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Review

Thalamic contributions to the state and contents of consciousness

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SUMMARY

Consciousness can be conceptualized as varying along at least two dimensions: the global *state* of consciousness and the *content* of conscious experience. Here, we highlight the cellular and systems-level contributions of the thalamus to conscious state and then argue for thalamic contributions to conscious content, including the integrated, segregated, and continuous nature of our experience. We underscore vital, yet distinct roles for core- and matrix-type thalamic neurons. Through reciprocal interactions with deep-layer cortical neurons, matrix neurons support wakefulness and determine perceptual thresholds, whereas the cortical interactions of core neurons maintain content and enable perceptual constancy. We further propose that conscious integration, segregation, and continuity depend on the convergent nature of corticothalamic projections enabling dimensionality reduction, a thalamic reticular nucleus-mediated divisive normalization-like process, and sustained coherent activity in thalamocortical loops, respectively. Overall, we conclude that the thalamus plays a central topological role in brain structures controlling conscious experience.

INTRODUCTION

Different functional modes of the brain vary profoundly in terms of whole-brain dynamics, their associated computational capacities, and the nature of the corresponding conscious experiences. These different modes of conscious processing can be framed as varying across at least two axes[1–3]: "conscious state," an organism's level of arousal and associated global changes in behavioral state, such as wakefulness, sleep, and anesthesia; and "conscious content," the relatively local variations in the informational composition of an individual conscious experience that occur against the backdrop of a particular global state of consciousness, including moment-to-moment changes in both the content of and threshold for awareness. Progress has been made regarding the neural mechanisms that together support both conscious state and contents—from classical animal studies of state to more recent theoretically driven human neuroimaging studies of content. However, the lack of consensus regarding detailed neurobiological mechanisms means that it is exceedingly difficult to differentiate among competing theories of consciousness,[4] with identical results often interpreted as supporting apparently contradictory theories.[5]

Here, we review a growing body of work in systems, cellular, and theoretical neuroscience to suggest a neural foundation of cellular and systems-level processes that support conscious experience.[6–14] We survey a rich literature outlining the contribution of the thalamus to the state of consciousness, such as the distinction between sleep, wake, and anesthesia, drawing empirical evidence from a wide variety of model organisms and computational approaches. We next appraise more recent empirical and computational evidence for a thalamic contribution to the content of consciousness and offer a set of provisional conclusions designed to provoke further empirical investigation. By integrating neurobiological insights across scales and model organisms, we argue that dynamic interactions between specific microcircuits connecting the thalamus and cerebral cortex form the basis of the micro-, meso-, and macroscopic neural dynamics that support both the state and content of consciousness.

THE ANATOMICAL BASIS OF THALAMOCORTICAL CONNECTIVITY

The thalamus is a highly conserved subcortical structure that is robustly and precisely interconnected with the rest of the brain at the microscale (Figure 1A), mesoscale (Figures 1B and 1C), and macroscale (Figure 1D). At the microscopic level, the thalamus is intimately connected with the cerebral cortex. Corticothalamic projections originate from the deep, infragranular layers (thick-tufted L5B pyramidal [ttL5B] and L6 cells), while reciprocal

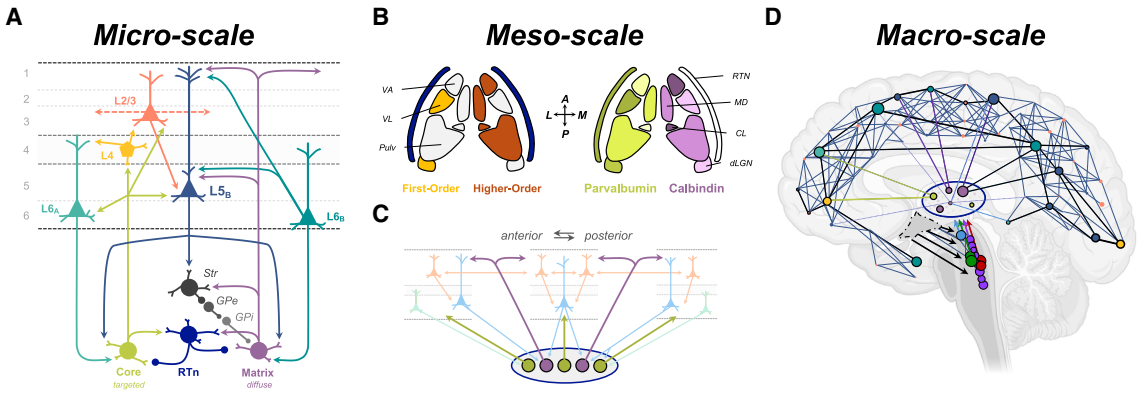

Figure 1. The microscale, mesoscale, and macroscale organization of the thalamocortical system

(A) At the microscale, distinct excitatory cell types in the thalamus (core [olive] and matrix [plum]) project to distinct layers (numbered 1–6) of the cerebral cortex, wherein they make contact with specific cell type populations that have different impacts on cortical computations. Core cells send targeted projections to stellate cells (L4, light orange) in the middle (granular) layers, which then innervate superficial (L2/3, tangerine) and deep (L6A, teal) pyramidal neurons, which project either back to the thalamus (L6A) or within the cerebral cortex (L2/3). In contrast, matrix cells innervate superficial (L1) and deep (L5) layers, with particular targeting of large, thick-tufted pyramidal tract (PT)-type pyramidal neurons (ttL5B, blue) that are the sole cortical output beyond the midbrain. Both ttL5B and matrix cells are also strongly connected with orexin-sensitive layer 6 pyramidal neurons (L6B, teal). There is also extensive inhibitory control over thalamic spiking: e.g., the reticular nucleus of the thalamus (RTn, dark blue), which is excited by thalamic projection neurons and cortical inputs to the thalamus (not shown), and the globus pallidus internus (GPi), which is gated by ttL5B inputs to the globus pallidus externus (GPe, medium gray); NB: this is an idealized diagram intended to convey a general overview of the main circuits, and hence, not all known connections are shown.

(B) The different nuclei of the thalamus can be characterized according to (left) first order (light orange) and higher order (brown), depending on whether driver inputs come from the subcortex or cerebral cortex, respectively; and (right) the expression of parvalbumin (in core cells) and calbindin (in matrix cells). Note that individual nuclei contain a blend of both cell types (denoted approximately by relative color intensity; distribution within individual nuclei not depicted).

(C) At the mesoscale, the thalamus is proposed to control the local (core) and long-range (matrix) excitability of distributed regions of the cerebral cortex through projections that augment local or distributed resonance in corticothalamic loops across the cortical mantle.

