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Perspective

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The impact of the human thalamus on brain-wide information processing

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Abstract

The thalamus is a small, bilateral structure in the diencephalon that integrates signals from many areas of the CNS. This critical anatomical position allows the thalamus to influence whole-brain activity and adaptive behaviour. However, traditional research paradigms have struggled to attribute specific functions to the thalamus, and it has remained understudied in the human neuroimaging literature. Recent advances in analytical techniques and increased accessibility to large, high-quality data sets have brought forth a series of studies and findings that (re-)establish the thalamus as a core region of interest in human cognitive neuroscience, a field that otherwise remains cortico-centric. In this Perspective, we argue that using whole-brain neuroimaging approaches to investigate the thalamus and its interaction with the rest of the brain is key for understanding systems-level control of information processing. To this end, we highlight the role of the thalamus in shaping a range of functional signatures, including evoked activity, interregional connectivity, network topology and neuronal variability, both at rest and during the performance of cognitive tasks.

Sections

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Introduction

The brain expresses rich, dynamic patterns of neural activity across multiple spatial and temporal scales. At the local level, the amplitude and tuning properties of neural responses exhibit task-dependent sensitivity[1]. Local neural responses are, in turn, transmitted across brain networks via white matter connections[2], wherein interregional communication can be adjusted in response to cognitive and behavioural demands[3–6]. When considering the structural organization of brain networks (that is, topology), both microscale and macroscale white matter connections in the brain can be described as encompassing a modular architecture[7], with tight interconnections between regions forming communities, which are then weakly connected to one another. This particular anatomical organization strikes a balance between segregated processes within local circuits and brain-wide integration[2,8], and can be well described by biophysical models[9–11]. In short, dynamic neural activities are richly expressed over seconds to minutes, and in circuits and systems, to facilitate a wide range of complex behaviours.

How does the brain instantiate this wide variety of spatiotemporal dynamics? An implicit assumption inherent within much of the human neuroimaging community is that these features arise due primarily to the organization of the cerebral cortex. As discussed in other reviews[12–14], in this Perspective we argue that many features of neural activity, connectivity and topology measured by standard whole-brain neuroimaging approaches are inextricably linked to the organization of the subcortex — in particular, we focus our attention on the thalamus. A small, bilateral structure in the diencephalon (Box 1), the thalamus is highly interconnected with various structures in the CNS. It is sensitive to neuromodulatory input[15,16], receives excitatory projections from both the superficial and deep superior colliculus[17–19], integrates inputs from the cerebellum and the basal ganglia[14,20], and projects to the cerebral cortex with a diverse range of different anatomical connectivity motifs[21,22] (see refs. 22–25 for excellent reviews of the complex anatomy of the thalamus and its connections with the rest of the nervous system) (Box 1). This dense interconnectivity places the thalamus in an ideal position to shape multiple aspects of brain dynamics and to contribute to diverse cognitive and behavioural functions.

Decades of important work in animal models — particularly in rodents, cats and non-human primates — has confirmed that the thalamus has a critical role in a wide range of cognitive processes. In more recent years, rodent models have enabled precise measurements and causal manipulations demonstrating key circuit properties of the thalamus. Many of these properties probably generalize to the human brain, as there is widespread homology in the morphology, physiology and gene expression of the thalamus across species[26,27]. There are, however, some differences between the rodent and the human thalamus. For example, in humans there is a greater proportion of GABAergic neurons in thalamic sensory nuclei[28]. Moreover, different mammalian species, including rodents, non-human primates and humans, have distinct neuromodulatory innervation pathways[29,30]. For these reasons, a deeper understanding of the human thalamus is needed, both to understand its shared and distinct functions relative to the thalamus in other species and to understand its role in complex higher-order cognition.

Although the physiology of the thalamus has been less studied in humans than in other species, the human thalamus is similarly implicated as a key node for coordinating cognitive function. Indeed, human lesion studies strongly suggest that the thalamus is involved in a wide range of cognitive functions. For instance, thalamic lesions are associated with aphasia[31], amnesia[32], executive dysfunction[33], neglect and attention deficits[34]. Despite these compelling case reports and other tantalizing clues from early studies using electrophysiology[35,36] and thalamic functional MRI (fMRI)[37,38], there are few whole-brain neuroimaging approaches that directly study the thalamus. This is partly because MRI head coils are typically designed to augment signal quality in superficial structures (that is, the cortex). In addition, there have long been (perhaps overemphasized) concerns that the proximity of subcortical regions to ventricular structures can make it difficult to disentangle putative neural signals from ventricular noise[39]. However, as the resolution and sensitivity of fMRI have advanced in recent years, so too has our ability to detect and measure thalamic dynamics, leading to a rich set of new investigations of thalamocortical function in the human brain (Box 2). In addition, computational modelling approaches have further enhanced our understanding of thalamic computational properties in humans.

