Synchrony in the Interconnected Circuitry of the Thalamus and Cerebral Cortex

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The corticothalamic system is organized to play a key role in synchronizing the activities of thalamic and cortical neurons. Its synapses dominate the inputs to relay cells and to the GABAergic cells of the reticular nucleus; its organization in focused and diffuse projections promotes both coherent activity of relay neurons and the spread of activity across the cortex and thalamus. The capacity of relay neurons to operate in voltage-dependent tonic or burst mode permits corticothalamic inputs to directly excite the relay cells or indirectly inhibit them via the reticular nucleus. This enables the corticothalamic projection to synchronize high- or low-frequency oscillatory activity, respectively, in the thalamo–corticothalamic network. Differences in the subunit composition of AMPA receptors at synapses formed by branches of the same corticothalamic axon in the reticular nucleus and dorsal thalamus are an important element in the capacity of the cortex to synchronize low-frequency oscillations in the network. Intrinsic voltage-gated calcium channels of different kinds expressed in the relay neurons form a substrate for corticothalamic interactions with the relay cells that promote high- or low-frequency oscillations. Focused corticothalamic axons arising from layer VI cortical cells and diffuse corticothalamic axons arising from layer V cortical cells, in conjunction with the core and matrix cells of the dorsal thalamus, form a substrate for synchronization of widespread populations of cortical and thalamic cells during high-frequency oscillations that underlie discrete conscious events.

Key words: **thalamus; thalamocortical; corticothalamic connections; core and matrix cells; oscillations; electroencephalogram; intrinsic properties**

Introduction: Types of Thalamic Nuclei

It was once thought that only the principal sensory nuclei of the thalamus received subcortical input and projected to the cerebral cortex; others, such as the ventral anterior and intralaminar nuclei, were thought not to project to the cortex. It is now known that every nucleus in the dorsal thalamus receives some kind of subcortical input and projects to the cerebral cortex. The thalamus also has substantial projections, unknown to earlier investigators, to the striatum, amygdala, and certain other basal telencephalic centers. We can now divide the dorsal thalamic nuclei into those that project to the cerebral cortex and those (primarily the intralaminar nuclei) that project to the cortex and striatum. However, those projecting to the cortex do so in different ways. The classical, topographically organized projection arising in the sensory relay nuclei (the lateral geniculate, medial geniculate, and ventral posterior nuclei) and focused on layer IV of a single cortical area (or at most a pair of areas) is the least common. Many other thalamic nuclei project upon several cortical areas and often do so in a rather diffuse manner, the fiber terminations commonly ending in one or more of several layers other than layer IV. Cortical layers I and VI are the most common that receive diffuse inputs but no layer is exempt from a thalamic input: it depends on the area of cortex in

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which the layer is situated and on the thalamic nucleus or nuclei projecting to it (reviewed by Jones [2007][1]). Further complexity has been added by the accumulating evidence that many nuclei of the dorsal thalamus can contain two or more populations of cells, one projecting in a focused manner upon a single cortical area and others projecting diffusely upon several areas, often with terminations in different layers of the cortex. In this lies a key to understanding how the thalamus is able to play a key role in effecting synchrony of the interconnected thalamo–corticothalamic network and probably of the cortico–basal ganglia–thalamocortical network as well.

The Core and Matrix of Thalamic Organization

Information that has come from the identification of thalamic relay cells in primates and certain other species in terms of expression of three common calcium-binding proteins, parvalbumin, 28-kDa calbindin, and 29-kDa calretinin, has resulted in a new view of the dorsal thalamus and its cortical projection in primates in terms of a core and matrix pattern (Fig. 1). In this scheme[2,3]) (see also several reviews by the author[1,4,5]), a diffuse matrix of calbindin cells is found throughout all dorsal thalamic nuclei, while upon the matrix, in some nuclei only, particularly the major sensory and motor relay nuclei, a core of parvalbumin cells is imposed. Although the biochemical or metabolic significance of this differential expression of calcium-binding proteins is unknown, this differential expression is associated with distinct patterns of projection of the two classes of relay cells: the parvalbumin cells are innervated by the major subcortical sensory and motor pathways and project with a high degree of topographic order on a single cortical area, the axons terminating in middle layers of the cortex (IV and deep III); the calbindin cells of the matrix customarily receive subcortical inputs from less-well-defined subcortical pathways and project

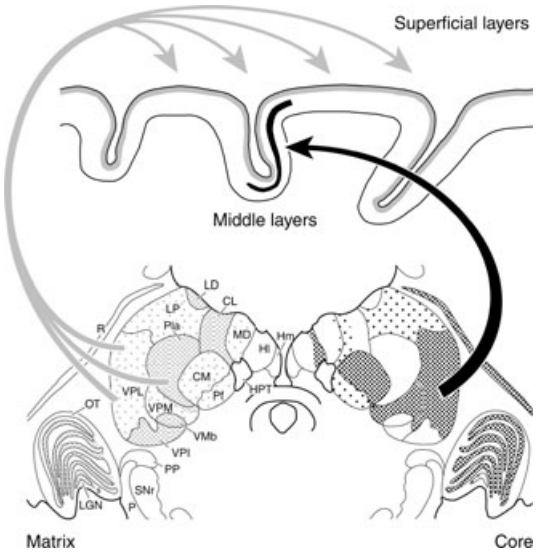

Figure 1. A frontal section through the middle of a macaque monkey thalamus (lower part of the illustration), with the relative distributions and concentrations of calbindin matrix cells (left) and parvalbumin core cells (right) plotted. Densities of dots represent the relative density of each cell type. The upper part of the figure shows schematically the projection of the matrix to superficial layers of the cerebral cortex over a relatively wide extent. Core cells restricted to individual nuclei, here exemplified by the ventral posterior nucleus, project in a topographically ordered manner to middle layers of single cortical fields. (From Jones [2007][1].)