(D) At the macroscale, the thalamus is deeply interconnected with the entire cortical mantle, with axonal connections originating in both the cerebral cortex and thalamus that together form a distributed network that shapes conscious experience. Of particular importance is the presence of both convergent (multiple cortical areas projecting to one thalamic area) and divergent (single thalamic areas projecting to multiple cortical areas) architectures within the same system. The hypothalamus (dashed line) projects to multiple hubs within the ascending arousal system, wherein specialized cells release a variety of neuromodulatory neurochemicals (dopamine, light blue; acetylcholine, green; noradrenaline, dark red; serotonin, purple). Key: CL, central lateral; dLGN, dorsal lateral geniculate nucleus; MD, mediodorsal; Pulv, pulvinar; RTN, reticular thalamic nucleus; VA, ventral anterior; VL, ventral lateral nucleus.

thalamocortical projections predominantly terminate in either the middle (granular L4 and deep L3) or the superficial, supragranular (L1) layers, with relatively sparse (though potentially impactful[15,16]) projections to the deeper layers (Figure 1A). Thalamic neurons projecting to the middle cortical layers (known as "core" neurons) typically contain the calcium-binding protein parvalbumin.[17–19] In contrast, thalamic neurons projecting to the superficial or deep cortical layers (known as "matrix" neurons) contain the calcium-binding protein calbindin.[17–19] Core neurons tend to have strong effects on their cortical targets—i.e., cause large excitatory postsynaptic potentials (EPSPs) via ionotropic glutamate receptors—and thus are considered "drivers." Matrix neurons tend to have weaker, graded effects—i.e., smaller EPSPs via both metabotropic and ionotropic glutamate receptors—and are thus considered "modulators."[20,21] Spiking activity from the sensory organs is transmitted to the thalamus (mainly via first-order thalamic nuclei, such as the lateral geniculate nucleus or medial geniculate body), which in turn sends dense axonal projections to primary sensory cortices. Information transmission between cortical neurons occurs via direct cortico-cortical connections and via higher-order thalamic nuclei (e.g., the pulvinar and intralaminar nuclei) that interconnect widespread cortical areas via robust cortico-thalamo-cortical pathways.[22]

At the mesoscopic scale, the thalamus has been divided into at least 30 nuclei, based on connectivity as well as cytoarchitectonic, neurochemical, and functional criteria.[23] The distribution of core and matrix neurons differs across thalamic nuclei (Figure 1B): core neurons predominate in first-order thalamic nuclei that receive driver inputs from the sensory periphery, whereas matrix neurons predominate in the higher-order intralaminar thalamic nuclei (except in the centromedian [CM] nucleus of the posterior intralaminar thalamus, which is parvalbumin-rich[24,25]). Most thalamic nuclei contain a blend of both cell types, with different proportions across nuclei (Figure 1B, right).[25,26] Fascinatingly, there are also thalamic neurons that exhibit both core- and matrix-like properties.[19] This includes intralaminar nuclei, many of which have broad projections to the cerebral cortex (similar to those seen in matrix neurons) but with stronger projections to the striatum.[27–29] Through the unique projections of each type of thalamic neuron, the thalamus can simultaneously influence both local and distant patterns of neuronal spiking activity (Figure 1C). The excitatory projection neurons of the thalamus are also embedded within a dense inhibitory network of cells that both surround and intersperse the excitatory cells. Specifically, the thalamus is bordered by the shield-like reticular nucleus, which is composed entirely of inhibitory GABAergic cells that are excited by both excitatory cortico-thalamic and thalamocortical projections and then release (inhibitory) GABA onto a broader population of thalamic cells than the population from which they were excited.[30–32] This organization is thought to dampen ongoing thalamic activity and may also

play a role in more selective features of attention and consciousness.[8,32,33]

At the macroscale, the thalamus acts as a hub connecting the ascending sensory pathways and arousal system from the brainstem with the massive projections from the cerebellum, basal ganglia, and colliculi, as well as the vast reciprocal connections with the entire cerebral cortex.[8,12,21,34–36] Generally speaking, directly connected cortical areas are mirrored (with some blurring) by cortico-thalamo-cortical projections.[37,38] In addition to acting as a key topological hub in the brain, corticothalamic projections have the key feature of convergence (Figures 1C and 1D), which forces high-dimensional activity patterns in the cerebral cortex—useful for distinguishing between similar situations and supporting a wide range of behaviors—to be compressed, giving rise to lower-dimensional patterns in the thalamus that coincide with simpler, latent variables.[39,40] This lower-dimensional information can then be shared via divergent outputs from the thalamus to the cerebral cortex, ensuring efficient, robust information processing across the brain.[8,41,42] With this key feature in mind, it is clear that the macroscopic location of the thalamus between the cortex, subcortex, and ascending arousal system places the structure at a crucial nexus for understanding the neural mechanisms of conscious state and content.

THALAMIC CONTRIBUTIONS TO CONSCIOUS STATE

The profound transition in conscious experience from sleep to wake reflects a corresponding change in whole-brain dynamics so pronounced it is electrically detectable from the scalp.[43] In this transition to the waking state, a regime of low-frequency, synchronized activity indicative of sleep shifts into a high-frequency, desynchronized (i.e., asynchronous, irregular) mode reflective of a high-conductance state.[44] This transition is thought to emerge from a switch-like mechanism that originates in the lateral hypothalamus,[45] wherein neurochemicals, such as orexin, are released, recruiting brainstem and forebrain regions within the ascending arousal system.[46–48] Widespread projections from these areas then release neuromodulatory chemicals, such as norepinephrine, acetylcholine, serotonin, and dopamine, which globally increase neural excitability,[49] motivating the transition from sleep to wakefulness.[45] The thalamus is a particularly important downstream target of the ascending arousal system, and its specific interactions with cortical circuits plays a crucial role in restoring conscious functionality to the whole-brain dynamical regime.

Thalamocortical microcircuit contributions to conscious state

A key mechanism through which arousal-based neuromodulatory inputs exert their effect is via T-type calcium channels and non-specific I*h* channels in the thalamus. In the waking state, T-type channels are inactive, and the cells operate in a "tonic" mode, firing regular action potentials at variable rhythms. At moderate levels of hyperpolarization, T-type calcium currents are open, causing an inhibition-induced burst that operates in the typical spindle frequency. Further hyperpolarization then opens non-specific I*h* channels, which paradoxically depolarizes the cell, reducing the rate of inhibition-induced slow-wave bursts to a delta frequency. As the cells cycle rhythmically through these up and down states, they set the pace of cortical rhythms[50–55]: the sleep spindles that are emblematic first of early stages of non-rapid eye movement (NREM) sleep then of "slow-wave activity" (SWA) that characterizes later stages of sleep. *In vivo* thalamic manipulation experiments have further reinforced the role of the thalamus in electrophysiological signatures of brain states: thalamic inhibition in freely moving rats has been shown to alter both sleep spindles and slow cortical waves, while optogenetic activation entrains slow-wave frequencies within a narrow band (0.75–1.5 Hz).[56] Importantly, this pacemaker mechanism for cortical SWA in NREM sleep is also characteristic of SWA in anesthetic-induced unconsciousness.[57]

Why should the thalamus play such a crucial role in shaping the expression of overall brain states? The weight of evidence suggests that (neuromodulatory-controlled) thalamic bursts influence the onset and timing of cortical up states.[51,57] More broadly, thalamus may influence conscious state by tuning integrative properties of the cerebral cortex, such as oscillatory synchrony, neuronal resonance (responsiveness to inputs at specific frequencies), and functional connectivity[12,58–61] (for general reviews of control of oscillatory synchrony, see Singer[62] and [63]). Signals that arrive in an area during a depolarized up state more readily translate into spiking activity, while signals that arrive during down states may fail to depolarize cells, leading to signal loss. This expected dysfunction in communication is readily observed in perturbation experiments during less-conscious states. When stimulations such as transcranial magnetic stimulation are delivered during wakefulness and REM sleep, they produce a complex electroencephalogram (EEG) response that resonates across regions, while pulses delivered during NREM sleep, anesthesia, and coma yield simple EEG responses that rapidly die out.[64–67] Similar experiments in rodents hint at a thalamocortical basis of the phenomenon, as electrical or optogenetic stimulation of the deep cortical layers (which project to thalamus; Figure 1) trigger complex responses in conscious states not triggered by superficial layers.[68,69] Further evidence suggests that response complexity depends on thalamic responses to the deep-layer perturbation: in wake or REM sleep, brief bursts in thalamus give way to rebound excitation, while in NREM sleep or anesthesia, longer periods of thalamic bursting trigger lingering cortical down states.[69]

