Thalamocortical Dysrhythmia

Synonyms

TCD

Definition

A pathophysiological chain reaction at the origin of neurogenic pain. It consists of: 1) a reduction of excitatory inputs onto thalamic cells, which results in cell membrane hyperpolarization, 2) the production of low-threshold calcium spike bursts by deinactivation of calcium T-channels, discharging at low (theta) frequency, 3) a progressive increase of the number of thalamocortical modules discharging at theta frequency, and 4) a cortical high frequency activation through asymmetric corticocortical inhibition. These events have been documented by thalamic and cortical recordings in patients suffering from peripheral and central neurogenic pain.

► Thalamotomy for Human Pain Relief
► Thalamus, Dynamics of Nociception

Thalamocortical Fibers

Definition

Axons with cell bodies located in the thalamus and terminations in the cortex.

► Corticothalamic and Thalamocortical Interactions

Thalamocortical Loops and Information Processing

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Synonyms

Cortical Information Flow; Corticortical Pathways

Definition

Until recently, communication among related cortical areas (e.g., those for somatosensation and pain) was thought to involve direct connections. We (Sherman and Guillery 2001; Sherman and Guillery 2002; Guillery and Sherman 2002a; Guillery and Sherman 2002b) suggest a radically new view in which many and perhaps all corticocortical communications involve a cortico-thalamo-cortical route.

Characteristics

To understand how information is processed in a thalamocortical system, it is important to identify and follow the route of information transfer. A recent suggestion based on thalamic circuitry is that not all pathways are equivalent, but instead can be divided into "drivers" which are the information bearing pathways and "modulators" which serve to modulate the flow of information rather than transmitting it. How this might apply to cortical processing in general and cortical processing of pain more specifically is best explained by considering how this idea has led to important changes in our thinking of thalamic circuitry.

Drivers and Modulators

Figure 1 shows the basic circuit of the thalamus, which varies only slightly among thalamic relays. As argued previously, the inputs to relay cells can be divided into two basic types, "drivers" and "modulators" and these differ on a number of different morphological and functional grounds that are briefly summarized in Table 1 (for details, see Sherman and Guillery 2001, 2002; Guillery and Sherman 2002a). The first pair of listed differences are properties limited to thalamus, but the remainder represent criteria that can be applied anywhere in the central nervous system. The drivers are the input that brings the information to be relayed. Examples are retinal input to the lateral geniculate nucleus, medial lemniscal input to the ► ventral posterior nucleus and, as noted below for some thalamic relays, layer 5 input from cortex. The modulators are everything else and their main function is to control the level and type of information relayed from drivers through thalamus to cortex. Examples are the local ► GABAergic cells (i.e., interneurons and cells of the thalamic reticular nucleus), feedback from cortical layer 6 and a projection from the brainstem reticular formation. Drivers represent relatively few of the synaptic inputs to relay cells (only about 5–10%), but their synapses are relatively powerful. The other 90–95% of synapses onto relay cells are divided roughly equally among modulatory inputs from local GABAergic cells, from cortical layer 6 and from the brainstem. The modulators require the vast majority of inputs for many subtle roles that affect the relay of driver inputs (Sherman and Guillery 2001, 2002; Guillery and Sherman 2002a).