more diffusely upon the cortex, their projection unconstrained by architectonic or functional borders between cortical areas and their axons terminating in superficial layers (I, II, and upper III) (Fig. 1). In the three great sensory relay nuclei, the parvalbumin-rich domain is the target of the medial lemniscus, P and M ganglion cells, and central nucleus of the inferior colliculus, while the calbindin matrix is the target of the spinothalamic system, of the blue-on ganglion cell system, and the less specific auditory pathways arising in the brain stem and reaching the medial geniculate nucleus via the lateral tegumental system of fibers (Fig. 2). Similar parallelism may hold in the motor relay nuclei and in some of the nuclei of the pulvinar. In nuclei and in parts of nuclei from which the parvalbumin core is lacking,

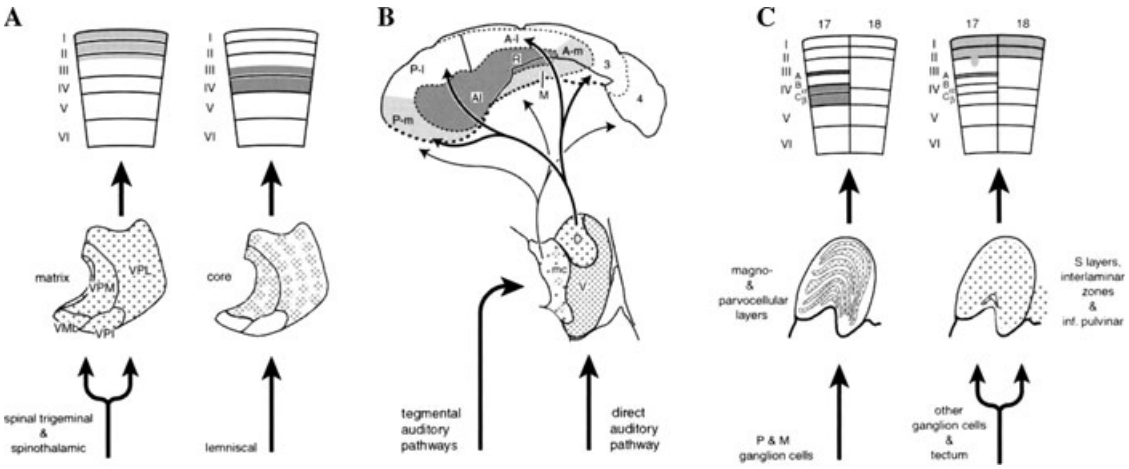

Figure 2. Schematic views of the diffuse and specific subcortical inputs that terminate in the matrix and core compartments of the ventral posterior (**A**), medial geniculate (**B**), and dorsal lateral geniculate (**C**) nuclei of macaque monkeys and the layer-specific and diffuse or focused projections of these compartments to the cerebral cortex. In panels A and C, cortical areas are indicated by schematic vertical sections, with the layers indicated; panel B shows the surface of the supratemporal plane, with the different auditory fields delineated. (Based on Jones [2001][5].)

there is commonly an enhancement of the calbindin population of cells and there is a denser calbindin projection. The intralaminar nuclei are not a homogeneous single entity but contain zones enriched with either calbindin- or parvalbumin-immunoreactive cells. At the cortical level, the parallel inputs via the projections of the calbindin- and parvalbumin-expressing relay cells can predominantly target different areas of the sensory cortex, with the parvalbumin-expressing cells of the medial geniculate nucleus, for example, targeting the primary areas and the calbindin-expressing cells of the matrix targeting mainly the surrounding belt areas. Of greater import, however, are the terminations of the two sets of afferents ending at different laminar levels in the cortex, for this should set up a coincidence-detecting circuit that is important for ensuring thalamocortical synchrony.

Fundamental Thalamic Circuitry

Thalamic relay neurons in all nuclei of all species display a symmetrical, bushy dendritic field that was originally described by Kölliker in the 1890s. This characteristic is only significantly modified in the X-cells in the dorsal lateral geniculate nucleus of the cat, the dendritic fields of which are more elongated and the dendrites of which possess a far greater proportion of dendritic protrusions.

Relay cells share a common synaptic geography.[6–8] Cells in the ventral posterior nucleus and in the dorsal lateral geniculate nucleus of the cat receive approximately 5000–8000 synapses over their whole soma–dendritic membrane. Approximately 44% of these synapses are derived from corticothalamic fibers and are concentrated on secondary and tertiary dendrites. Approximately 16% are derived from medial lemniscal or optic tract fibers and are concentrated on proximal dendrites, the terminals making multiple points of synaptic contact on dendritic protrusions as well as on the shafts of the dendrites. The remaining 40% of synapses are inhibitory and tend to be concentrated on proximal and secondary dendrites and on the soma, and the majority are derived from axons of the reticular nucleus.[9] A small number of inhibitory synapses (~5% of the total) are derived from presynaptic dendrites of intrinsic interneurons.