In this Perspective, we review recent human neuroimaging studies of the thalamus that highlight various unique functional signatures through which the thalamus impacts the dynamics in the rest of the brain. Specifically, we highlight the highly diverse functional repertoire of the thalamus: it modulates neuronal activity, supports interregional connectivity, facilitates shifts in network topology, mediates heightened neuronal variability and is involved in modulating both subtle and overt shifts in systems-level arousal (Fig. 1). Through this approach, we argue that multimodal human neuroimaging approaches have helped the field to move away from the notion that the thalamus is a simple 'relay'[25] to the cerebral cortex and, instead, have provided evidence to support a nuanced perspective of the thalamus as a structure that facilitates flexible, multiscale, coordinated dynamics that characterize arousal, cognition and conscious awareness.

The functional repertoire of the thalamus

Modulating local cortical-evoked activity

There is a large body of neuroimaging literature linking task-related activity in the human thalamus with a wide array of different behaviours, including attention, motor coordination, working memory and sleep–wake cycles[6,35,40–44] (Box 2). Insights from animal studies can help interpret thalamic activity reported in human neuroimaging studies. For instance, findings from mice and non-human primate studies indicate that across each of these behavioural domains, the thalamus is capable of enhancing (or inhibiting) local activity patterns in the cerebral cortex[45–47], potentially through recruitment of the inhibitory reticular nucleus (RTN) (Fig. 1a). For example, pharmacological or optogenetic inhibition of the pulvinar or the RTN during a visual selective attention task reduced attentional modulation of evoked responses recorded in the visual cortex[47,48]. Specifically, the attentional enhancement in evoked response amplitude for the attended target was greatly reduced, suggesting that thalamocortical interactions are necessary for attentional amplification of task-relevant evoked responses, a process that has long been hypothesized to be mediated by top-down biasing signals.

The above studies suggest that thalamocortical projections can modulate cortical-evoked activity (Fig. 1b) associated with cognitive processes that depend on top-down attentional biasing, such as working memory. For working memory, neural activity occurring after the presentation of a sensory input and before the contingent response (known as 'delay activity')[49] is thought to support the active maintenance of working memory content[50]. Persistent delay activity during working memory-related tasks has been found in the mediodorsal thalamus in both non-human primates and human fMRI studies[51–56].

Box 1

Thalamic neuroanatomy

The thalamus is anatomically perched between the tectum and midbrain at one end, and the hypothalamus and telencephalon (that is, the cerebral cortex, basal ganglia, hippocampus and so on) at the other. Similar to many other regions in the CNS, the thalamus comprises both excitatory and inhibitory neurons; however, their projection patterns are quite distinct. Excitatory thalamic neurons project primarily outside the thalamus, albeit with fewer local synapses onto inhibitory neurons, such as those in the reticular nucleus (RTN). By contrast, inhibitory neurons have predominantly local effects. For instance, the GABAergic RTN engulfs the excitatory cells of the thalamus[164], providing crucial inhibitory dampening of ongoing thalamic activity[123,165] that is thought to play a crucial computational role in shaping feedback projections to the cerebral cortex[166]. By blanketing the thalamus with inhibition, the preferential lack of inhibition to a specific subset of thalamic neurons acts to boost the signal-to-noise properties of precisely the subset of regions that escape the reticular inhibition, particularly when compared with the surrounding, inhibited regions[164,165,167]. Optogenetic studies in rodents have provided empirical support for this hypothesis[123,168]. Specifically, focal stimulation of the RTN leads to sleep-like dynamics in the cortex that are spatially restricted to the area of inhibited thalamic projections[123], suggesting that the RTN contains a spatially organized circuit that can enable focal enhancement or suppression of cortical processing (that is, what some might call the attentional searchlight)[166]. The thalamus also receives inhibitory inputs from the pretectal nuclei and the zona incerta[24,169], which in turn provide other circuits through which thalamic activity can be modulated.