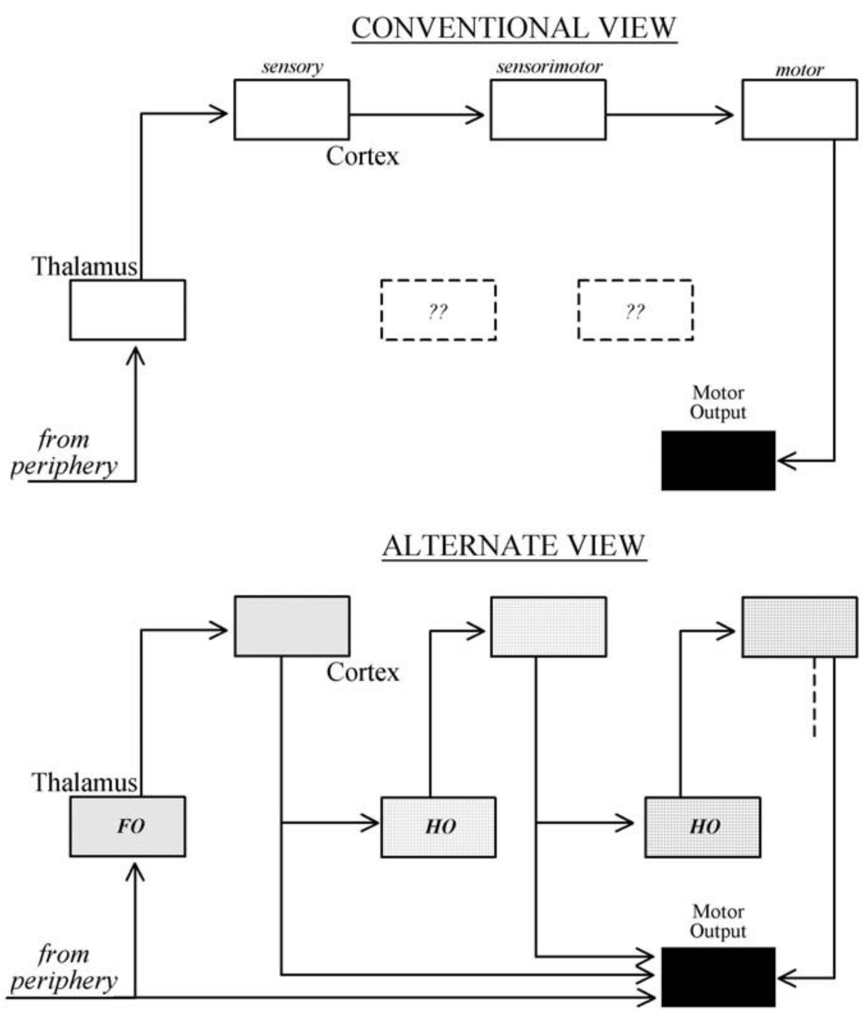
The main difference between thalamic relays is the origin of the driver input; the modulators are basically similar throughout thalamus, although there is some variation (Jones 1985; Sherman and Guillery 2001).

The understanding that inputs to relay cells can be divided into drivers and modulators and that the former largely define the function of a thalamic relay has implications that may extend beyond thalamus (see also below). Thus the ► lateral geniculate nucleus is largely defined as a relay of retinal information. It is important to understand that consideration of anatomical information

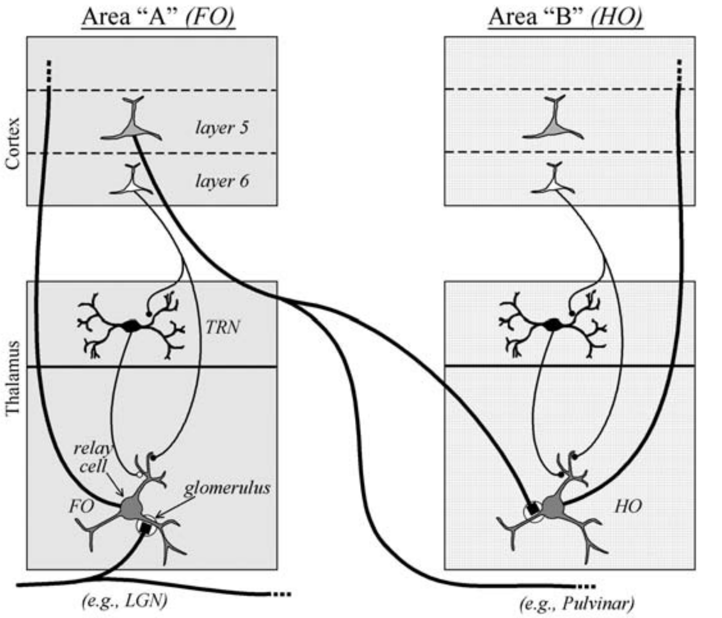
thalamus is a corollary of motor commands and it is these motor commands that serve as the basis of perceptual information acted upon and further elaborated by cortex (Guillery and Sherman 2002 a, b; Guillery 2003).
It is also worth noting that, as sufficient information regarding various thalamic relays develops regarding the division into first order and higher order, the large majority of thalamus seems to be devoted to higher order relays.