Neural changes associated with conscious state transitions depend on intimate connections between the cerebral cortex and matrix thalamus at the microcircuit level (Figure 2A). Deep layers of cortex, particularly L5B and L6B, project to higher-order thalamic nuclei rich with matrix cells. These matrix cells in turn project diffusely back up to the cerebral cortex, wherein they target ttL5B neurons at both their apical dendrites, located in L1, and oblique dendrites, located in L5A.[17,19,70] These ttL5B neurons participate in cortical processing in intracolumnar, lateral, feedforward, and feedback pathways and are thus suspected by many to play a key role in consciousness.[13,19,70–79] Importantly, the matrix thalamus is ideally placed to modulate the activity of these neurons (Figure 2A).

Optogenetic stimulation experiments *in vivo* demonstrate that ttL5Bs, more so than L2/3 pyramidal neurons, generate cortical slow waves (1 Hz)[84,85]; for reviews, see Neske[51] and [86] ttL5Bs also uniquely synchronize in up-down states across cortex under

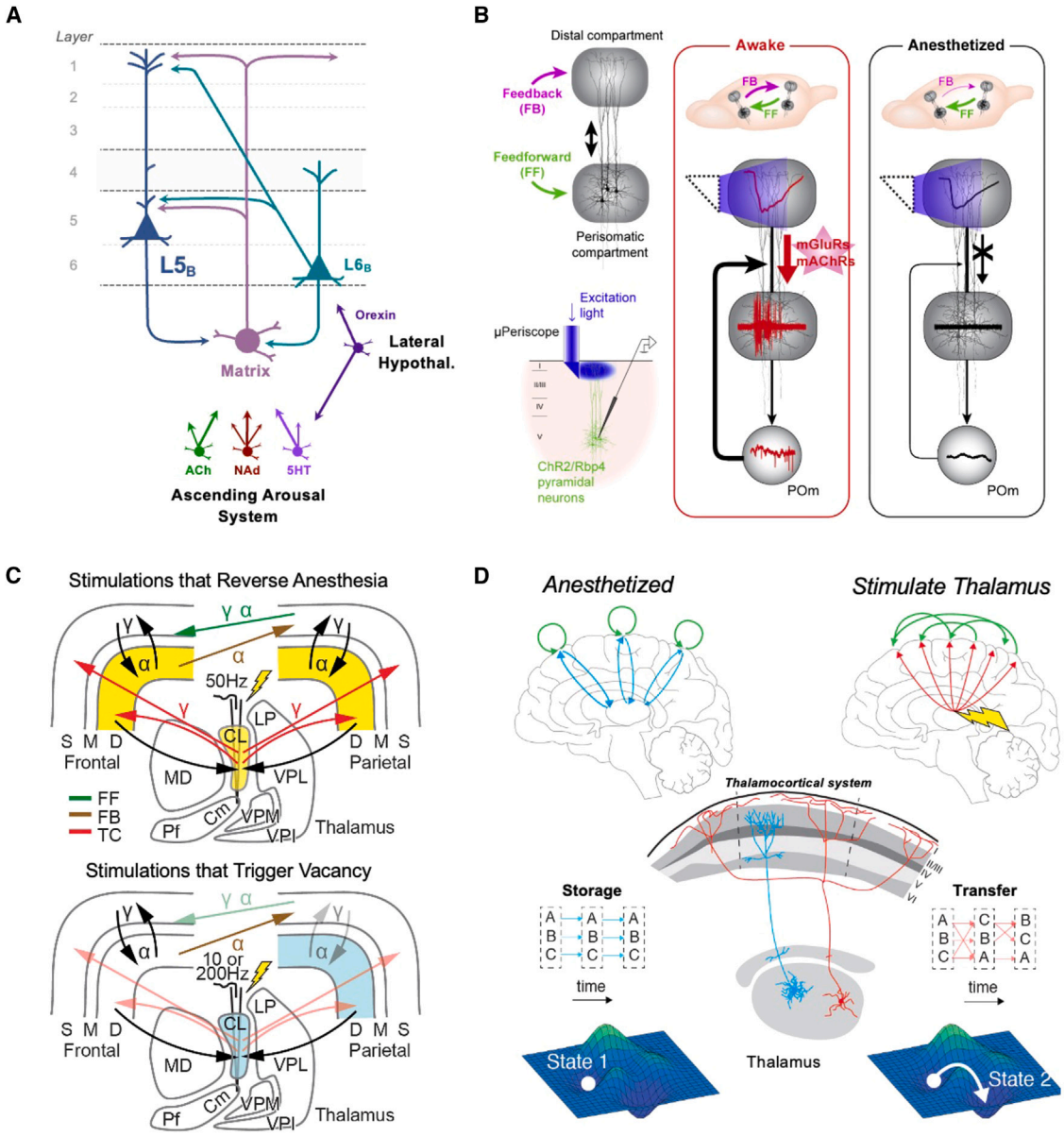

Figure 2. Matrix thalamic inputs interface with the cerebral cortex at different scales to alter conscious state

(A) Thalamocortical circuits implicated in conscious state. Matrix thalamic cells (purple) are important targets of the reticular activating system. They reciprocally connect to ttL5B (dark blue) neurons and are ideally positioned to modulate their excitability. Orexin-gated L6B neurons further modulate these thalamocortical interactions.

(B) During wakefulness, matrix thalamic inputs excite L5 pyramidal neurons via metabotropic glutamatergic inputs to the oblique dendrites, allowing calcium spikes in the apical dendrites to influence somatic activity. Under general anesthesia, in the absence of thalamic excitation, L5 pyramidal neurons fail to propagate signals from the dendrites through to the soma, contributing to functional dissociation of brain areas. Figure adapted with permission from Suzuki and Larkum.[80]

(C) Minimally sufficient mechanism for CL thalamic DBS to restore or disrupt consciousness. Top: thalamocortical (TC), feedforward (FF), and feedback (FB) connections most altered by thalamic stimulations that successfully reversed general anesthesia (propofol and isoflurane) in macaques. Higher-frequency (50 Hz) thalamic DBS simultaneously via 16 contacts of a linear array (200 μm spacing) centered in CL mimics wake-state firing (yellow) from thalamocortical efferents. This increases firing in deep cortical layers (yellow), which reinstates intracolumnar, feedforward, and feedback communication at alpha and gamma frequencies despite inhibitory pressure from anesthesia. Adapted with permission from Redinbaugh et al.[81] Bottom: low- (10 Hz) and very-high- (200 Hz) frequency DBS centered on CL in awake macaques instead produces a vacant state similar to the symptoms of absence epilepsy. Low activity in thalamus and deep cortical layers (blue) leads to perturbed connectivity in parietal intracolumnar circuits and disrupted feedforward communication (light shading). Based on results from Redinbaugh et al.[82]