Based on the patterns of afferent connections, excitatory thalamic nuclei are generally divided into two classes[40]: first-order thalamic nuclei (for example, the lateral geniculate nucleus (LGN)), which are predominantly composed of neurons that receive 'driver' inputs from ascending sensory pathways (that is, large glutamatergic synapses that directly propagate action potentials in target cells)[40] or other subcortical brain regions and 'modulatory' input from the cerebral cortex (that is, change in the excitability and receptivity of target cells)[40]; and higher-order thalamic nuclei (for example, mediodorsal and pulvinar nuclei), which are composed of thalamic neurons that receive both driver and modulatory inputs from the cerebral cortex. Importantly, this two-class schema does not cover all glutamatergic thalamic populations — for instance, the intralaminar nuclei are a class of 'non-specific' nuclei whose projections innervate multiple cortical regions throughout the cerebral cortex[22] as well as the corpus striatum of the basal ganglia[170]. It is also possible to characterize thalamic regions according to their efferent projections to the cortex[22]. First, parvalbumin-staining 'core' cells (which are prevalent in sensory nuclei, but also exist within some higher-order thalamic nuclei) typically act as drivers of activity in relatively granular cortices, sending projections to layer IV of the cerebral cortex. Second, calbindin-staining 'matrix' cells (which are more common in higher-order nuclei)[22] fulfil a more integrative function by sending their projections to supragranular layers of cortex across multiple distinct neural regions, where they make contact with both cross-columnar layer II/III pyramidal cells and with apical dendrites of large, subcortically projecting thick-tufted, layer V pyramidal cells that recruit the involvement of diverse populations of subcortical regions[171,172]. It is important to note that the microarchitecture of the thalamus is highly diverse, with numerous individual neurons that are not easily classified into one of these groupings[21], suggesting it is best to conceptualize these extreme classes as different ends of a complex spectrum.

There are several important subcortical inputs to the thalamus. For instance, there are strong excitatory projections from the retina and cochlea into the LGN and medial geniculate nucleus, respectively[23], and the superficial superior colliculus acts as a way station between different thalamic nuclei, in that it receives inputs from the LGN but projects back to the pulvinar[18]. In the ventral tier of the thalamus, the core cells of the thalamus predominantly receive glutamatergic driver inputs, either from sensory nuclei or from the deep nuclei of the cerebellum[14,62], whereas the calbindin-staining matrix cells are instead under the GABAergic control of the globus pallidus internus, which represents the main inhibitory output from the basal ganglia[14,62]. There are also other structures that send inhibitory projections into the thalamus, such as the zona incerta, pretectal nuclei and pontine reticular formation (for a review in rodents, see ref. 24). Finally, there are many neuromodulatory structures in the brainstem, hypothalamus and basal forebrain that also strongly innervate the thalamus[15,16], including major histaminergic, noradrenergic, dopaminergic and cholinergic projections[36,113,173], wherein they alter the gain and timescales of ongoing neural processing[113]. With all this said, it bears mention that the majority of information we have about thalamic circuitry arises from non-human model organisms, and there may be features of thalamic anatomy that are distinct across species.

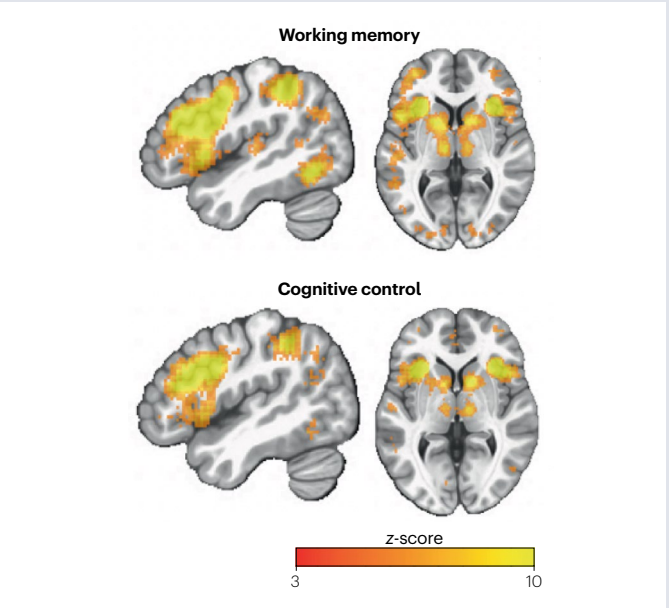
In rodents, inhibiting activity in the ventrolateral or mediodorsal nucleus (MD) diminished delay activity in the premotor[45] and prefrontal cortex[46] respectively, whereas stimulated mediodorsal thalamic activity enhanced information coding in rodents' medial frontal cortex[48]. In humans, analogous findings have been reported in which evoked responses in the thalamus can successfully predict evoked activity patterns in the cerebral cortex during working memory[57], language, motor, attention and perceptual tasks[58]. These findings highlight the potential role of thalamic activity in influencing the cortical signatures of working memory and other task contents via thalamocortical interactions.

