Overview

The thalamus: gateway to the mind

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The thalamus of the brain is far more than the simple sensory relay it was long thought to be. From its location at the top of the brain stem it interacts directly with nearly every part of the brain. Its dense loops into and out of cortex render it functionally a seventh cortical layer. Moreover, it receives and sends connections to most subcortical areas as well. Of course it does function as a very sophisticated sensory relay and thus is of vital importance to perception. But also it functions critically in all mental operations, including attention, memory, and consciousness, likely in different ways for different processes, as indicated by the consequences of damage to its various nuclei as well as by invasive studies in nonhuman animals. It plays a critical role also in the arousal system of the brain, in emotion, in movement, and in coordinating cortical computations. Given these important functional roles, and the dearth of knowledge about the details of its nonsensory nuclei, it is an attractive target for intensive study in the future, particularly in regard to its role in healthy and impaired cognitive functioning.

How to cite this article:
WIREs Cogn Sci 2013. doi: 10.1002/wcs.1256

INTRODUCTION

Open nearly any textbook of neuroscience or sensation and perception and you will find the thalamus described as a 'sensory relay'. Five of its roughly 50 nuclei in particular, the lateral (vision) and medial (hearing) geniculate nuclei, and various parts of the ventral-posterior nucleus (touch, pain, taste), do indeed function as relays, receiving inputs from sensory receptors and sending the information contained therein on to primary sensory cortices. The other 45 nuclei, however, receive the bulk of their input from the cortex and subcortex, and thus participate in complex cortical and subcortical networks, and have no primary sensory inputs whatsoever. These latter thalamic nuclei evolved along with the evolving neocortex as vertebrates' brains became more complicated over millions of years.[1] The precise functions of these nuclei have been elusive, although it is clear that they must be very important given the dire consequences of damage to them. To destroy the thalamus is to kill; a person cannot live without a thalamus although people and other animals can do quite well without major chunks of cortex. Indeed, decorticate rats behave very similarly to normal rats in many ways,[2] whereas de-thalamate rats die. Even a bit of damage to the thalamus can have dire consequences for perception, cognition, emotion, action, and even consciousness. The thalamus is a critical locus for anesthetics in rendering us unconscious, and participates in a critical cortical arousal system and in many if not all cortical networks. The thalamus has been proposed to be the 'brain's highest mechanism',[3] and indeed it has figured prominently in many theories of mental function for many years. And yet, in spite of all of this interest, and much evidence of critical functions, it remains one of the least well-understood regions of the brain. Its best-understood part, the lateral geniculate nucleus (LGN), is marvelous indeed, and plays a sophisticated and critical role in the visual system. But generalizations from this nucleus, as useful as they seem to be, have not prepared us for the complications that have recently been revealed, especially in regard to the nonsensory nuclei that form the bulk of the dorsal thalamus. This article provides an overview both of what we know and of what we are beginning to suspect about how the thalamus helps to integrate and regulate cortical and subcortical activity, and helps provide us humans with the delights and sorrows of our complex mental life.

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Conflict of interest: The author has declared no conflicts of interest for this article.

A SEVENTH LAYER OF CORTEX

The thalamus has been characterized as a central, convergent, compact 'miniature map' of the rest of the brain. Thus, it is well-positioned to integrate a wide variety of cortical computations with sensory inputs and to integrate both of these with limbic activity from the hypothalamus, amygdala, and other subcortical regions.

The human thalamus is comprised of about 50 nuclei and subnuclei, which do not connect directly with each other. Rather, each nucleus tends to connect reciprocally with one or more specific cortical areas, as well as with the thalamic reticular nucleus (TRN) that surrounds the dorsal thalamus.[4,5] Figure 1 shows the relatively larger projection from each cortical area to a specific dorsal thalamic nucleus (indicated by the thick lines on the left side) as compared to the much smaller thalamocortical reciprocal projection (thin lines on the right side) in the human brain.[7] This pattern of connection circuitry is common among mammals. The so-called 'higher' mammals have more cortical areas and thus more thalamic nuclei connected in this way. It seems that each new cortical area that evolved was accompanied by the addition of another nucleus in the dorsal thalamus.[1] The relationship between the dorsal thalamic nuclei and their reciprocally connected cortical areas is so close that some researchers have argued that the dorsal thalamic nuclei comprise a seventh layer of the cortex. The thalamus also has a reciprocal relationship with many subcortical areas, such as the basal ganglia, the striatum, the amygdala, the hypothalamus, the cerebellum, and so on. Thus, the thalamus interacts directly with, or is a target for, nearly every other part of the brain. It is likely that it plays a role in the integration of the outputs of, and communication between, all of the functional areas