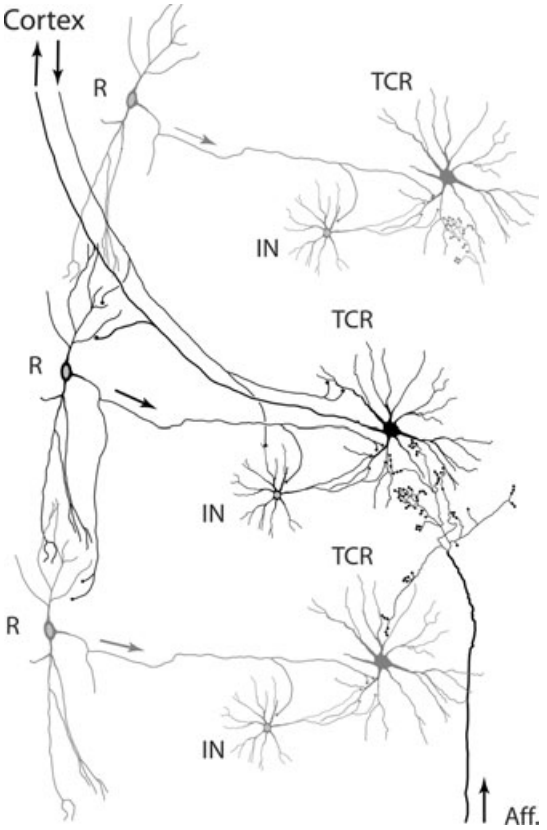

Figure 3. Schematic showing the basic circuitry of the thalamus, which is made up of connections between afferent fibers (Aff), thalamocortical relay cells (TCR), intrinsic interneurons (IN), reticular nucleus cells (R), and the cerebral cortex. (From Jones [2007][1].)

The GABAergic cells of the thalamic reticular nucleus occupy a central place in thalamic circuitry. They are innervated by collateral branches of thalamocortical and corticothalamic fibers as these traverse a sector of the nucleus defined by its connectivity with a particular dorsal thalamic nucleus and its associated cortical area. This bidirectional collateral input to the reticular nucleus and the projection of the reticular nucleus cells in that sector back to the particular dorsal thalamic nucleus form the basis of the fundamental circuit diagram of the thalamus (Fig. 3). Inputs coming to a nucleus of the dorsal thalamus from the periphery or from intrinsic brain structures excite relay neurons, and the collaterals of these neurons' cortically projecting axons excite reticular nucleus cells which, in projecting back to the same nucleus, form an inhibitory feedback connection to the relay cells. Fibers returning to the thalamus from the cortical area to which the dorsal thalamus projects excite, via their collaterals, cells in the same sector of the reticular nucleus, and in this case the projection of the reticular nucleus cells into the dorsal thalamus provides an inhibitory feed-forward to the relay cells. This bidirectional circuitry holds the key to understanding many aspects of thalamic function. The inputs from the reticular nucleus are the only inhibitory inputs to thalamic relay cells in most nuclei of rodents and some other species in which intrinsic interneurons are absent; they outnumber by far the inhibitory dendrodendritic synapses of intrinsic neurons in species in which intrinsic inhibitory neurons are present.

Corticothalamic terminals also predominate on reticular nucleus cells, accounting for nearly 70% of the synapses that these cells receive.[10] The small terminals of the corticothalamic collaterals have a single small postsynaptic density that appears to reflect the presence of a single vesicle release site, and they are distributed in more or less equal numbers over both proximal and distal dendrites of a reticular nucleus cell. The less frequent synapses derived from collaterals of thalamocortical fibers are mainly located on the proximal dendrites of the reticular nucleus cells and, although in the minority, are distinguished by a larger size and by the presence of large, perforated postsynaptic densities indicative of multiple vesicle release sites (Fig. 4). These differences are reflected in the variability, amplitudes, and rise times of unitary excitatory postsynaptic currents induced in these cells by stimulation of the two sets of collaterals.[11,12] GABAergic synapses between reticular nucleus cells, formed by intrareticular collaterals of reticular nucleus cells or by dendrodendritic synapses, are also key features of the circuitry and play a major role in setting up the synchronous action of reticular nucleus cells.