Beyond working memory maintenance, thalamocortical modulation of local cortical activity can be extended to inputting and updating task-relevant information into working memory. Computational models suggest that the process of inputting and updating working memory content can be implemented via a 'gating' mechanism[59]: when the gate is 'open', new information can enter the working memory system, whereas when the gate is 'closed', no new information can be entered into working memory. Crucially, this process is hypothesized to be mediated by the striatal–thalamic circuit[60,61], wherein the striatum disinhibits a thalamocortical loop to facilitate new information to

Box 2

Neuroimaging the thalamus: past, present and future

Cognitive neuroimaging has the potential to reveal how mental functions are supported by distributed brain regions and systems, owing to the whole-brain coverage of imaging methods such as functional MRI (fMRI). However, although fMRI can image functional signals from both cortical and subcortical structures, the field has remained largely cortico-centric. For example, neuroimaging studies on cognitive control have largely focused on determining the functional specialization and interactions of the frontoparietal systems, with relatively fewer studies focused on thalamic nuclei that are known to project to frontal parietal cortices. Nevertheless, the few studies that investigated thalamic contributions have reported notable task-linked activity in thalamus. This relative negligence of the thalamus may be due to several unfounded biases: the thalamus is small (relative to the resolution of typical functional neuroimaging scans), close to noise sources (for example, the ventricles) and not traditionally associated with higher-level mental functions, such as cognitive control. As a result, findings in the thalamus from human neuroimaging studies are often either omitted, reported with no interpretation or discussed without consideration of its anatomical organization (that is, not describing the subregions involved, despite the major functional and anatomical differences between thalamic nuclei). Contrary to these pervasive biases, neuroimaging studies indeed obtain reliable task-related signals from the human thalamus with anatomical specificity that directly reflects cognitive capacities typically ascribed primarily to the cerebral cortex. Indeed, an automated meta-analyses performed by the Neurosynth database[174] found that the mediodorsal, anterior, ventral lateral and intralaminar nuclei were frequently associated with the terms 'working memory' and 'cognitive control' in the literature (meta-analyses performed in June 2022; see the figure). In the figure, maps were created by entering the terms 'working memory' and 'cognitive control' individually into the Neurosynth database. These maps depict results from the 'uniformity test', which reports *z*-scores (thresholded at $z > 3$) summarizing the likelihood of a voxel being reported in studies that included the selected terms. Specifically, the Neurosynth query tool performs a one-way analysis of variance test to determine whether the proportion of studies reporting activation at a given voxel differs from the rate that would be expected if activations were uniformly distributed throughout grey matter. Importantly, these results showed that in the fMRI literature corpus, reliable and robust task-related signals have already been consistently reported in specific thalamic regions. With the results of the aforementioned human fMRI studies in mind, we foresee excellent opportunities for the field to leverage reliable neuroimaging signals to improve our understanding of thalamic function. Future studies would benefit from combining the inferential power of computational modelling, model-based analysis and cutting-edge neuroimaging techniques with improved spatial and temporal resolution (for example, 7 T MRI and fast blood oxygen level-dependent (BOLD) imaging), greatly increasing sensitivity to thalamic activity. In addition, haemodynamic responses in the subcortex are often faster than those in the cortex[175], which should be leveraged to take full advantage of the most advanced neuroimaging methods[176]. Researchers also must improve anatomical specificity when reporting thalamic results. To that end, there are now thalamic atlases widely available, parcellating the thalamus based on various structural, histological and functional information[177,178].



enter cortical circuits through targeted thalamocortical projections. Although these models typically model the thalamic nodes according to known features of core-type thalamocortical projections (Fig. 1a and Box 1), it is unclear whether similar capacities will be associated with the gating of matrix-type projections, which are typically more diffuse and far more prominent targets of basal ganglia-mediated inhibition than core-type neurons[14,62]. Given that different cortical regions may be encoding different features, categories or modalities of working memory content[63], having a specific thalamocortical projection pathway that is selective for specific information may be advantageous, as different core cells can be selectively activated to allow precise control over distributed cortical activity.

