuits, including thalamic afferents. There is nonetheless enough scattered evidence to make the case that driver afferents to thalamus frequently, and perhaps always, branch and thereby also target other subcortical sites.

Figure 6 shows various examples of this. This includes first order relays, involving both intracellular staining of single axons (Fig. 6A) and a Golgi study from Cajal (Fig. 6B), as well as higher order relays involving staining of single axons (Fig. 6C). What is particularly interesting in these and other examples is the identity of many of the extrathalamic targets of these axons, because these can be regarded as motor control centres. For instance, retinogeniculate axons branch to innervate midbrain sites involved with head and eye movements, pupillary control and focusing (Fig. 6A). Inputs to the ventral anterior/ventral lateral nuclear complex of the thalamus from cerebellar nuclei branch to target also the red nucleus and midbrain reticular nuclei, sources of the rubrospinal and reticulospinal pathways (Fig. 6B). Figure 6C shows the branching of a layer 5 cell from motor cortex: the axon innervates thalamus (blue dashed perimeter) but also branches to innervate brainstem motor sites in addition to the spinal cord itself (red arrows).

Just as the ascending branch of the afferent in Fig. 5 can be considered to be carrying an efference copy, so can the examples of inputs to thalamus illustrated in Fig. 6. And just as the message carried by the ascending branch in Fig. 5 can also be thought of as having two meanings—sensory and efference copy—so can the message carried by inputs to thalamus. Thus, for instance, retinogeniculate inputs can inform cortex via the lateral geniculate nucleus about a new visual stimulus as well as the possible eye movement elicited by that stimulus; and higher order thalamic relays can pass information up the cortical hierarchy both about general computations carried out by lower cortical areas and motor commands sent out by those lower areas.

As noted above, evidence for branching axons is relatively sparse due to technical difficulties of obtaining such data, and therefore examples of driving inputs to thalamus involving branching axons are few in number. The possibility exists that many such inputs do not involve axons that branch to innervate extrathalamic targets, although such examples have not yet been clearly documented, and it is also the case that branching axons do not necessarily mean that the message carried to thalamus is an efference copy. Nonetheless, more evidence is clearly needed to establish the pattern of driver input to thalamus with regard to this issue.

Efference copies from an evolutionary perspective

As noted above, efference copies must have evolved very early in biological history, because they are needed for any organism with complex behaviour. We can thus assume that our earliest vertebrate ancestors, which operated chiefly through spinal circuits, had efference copies. One plausible substrate for an efference copy in such a primitive vertebrate is shown in Fig. 5B. As evolution added bulbospinal control centres (e.g., via rubrospinal, tectospinal, and reticulospinal pathways), which provide more sophisticated behavioural control, additional efference copy circuits must have evolved with these supraspinal centres. We may regard the final evolutionary addition to neuronal substrates of behavioural regulation being that of corticofugal control.

However, the evolution of cortex did not parallel the creation of a motor plant to which cortex has privileged access. Instead, the only way cortex can influence behaviour is by acting through older evolutionary centres, such as bulbospinal pathways, and, in the case of pyramidal tract neurons, more directly with spinal circuits. It is also worth emphasizing that this ability of cortex to affect behaviour is carried solely by layer 5 corticofugal axons, which represent the only useful way in which cortex can influence the rest of the neuraxis and thus behaviour.

One feature of neuronal evolution we think we understand is that successful brain circuits, once they evolve, are rarely discarded.