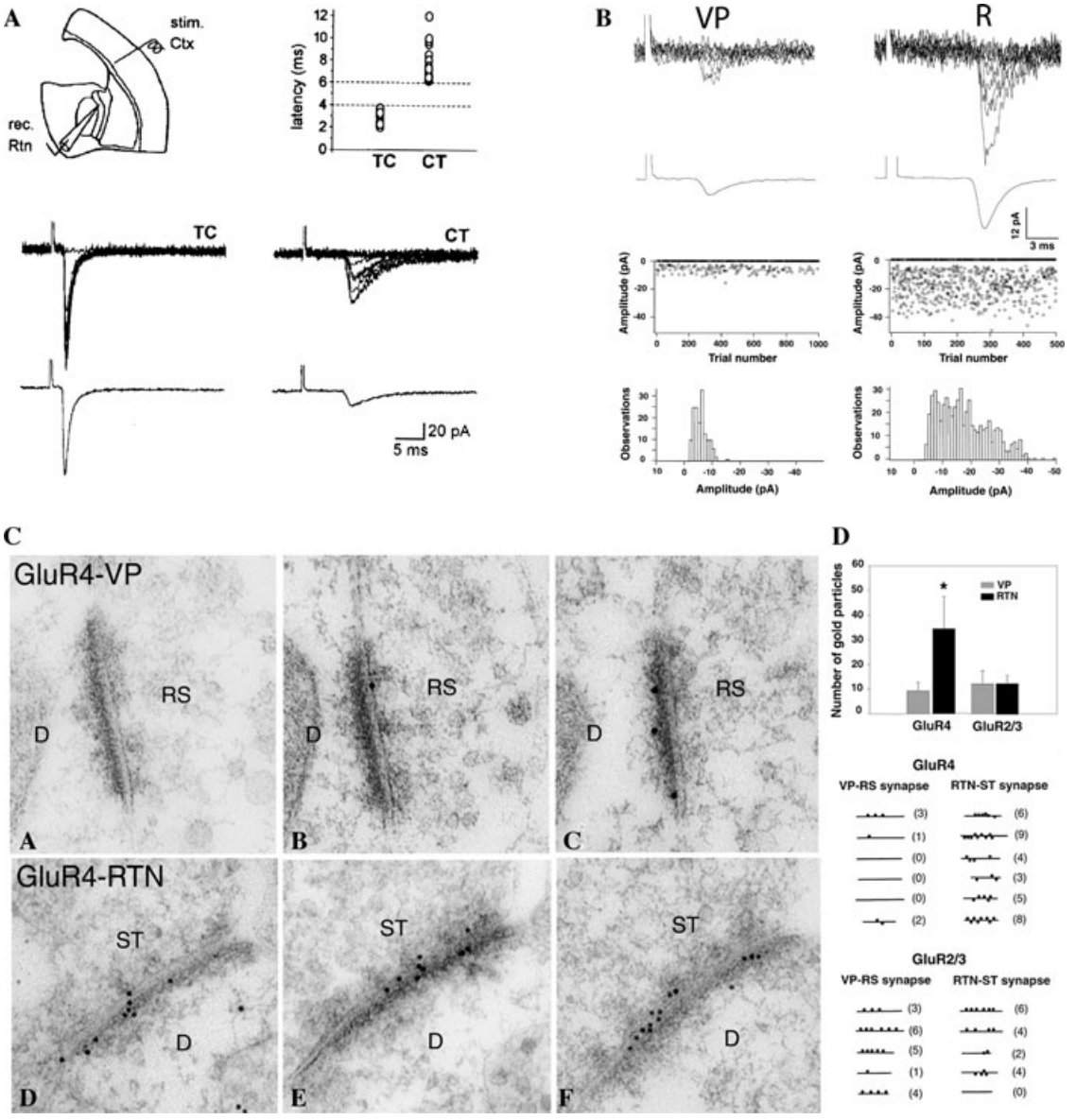

Figure 4. (**A**) A mouse thalamocortical slice preparation, showing the location of a recording electrode (rec.) in the thalamic reticular nucleus (Rtn) and a stimulating electrode (stim.) in layer VI of the somatosensory cortex (Ctx). Latencies of synaptic responses of neurons in the reticular nucleus following stimulation of layer VI are shown in the graph. The shorter latency responses at 2–4 ms stem from antidromic activation of thalamocortical axons (TC) and invasion of their collaterals in the reticular nucleus. The longer latency responses at 6–10 ms stem from orthodromic activation of corticothalamic fiber collaterals (CT). The lower panels show overlays of 10 voltage clamp traces from a reticular nucleus neuron following minimal stimulation of TC and CT fibers, and averages of the 10 traces are shown beneath each overlay. Minimal thalamocortical excitatory postsynaptic currents (EPSCs) are of greater amplitude, have faster rise and decay times, and exhibit fewer failures than minimal corticothalamic EPSCs. (**B**) Data obtained from the same preparation as shown in panel A, including the following: overlay of 10 voltage clamp traces from a neuron in the ventral posterior nucleus (VP) and from one in the reticular nucleus (R) following minimal stimulation of corticothalamic fibers; their average response; trial–to–trial variability in peak amplitudes of EPSC successes, indicating that minimal EPSC amplitudes are larger in the reticular nucleus neuron; the narrow distribution of amplitudes of EPSC

Two Modes of Action of Thalamic Neurons

Relay cells possess not only a common set of membrane properties but also share a common morphology and a common synaptic circuitry in which the nonspecific brain stem afferent systems, especially the cholinergic, tilt them towards either burst or tonic mode in order to make the transfer of afferent information either less or more effective and in which the reticular nucleus and corticothalamic inputs serve to create functional assemblies that oscillate in tune with our states of consciousness. The complexity lies not in the circuitry but in the functional states that it subserves.

A thalamocortical relay neuron is a more efficient transmitter of sensory information to the cortex in an awake than in a drowsy animal.[13] Seminal studies by Llinás and colleagues[14–16] *in vitro* and by Steriade and colleagues[17,18] *in vivo* revolutionized study of the thalamus by revealing that all thalamic neurons have the capacity to switch their firing behavior between two states depending on their membrane potential. At membrane potentials negative to minus 60 mV, the cells exhibit bursting behavior when subjected to a brief depolarizing current injection or when stimulated directly, antidromically, or by means of afferent synapses. After activation, there is a refractory period of 150–180 ms. At membrane potentials positive to minus 55 mV, thalamic cells, when stimulated as above, fire the repetitive fast spikes typical of thalamocortical relay cells in the awake state. The bistable membrane state of thalamic relay cells is another clue to understanding the synchrony in forebrain networks that underlies consciousness and unconscious states.

When relatively depolarized under the drive of the arousal systems of the brain stem and with the influence of the reticular nucleus at its least effective, cortically projecting neurons of the thalamus are capable of relaying activity from the peripheral sense organs with little or no degradation of temporal or spatial information or of sensory quality. This is what makes the thalamus such an efficient relay for sensory information from the periphery to the centers for perception in the cerebral cortex.

There is a dramatic contrast between the tonic activity of relay neurons in the awake, attentive state and the activity of these neurons during drowsy inattentiveness and sleep, when the brain stem drive is weakened, the neurons are hyperpolarized, and the influence of the reticular nucleus is at its peak. In this state, high-frequency bursts of action potentials are discharged at a slow rhythm that is communicated to the electroencephalogram (EEG) as high-amplitude slow waves of spindle and delta frequencies.