Although these observations mostly came from electrophysiology findings in model systems, various techniques can be used to study the effects of thalamic modulation on cortical activity in humans. In rare cases when electrophysiological activity can be simultaneously recorded from the human thalamus and the cortex, thalamic activity has been found to influence the level of high-frequency cortical activity[64]. Deep brain stimulation-mediated manipulation of mediodorsal thalamic activity in humans affected working memory performance[43],

and anterior thalamic activity recorded with an intracranial electrode showed increased synchrony with neocortical activity measured by electroencephalography (EEG) during successful memory encoding[65]. fMRI studies have also successfully imaged thalamic activity during visual attention tasks and have shown that such activity is correlated with local sensory responses and attentional modulation[66,67]. Technical developments in high-field fMRI have improved its spatial resolution, positioning it as an effective tool for detecting task-related thalamic activity for different cognitive functions. Thalamocortical interactions have also been found to be altered in disease states, suggesting that disrupted thalamocortical modulation of cortical-evoked activity may be a core deficit in some psychiatric and neurological disorders[68]. Altogether, evidence from animal and human studies highlights the critical importance of thalamocortical function for modulating cortical-evoked responses, and a major challenge is to determine how this mechanism is involved in diverse range of cognitive functions, beyond memory and attention.

Mediating interregional coupling

Cognition and behaviour are not only correlated with localized evoked activity in individual brain regions but also influenced by the interactions among circuits, regions and systems. In recent studies, interregional communication between brain regions has been proposed to be facilitated via coherence of local neural oscillations[69,70], in which modulating the consistency in phase relationship between neural oscillations regulates patterns of information processing. Different classes of oscillations (that is, alpha-band, beta-band and gamma-band oscillations) have been demonstrated to be controlled by different cortical GABAergic inhibitory interneurons[23,71,72], which in turn may be crucial targets for thalamocortical projections to control and facilitate interregional communication. Indeed, distinct families of GABAergic interneurons are known to be innervated by different classes of thalamocortical projections[73,74]. In addition, the inactivation of the thalmus diminishes cortico-cortical communication[75], suggesting that the thalamus is directly or indirectly involved in facilitating information transfer between cortical regions.

There is evidence that the thalamic control of interregional communication supports a wide range of cognitive and behavioural processes (Fig. 1b). For instance, when monkeys performed a visual attention task, the level of alpha-band neural synchrony between V4 and the inferior temporal area of the cerebral cortex was modulated by the level of attention directed to the specific spatial receptive field[42]. A subsequent Granger causality analysis suggested that the thalamic pulvinar nucleus modulated alpha-band activity in both V4 and the temporo-occipital area[6]. Importantly, the regions that were functionally coupled also belong to similar thalamocortical projection zones determined via diffusion tensor imaging[76], suggesting that thalamic regions are involved in coordinating the functional interactions between regions. These findings were further corroborated by a study demonstrating that pharmacologically inactivating the macaque