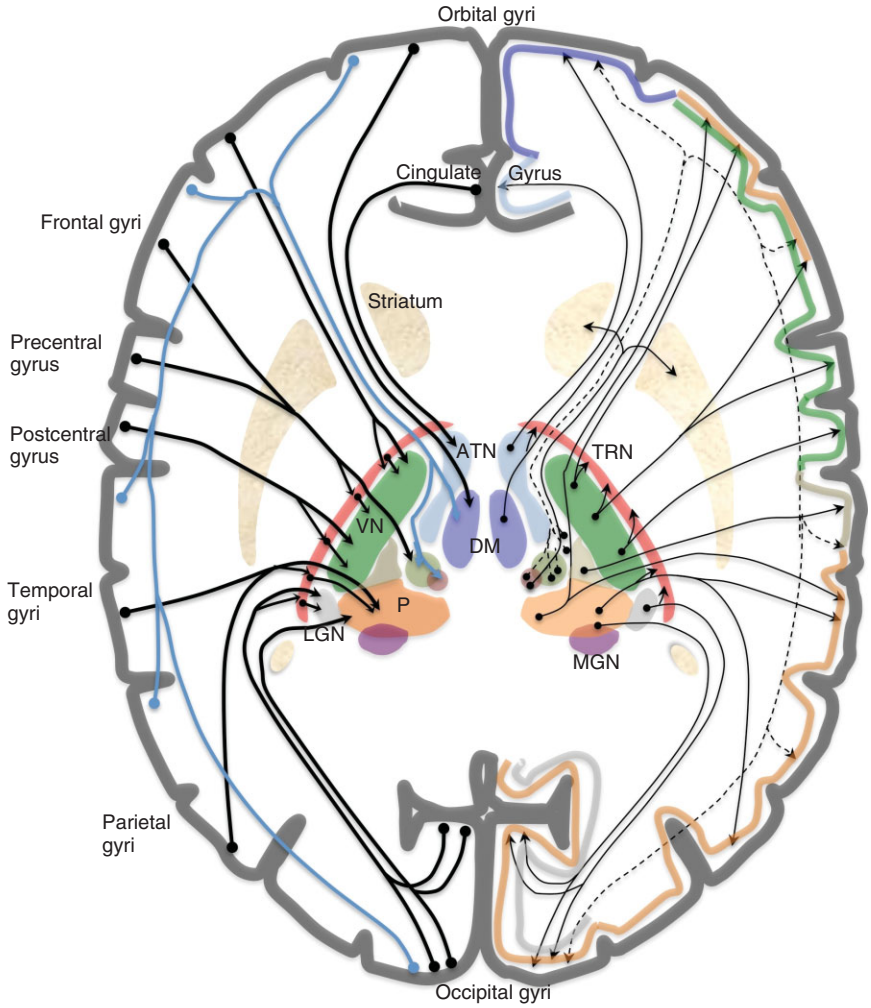

FIGURE 1 | Corticothalamic (left side) and thalamocortical (right side) connections. (Reprinted with permission from Ref 6. Copyright 2011 Elsevier.)

of both hemispheres of the brain: sensory, cognitive, limbic, and motor.[8]

The dorsal thalamic nuclei (excluding TRN) are comprised of about 70% glutamatergic excitatory neurons and about 30% GABA-ergic inhibitory interneurons. The interneurons form reciprocal connections with nearby excitatory neurons only within a particular nucleus. The dorsal thalamic excitatory neurons are very different from cortical pyramidal neurons (Figure 2). The thalamic neurons are larger and have more extensive dendritic trees, where they receive cholinergic, noradrenergic, and serotonergic inputs from other subcortical areas, excitatory synapses from the cortex, and inhibitory synapses from nearby interneurons and from the TRN.[9] The neurons of the TRN (Figure 2) are similar to cortical interneurons, and are all GABA-ergic inhibitory neurons. The TRN is also parcellated into sectors that interact with specific thalamic nuclei and receive collaterals from the corresponding cortical areas, although the parcellation is not as well-defined for the nonsensory nuclei.

The Sensory Nuclei

Sherman and Guillery called the relay nuclei that innervate the primary sensory projection areas 'first-order' relay nuclei.[10] In humans, these are the lateral geniculate (visual), medial geniculate (auditory), ventrolateral (tactile), posterior ventromedial (pain, temperature),[11] and ventrocaudal (taste and other somatic sensations) nuclei.[12] Some of these are shown with their projections to cortex in Figure 3. Their primary function has been thought to simply relay basic afferent information from the peripheral receptors to the cortex for sophisticated processing. This is far from a complete description of their role, however. Cortical feedback has been shown to locally enhance or suppress activity in sensory thalamic nuclei.[13] In turn, sensory thalamic bursts potently activate cortical circuits.[14] The TRN gates the relay of sensory information to cortex by fine-tuning of gain in feedback inhibition circuits between TRN and sensory relay nuclei: high gain in those circuits disconnects the relay from cortex whereas low gain enhances transmission from the relay to cortex.[15] It is becoming clear that considerable processing of sensory information takes place in these nuclei, partly because of feedback from cortex, as in vision, and partly because of that feedback combined with sophisticated processing in even more peripheral nuclei of the brain stem, as in hearing.