The possession of two different modes of action potential generation and the capacity to switch from the tonic, relay mode to burst mode, in which thalamic projection neurons are less effective transmitters of information whether centrally or peripherally generated, makes the thalamus a key structure in virtually every aspect of forebrain function. In the tonic mode, when under the influence of the nonspecific brain stem afferents, relay cells are

successes in the ventral posterior neuron and the wider range in the reticular nucleus neuron. (**C**) Serial electron micrographs of single corticothalamic synapses in the ventral posterior and reticular nuclei stained by the immunogold technique for GluR4 glutamate receptor subunits, showing the small number of gold particles at the synapse in the ventral posterior (VP) nucleus (A–C) and the larger number at the synapse in the reticular nucleus (RTN) (D–F). (**D**) Comparison of the number of GluR4 and GluR2/3 immunogold particles found at two serially sectioned corticothalamic synapses in the RTN and VP nucleus. GluR4 subunits at the corticothalamic synapses in the reticular nucleus clearly outnumber those at the corticothalamic synapses in the ventral posterior nucleus, but the number of GluR2/3 subunits is approximately equal. (From Jones [2007][1].)

relatively depolarized and firing trains of single action potentials and the thalamus is capable of operating as the simplest of relays, conveying sensory information to the cerebral cortex with little or no decrement in spatial or temporal properties. Under these conditions the influence of the reticular nucleus is at its least, serving only to sharpen the contrast between signal and noise, and corticothalamic feedback is influential in assembling relay neurons into ensembles that fire coherently at ~40 Hz. It is in the tonic state of relay cell function that the properties of relay cells that most befit them for a role as conduits in the pathways to perception are most clearly revealed. The outputs of the cells then become faithful facsimiles of the inputs, with the capacity to follow a repeated peripheral stimulus only failing at high repetition rates. The further grouping of relay neurons into assemblies discharging synchronously at ~40 Hz and leading to an act of perception also appears to be a key element in the effective transfer of information to cortical neurons that can be brought into action under the influence of remarkably few thalamocortical synapses.

State-Dependent Activity of Thalamocortical Relay Cells

The two modes of spike generation, dependent on the inactivation or deinactivation of the voltage-dependent T-channel, have their functional expression in the two modes of relay cell behavior during arousal and sleep (reviewed by McCormick and Bal [1997][19] and Steriade [2003][20]). During wakefulness, directed attention, and higher cognitive performance, relay neurons, under the influence of the nonspecific brain stem systems, primarily the cholinergic, are relatively depolarized and fire tonically in response to peripherally or centrally generated afferent activity. By contrast, during drowsy inattentiveness and slow wave sleep, the neurons, in the absence of the same brain stem influence, drift towards hyperpolarization, to deinactivation of low-threshold calcium channels, and to burst firing. It is during this state that the influence of the reticular nucleus is at its strongest in its capacity to entrain relay cell bursts at spindle frequencies and under certain circumstances at lower frequencies. The power of the reticular nucleus in this regard is substantially enhanced by the feedback from layer VI neurons of the cerebral cortex, even a single corticothalamic volley being sufficient to set up a spindle oscillation in the thalamus and throughout the entire thalamo–corticothalamic network. And massive, sustained corticothalamic activity, as in an epileptiform seizure, may cause the reticular nucleus to shut off activity altogether in relay neurons. In mice null for the gene encoding T-type calcium channels, thalamic relay cells lack burst discharges and slow wave synchrony and the animals display resistance to pharmacologically induced spike and wave discharges.[21]

The reticular nucleus is at its least effective when during the conscious state relay neurons are relatively depolarized, their T-channels inactivated, and they are firing tonically. Under these circumstances the power of the corticothalamic system is brought to bear directly on the relay cells rather than on the reticular nucleus. As the membrane potentials of relay cells become more positive and just before tonic firing commences, a remarkable ~40-Hz membrane oscillation is revealed, dependent on high-threshold (P/Q) calcium channels. When engaged by corticothalamic synaptic activity, the tonic firing of the relay cells now becomes entrained at ~40 Hz, and this is communicated to the whole thalamo–corticothalamic network.[22,23] In mice null for the genes coding for P/Q channels, relay cells lack the subthreshold ~40-Hz oscillations and EEG recordings show little activity in the gamma range of frequencies.[24]

We now recognize that an EEG or electrocorticogram reflects neuronal activity not in the cerebral cortex alone but in the whole thalamo–corticothalamic network. The high-amplitude spindle waves that herald the drift into and out of slow wave sleep have their origins in the

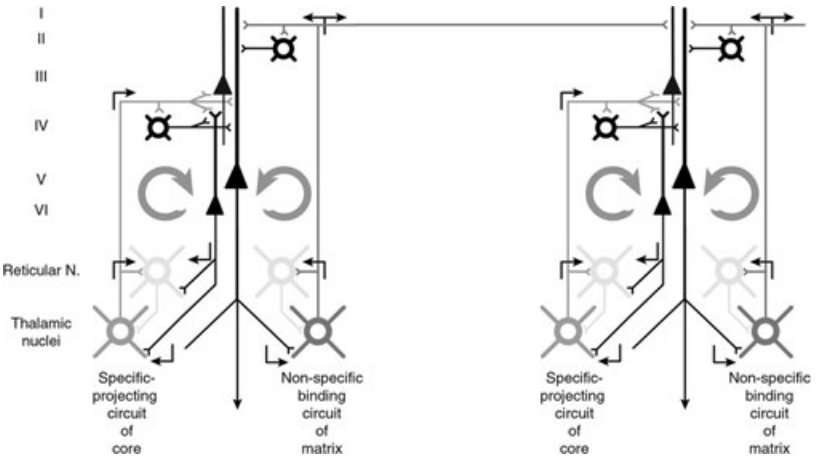

Figure 5. Synchrony of the thalamus and cortex. The schematic view shows how assemblies of thalamic and cortical neurons firing synchronously can be formed under the influence of coincident inputs of the core and matrix projections to cortical pyramidal cells of all layers and how re-entrant corticothalamic circuitry can maintain a local assembly. In addition, because of the divergence of the matrix projection and of the layer V corticothalamic projection, activity in one assembly can be transferred to new assemblies across the cortex and thalamus. (From Jones [2007][1]; based in part on Llinás and Paré [1997].[35])