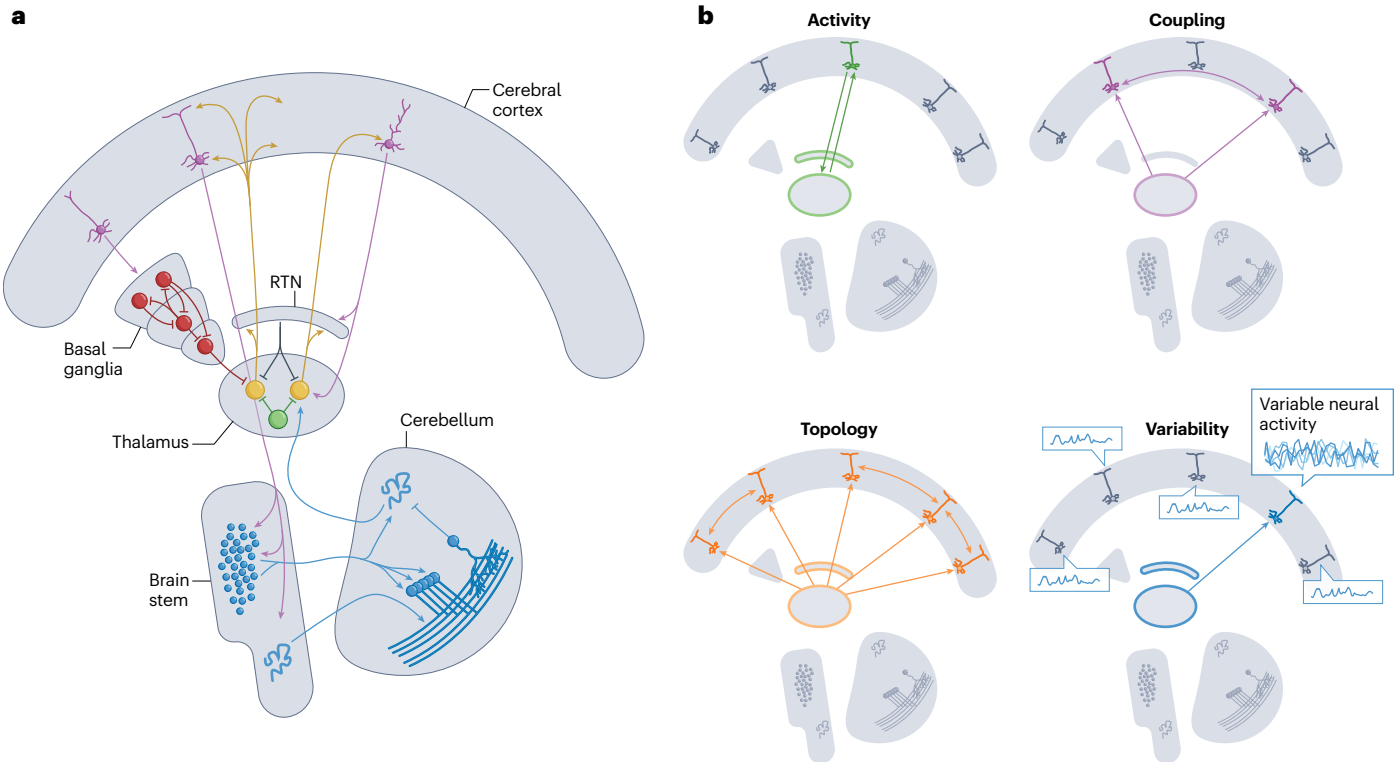


Fig. 1 | The functional neuroanatomy of the thalamus. a, The thalamus is embedded in a distributed neural architecture: different populations of neurons in the thalamus (yellow) are interconnected with pyramidal neurons in the cerebral cortex (purple), inhibitory input from the basal ganglia (red), excitatory input from the cerebellum (blue) and local inhibition, both from the reticular nucleus (RTN; grey) and GABAergic interneurons (green). **b**, The thalamus has a crucial role in at least four partially overlapping canonical functions: promoting focused cortical activity (green), facilitating interregional coupling (purple), supporting changes in network topology (orange) and dimensionality (that is, the higher-order structure of the interactions between neurons), and enabling and modulating temporal neuronal variability (blue).

pulvinar reduced attention-driven neural synchrony between V4 and the inferior temporal cortex[47]. These findings are consistent with studies that have mapped the resting-state correlations between the pulvinar and the cerebral cortex (using fMRI)[77], as well as those that found pulvinar lesions in human patients are associated with various attention deficits[34]. Importantly, there is detailed computational modelling work that reinforces the plausibility of these mechanistic explanations[78]. It remains an open question as to whether context-dependent shifts in interregional coupling observed in fMRI[79] are also associated with similar thalamocortical interactions[80,81], although there is emerging evidence that supports this hypothesis[82].

Thalamic control of interregional communication may also be particularly important for top-down cognitive control, during which a hypothetical control signal (also referred to as a 'top-down biasing' signal) is communicated to regulate perceptual and motor functions to facilitate goal-directed behaviours[83,84]. This top-down control mechanism requires selectivity and flexibility to allow control signals to reach targeted brain regions accurately and selectively. As described in the previous section, the thalamus is well placed to mediate the communication of top-down biasing signals, such as those that occur when selected cortical activity needs to be enhanced or inhibited via attentional modulation[85]. Many fMRI studies typically link attention modulation as observed in changes in blood oxygen level-dependent (BOLD) signal amplitude to biasing effects from the frontoparietal and dorsal attention networks[86], but evidence discussed in the above section strongly implicates thalamocortical interactions contributing heavily to this biasing mechanism. Because the thalamic regions supporting this frontoparietal network span both the MD and the pulvinar[87], it is possible that effective attentional performance may require heretofore underexplored coordination between different thalamic subnuclei.