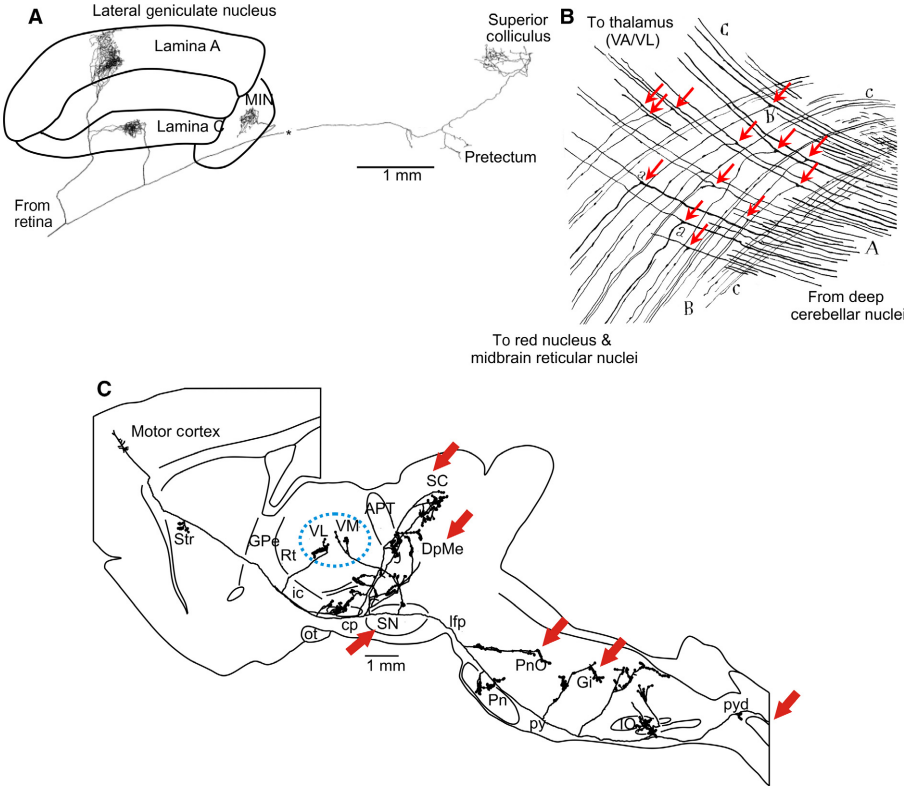

FIG. 6. Examples of branching axons innervating thalamus. A: Example from retinogeniculate axon of cat; redrawn from Tamamaki *et al.* (1994). B: Example of cerebellar inputs to the ventral anterior and ventral lateral nuclei (VA/VL); redrawn from Cajal (1911), and thanks to Javier deFelipe for providing this image. C: Branching axon from layer 5 pyramidal tract cell of rat motor cortex; redrawn from Kita & Kita (2012); tracing of reconstruction generously supplied by H. Kita. Branches innervating thalamus are indicated by the dashed blue circle, and brainstem motor regions are indicated by red arrows. cp, cerebral peduncle; DpMe, deep mesencephalic nuclei; Gi, gigantocellular reticular nucleus; GPe, globus pallidus external segment; ic, internal capsule; IO, inferior olive; Pn, pontine nucleus; PnO, pontine reticular nucleus, oral part; py, medullary pyramid; pyd, pyramidal decussation; Rt, thalamic reticular nucleus; SC, superior colliculus; SN, substantia nigra; Str, striatum; VL, ventrolateral thalamic nucleus; VM, ventromedial thalamic nucleus.

Thus, our central nervous system is a rather messy concatenation of hierarchically related circuits that reflect our evolutionary history. Thus, much movement control involves spinal circuits that can act on their own via spinal reflexes, and these circuits can be influenced or controlled by later evolved bulbospinal pathways, and these bulbospinal pathways can, in turn, be influenced by layer 5 cortical outputs, which represent the newest evolved motor command system. This picture of evolution and the need for efference copies related to movement commands indicates that each of these evolutionary stages included efference copies. We do not know precisely what their anatomical substrates are, but a few plausible examples help illustrate what we believe is an unappreciated problem. Figure 5B illustrates an efference copy pathway that credibly evolved during the appearance of our earliest vertebrate ancestors. As bulbospinal and, later, corticofugal motor pathways evolved, these must also have included efference copies. The result is not consistent with the simplistic view that there is a single efference copy associated with each sensorimotor command, but rather multiple messages relating to efference copies at various hierarchical and evolutionary levels associated with motor commands. Thus, when layer 5 cortical outputs generate a behavioural response, efference copies could be generated at cortical, brainstem, and spinal levels. How does the brain deal with multiple efference copies, especially given the possibility that not all are associated with actual behaviour? For example, a layer 5 output from cortex might generate an efference copy, but if that output fails to activate its brainstem or spinal targets, no actual behaviour will ensue. The answer to this question is presently unavailable, but the question itself is worth pondering.