thalamus, and slower waves in the delta range can be generated in the cortex or thalamus. The lower-voltage waves in the gamma range (20–80 Hz) that lie within what was once regarded as a "desynchronized" EEG and which are typical of attentive wakefulness are now recognized as accompaniments of directed attention, perception, and higher cognitive states. Magnetoencephalography demonstrates the movement of gamma oscillations across the cerebral cortex during conscious perception,[25] and the power spectrum of gamma band activity is reduced in areas such as the prefrontal cortex in psychosis.[26] Recognizing that the EEG is a reflection of the activity of many hundreds or thousands of cortical and thalamic cells firing synchronously, it is incumbent upon us to attempt to explain how assemblies of thalamic and cortical neurons that fire synchronously in the gamma range can be formed and how the synchronous activity can be transferred to new assemblies as a substrate for the movement of activity across the cortex during the process of "binding" all the elements of an experience into a single cognitive event. The re-entrant circuitry (Fig. 5) provided by the layer VI corticothalamic cells appears to be a key element in the establishment of local assemblies of thalamic and cortical neurons, ensuring that any 40-Hz activity generated in tonically firing relay cells and communicated to the layer VI cells by their monosynaptic thalamocortical inputs will be re-entered at the relay cells and the oscillations reinforced. The somewhat divergent thalamic terminations of layer VI corticothalamic axons should recruit other relay cells into an assembly, including both focally projecting core cells and diffusely projecting matrix cells. At the cortical level, relay cell oscillation will be conveyed via monosynaptic inputs to middle layers, that is, to pyramidal cells of layers III–VI, and the terminations of the axons of matrix cells in superficial layers on the apical dendritic sprays of these cells should set up a coincidence detection circuit that will further reinforce synchrony in the assembly. The engagement of new assemblies and the spread of activity across assemblies would in this scheme occur via layer V corticothalamic projections to new thalamic nuclei and via matrix cells to their cognate cortical areas (Fig. 6). Eventually, in this view, the whole dorsal thalamus and cerebral cortex could be engaged in synchronous gamma frequency oscillations.

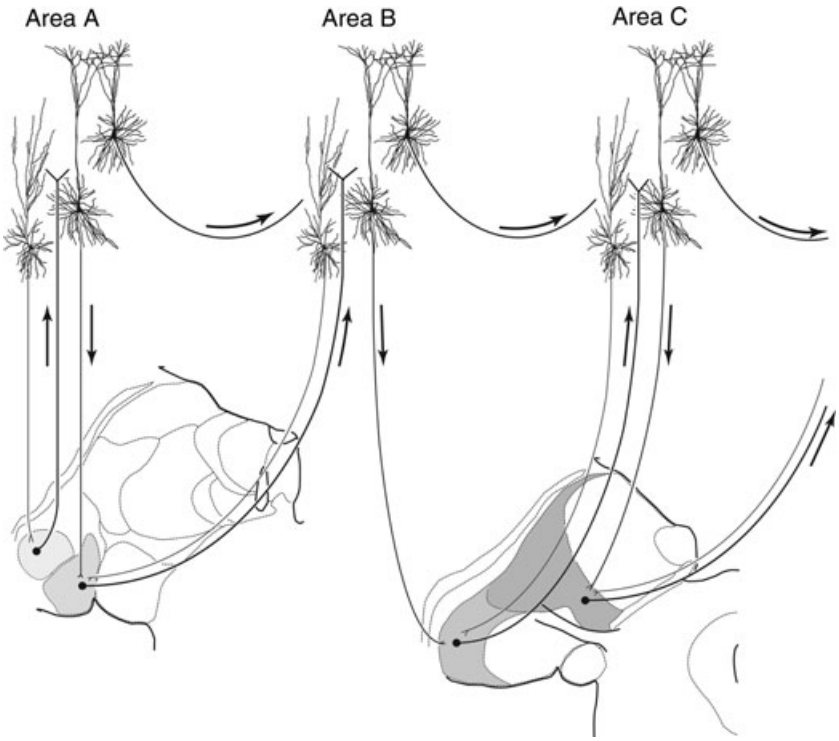

Figure 6. Schematic illustration of how corticothalamic fibers arising from layer V cells of one cortical area and projecting to nuclei of the pulvinar other than that which provides input to that cortical area could serve to provide a series of cortico–thalamocortical loops that parallel the hierarchical progression of cortico–cortical connections from a primary sensory area (area A) to other cortical areas (areas B and C, etc.). (From Jones [2007][1].)

Interpolations of an abnormal, lower-frequency rhythm at some point, such as one induced in the ventral lateral anterior nucleus by heightened inhibitory inputs from the internal segment of the globus pallidus in Parkinson's disease, would potentially disrupt the normal sequence and cause a disturbance of behavior, e.g., tremors in the case of Parkinson's disease, or an abnormal sensory experience, perhaps pain, in the case of altered input from the periphery. Other comparable thalamic dysrhythmias may be the accompaniments of psychotic states and could potentially be the basis of hallucinations.