We know most about the function of the LGN.[16] It precisely maintains the spatial topography of the retina, while at the same time separating magno- and parvocellular retinal inputs into interleaved layers for input into specific sublayers of layer IV of cortical area V1. This means that it might be possible to create a prosthetic for vision by stimulating the LGN directly, and this possibility is confirmed by the fact that phosphenes (phantom visual sensations) can be generated by electrical microstimulation there.[17] With modulatory inputs from V1, TRN and several subcortical areas, LGN is a site of early modulation of visual information arriving from the retina. It leads the cortex in the detection of oddball visual targets, and presumably enhances the cortical response to them.[18] The LGN improves the coding efficiency of retinal signals by preferentially relaying spikes that arrive after short interspike intervals. The LGN is also a locus of attention enhancement and suppression via the TRN (see section *Attention*). Some of this is apparently accomplished via modulation of synchronization of oscillatory responses between LGN and cortex.[19]

The medial geniculate nucleus (MGN) receives already highly processed afferent input from the top of a chain of other brain stem auditory nuclei, comprised of the inferior colliculus, the superior olive, and the cochlear nucleus. These early nuclei maintain the tonotopic sound frequency mapping created by the cochlea and also contain localization neurons sensitive to sound timing and intensity differences between the two ears. The MGN sends all this information to the primary auditory cortex and receives modulatory inputs similar to the LGN, and thus most likely is a site of attentional gating of auditory stimuli. Neurons in the auditory TRN adapt very quickly to repeated stimuli, and thus function very sensitively as deviance detectors.[20] They also modulate the responses of the MGN to the deviant stimuli. The auditory TRN also receives visual and tactile afferents so that it might be involved in cross-modal modulation as well.[21,22] Behavioral experiments have demonstrated that visual cues can affect thalamic responses to auditory stimuli, consistent with such a role.[20,23] The MGN is also connected to the spatial maps of the superior colliculus. It is likely that the spatial information extracted by the brain stem auditory nuclei, rather than being directed to the auditory cortex (which contains no spatial maps), is sent to the spatial maps comprised of multimodal neurons found in deep layers of the superior colliculus.[24]

The other sensory nuclei apparently function similarly to the LGN and MGN but also likely display modality-specific differences. For example, stimulation of ventrolateral nucleus generates phantom limb sensation in amputees,[25] much like the phosphenes from the LGN. Phantom pain can also be elicited by

pathology of the pain nuclei, or other nearby nuclei, associated with diabetes.[26] Activation of the ventral posterolateral nucleus has been implicated in causing the head pain in migraine.[27] Thalamocortical circuitry that would enhance processing of information from rodent vibrissae has been described,[28] and some specifics of this function have now been demonstrated. Adaptation to stimulation decreases synchrony in tactile thalamus, reducing the ability of barrel cortex to detect stimuli but enhancing its ability to discriminate them based on vibrissae movements.[29] Thalamic activity is necessary for the desynchronized cortical state that prevails during whisking (moving whiskers to detect and discriminate tactile stimuli) in mice and optogenetic stimulation of tactile thalamus produces a similar state in cortex to the desynchronized whisking state.[30]

Drivers and Modulators

As described in the previous section, some parts of the thalamus do function as sophisticated sensory relays or gates. Most thalamic nuclei, however, called 'higher order' by Sherman and Guillery,[10] receive the vast majority of their input from the cortical area(s) to which they are reciprocally connected. Guillery and Sherman argued that these higher-order nuclei function exactly as do the first-order relay nuclei: they relay information.[10,31] In other words, Sherman and Guillery extended the classical notion of the thalamus as a sensory relay from sensory nuclei such as the lateral geniculate and the medial geniculate, to *all* thalamic nuclei. They did add a twist, however, based on their observation that cortico-thalamic inputs originating in layer V of the cortex also branch to motor areas (at least in the visual and somato-sensory systems). Moreover, those inputs from cortical layer V do not return to the thalamic nucleus associated with the same cortical area, but rather to other, higher-order thalamic nuclei (at least for vision) associated with a later cortical area. Finally, they are of the 'driver' type of inputs (fast, ionotropic synapses, large axons and large synaptic boutons). On the basis of these facts, Sherman and Guillery proposed that the higher-order thalamic nuclei functioned to relay *motor* information from one cortical area to another, effectively an efference copy of action-related information sent by the cortex to motor areas, such as the superior colliculus (which controls eye movements), brain stem, and spinal cord, from these perceptual areas. Information transmission via this corticothalamocortical pathway has been demonstrated for spatial vision stability relating to eye movements[32,33] and for the somatosensory system.[34]

Sherman and Guillery also observed that many, if not most, of the corticothalamic inputs that originate in layer VI of the cortex terminate in the thalamic relay nuclei in slow, metabotropic synapses, which have small fiber and synaptic bouton size and require cascades of intracellular processes to open ion channels.[10] They classified such terminals as 'modulators', which do not transmit information