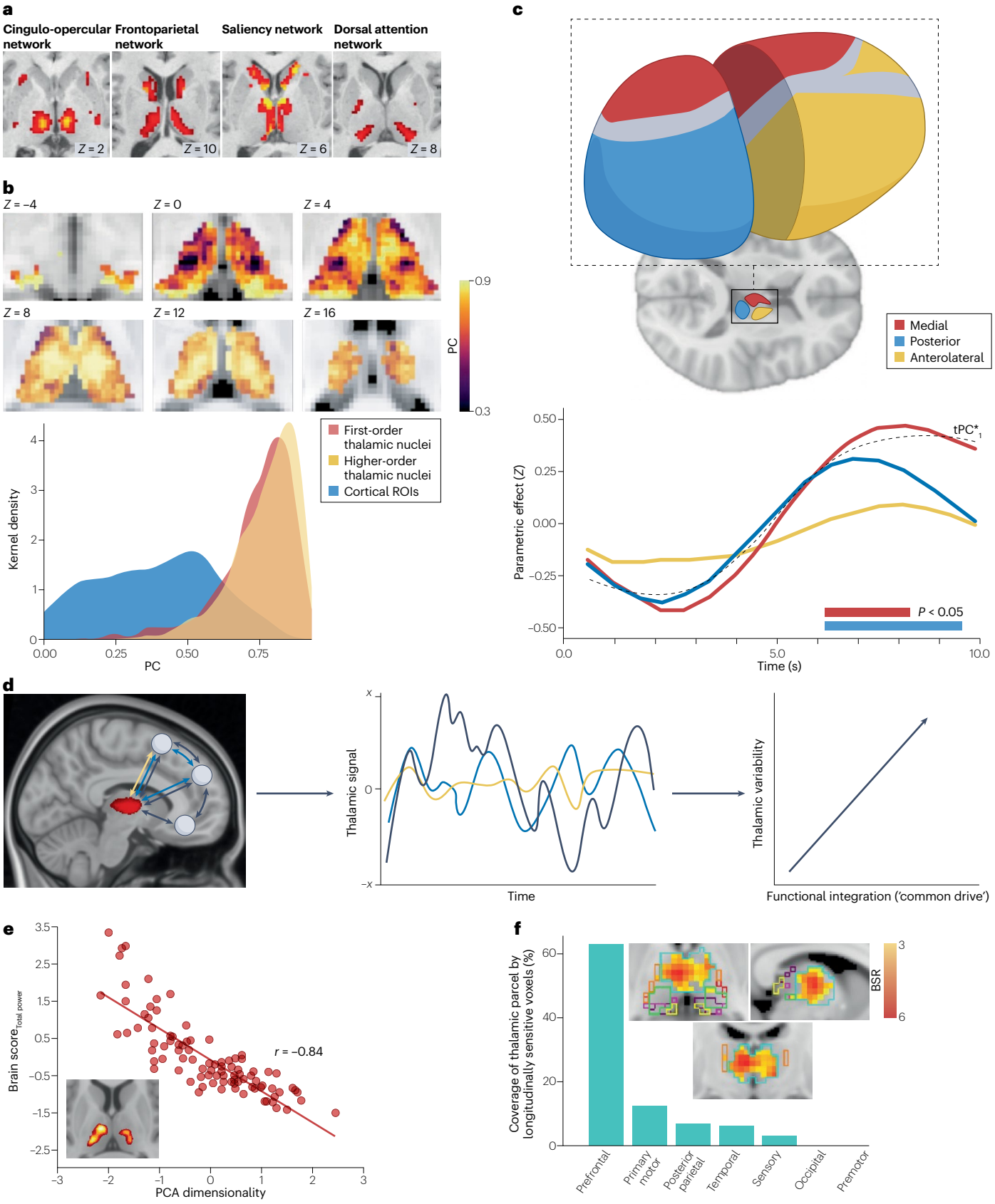
Topology and dimensionality

Functional connections in the brain are not limited to pairwise interactions — indeed, the human brain can be conceptualized as a complex network consisting of interconnected circuits, brain regions and neural systems[2]. The architecture of brain networks can be effectively studied by graph theory-based methods, in which brain networks are represented as graphs, brain regions are modelled as nodes and connectivity among regions is modelled as edges[88]. Studies of brain network organizations have consistently reported that they have a modular structure[7], in which brain regions within the same module have many connections with other brain regions in the same module, and fewer connections with brain regions outside the module. For example, distributed regions within the sensory and motor cortices form visual, auditory and somatomotor networks, whereas regions within the frontoparietal association cortices form several distributed networks including the dorsal attention, ventral attention, cingulo-opercular and frontoparietal networks[89]. In addition to revealing the modular structure of functional brain networks, graph theoretic approaches can also be used to study network properties of individual brain regions in a functional network. For example, a brain region with many between-network connections has a strong 'connector hub' property, presumably to mediate interactions between functional networks[90]. Studies have found that in the cerebral cortex, such hubs are primarily located in frontal and parietal association areas that have been implicated in higher-order, integrative functions[5,91,92].