Two Classes of Corticothalamic Neurons

The cerebral cortex provides feedback to the thalamus via the projections of two distinct classes of pyramidal cells with somata located in different layers. The majority of cells projecting to a particular thalamic nucleus have somata located in layer VI of the cortical area receiving input from that nucleus. A smaller number are found in layer V of the same area and project mainly to different although functionally related thalamic nuclei (reviewed by Steriade *et al*. [1997][27] and Jones [2007][1]). The layer VI and layer V corticothalamic cells have very different morphologies, and their axons have different patterns of ramification and termination in the thalamus as well as collateral branches, with very different distributions within the parent area of the cortex (Fig. 7).

Corticothalamic neurons of layer VI are small, pyramidal cells with a narrow, vertical dendritic field that ends in the middle layers of the cortex among the terminations of thalamocortical fibers from which the cell receives

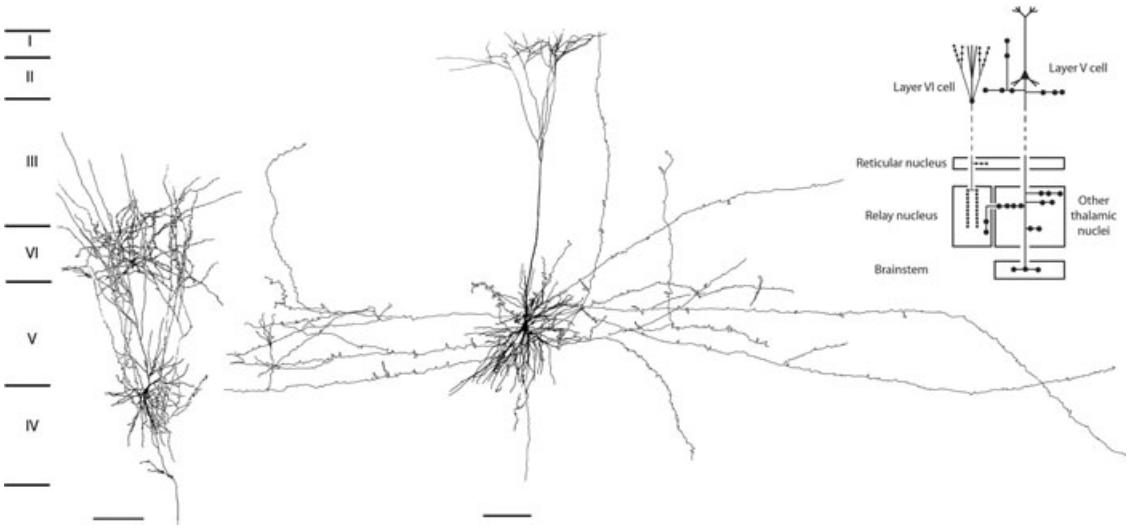

Figure 7. Camera lucid drawings of corticothalamic cells in the auditory cortex of the cat, intracellularly labeled with horseradish peroxidase or biocytin. Corticothalamic cells in layer VI have a vertical organization of intracortical axon collaterals, while corticothalamic cells in layer V have a horizontal distribution of intracortical collaterals. The inset shows the terminal distribution of axons of layer VI and layer V corticothalamic cells in the thalamus, illustrating the focused nature of a layer VI projection, with collaterals in the reticular nucleus, and distributed nature of a layer V projection without collaterals in the reticular nucleus. (From Jones [2007][1]; based on Ojima *et al*. [1992][28] and Ojima [1994][29]).

monosynaptic inputs from the thalamus. The axon of a layer VI corticothalamic cell, before leaving the cortex, gives off two or three recurrent collaterals which ascend within the confines of the vertical dendritic field of the cell.[28,29] Each cell, therefore, influences a relatively narrow zone of the cortical area in which it lies. The principal axon of the cell projects subcortically only to the thalamus. As it traverses the reticular nucleus it gives off one or two short collaterals in the reticular nucleus. On entering the dorsal thalamic nucleus from which its parent cortical area receives input, it terminates in a relatively narrow zone, in appropriate topographic order. Although ending in a relatively restricted zone of the related thalamic nucleus, the terminals of a single layer VI corticothalamic cell can apparently influence thalamic relay cells that project to regions of cortex outside the narrow cortical zone in which it resides.[30] For example, a corticothalamic axon projecting to the dorsal lateral geniculate nucleus can influence an extent of the visual field representation in the lateral geniculate nucleus many times greater than that represented in the cortical column in which its parent cell resides. In another example, fibers derived from a cell located beneath a single cortical barrel in the somatosensory cortex extend terminals in the ventral posterior nucleus of the thalamus into regions adjacent to the cluster of cells that provides input to that cortical barrel, and thus into thalamic regions representing other facial vibrissae.[31,32]

Corticothalamic cells whose somata lie in layer V are characterized by far more extensive axonal ramifications in the cortex and thalamus. The layer V cells are large, pyramidal in form and have a thick apical dendrite that ascends to layer I of the cortex, where it ends in a tuft of branches (Fig. 7). The axon gives off a number of long horizontal collaterals that extend for a great distance through layers III and V of the cortex and then descends to the thalamus and to other subcortical sites, such as the tectum, other parts of the brain stem, or the spinal cord. Unlike the axon of a layer VI corticothalamic cell, the axon of a layer V cell does

not give off collaterals to the reticular nucleus and within the dorsal thalamus its terminations are not restricted to the nucleus from which its parent cortical area receives inputs. The terminations extend into one or more adjacent nuclei, although in each nucleus the terminals can be more highly focused than those of the axons of layer VI cells. The axons terminate in small numbers of large boutons, quite unlike the numerous small boutons of layer VI corticothalamic cells. These larger boutons often enter into synaptic relationships with relay cells that resemble those of ascending afferent fibers rather than those of the terminals of the layer VI cells. The additional nuclei receiving input from layer V corticothalamic cells commonly include those of the intralaminar system, but nuclei of the pulvinar–lateral posterior complex and the dorsal and magnocellular nuclei of the medial geniculate complex are also targets. A common feature is that these additional target nuclei are commonly those in which the calbindin matrix of thalamic cells is most highly represented.