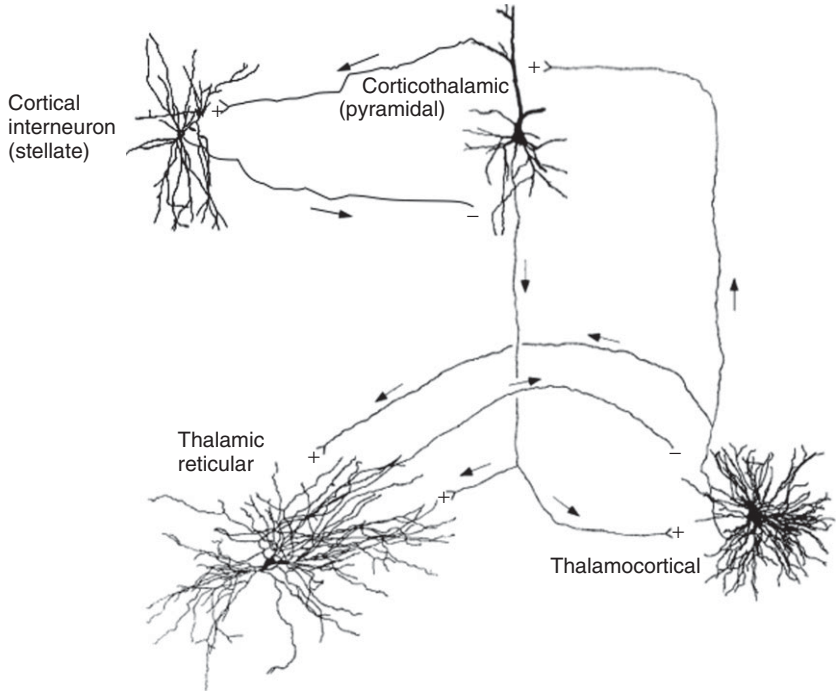

FIGURE 2 | Thalamic neurons compared with cortical neurons. (Reprinted with permission from Ref 6. Copyright 2011 Elsevier.)

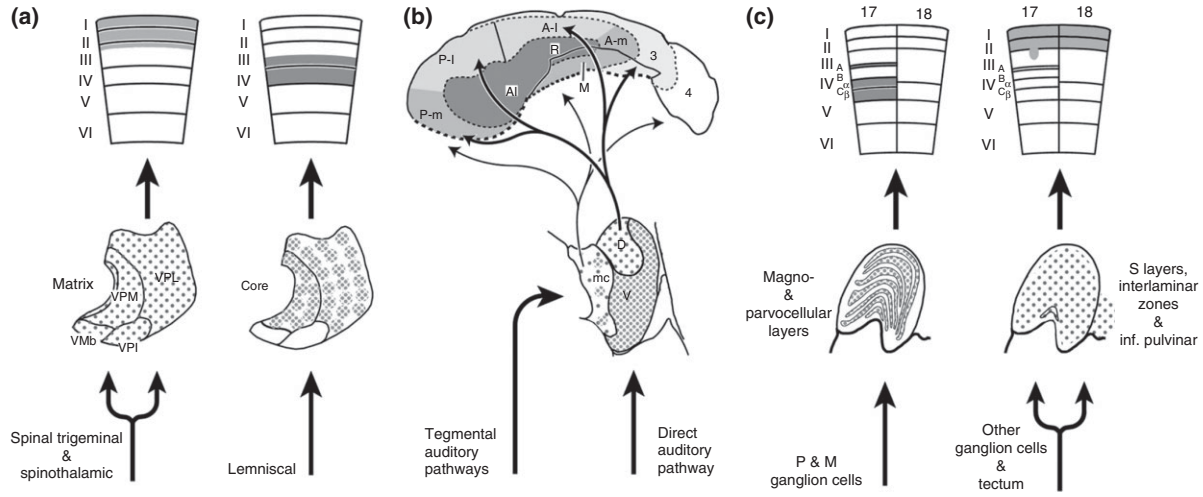

FIGURE 3 | Connections between thalamic sensory nuclei and the cortex. (a) Tactile system—ventrolateral nucleus; (b) auditory system—medial geniculate nucleus; (c) visual system—lateral geniculate nucleus. (Reprinted with permission from Ref 9. Copyright 2002 Royal Society Publishing.)

but only change the way that their targets respond to driving inputs. Importantly, though, it seems that both ionotropic and metabotropic synapses can perform either function. This is because, rather than by type of synapse, gain modulation is better characterized functionally as arising from balanced excitatory and inhibitory background synaptic input, whereas driving input arises from unbalanced input.[35] Thus, while it is possible that the higher-order nuclei function as information relays, it is not clear that this is their only function or even their primary function.

The Core and the Matrix

Another important distinction between the first- and higher-order thalamic nuclei arises from the discovery by E.G. Jones of two different types of excitatory thalamic neurons.[36] They are distinguished both chemically and anatomically: the 'core' neurons express a calcium-binding protein called parvalbumin and are found mostly in the first-order and motor nuclei, whereas the 'matrix' neurons express a different calcium-binding protein called calbindin and are found throughout the dorsal thalamus with a higher concentration in the higher-order nuclei (Figure 3). The core neurons project to interneurons in layer IV and to pyramidal neurons in layers III, V, and VI in sensory- or motor-specific cortical areas. The matrix neurons, however, project diffusely to interneurons in layers I and II of several related cortical areas, mostly from nonsensory nuclei and especially to frontal areas. Both core and matrix neurons receive projections from cortical layer V pyramidal neurons and the core neurons also receive back projections from layer VI pyramidal neurons.