Role of Thalamus in Corticocortical Communication

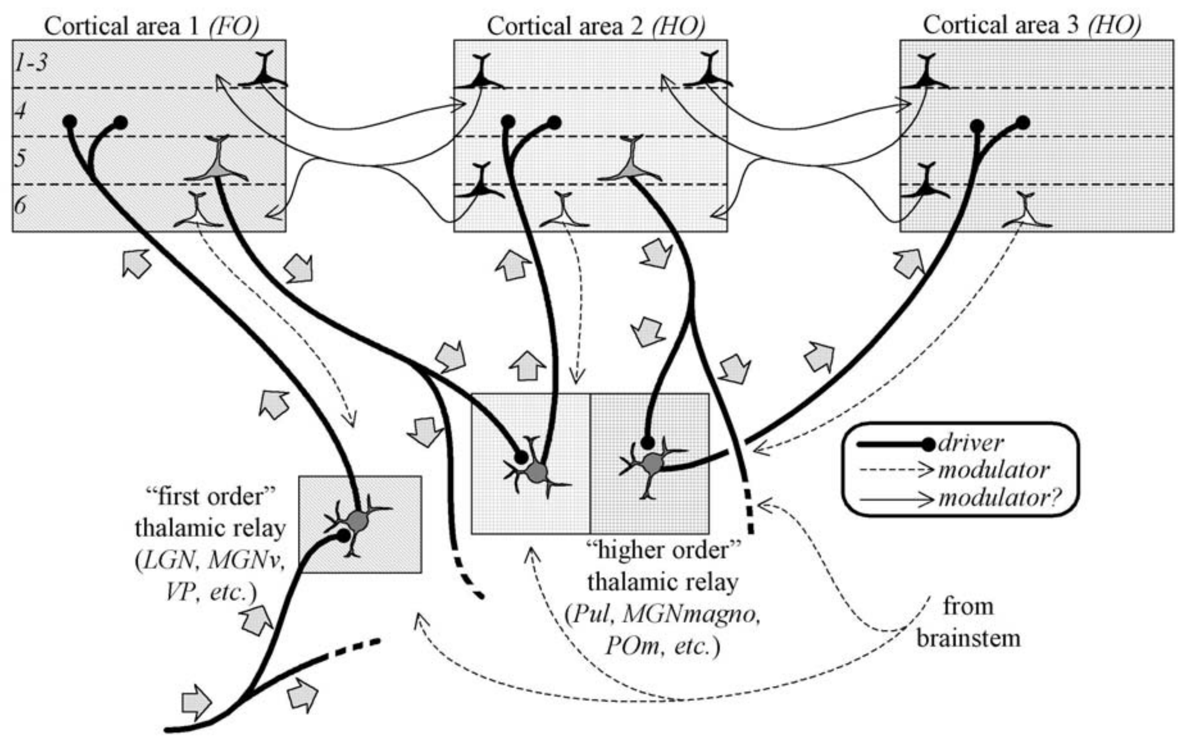
Figure 3 summarizes the major implication of this division of thalamic relays into first order and higher order for cortical functioning. Information of a particular sort first reaches cortex *via* a first order relay; this can apply to primary information about vision, sounds, pain, etc. Further cortical processing of this primary information is based on cortico-thalamo-cortical pathways involving higher order thalamic relays. This view of corticocortical processing has the interesting feature that any new information reaching a cortical area, whether initiated subcortically or in another cortical area, benefits from a thalamic relay. Such benefits are beyond the scope of this essay to cover, but the reader can learn more of this from other sources (Sherman and Guillery 2001; Guillery and Sherman 2002a).
To place this scheme in the proper perspective, it is important to appreciate that most prevailing conceptions about functioning of cortical areas are based on direct connections between areas. For instance, the best studied is visual cortex, which is divided into more than 30 discrete areas in humans and the detailed scheme of functional organization is based almost entirely on the pattern of direct corticocortical connections, with no place for thalamus (Van Essen et al. 1992; Kandel et al. 2000). A similar view dominates thinking about the organization of somatosensory cortical areas responsible for the cortical processing of pain. Understanding how cortical areas process information requires first identifying the routes of information and, if the driver/modulator distinction holds for cortical pathways as it seems to in thalamus, it then becomes essential to distinguish among the direct corticocortical pathways those that are drivers from those that are modulators. As it happens, the cur-



Thalamocortical Loops and Information Processing, Figure 4 Conventional (upper) versus alternate (lower) views of cortical processing.