The focusing of the layer V corticothalamic projection in comparison with the more divergent layer VI projection does not imply a greater degree of topographic specificity, for the axons of these cells, in addition to their terminations in the thalamus, have terminations in the striatum, brain stem, and even spinal cord. And, their intracortical projections are widespread, unlike those of the layer VI cells, which are highly columnar. The chief function of the layer V cells may, therefore, be more in the nature of a general activator of the thalamus in conjunction with the rest of the brain. Because the layer V-originating axons do not innervate the reticular nucleus, they have direct excitatory access to the relay neurons of the dorsal thalamus. Hence, the layer V corticothalamic projection may serve both as a means of directing attention during wakefulness and as a basis for a "wake-up call" during sleep and inattentiveness. The offsetting of the layer V projection from the primary thalamic source of input to a cortical area and especially its predilection for the matrix of the dorsal thalamus could be an important means of bringing attention to bear upon the context under which the content of a sensory message is being relayed through the primary nucleus.

Despite the preceding comments, the layer VI-originating corticothalamic projection cannot be seen as subservient to the layer V-originating projection or simply as a "modulator" of thalamic relay function. The layer VI corticothalamic projection can operate most powerfully in both the sleeping and the alert states.[33,34] In the former, when it is focused on the reticular nucleus and its influence over the hyperpolarized relay cells is weak, the effect of corticothalamic stimulation is strong disynaptic inhibition of the relay cells, and in this it promotes low-frequency oscillations in the cortico–thalamocortical network as the cells begin to burst. In wakefulness, the excitatory postsynaptic potentials (EPSPs) elicited by the layer VI corticothalamic projection become more effective because of the functional expression of high-threshold calcium channels in the dendrites and the corticothalamic system now serves to entrain the natural ~40-Hz intrinsic oscillations of the cells, thus setting up and maintaining high-frequency synchronous activity in the thalamocortical network as described above.

Interactions of Core and Matrix Cells and Corticothalamic Projections in Promoting Widespread Synchrony in the Thalamo–Corticothalamic Network

The relay cells that make up the core of the thalamus have focused projections to an individual cortical area and form the basis for the relay of place- and modality-specific information to the cortex. Those of the matrix form a basis for the dispersion of activity in the thalamocortical network across larger areas of cortex. Within a zone of cortex, the terminations of core cell axons on more-proximal dendrites in middle layers and those of matrix cell axons

on distal dendrites in superficial layers form a coincidence detection circuit that should provide a high degree of temporal integration between inputs coming from the core and matrix cells[35] (Fig. 6). Coincidence of inputs should promote synchronous activity in the cells of cortical columns activated by a peripheral or internally generated stimulus. Activity in these columns should then be returned via layer VI corticothalamic cells to the thalamic nucleus from which they receive input, and thus thalamocortical synchrony would be reinforced. Activity would be spread to other cortical columns in the same cortical area and to those in adjacent cortical areas via the diffuse projections of matrix cells in the thalamic nucleus that was first activated and to which the layer VI projection returns. Other thalamic nuclei would be recruited via the more widespread corticothalamic projection of layer V neurons and then, through the cortical projections of matrix cells in these nuclei, other cortical areas would become involved (Fig. 6). Intracortical spread of synchrony would also be promoted by the widespread horizontal collaterals of layer V corticothalamic cells within the cortex. By means of the systematic recruitment of cortical and thalamic cells by layer V corticothalamic cells and by thalamic matrix cells, large-scale, coherent activity would be set up throughout large regions of cortex in response to an externally or internally generated stimulus. In this way temporary functional links would be provided between discrete populations of cortical and thalamic cells in the process of binding the different aspects of a stimulus into a single experiential event.[25,36–40] The links would be broken as an oscillation faded but could be reformed in new patterns in response to new external or internal inputs to the thalamus. Coherency of fast (20- to 40-Hz) activity in the cerebral cortex and thalamus has been demonstrated by multisite recording of field potentials and intracellular activities in different neocortical areas[41,42] and within thalamic nuclei connected with these areas by thalamocortical and corticothalamic connections.[43]

In the cortex of awake humans, high-frequency cerebral oscillations accompanying cognitive events tend to engage areas of the cortex that, although large, are regionally restricted, as though representing input through a single thalamic relay nucleus. During a discrete conscious event, 40-Hz activity, as revealed in magnetoencephalographic traces, being at first regionally restricted, moves across the cortex as new areas are recruited,[44] as though following the progression of cortico–thalamocortical recruitment predicted above. The spread of activity predicted is also consistent with the time course of peripherally elicited or internally generated sensory experiences.[25,45,46] Cortico–cortical connections undoubtedly play a prominent role as well, but they are seen as running parallel to a system of cortico–thalamocortical loops in spreading activity across the cortex and thalamus (Fig. 6).

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Conflicts of Interest

The author declares no conflicts of interest.

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