Jones proposed that core neurons relay information within specific sensory and motor pathways, whereas matrix neurons bind together the activities of thalamus and cortex.[36,37] He proposed these distinct roles in the context of the two major modes of action in the thalamocortical circuitry: burst mode inducing drowsiness and sleep and tonic mode inducing wakeful consciousness and action. In burst mode the brain stem arousal system is inactive and core and matrix neurons are inhibited by the TRN.[38] In tonic mode the brain stem arousal system is active and inhibition from TRN is weak. In tonic mode, thalamocortical and cortico-cortical synchronization are both enhanced by the binding influence of matrix neurons, and sensory information is efficiently relayed to the cortex by the core. In this scheme, the TRN and the brain stem arousal system together determine whether the thalamus will facilitate thalamocortical synchronization at 40 Hz (conscious wakefulness) or at much lower frequencies, in the delta (2–3 Hz) range (sleep).

AROUSAL AND SLEEP

It is generally agreed that the thalamus plays a critical role in the sleep–wakefulness cycle of the brain, although it is only part of the necessary machinery. Figure 4 abbreviates the complex neural circuitry involved in the circadian sleep–wake cycle.[39] The special role of the thalamus was first described in detail in the early 1990s.[40] It involves the generation of regular slow rhythms in the thalamocortical system

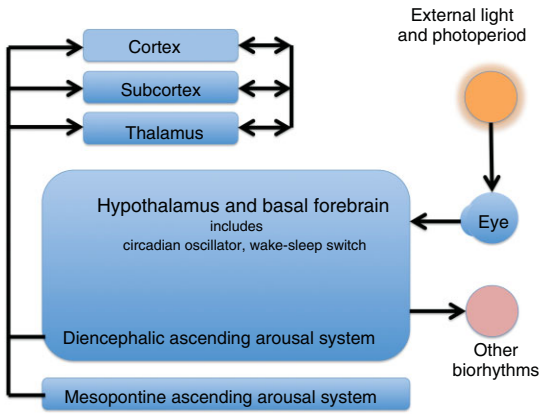

FIGURE 4 | Important brain areas and connections in the sleep and arousal networks. Source: Pace-Schott and Hobson[39].

during sleep and irregular faster rhythms during wakefulness. The isolated TRN generates sleep spindle oscillations, thus indicating that it is probably the origin of the slow rhythms.[40] When the TRN is inhibited the slow rhythms disappear and the faster rhythms of the waking (and rapid-eye-movement sleep) state recur.

The intralaminar and midline nuclei of the thalamus are important parts of the forebrain arousal system.[41] These nuclei have a high density of matrix neurons that project diffusely to frontal cortex as well as to the striatum and the basal ganglia (responsible for actions).[9,36,37] One study showed that the intralaminar nuclei and the brain stem reticular system were both activated when human subjects went from a relaxed awake state to one that required focusing on an attention-demanding reaction-time task.[42] Although there are other pathways from the reticular activating system to cortex, the forebrain system is especially important in enabling the 'higher' brain functions of the frontal cortex. It is likely that the role of the midline nuclei of the thalamus in arousal directed specifically toward frontal cortex is the reason that infarctions of the intralaminar nuclei initially have the dramatic effect they seem to on consciousness.[43] Merker argued, however, that lesions of the intralaminar nuclei cause effects on the sleep–wakefulness axis rather than on consciousness *per se*, relaxing the subject to a somnolent state that, although debilitating and suggestive of unconsciousness, is very different from, e.g., the awake but unconscious state displayed in absence epilepsy.[44] Thus, nonspecific generalized arousal from the reticular activating system might be sufficient to bring the brain to a state of 'relaxed' wakefulness but not to provide the ideal, alert, focused wakefulness demanded by coordinated thought or action, particularly that mediated by activity in frontal regions of the cortex.

The consequences of disabling the midline-thalamic arousal system can be seen in some brain-damaged patients who persist in a minimally-conscious state. Such patients can only briefly sustain attention on an object or movement, and show disordered speech and behavior and little evidence of thinking. In one such patient, stimulation by electrodes implanted in the intralaminar and midline nuclei resulted in a dramatic improvement in his behavior, including the ability to speak coherently and to eat by himself.[45] Discontinuation of the stimulation caused an immediate return to the minimally-conscious state. In general, electrical stimulation of the central thalamus may enhance cognitive performance through neocortical and hippocampal neuronal activation and also through specific regulation of gene expression.[46]

More evidence for a role of the midline-thalamic arousal system in providing optimal conditions for cognitive functioning is provided by a study of connectivity in thalamocortical loops involving the intralaminar nuclei, frontal cortex, and anterior cingulate cortex in one vegetative state patient. Connectivity in these loops was significantly reduced during the vegetative state in comparison to healthy controls but was roughly normal after that patient had recovered consciousness.[47] Moreover, anterior thalamic nuclei also appear to drive high metabolic activity in posterior midline cortical areas such as precuneus, posterior cingulate, and retrosplenial cortices.[48] These cortical areas are associated with self-awareness and self-reflection, have the highest cortical glucose metabolism in the adult human brain, and are significantly depressed during absence epilepsy, sleep, and anesthesia. Interestingly, vegetative patients can be differentiated from minimally conscious ones by a difference in glucose metabolism in these regions,[48] and these regions are the first to show increases in glucose metabolism during the recovery trajectory from coma though vegetative state to minimal or full consciousness.[49]