(D) A large-scale corticothalamic neural mass model (imbued with matrix and core thalamic cells) that replicated recovery of consciousness with thalamic stimulation following propofol anesthesia in macaques. Simulated stimulation of matrix, but not core, cells increased cortical excitability, allowing interareal information transfer and more complex, less stereotyped dynamics. At the macroscale, this was reflected in a flattening of the whole-brain energy landscape that is typical of the waking state. Figure reproduced with permission from Müller et al.[83]

general anesthesia relative to neurons in other cortical layers.[87] Empirical evidence suggests that thalamic bursting drives the rhythmic properties of these cells,[51,58,68] and neuromodulatory input from the thalamus may more generally control their responsiveness to other inputs. Indeed, a recent study pairing optogenetic stimulation of dendrites in L1 with patch-clamp recordings of the apical dendrites and soma of the same neurons showed that dendrites and soma are largely synchronized in response to dendritic activation during wakefulness but decoupled under multiple types of anesthesia (Figure 2B).[80] This effect could be replicated by the application of mGluR antagonists (intended to block glutamatergic thalamic input to the "coupling zone" that allows activity to propagate between apical and somatic compartments), as well as direct inactivation of the thalamus with muscimol.[80] When decoupled, ttL5Bs are unable to combine activity from feedback projections terminating in superficial layers with activity from feedforward projections terminating in deeper layers[74,76] or activity even within the cortical column. Thus, thalamic dynamics can directly contribute to a breakdown in feedforward and feedback information flow associated with a drop in conscious state.[13]

Other deep-layer neurons that interact with thalamus and ttL5B neurons to influence conscious states are L6B pyramidal neurons, which provide modulatory input to the matrix-rich, higher-order thalamic nuclei,[15,22,34,88] and also send axonal projections to L1, wherein they contact the apical dendrites of ttL5Bs (Figure 2A). Activation of these L1 efferents generates calcium spikes in the apical dendrites of ttL5Bs, an effect that is eliminated by the application of an NMDA receptor (NMDAR) antagonist.[15] This pathway has unique ties to conscious state and arousal because, while all cortical neurons express receptors for different classes of neuromodulatory inputs,[48] layer 6B pyramidal neurons are the only cortical cells sensitive to orexin.[15]

Thalamocortical mesocircuit contributions to conscious state

The breadth of thalamocortical projections expands this microcircuit motif into the mesoscale (Figure 1C). Stemming from a variety of higher-order thalamic nuclei, matrix efferents span the cerebral cortex and target many circuits associated with specific higher-order functions.[34,89] During wakefulness, tonic spiking in the thalamus tunes the responsiveness of networked cortical areas to optimize efficient information transmission[60,90] and, in doing so, contributes to a responsive, functionally coherent conscious state.[59] In less-conscious states, bursting thalamic activity instead sets the pace of cortical slow waves in a way that contributes to the area's functional isolation from the rest of the network. During NREM sleep, it has been shown that distinct brain areas oscillate at different frequencies and relative phases.[91] By desynchronizing up states between brain areas, matrix thalamic projections are well placed to ensure the functional isolation required for modular processing,[12] rendering cortical communication sparse, inconsistent, and dissociated from normal sensory pathways. As the network function shifts instead toward mechanisms of synaptic homeostasis and memory consolidation,[51,92] the resulting drop in network topology and coherent transmission of content would contribute to a loss of consciousness.[93,94]

Important causal evidence for the role of the thalamus in the generation and maintenance of conscious states comes from clinical observations related to disorders of consciousness, especially coma and absence epilepsy. Broadly, coma is associated with lesions that affect the brainstem; however, bilateral thalamic lesions[95] and lesions that decouple the thalamus from the reticular activating system[96,97] can also cause coma, and recovery from coma is associated with improved function in thalamocortical, thalamostriatal, and frontoparietal circuits.[43,98–103] A number of studies have now demonstrated that thalamic deep brain stimulation (DBS), specifically of the central thalamus, i.e., intralaminar nuclei, leads to improvements for patients in coma[104–107] (for review, see Cao et al.[108]). Interestingly, most studies target stimulation to the central lateral (CL) or CM nuclei, and many highlight beneficial clinical effects with moderate stimulation frequency (40–100 Hz).[108] This finding is particularly noteworthy because parallel clinical literature suggests that low-frequency ($\leq$10 Hz) intralaminar stimulation instead triggers seizures characteristic of absence epilepsy.[109,110] Ictal episodes of absence seizures are associated with loss of consciousness (individuals are often caught "staring off into space") but with no discernible reduction in overall arousal. Thus, the intralaminar nuclei appear to exert bidirectional control over conscious state.

Mechanistic insights into the role of the thalamus in controlling conscious state have come from three recent studies that have used central thalamic DBS to reverse the effects of general anesthesia in macaque monkeys.[81,111,112] Despite methodological idiosyncrasies (for example, targeting CM vs. CL nuclei), in all cases, animals were demonstrably roused from anesthesia (i.e., they began to make voluntary movements and respond to external stimuli) following central thalamic stimulation, despite constant administration of anesthetic agents. One experiment also demonstrated restoration of neural responses to a local-global auditory oddball paradigm, implying the reinstatement of conscious processing.[112] Indeed, central thalamic DBS reversed many signatures of loss of consciousness and was shown to restore cortical interactions and functional connectivity in ways more typical of wakefulness.[81,111,112]

Even though animals were roused by stimulation, CL DBS did not always eliminate SWA in the cerebral cortex or the dominance of slow-wave coherence in intra-cortical communication pathways. Specifically, 50 Hz DBS targeted to CL nuclei—likely increasing local CL nuclei activity[113]—reinstated firing in the deep layers of cortex, as well as high-frequency intracolumnar, feedforward, and feedback coherence (Figure 2C).[81] This finding suggests that the function of the thalamus goes beyond providing the cortex with excitatory tone. Rather, it is crucial for driving distinct functional modes in the cortex, even in spite of the typically overwhelming inhibitory influence of anesthetics. In contrast, both lower- (10 Hz) and much higher-frequency (200 Hz) stimulation of CL nuclei—likely leading to reduced CL nuclei activity[114]—has been shown to produce absence-like events in wakeful macaques.[82] Without any noticeable drop in arousal, animals stared vacantly into space, occasionally making repetitive movements with the mouth (similar to absence seizure pathology). These vacant events were accompanied by altered intracolumnar dynamics and a broadband breakdown in feedforward functional connectivity (Figure 2C).[82] Indeed, many of the

same complex network dynamics restored by 50 Hz CL DBS under anesthesia were perturbed when DBS frequencies were more extreme[9,81,82]—i.e., more dissimilar from natural wakeful dynamics of the nucleus.[54,81,82,115] These results directly suggest that abnormal thalamic activity can disrupt normal cortical function even without a clear drop in arousal.