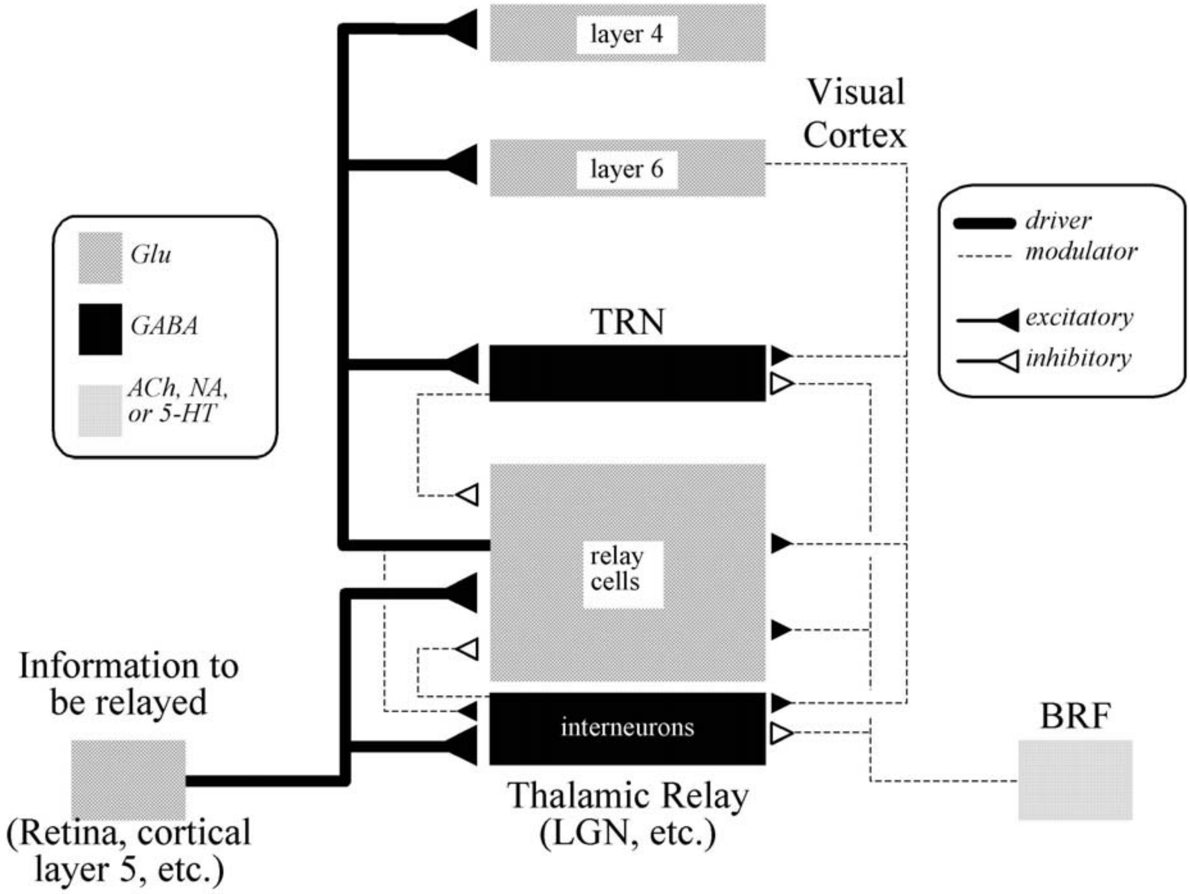


Thalamocortical Loops and Information Processing, Figure 2 First order (FO; left) and higher order (HO; right) thalamic relays. For simplicity, connections to relay cells from interneurons and brainstem are omitted. "Glomerulus" refers to a complex synaptic zone that is ubiquitous to thalamus and that is often associated with driver input.



Thalamocortical Loops and Information Processing, Figure 3 Involvement of higher order thalamic relays in corticocortical communication. For simplicity inputs from interneurons and cells of the thalamic reticular nucleus omitted. Abbreviations as in Fig. 1 plus: MGNv, ventral region of medial geniculate nucleus; MGNmagno; magnocellular region of medial geniculate nucleus; POm, posterior medial nucleus; VP, ventral posterior nucleus.

afferents, both subcortical to first order relays and from layer 5 for higher order relays, are branches of axons that also innervate an extrathalamic target, which tends to be "motor" in nature; this is true for many and perhaps all driver inputs (for details, see Guillery and Sherman 2002 a, b; Guillery 2003). For instance, many or all retinal afferents to the lateral geniculate nucleus branch to also innervate midbrain structures associated with control of pupil size, eye movements, etc and many layer 5 afferents to higher order thalamic relays also innervate many levels of the brainstem and may extend input to spinal levels. It is as if the information relayed to cortex through



Thalamocortical Loops and Information Processing, Figure 1 Schema of inputs to thalamic relay cells. Abbreviations: 5-HT, serotonin; ACh, acetylcholine; BRF, brainstem reticular formation; GABA, gamma-aminobutyric acid; Glu, glutamate; LGN, lateral geniculate nucleus; NA, noradrenalin; TRN, thalamic reticular nucleus.

alone can obscure this. For the lateral geniculate nucleus for instance, only 5-10% of synapses onto relay cells derive from retina and roughly one third derive from brainstem. If we had only these anatomical data, most of us would conclude that the lateral geniculate nucleus relayed brainstem information and that retinal input provided some obscure, minor function. In other words, we would badly misconstrue this thalamic relay.