ATTENTION

In Posner and colleagues' influential model of attention orienting,[50] the pulvinar nucleus of the thalamus is responsible for (re-)engaging attention at a particular locus in visual space; the posterior parietal cortex disengages attention from that locus and the superior colliculus shifts it to a new locus where the pulvinar again engages attention. Consistent with this interpretation, Laberge argued that the pulvinar is where the attention 'filter' is implemented.[51] Earlier Laberge and Buchsbaum had found that the pulvinar is especially active when attention must be focused on

a particular region of the visual field while excluding other regions.[52] In contrast, Crick emphasized the role of the TRN in selective attention.[53] It is likely that both are important in selecting sensory/perceptual information on which to concentrate processing and in updating the contents of consciousness.[6]

The Pulvinar Nucleus

The pulvinar nucleus is comprised of subnuclei that interact with several different cortical and subcortical regions. The inferior and ventral parts of the lateral subnucleus make extensive reciprocal connections to the visual cortex and receive input from superficial superior colliculus. In contrast, the medial and dorsal parts of this subnucleus seem to be more related to attentional focusing. They make connections to orbitofrontal, parietal, temporal, and cingulate cortex and to the amygdala, and receive input from intermediate layers of the superior colliculus.[54] The oral pulvinar is a polysensory section, making connections to parietal and temporal cortices as well as to visual cortices. The pulvinar nucleus is thus a prime locus for a salience map that could coordinate sensory (visual, auditory, and touch) and motor activity directed toward particular locations in space.[55] The pulvinar also is thought to integrate bottom-up orienting, either through sensory systems or from subcortical inputs such as the amygdala that would signal danger, with top-down orienting, driven by goals and context associated with frontal and other association cortex activity.[6,16]

The TRN

Crick suggested that the TRN is the locus of an 'attention spotlight' implemented by TRN modulation of thalamic relay neuron activity.[53] This general idea (but not Crick's suggested mechanism) is now widely accepted.[10] Attention gating involving the TRN has been confirmed both during classical conditioning[56] and in visual perception of simple patterns.[57]

The neurons of the TRN make inhibitory connections to all of the nuclei of the dorsal thalamus. The TRN neurons in turn receive excitatory input from both cortex and dorsal thalamus, and they also make exclusively inhibitory connections with each other. The TRN is parcellated in much the same way as the dorsal thalamus is, so that particular parts of TRN, cortex, and dorsal thalamic nuclei all serve the same function(s).[58] The sensory sectors contain similar topographic maps and form open loops with their associated thalamic sensory nuclei, allowing them to regulate firing in those nuclei. In turn their own activity is modulated by the associated cortical and thalamic regions. These parts of TRN probably influence only the nearby neurons by enhancing transmission of salient information.[59]

We know less about the nonsensory parts of the TRN. They lack the specificity of the sensory sectors, and so probably exert more global effects on activity in their associated nuclei. One important nonsensory circuit, however, has been elucidated recently in monkeys. The amygdala and orbitofrontal cortex project very broadly to the TRN, including even to the sensory parts, as does the mediodorsal nucleus of the thalamus.[60] It has been argued that these areas, along with the anterior cingulate cortex, regulate behavior relative to the emotional state of the organism and provide an efficient way of focusing attention on emotionally salient information through activation of the TRN, which in turn would inhibit irrelevant sensory and cognitive processing by shutting down parts of the thalamocortical pathways.

Reciprocal inhibition between TRN neurons is important in creating the sleep state.[61] Moreover, the thalamocortical system as a whole can recruit the entire TRN through either cortical or thalamic input.[61] Importantly, focal stimuli initiate TRN oscillations that persist for some time, so that intrareticular inhibition could be responsible for keeping those stimuli in the attention spotlight.[62] Even the strictly parcellated sensory-specific relay nuclei can interact because they all connect to the TRN.[63] Such interactions could allow thalamic sensory relay neurons responding to a salient stimulus to influence the activity of higher-order neurons in the same modality, or those in a multimodal salience map in the pulvinar, thus helping to implement bottom-up attention orienting.

EMOTION

The thalamus is sometimes considered to be part of the 'limbic brain'—deeply involved in creating emotional experiences. Indeed some early speculations attributed to it the affective tone of all perceptions and cognitions, including the moral emotions,[64] and its role in the moral emotions has since been confirmed.[65] As mentioned above it is connected to many emotion-associated areas, including the amygdala and the insula, and to various parts of the frontal cortex, as well as to the hippocampus, from whence come emotional memories. According to some studies the thalamus is rather nonspecific regarding emotion, being activated by a wide range of positive and negative emotion-generating stimuli.[66]

There do seem to be some very specific functions of the thalamus in emotion, however. For example, the

posterior thalamus codes reward value.[67] Thalamic projections to nucleus accumbens seem to be especially important in reward processing.[68] Moreover, some neurons in the intralaminar nucleus, connected to the striatum, respond preferentially to the smaller of two rewards rather than simply firing more the bigger the reward.[69] The cortex and the thalamus together prime the amygdala in fear conditioning,[70] and reward devaluation effects[71] and fear extinction[72] are both modulated by activity in the mediodorsal nucleus. In general, circuits made with the basal ganglia and the striatum are likely involved in integrating emotion, motivation, and perceptual information with memory to select appropriate behaviors.[73]