While the matrix thalamus clearly contributes to cortical functional modes, the intralaminar thalamus is particularly involved in the control of conscious states. However, substantial differences in the anatomical properties of different intralaminar nuclei (CL and CM) make the mechanism unclear. CL neurons are part of the anterior intralaminar group, stain strongly for calbindin[17] (signifying matrix-style projections), and target frontoparietal circuits as well as the basal ganglia.[34,116,117] In contrast, CM nuclei are part of the posterior intralaminar group and predominantly stain for parvalbumin.[17] While this pattern is usually associated with core thalamic projections, most of CM's efferent projections target the basal ganglia[118] (which is unlike other core nuclei), with the few remaining cortical projections targeting motor areas and appearing relatively "matrix-like."[119–121] If both nuclei influence consciousness by a shared mechanism, it likely involves restoration of frontoparietal and basal ganglia circuits. This is consistent with the mesocircuit hypothesis that disruptions in intralaminar thalamus contribute to reduced excitation of the basal ganglia, triggering unconstrained tonic inhibition throughout the thalamus and substantial thalamocortical dysfunction.[103] If this proves true, CM nuclei may dominate the effect, as they have stronger basal ganglia connectivity. CM nuclei have also been shown to counter prepotent responses, via the thalamostriatal pathway, enabling behavioral flexibility.[122] Similarly, CM stimulation effects on the striatum may help counter the dominant neural dynamic of the low arousal state, enabling a greater repertoire of potential neural activity patterns.

Alternatively, CL nuclei may drive the intralaminar influence over consciousness. Evidence from many studies suggests that 40–100 Hz central thalamic stimulation induces conscious state transitions in rodents, macaques, and humans.[81,104,110,123] Many neurons within CL nuclei present with a high, tonic, spontaneous firing rate (around 40–50 Hz) during wakefulness, which slows during general anesthesia and NREM sleep.[81,115] It is possible that these CL neurons mediate the DBS rousing effect, with higher-frequency stimulation mimicking their wake-state firing patterns. Most of the DBS experiments covered in this review use clinical DBS electrodes, which have relatively large contacts and are likely to affect multiple regions by current spread. CM and CL nuclei are in close anatomical proximity, and thus, most traditional DBS experiments stand a strong chance of influencing both nuclei with stimulation events. The use of a more-targeted, low-current ($\leq$200 μA) microstimulation approach has shown that emergence from anesthesia was more likely when the stimulation array was centered in CL nuclei as opposed to neighboring nuclei like CM or mediodorsal (MD).[81] Similar arousals observed in the other macaque experiments used substantially higher current (>1 mA) targeted at CM nuclei, and weaker stimulation could not produce the same effects.[111,112] This might suggest that higher current levels are needed to recruit activation of CL in order to restore consciousness.

One final but important clue about the underlying mechanism comes from a recent modeling study, where the CL-nuclei-specific stimulation findings were recapitulated *in silico* using a biophysical neural mass model incorporating core and matrix thalamic projections. Simulated stimulations of the matrix-like, calbindin-rich thalamus (e.g., CL nuclei), but not core-like, parvalbumin-rich thalamus (e.g., CM nuclei), were shown to reinvigorate cortex and push the network toward a quasi-critical regime—where individual nodes in the network are highly susceptible to perturbations while also remaining stable at a network level—that is typically associated with wakefulness (Figure 2D). Through information theoretic analysis, this study showed that the shift back toward quasi-criticality allowed information to once again propagate across the network, restoring a coherent, wake-like state of bidirectional information flow despite the ongoing inhibitory pressure and reduced functional connectivity imposed by the simulated general anesthetic.[83] In spiking networks, analogous traveling waves have been shown to increase the response gain of individual neurons receiving input aligned with the wave's phase and to gate perception of close-to-threshold visual stimuli,[124,125] thus providing a plausible link between the matrix-mediated changes in the state of consciousness discussed above and matrix-mediated gating of conscious content (a topic we discuss in detail in the next section). Although there are limitations to such neural modeling experiments, the results suggest that regions like CL nuclei, with strong matrix-like projections to multiple cortical areas, are better candidates to recruit cortical function than CM nuclei.

In sum, there is robust evidence that the thalamus exerts vital control over conscious state. At the microscale, the thalamus interfaces with the reticular activating system to tune ttL5B pyramidal neurons, controlling SWA and receptiveness of cortex to input. At the mesoscale, this translates into a broader mechanism by which the wakeful thalamus influences cortical functional connectivity and synchrony. The intralaminar nuclei, and perhaps CL nuclei in particular (with broad projections to both frontal and parietal cortex), may specifically control consciousness by tuning these cortical properties toward heightened conductivity at the macroscale. Overall then, while thalamus clearly plays a vital role in the arousal component of consciousness, the true power of its function seems to lie in the ability to reignite whole-brain dynamics in ways that overcome inhibitory pressures of brain damage or anesthesia. In the rest of this review, we will make the case that thalamic circuits directly contribute to the contents of conscious experience.

THALAMIC CONTRIBUTION TO CONSCIOUS CONTENTS

Although thalamocortical loops play a prominent role in several theories of consciousness,[10,75,126] the search for the neural correlates of conscious content has historically focused on the cerebral cortex (e.g., Bisenius et al.[127]). Rather than actively shaping experience, the thalamus (if it is considered at all) has typically been relegated to a role in gating contents into consciousness.[128] Here, we advance the hypothesis, based on first-principles anatomical considerations, that both core and matrix thalamic cells also play crucial computational roles in shaping experiential properties. The diffuse connectivity of

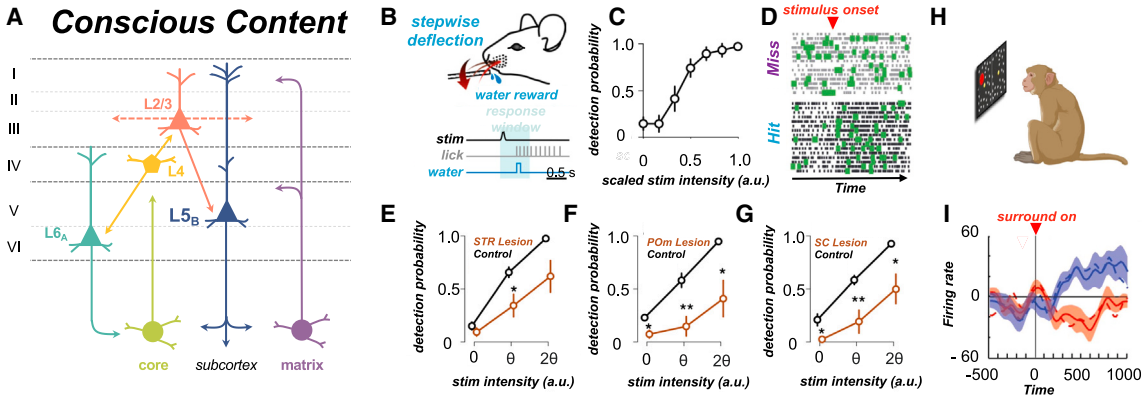

Figure 3. Thalamic contributions to conscious contents

(A) Thalamocortical circuit hypothesized to support the contents of consciousness. Matrix thalamic cells (purple) project to the apical dendrites of ttL5B (dark blue) and L2/3 (orange) pyramidal cells and the oblique dendrites of ttL5B cells in L5A. The projections to the oblique dendrites depolarize the trunk of the cell through the action of metabotropic glutamatergic (and cholinergic) receptors, which has been hypothesized and shown to facilitate coupling between the apical and somatic compartments allowing sodium spikes to backpropagate from the soma to the apical dendrites contributing to the generation of calcium spikes and vice versa. Both matrix and core (light green) thalamic cells receive driving inputs from ttL5B cells. Core cells send driving projections to L4 IT-type cells and L2/3 pyramidal cells (not shown). L4 IT-type cells then form a closed excitatory loop with core cells via L6A neurons (cyan). Similarly, excitatory output from L4 cells target the basal dendrites of ttL5B via L2/3.