Efference copies and cortical circuitry

Much of our behaviour is not under cortical control. Obvious examples include normal breathing and other reflex activity. Furthermore, everyday common activities, such as chewing gum or walking a familiar path, are probably not guided by cortical outputs. Cortex likely provides major control in situations that require attention and concentration, such as learning a new task or navigating through a dangerous situation. Under such conditions when cortex is in control of behaviour, the need for efference copies associated with these cortical outputs arises. Thus, as cortical areas generate layer 5 outputs to influence behaviour, these outputs must be associated with efference copies that are fed back into further cortical processing to disambiguate effects of the new behaviour from environmental events. What are plausible circuits for these cortically related efference copies?

Figure 7 illustrates the problem via two proffered examples of cortically related efference copies. Figure 7A represents a common view of efference copies: that they are generated only at the end of a circuit controlling motoneurons. In this case, the efference copy would be generated via some spinal neurons innervating motoneurons. (As motoneurons have no axonal branches innervating the central nervous system, these cells cannot contribute to efference

copies.) The problem is getting this efference copy information back into appropriate cortical circuits in a timely fashion, which, in turn, means involving a thalamic relay. The spinothalamic pathway can be ruled out as a possibility, because the cells of origin in the dorsal horn have no known cortically influenced inputs. Thus, any yet-to-be-discovered route through thalamus must involve at least two synapses prior to the thalamic relay, and this would appear to make such an input too late to create the forward model in cortex associated with efference copies. Figure 7B, which illustrates our suggestion, is that efference copies are produced from branches of the very same layer 5 cells generating the motor commands, and these branches are passed through thalamic circuitry up the cortical hierarchy. The anatomical basis for this is well established, and it is difficult to imagine other plausible anatomical substrates for timely efference copies required by cortex in control of behaviour.

Efference copies and the thalamus

A glance at the scheme of Fig. 7B should make clear that the branch of the layer 5 axon intended as an efference copy could directly innervate the higher cortical area without a thalamic relay. This raises the question: Why is this information route directed through a thalamic relay? This may be related to the problem raised in the previous section that evolution has left us with multiple efference copies at various hierarchical levels, some of which might not actually be related to eventual movements. This would require a means of negating or blocking such inappropriate efference copies. Just as a lack of efference copies associated with movement is a problem, so would the opposite. This may offer a reason for passing the efference copies in cortex through the thalamus, because the thalamus can act as a gate capable of being closed by powerful GABAergic inputs, and such inputs do exist (e.g., Kultas-Ilinsky *et al.*, 1985; Barthó *et al.*, 2002; Wanaverbecq *et al.*, 2008).

Concluding comments and questions

Ray and I engaged in a good deal of speculation, much of which we published. It seems useful to separate the new facts we highlighted from the speculation, which I would like to think of as still useful hypotheses worthy of testing.

Glutamatergic drivers and modulators

Regarding our ideas about drivers and modulators, it seems a clear fact that a classification of glutamatergic pathways in both thalamus and cortex reveals at least two distinct types of underlying synaptic input (see Fig. 2). More types may be discovered as the classification is extended to more neuronal regions. So whereas the classification is clear enough, the question about the functional significance thereof is anything but resolved. Based initially on knowledge of the functional circuitry of thalamus, we hypothesized that drivers are the main conduits of information, and glutamatergic modulators act like classical ones (e.g., ACh and 5-HT) to affect various aspects of how driver input is processed; we also suggested that what is unique about glutamatergic modulators is their high degree of topography compared to the classical ones.