CONSCIOUSNESS

Clearly, given its dominant roles in all of perception, cognition, emotion, and action, thalamic function is critical in every aspect of human life, including even the ineffable and mysterious experience of conscious awareness. Some theories of consciousness emphasize cortical processing,[74] whereas others promote corticothalamic interactions.[75] But for many years the thalamus itself has been implicated more directly.[3,76] Most recently, it has been proposed that conscious awareness arises from the synchronized activity of neurons in some higher-order nuclei of the thalamus, mediated by the lateral inhibitory interactions of neurons in the TRN.[6] Four specific bodies of evidence support this latter proposition. First, phenomenal and access consciousness are restricted to the *results* of cortical computations only, with little or no experience of or access to the computational processes themselves. Second, the thalamus is the most likely common brain locus of brain injury resulting in vegetative state and of the effects of general anesthetics on consciousness (see next section). Third, the anatomy and physiology of the thalamus and its relationship to the cerebral cortex imply that corticothalamic loops play a key role in consciousness and attention, consistent with the position of Llinás et al.[75] Finally, neural synchronization is a strong neural correlate of consciousness, consistent with the cortical dynamic core proposed by Tononi and Edelman.[77] As most scientific theories, this one is probably not the whole story, and many of its competitors also undoubtedly contain elements of a more complete theory. But whatever the final theory, it seems that the thalamus will be a central player.

Anesthetics

Anesthesiologists are used to turning consciousness on and off with impunity but they still do not know exactly how they manage to do this. An important body of evidence indicates a key role of the thalamus in this process.[78] Several studies have indicated that the thalamus is one of only two brain regions that are suppressed by all general anesthetics tested so far;[79–81] the other is the brain stem reticular activating system, which is implicated in the sleep–wake cycle as indicated earlier. Importantly, sensory cortex remains responsive to stimuli even under large doses of anesthetics.[82] Of course, several critical cortical regions are also involved in the return of consciousness,[83] as is the flow of information between thalamus and cortex.[84] Closely related to the role of midline nuclei in vegetative and minimally conscious states, blockade of potassium channels in the central medial thalamic nucleus of rats reverses desflurane anesthesia.[85] Moreover, propofol, a much-used general anesthetic, preferentially depresses functional connectivity in non-specific (matrix) thalamocortical systems.[86] Thus, it is likely that any explanation of the mechanism by which anesthetics abolish consciousness will centrally involve the thalamus, and likely the nonsensory nuclei in particular.

THALAMIC BRAIN DAMAGE AND COGNITION

Much of what we know about thalamic function, and thalamic participation in brain networks, in humans comes from reports of the effects of thalamic lesions on perception, cognition, and behavior. Clearly lesions in the primary sensory nuclei dramatically affect the specific sensory–perceptual system involved, often in very specific ways, depending on the particular thalamic area involved.[87] But thalamic lesions, often caused by vascular incidents involving the blood supply to specific nuclei, can also affect every other aspect of brain function. Thalamic lesions can cause all sorts of disordered cognition, including delirium, aphasias, confusion, hallucinations, disordered speech, somnolence, and loss of consciousness. Moreover, damage to other parts of the brain can cause reversible thalamic malfunction via diaschisis (depression of blood flow and/or metabolism in one area by damage to a distant area), and often eventually results in permanent thalamic damage because of retrograde degeneration. Thus, because the thalamus is so connected to the rest of the brain, brain damage of any sort impacts thalamic function and damage to the thalamus impacts the function of associated brain networks.

Effects on Cognition

Because we know so little about the higher-order nuclei, information gained from lesions in those nuclei is particularly valuable. Infarcts (dead tissue caused by loss of blood supply) occur in the thalamus, and the nuclei in which they occur are thereby rendered dysfunctional, either temporarily or permanently. Four major systems of blood vessels supply the thalamus, each bringing oxygen and nutrients to a different subset of nuclei, leading to four general infarct syndromes.[87] Neuroimaging studies, while still not ideal, have revealed that these syndromes can be complex, involving most cognitive and behavioral functions.

The tuberothalamic artery supplies a large number of ventral and medial nuclei, including especially the mammillothalamic tract (to hippocampus), the TRN, and the ventral part of the mediodorsal nucleus. Blood clots or leakage affecting these nuclei lead to a host of memory problems, personality changes, executive dysfunction, language problems (if on left), and hemispatial neglect (if on right).[87–89] Some of these can be subtle, as when a left lateral posterior nucleus infarct caused a semantic paralexia, in which a reader substituted content-related words for words seen,[90] as well as other lexical-semantic deficits.[91] Also, certain lesions of the mammillothalamic tract can lead to specific long-term episodic memory impairment.[89] Importantly, intense electrical stimulation of these nuclei results in similar types of deficits, confirming their role in language and memory in particular,[92] whereas minimal electrical stimulation can actually enhance memory performance.[93] Blood flow interruptions in the paramedian artery affect the midline and intralaminar nuclei, the mediodorsal nucleus, and parts of the pulvinar, leading to a similar set of problems, but including in addition attention[89] and arousal problems, and coma if bilateral.[87] The inferolateral and posterior choroidal arteries supply the sensory and motor nuclei and the pulvinar, and their interruptions result in various sensory and motor disorders, including paralysis.[87]