(B) Illustration of the threshold-detection paradigm used in both studies by Takahashi and colleagues.[16,145]

(C) Psychometric function showing response probability (mean ± SD) as a function of (scaled) stimulus intensity across mice and recording sessions.

(D) Example raster plots for the soma of ttL5B cells in hit and miss trials. Sparse bursts (green) occur in both conditions but are time locked to stimulus onset on hit trials.

(E–G) Detection probability (mean ± SEM) in the threshold-detection paradigm as a function of stimulus intensity comparing the control condition to (E) striatal inhibition, (F) POm inhibition, or (G) superior colliculus inhibition from Takahashi et al.[16]

(H) Generalized flash-suppression paradigm used by Wilke et al.[146] Monkeys fixated on a central location for 1.5 s, at which point the target stimulus (red disk) appeared in the visual periphery. 2 s following the onset of the target stimulus, a surround pattern appeared, rendering the target stimulus invisible with a probability proportional to the density of the pattern. Monkeys were trained to report the disappearance of the stimulus with a lever press.

(I) Average firing rate (±SEM) of neurons in the dorsal and ventral pulvinar that were suppressed by the disappearance of the stimulus (red) or were activated by the disappearance of the stimulus (blue). Dashed lines show pulvinar responses for the physical removal of the stimulus, while solid lines show the pulvinar responses to the perceived disappearance.

(B)–(I) were recreated with permission from Takahashi et al.[16,145] and Wilke et al.[146]

modulatory matrix cells,[19,129] combined with the widely branching apical dendrites of ttL5Bs[130] to which they project, seemingly does not possess adequate specificity to support the specificity of conscious contents. Rather, they offer a plausible mechanism for explaining how sensory content enters consciousness, irrespective of the properties of the specific content. Core thalamic neurons possess more precise driving connections to L2-4 IT-type neurons[19,129] and interact with the inhibitory reticular nucleus, which introduces a mechanism akin to divisive normalization[131,132] for selectivity into their dynamics. We argue that an appreciation of the nuanced neuroanatomy of the core (in addition to matrix) thalamic nuclei, and their embedding within the rest of the brain, may explain key properties of the contents of consciousness in typical waking experience, including its "integrated" (i.e., unified),[35,133–135] "segregated "(i.e., differentiated),[10,126,136] and seemingly "continuous" nature[14,137,138] (Figure 4). Although emphasis on the importance of these properties differs across theories of consciousness, these concepts have a long history in the philosophy[135,138,139,140] and science[10,14,136,141,142] of consciousness and have been discussed by a wide range of theorists with divergent starting assumptions (see articles in this issue).

Thalamus gates the threshold for conscious contents

The threshold for conscious perception is typically studied by contrasting neuronal responses to stimuli that are as close to physically matched as possible but vary according to whether the subject is conscious of the stimulus (operationalized through direct or indirect behavioral reports[143,144]). Recent work has keenly employed this approach in a mouse model of perception demonstrating a role for the same matrix thalamus-ttL5B circuit implicated in the anesthetic control of conscious state[80] in controlling the threshold of conscious perception (Figures 2A and 3A).[16,145]

In a whisker-deflection threshold-detection task (Figures 3B and 3C), synchronous bursting (interspike interval < 12.5ms) in ttL5Bs was shown to be time locked to stimulus onset (Figure 3D) and also to distinguish "hits" and "false alarms" (trials on which the animal reported perceiving a stimulus) from "misses" and "correct rejections" (trials on which the animal did not report perceiving the stimulus as present). As mentioned above, the bursting state of ttL5Bs *in vitro* is controlled by NMDAR-driven calcium spikes in apical dendrites, a prominent site of matrix thalamic inputs.[20] When there is a calcium spike in the apical dendrites and coincident input (within 25–30 ms) to the basal dendrites, the somatic spikes of ttL5B neurons shift from a regular spiking to a bursting regime.[147] Crucially, in the context of threshold detection,[145] optogenetic stimulation and pharmacological inhibition of apical dendrites has been shown to shift the threshold for stimulus detection by making apical dendrites more or less likely to burst. Specifically, optogenetic activation of ttL5B apical dendrites lowers the perceptual

threshold of the animals, while a $GABA_B$ agonist increases the perceptual threshold.[16] Importantly, it was also shown that targeted inhibition of POm (a higher-order somatosensory thalamic nucleus rich in both core and matrix cells), superior colliculus, and the striatum—all of which project either directly or indirectly to the apical dendrites of ttL5B through matrix cells—increased the animal's perceptual threshold (Figures 3E–3G). Crucially, the synchronous burst response that was time locked to stimulus onset was not found in a response/reward-only condition, suggesting that the synchronous bursting associated with conscious perception was unlikely to be driven by motor preparation or reward expectation. This implies that the threshold for the contents of conscious perception may be mediated by the formation of a reentrant loop between matrix thalamus and ttL5B cells transitioning the cortical ttL5B cells from a regular spiking (unconscious) to a bursting (conscious) regime.[8,13,14] Recent modeling work[148] has provided support for this perspective, showing that diffuse drive targeting the apical compartment of a large neuronal population of ttL5Bs—analogous to the projections of matrix thalamus—controlled the propagation of activity across the cortical sheet.

Although the cellular-level study of the contents of consciousness in rodent models is still in its infancy, evidence from invasive recordings in human surgical patients[149] and non-human primates[146] as well as non-invasive human neuroimaging,[150–152] combined with biophysical modeling[153,154] and the anatomy of the matrix-ttL5B circuit (Figure 3A), suggests that this circuit may be a key component in the general mechanisms underlying perceptual consciousness in humans, non-human primates, and rodents alike. In humans, biophysical modeling of source-localized MEG recordings found that the auditory awareness negativity—an evoked electrophysiological response thought to characterize perceptual awareness of auditory stimuli in an auditory threshold-detection task—was best explained by increased input to superficial layers of the cortical column housing the apical dendrites of ttL5Bs.[154] Given the known projections from matrix cells in higher-order thalamus to superficial layers of the cerebral cortex, a reasonable interpretation of this finding is that increased thalamic feedback in the aware condition led to widespread bursting in ttL5Bs. More direct evidence for thalamic involvement comes from a study of human patients with chronically implanted thalamic electrodes.[149] Performance in a visual masking task revealed a large awareness-selective response in the matrix-rich intralaminar nuclei of the thalamus. Similar thalamic correlates of awareness, though coarser in grain, were confirmed using fMRI in healthy controls with a version of the task that controlled for report-related confounds. This suggests that the thalamus is sensitive to perception above and beyond mechanisms needed to explicitly report perception.

In non-human primates, single-unit recordings during generalized flash suppression (Figure 3H) have shown that cells in ventral and dorsal pulvinar (higher-order thalamic nuclei, containing a mixture of matrix and core cells) are selectively modulated by an animal's awareness of a stimulus rather than its physical presence, independent of report demands (Figure 3I). In contrast, the first-order lateral geniculate nucleus (i.e., whose main driving input is from the retina) is selectively modulated by the physical presence of the stimulus, but not its subjective visibility.[146] This result is reinforced by three recent human neuroimaging studies of bistable perception, each of which found that visual-rivalry-induced activity in the pulvinar strongly differentiated between competing percepts.[150–152] This finding is also complemented by the result that lesions to pulvinar can lead to changes in conscious content, including perturbed feature binding[155] and hemineglect,[156] which, in the context of the current framework, would manifest as a near absence of pulvinar-ttL5B reentrant interaction preventing visual activity within the affected hemifield from achieving widespread propagation.