This hypothesis seems pretty solid with regard to thalamic circuitry. The lateral geniculate nucleus serves as an example. The input with driver properties is retinal, and it has been clear for decades that this glutamatergic input carries the main information for geniculate relay cells to pass on to cortex. The other main glutamatergic input to these cells, which is from layer 6 of cortex, clearly has a different function, and as noted above, that function is to affect the detailed nature of retinogeniculate transmission, including gain control and switching between burst and tonic modes of firing for the relay cells. However, cortical circuitry is much more complicated, and although we consider the idea that drivers and modulators in cortical circuitry subserve the same general functions they do in thalamus, rigorous and direct experimental tests of this hypothesis remain wanting.

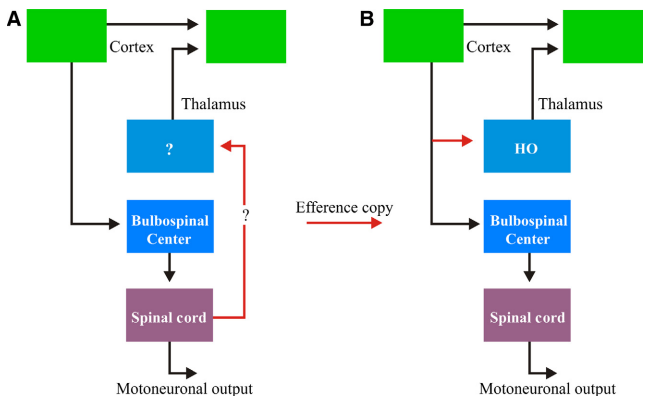

FIG. 7. Schematic diagrams of presumed circuits for efference copies related to cortically initiated motor commands. A: Conventional view. B: Our alternative view. See text for details.

Higher order thalamic relays and efference copies

The idea that at least some if not all higher order thalamic relays represent a link in transthalamic corticocortical networks seems quite well established from anatomical and physiological data. There are a number of key questions here, such as how common these circuits are and how they relate to direct corticocortical circuits (see below for details), but their presence seems well established.

What is not at all clear is the functional significance of these transthalamic pathways. However, another anatomical fact offers some insight. That is, most if not all of the driving inputs to thalamic relays cells, both first order and higher order, arrive via branching axons. This means that whatever message is being sent to thalamus to relay to cortex is copied to other spinal or brainstem centres. This is in contrast to direct corticocortical projections, which do not generally involve axons with subcortical branches (Petrof *et al.*, 2012). Furthermore, some of the extrathalamic branches of these driving inputs seem to target brainstem, and sometimes spinal, motor centres. This led to our hypothesis that, because the messages relayed by cortex appear to be copies of messages targeting motor centres, these serve as efference copies. It is important once again to separate fact from hypothesis: the anatomy of branching driving inputs to thalamus and their extrathalamic targets are well-documented observations, but their meaning suggested by us remains pure speculation.

Questions arising

Ray and I often finished our writing efforts with questions that we regarded as interesting and arising from issues that we raised. It thus seems appropriate to finish this piece the same way:

- What is the functional significance of the glutamatergic driver/modulator classification, especially for cortical circuitry?
- Do other classes of glutamatergic inputs exist beyond driver and modulator?

- How frequently are direct corticocortical pathways paralleled by transthalamic ones? Or, how often are cortical areas connected by just one or the other?
- What is different in the information content of direct versus transthalamic corticocortical pathways?
- Why are transthalamic pathways filtered through thalamus?
- What is the significance of the branching of driver inputs to thalamus?
- Feedforward transthalamic pathways have been identified (e.g., V1 through pulvinar to V2), but do feedback such circuits also exist (e.g., V2 through pulvinar to V1)?
- Do any driving inputs to thalamus not involve branched axons, and if so, how do their messages differ from those carried by branched axons?
- How do efference copies generated in response to motor commands issued by cortex coordinate with those generated by subcortical circuits?

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Conflict of interest

There are no conflicts of interest.

Author contributions

This article was written solely by the author.

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