Effects on Consciousness

One of the most devastating possible effects of thalamic brain damage is a disorder of consciousness. Such disorders can range from coma through vegetative state and minimal consciousness to more or less normal consciousness accompanied by more or less severe cognitive deficits that compromise normal living. After severe brain damage, either by trauma or from oxygen deprivation leading to infarcts, the normal progression is from coma (no response to stimulation), to vegetative state (sleep–wake cycle but no response to stimulation), to minimal consciousness (some inconsistent response to stimulation), to partial or full recovery. Death, of course, can happen at any stage before recovery. A classic case of massive thalamic damage from hypoxia is that of Karen Ann Quinlan. She emerged from coma into a vegetative state after a cardiopulmonary arrest and persisted for 10 years in that state before dying of systemic infection. An autopsy of her brain revealed that her cortex and inferior brain stem were largely intact but her thalamus was massively damaged. Kinney et al. concluded that '…the disproportionately severe and bilateral damage in the thalamus as compared with the damage in the cerebral cortex supports the hypothesis that the thalamus is critical for cognition and awareness and may be less critical for arousal.' (p. 1474).[94] Several studies of the brains of vegetative state patients have since confirmed that severe thalamic damage is invariably associated with vegetative state.[95–98] Damage to the mediodorsal nucleus, in particular, seems to be especially disruptive to consciousness.[99] Finally, thalamocortical connectivity, both specific and nonspecific, is dramatically reduced by various forms of brain damage that lead to the vegetative state, including both traumatic and nontraumatic (e.g., hypoxia) damage.[100]

Mental Illness

Given its extensive connections with the rest of the brain, it should not be surprising to find that thalamic dysfunction has been associated directly with mental illness, particularly with the various manifestations of schizophrenia. It has been proposed that disruption of connectivity between prefrontal regions, their associated thalamic nuclei, and the cerebellum produces 'cognitive dysmetria,' which is characterized by difficulty in prioritizing, processing, coordinating, and responding to information.[101] These dysfunctions in turn are prominent in schizophrenia and can account for its broad diversity of symptoms. It is also known that thalamic connectivity to the lateral prefrontal cortex is sparser, and the associated thalamic regions smaller, in schizophrenia, correlating with working memory deficits in that condition.[102] It is possible also that abnormalities in the TRN might explain the altered slow-wave sleep patterns and loss of self-reference in schizophrenia.[103]

Schizophrenia is not the only mental illness associated with thalamic dysfunction. Bipolar disorder has been associated with disruptions in striatum-thalamus and thalamus-pre-frontal connectivity.[104]

And, using a monkey model, it has been shown that over-activation of the ventral anterior and mediodorsal nuclei of the thalamus provokes the compulsive-like behaviors and the neurovegetative manifestations usually associated with the feeling of anxiety in obsessive–compulsive disorder.[105] It is likely that in the future even more mental disorders will come to be seen to closely align with subtle damage to thalamic mechanisms.

Therapy by Stimulation

The thalamus plays a major role in movement through a variety of complex pathways involving the motor cortex, cerebellum, and various subcortical regions. When some part of this complex circuitry is compromised a movement disorder can result. For example, Parkinson's disease is associated with death of the dopamine-producing neurons in the substantia nigra, which eventually results in dysregulation of other parts of the motor circuitry, including the intralaminar and other nuclei of the thalamus.[106] Because the thalamus acts as a gate for movement, combining information from subcortical areas to feed back into the motor cortex, dysregulation of these thalamic nuclei compounds the disorder. Although medication is somewhat effective in alleviating symptoms such as tremor and rigidity, electrical stimulation of the subthalamic nucleus to block some of the aberrant signals into the thalamus is even more effective.[107] Thalamic stimulation of other nuclei is also effective in alleviating symptoms of other disorders, e.g., essential tremor,[108] Tourette's syndrome,[109] epilepsy,[110] and even obsessive–compulsive disorder, although deep brain stimulation of targets other than the thalamus seems to be more effective in the latter case.[109,111] Moreover, it has recently been shown that optogenetic inhibition of thalamocortical neurons can control epileptic seizures resulting from cortical strokes because thalamic hyperexcitability is required to sustain the seizure.[112]

CONCLUSION

The thalamus is centrally located and densely connected with nearly all of the rest of the brain. Given its anatomy, physiology, demonstrated functional interactions with cortical and subcortical systems, and its influence on perception, cognition, emotion, and behavior, more intensive study is surely warranted. Some parts, such as the LGN, are understood in detail, although even there recent investigations are uncovering evidence of ever-more-sophisticated interactions with cortex and other brain areas. The study of the higher-order nuclei should repay intense study even more richly, with the promise of uncovering some of the central mysteries of higher cognition and consciousness, as well as forming a useful locus for therapeutic intervention.

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