In support of the above interpretation of the role of the pulvinar in visual consciousness, a recent thalamocortical spiking neural network model of visual rivalry[153] found that the same matrix-mediated, ttL5B gating mechanism known to underlie threshold detection in rodents could also account for perceptual awareness across visual rivalry paradigms. Under the tenets of the model, perceptual dominance was determined by the formation and maintenance of a cortical bursting state through recurrent connections between ttL5B cells and a matrix-like population of thalamic cells. Importantly, the model conformed to a number of key psychophysical benchmarks (Levelt's laws[157]) and reproduced the visibility-specific pulvinar responses observed in non-human primates.[146]

Thalamic contributions to properties of conscious contents

Conscious experiences in the typical waking state are *integrated*, meaning percepts are experienced as unified wholes,[10,14,126,135,139] not disparate, disconnected component pieces (for exceptions, see Bayne[135,139]). When perceiving a visual scene, we do not sequentially perceive individual features of objects; the contents of the scene are experienced *en masse* in a common visual space. With others,[10,14,126] we (at least partially) attribute this property to the anatomical and functional properties of thalamocortical loops. In particular, the thalamus contains orders of magnitude fewer cells than the cerebral cortex,[158,159] meaning that information embedded within cortical circuits will, by necessity, be compressed when processed through the thalamus before returning to the cerebral cortex[8,12,160](Figure 4A). We propose that this pervasive motif of information compression contributes to the unified, low-dimensional "gist" quality of conscious contents. Specifically, the low-dimensional nature of the representation could not resemble the rich, detailed content ever present in visual experience, but it might give rise to the gist of scenes or events (e.g., informationally compressed versions of the scene) perhaps contributing to less vivid but still adaptive aspects of experience. Consistent with the neural aspects of this hypothesis, thalamic activity in humans has been shown to be temporally coincident with low-dimensional network integration in complex cognitive tasks.[12,40,41,161] The resolution of these data is not sufficient to resolve whether this support occurred via core or matrix nuclei (or both); however, there is evidence that the expression of genetic markers differentiating core and matrix populations covaries with similar low-dimensional cortical patterns.[18]

Another key feature of consciousness is that perceptual contents are typically segregated from one another and experienced as distinct, differentiated perceptual objects.[10,126,136] Successive

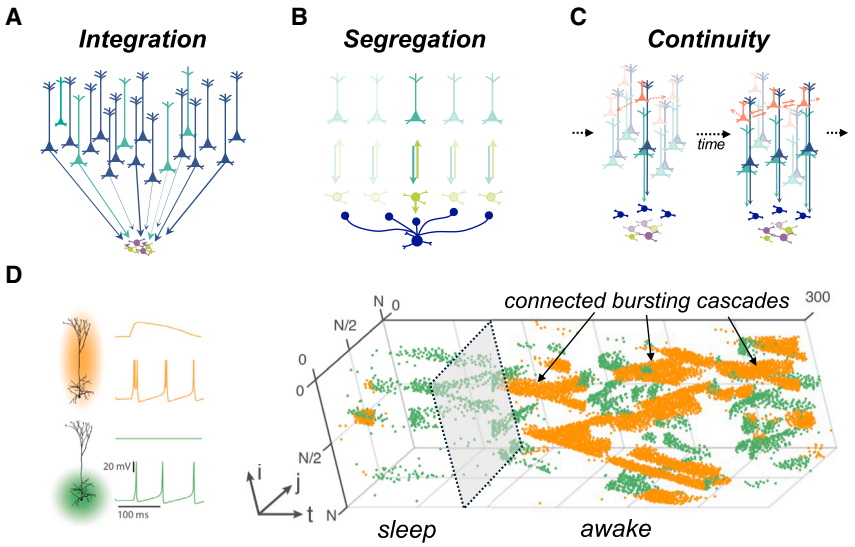

Figure 4. Thalamic contributions to the character of conscious contents

(A–C) The constraints placed on ongoing dynamics by the organization of the thalamus may help to explain key features of conscious information processing, such as (A) integration, which we argue arises as a product of the dimensionality reduction imposed by the converging inputs to the smaller number of cells in the thalamus (lower row), relative to the cerebral cortex (upper row); (B) segregation, which is a natural byproduct of the divisive normalization-like process that arises from activity-dependent recruitment of the inhibitory thalamic reticular nucleus (dark blue); and (C) continuity, wherein the combination of driver and modulatory roles in the thalamus imposes a "Matthew effect" on cellular populations that provides an activity boost to neurons that are connected to the currently dominant thalamocortical ensemble. The colors of cells in (A)–(C) match those in Figures 1, 2, and 3. (D) A spiking neural model was created to mimic a key feature of tt5LB cells—namely, that they shift from a regular-spiking (green; input to basal dendrites only) to a burst-firing (orange; simultaneous activation of apical and basal dendrites) mode when gated by matrix thalamic inputs. After fitting the model to electrophysiological data from anesthetized/awake humans and naturally sleeping macaques, the authors showed that the location in model parameter space best fit to sleep was associated with predominantly regular-spiking activity (green dots), whereas in the awake regime (following the gray dotted square), model tt5LB neurons (embedded on an $N = 100 \times 100$ cortical sheet) were capable of entering into a burst-firing mode that, in turn, triggered burst firing in synaptically connected neurons, leading to sustained activity that could propagate coherently across the cortical sheet, a process labeled as "connected bursting cascades." (D) was adapted from Munn et al.[148] with permission. Note that these mechanisms are simply intended to convey plausible, non-exhaustive means for enacting each feature.

conscious states are not exactly alike and are often mutually exclusive, suggesting the need for relatively isolated circuits that eliminate competing sources of information processing not currently involved in contributing to the contents of consciousness. What role might the thalamus play in the segregated nature of conscious experience (Figure 4B)? There are three key anatomical principles that support this capacity: (1) there are almost no excitatory connections between thalamic projection neurons[162] (only the posterior intralaminar nuclei exciting other excitatory thalamic neurons); (2) the inhibitory reticular nucleus is recruited in an activity-dependent fashion; and (3) individual cells within the reticular nucleus project in a "fan-out" fashion that ultimately inhibits more cells than were required to engage the inhibition. The confluence of these anatomical features results in a relatively global process of divisive normalization.[8,31,163,164] If a thalamic neuron is coerced into spiking (whether by subcortical or cortical inputs), then as it projects back to the cerebral cortex, the excitatory cell also engages a relatively broad inhibitory process that ultimately hyperpolarizes any thalamic cells in the nearby anatomical vicinity. Thus, these cells have to obtain more excitatory drive in order to fire, making it less likely that they will form a part of the ongoing active coalition of neurons reverberating through thalamocortical loops that support the contents of consciousness.