First and Higher Order Relays

Thus identifying the driver is a major key in determining the role played by a thalamic relay. For instance, we define the role of the ► lateral geniculate nucleus based on its relay of retinal axons and that of the ventral posterior nucleus based on its relay of ► medial lemniscus axons. However, until recently, the role played by many thalamic relays remained a mystery, because it was not clear what was being relayed. We used to think that the role of the thalamus was to relay subcortical information to cortex and for large regions of thalamus, such as much of the pulvinar, it was not clear what was the subcortical source being relayed.

However, the recent realization that drivers for many thalamic relays originate in layer 5 of cortex led to a division of thalamus into "first order" and "higher order" relays, and this is summarized in Fig. 2 (Sherman and Guillery 2001, 2002; Guillery and Sherman 2002a). First order relays transmit to cortex a particular type of information (e.g. retinal) for the first time, whereas higher order relays are involved in further transmission of such information between cortical areas. The higher order relay can be between a first order and higher order cortical area (as shown in Fig. 2) or between two higher order cortical areas (not shown). Higher order relays have been identified for the major sensory systems, the pulvinar for vision, the posterior medial nucleus for somatosensation (and thus for pain) and the magnocellular division of the medial geniculate nucleus for hearing. Other examples of higher order relays have also been identified (see Sherman and Guillery 2001, 2002).

Several features from Fig. 2 bear further emphasis. All thalamic relays receive a modulatory input from layer 6 of cortex that is mainly feedback, whereas only the higher order relays receive in addition a layer 5 cortical input and this is feedforward. Note also that the driver rent views of cortical organization consider only direct corticocortical connections that have been identified almost entirely with anatomical techniques and an implied assumption that needs to be made explicit is that all more or less contribute equally, in a sort of anatomical democracy, to information flow. This same logic applied to the thalamus would produce the misconception that the lateral geniculate nucleus relayed brainstem, not retinal, inputs to cortex (see above).

Given the nature of thalamocortical inputs, which have the morphological and functional characteristics of drivers, it seems very likely that the cortico-thalamo-cortical pathways shown in Fig. 3 are important information routes. It follows that understanding the relationships of cortical areas in various functional zones (e.g. visual, somatosensory and auditory among others) will require mapping out of all of the cortico-thalamo-cortical pathways involving higher order thalamic relays.

What, then is the function of the direct corticocortical pathways? An answer to this important question requires identifying these pathways, one by one if necessary, for function as driver or modulator. One extreme possibility is that all of these pathways are modulators. However, even if some are drivers, there is an important distinction to be made between such putative information routes and those involving higher order thalamic relays. That is, the former involve information that remains strictly within cortex, whereas the latter involve information, perhaps involving motor commands, that is shared with various subcortical centers.

Summary and Conclusions

To understand the implications of the proposal put forward here for the role of thalamus in corticocortical communication, it might be helpful to contrast it with the conventional view, and this is done in Fig. 4. In the conventional view (Fig. 4, upper), sensory information is relayed from the periphery by thalamus to a primary sensory cortical area. From there, the information is processed strictly within cortex, eventually *via* sensorimotor areas to motor areas and finally this leads to a motor output. Note that, in this view, the only role for thalamus is to get raw information to cortex in the first place and that most of thalamus, which we call higher order relays, has no specific role to play. In the alternate view (Fig. 4, lower) offered here, information relayed to cortex is, from the very beginning, corollary to motor commands and further corticocortical processing involves higher order thalamic relays of continuously elaborated and updated motor commands. Thus thalamus not only gets information to cortex in the first place but also continues to play an essential role in corticocortical communication.

This has important implications for cortical functioning generally and also for cortical processing of pain information more specifically. That is, the higher order thalamic relays involved in pain processing could be key. The best candidate for the higher order thalamic relay of pain information would be the posterior medial nucleus, which lies mostly medial to the ventral posterior nucleus, most of which is the first order somatosensory relay. We clearly need a better understanding of how pain is processed by somatosensory cortex and the purpose of this essay is to provide a different theoretical framework that might fruitfully guide further research through this topic.

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Thalamocortical Module

Definition

Anatomofunctional entity comprising of thalamic cells and their cortical partners, interconnected by thalamocortical and corticothalamic projections and sustaining perceptual, motor and cognitive hemispheric functions. The thalamocortical loop is accompanied by a shorter thalamoreticulothalamic loop. Every module may be subdivided in a specific, or content subpart, providing the substrate for the integration of a given function, and a non-specific, or context subpart, dealing with the interactions between functional domains.

► Thalamotomy for Human Pain Relief

Thalamocortical Neurones

Definition

Neurones located within the thalamus and projecting directly to the cerebral cortex.

► Spinothalamic Projections in Rat