A third crucial feature of typical conscious experience is the fact that transitions between conscious contents have a seeming continuity[14,137,138,165]—i.e., neural processes that can maintain coherence over protracted periods (Figure 4C). The most direct evidence for a core-type thalamic contribution to the experience of continuity comes from work on spatial constancy—the process underlying our stable perception of the world despite the saccadic eye movements that cause visual image displacement ~3×–4× per second, on average, in primates. Spatial constancy is thought to arise from the corollary discharges associated with eye movements (i.e., copies of eye movement commands) that traverse from the superior colliculus, to core-rich (calbindin-absent) lateral MD, and through to the cortical frontal eye fields.[166] This circuit enables remapping of the visual receptive field of frontal eye field neurons immediately before an eye movement—from the current receptive field location to the future location (i.e., the new location of the receptive field after the movement). Such spatial remapping across eye movements is commonly thought to contribute to our visual perception of a stable world.[167,168] Notably, prospective information about the upcoming saccade emerges earlier in the MD nucleus than in the frontal cortex,[169] with peak activity immediately before movement initiation.[170,171] This activity is movement-direction specific and transmitted to the frontal eye field for spatial remapping. Accordingly, muscimol-induced deactivation of these MD neurons prevented the remapping of frontal eye field neurons' receptive fields.[168] Moreover, MD deactivation perturbs corollary discharge processing and movement-related perception, but not the eye movement itself.[172] These experiments suggest that MD plays a crucial computational role in the stabilization of conscious contents. Further (albeit weaker) evidence comes from the fact that MD also has been shown to play a vital role in working memory processes.[173–176] Although consciousness and working memory can be dissociated,[177–180] the contents of working memory encoded in delay period activity are typically a part of the contents of consciousness.[178] In mice and primates, ongoing activity in the MD-frontal cortex loop has been shown to support task performance across delay periods, and deactivation of MD in mice and a thalamocortical computational model has been shown to prevent sustained spiking activity in frontal cortex and impair performance.[39,181–183] While these studies were not designed to dissociate conscious contents from post-perceptual processes, they suggest that core-cortex loops

may underlie temporally protracted, seemingly continuous aspects of conscious contents. Precisely controlled experiments that manipulate specific cellular populations in nuanced perceptual contexts will allow more direct tests of this hypothesis.

CONCLUSION

We have argued that thalamocortical loops are a crucial component in the neuronal mechanisms controlling both conscious state and conscious contents, with distinct contributions from matrix and core thalamic cells. Specifically, there is growing evidence to suggest that matrix thalamic cells and their reciprocal, reentrant interactions with ttL5B and L6B cortical neurons are vital for the desynchronized wake state.[80] Ultimately, the connections between these circuits (facilitated by orexin-sensitive L6B cells[15]) engage both broad (distributed) thalamocortical and local (intracolumnar) cortical circuitry, enabling the complex information-processing modes required to support the wakeful conscious state. In the context of matrix-enabled, high-conductance up states, core cells and their more targeted interaction with middle cortical layers are vital for sustaining activity patterns in thalamocortical loops.[181,182,184] Based on the current available evidence, we propose that these core-thalamocortical interactions maintain conscious contents and give rise to perceptual constancy.

In arguing for a thalamic contribution to the contents of consciousness, we drew on evidence showing that matrix-thalamus regulation of coupling between the apical and somatic compartments of ttL5Bs controls both conscious state and the threshold for the perception of conscious contents.[16] Because of the unique topological position of ttL5Bs in the cortical column, this coupling effectively decides whether activity can freely reverberate through cortico-cortical and thalamocortical loops, and thus achieve widespread influence throughout the brain, or whether it remains unconscious and isolated within an individual cortical column. A number of intralaminar nuclei, like CL, not only are predominantly constituted by matrix-type cells but also have thalamostriatal projections that regulate basal ganglia inhibitory influence over thalamocortical loops. This provides an explanation of why the intralaminar thalamus holds a special place in shaping consciousness and why it is well suited to DBS interventions in disorders of consciousness.

Based on the intimate connections between ttL5Bs and matrix thalamus in both the state and contents of consciousness, recent work has advocated for a matrix-centric cellular explanation of consciousness.[13,14,71] While we agree about the importance of matrix cells, we diverge by proposing the importance of the targeted connections between L2-4 cells and core thalamus in supporting the contents of consciousness over time. Substantiation of this conjecture requires more accurate identification of cell types and their link to perceptual experience. In addition, the pursuit of this goal of identifying correlates of conscious content down to the cellular level (whether matrix, core, intermediate, or other cell type) requires the use of experimental paradigms that can be run in parallel across human and model organisms alike[185]: animal models allow for high-resolution, high-density recording techniques from thalamocortical sites and causal interventions simply not possible in humans, whereas the lower-resolution data in human participants can be used to directly validate the veracity of psychophysical methods used to study conscious experience. Perceptual rivalry variants represent an obvious candidate paradigm to use across species, as the phenomenon has been well characterized psychophysically in humans and non-human primates, does not rely on explicit report,[186,187] and has more recently been studied in mice.[188] Masking and flash suppression are other paradigms to use across species,[189–191] although potential report confounds need to be carefully addressed.

How might a thalamocortical coalition—which functions as an integrated whole that is segregated from a background of competing thalamocortical coalitions and temporally continuous—evolve over time in a way that maintains the coherent character of typical experience? Recent modeling work has proposed that the extended thalamocortical circuit, when active, allows information to propagate across the cortical sheet through the matrix-dependent close-to-critical nature of ttL5b bursting coalitions.[148] We speculate that the activity of the dominant coalition reflecting the current content of consciousness propagates across the cortical sheet through matrix primed cortico-cortical connections while maintaining itself through reentrant interactions with core nuclei that also act to inhibit competing coalitions through the recruitment of the thalamic reticular nucleus (Figure 4D). This suggests that the dominant coalition may be able to leverage the "Matthew effect" of accumulated advantage[192]: that is, the thalamocortical coalition that is most active at a given time can enact a disproportionate influence[193] over the processes that define the *next* coalition that will be the most active,[8] because it can send spikes to all neurons connected to it without having to compete with other potential challenger coalitions (all of which have been hyperpolarized because of the influence of the activity-dependent reticular nucleus; Figure 4B).

In conclusion, taking into account the anatomy and functional evidence, it becomes impossible to relegate the thalamus to a mere background condition for consciousness. Close interactions between thalamus and cortex shape the neural landscape across micro-, meso-, and macroscales, giving rise to differences in information-processing capacity and network interactions associated with different states. Mounting evidence suggests that these thalamocortical interactions directly shape the contents of consciousness by gating access to perception. Beyond that, however, we argue that the anatomical relationship between the thalamus and cortex enables the integrated, segregated, and continuous nature of our experience. This gives rise to a number of testable predictions, including the possibility that the cerebral cortex alone may not be sufficient to explain the contents of consciousness.[133] Rather, the thalamus may contribute by compressing high-dimensional cortical dynamics into a context-rich, yet detail-poor, latent space. Accordingly, core cells may tune and stabilize high-dimensional cortical information processing, while matrix cells may constrain interpretations and large-scale network dynamics. If true, analogous to how damage to thalamocortical circuits alters the capacity for experience in disorders of consciousness, we would expect phylogenetic differences in cortical/pallial,[194] subcortical,[19,134] and thalamocortical anatomy to give rise to differences in the presumed nature and richness of experience across animal

species. Modern neuroscience tools make it possible to directly test these predictions. The time has come for detailed and dedicated study of the role of the thalamus and cortex, not as separate systems, but as a rich integrated circuit that contributes integrally to conscious experience.

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AUTHOR CONTRIBUTIONS

All authors wrote and edited the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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