Within the context of large-scale brain network organization, it has been shown that all cortical functional networks are strongly connected to distinct but also overlapping thalamic regions[87,93,94] (Fig. 2a). Critically, multiple thalamic nuclei have also been found to exhibit strong connector hub properties (Fig. 2b). The anterior, mediodorsal, intralaminar, ventrolateral, ventroposterior and pulvinar nuclei all exhibit strong connector hub properties, which were found to be stronger than cortical connector hubs[87] (Fig. 2b). This finding suggests that, similar to cortical regions such as the prefrontal and parietal cortices, thalamic nuclei are in a privileged position for supporting integrative functions across multiple functional networks[87,95].

This central topological position of the thalamus also makes specific predictions regarding its behavioural relevance. Given converging connectivity with multiple processing systems and functional networks, thalamic hubs should be involved in cognitive functions across multiple domains. This prediction can be best tested by studying human patients with focal thalamic lesions. As described in previous sections, lesions to different thalamic regions have been reported to be associated with behavioural impairments across many domains, including language[96], memory[32], executive function[33] and attention[34]. Furthermore, a recent study provides causal support of the behavioural significance of thalamic hubs, reporting that a single, circumscribed lesion to an anterior dorsal thalamic subregion in humans can produce

Fig. 2 | Functional parcellation, connector hub properties and variability profile of the thalamus. a, Thalamic regions associate with cortical functional networks that are putatively involved in cognitive control-related functions, namely the cingulo-opercular network, the frontoparietal network, the saliency network and the dorsal attention network. **b**, The medial, mediodorsal and posterior portions of the thalamus exhibit particularly strong connector hub properties, which are indicated by their higher scores on the participation coefficient (PC) axis. The colour bar depicts the PC scale, which is a measure of connector hubness and ranges from 0 to 1 (low to high) (top). Most of the thalamus exhibits connector hub properties that are stronger than those of cortical regions (bottom). **c**, The mean blood oxygen level-dependent (BOLD) signal in three different thalamic groups — medial (pink), posterior (blue) and anterolateral (orange) — is strongly aligned with the parametric effect of cognitive load on the low-dimensional distributed activity. Coloured bars designate significant parametric effects ($P < 0.05$ from non-parametric permutation testing) and the dotted black (tPC^*_1) line depicts mean low-dimensional trajectories. This indicates a low-dimensional relationship between activity in the thalamus and activity in the cerebral cortex. **d**, Toy example of three functional interaction scenarios between the prefrontal cortex and the thalamus. Here, the expectation is that with increasing functional connection (that is, going from 1 (yellow) to 2 (lighter blue) to 3 (darker blue) connected nodes; left panel), moment-to-moment brain signal variability expressed by the thalamus should increase in kind (middle panel). Accordingly, higher temporal variability in the thalamus may reflect higher functional integration among connected regions. **e**, Heightened BOLD variability in the thalamus was the strongest signature of lower principal component analysis (PCA) dimensionality (that is, higher moment-to-moment functional integration between brain regions). **f**, Thalamic regions projecting to the prefrontal cortex were particularly sensitive to joint longitudinal changes between BOLD signal variability, functional integration and cognition; individuals who maintained moment-to-moment thalamic variability also maintained functional integration and cognition over 2.5 years. BSR, bootstrap ratio; ROI, region of interest. Part **a** adapted with permission from ref. 94, Elsevier. Part **b** adapted with permission from ref. 87, Society for Neuroscience. Part **c** adapted with permission from ref. 82, Elsevier. Parts **d** and **e** adapted with permission from ref. 102, Elsevier. Part **f** adapted from ref. 108, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).


a
Cingulo-opercular network
Frontoparietal network
Saliency network
Dorsal attention network
Z = 2
Z = 10
Z = 6
Z = 8
b
Z = −4
Z = 0
Z = 4
Z = 8
Z = 12
Z = 16
PC
0.9
0.3
First-order thalamic nuclei
Higher-order thalamic nuclei
Cortical ROIs
Kernel density
PC
c
Medial
Posterior
Anterolateral
Parametric effect (Z)
tPC*1
P < 0.05
Time (s)
d
Thalamic signal
Time
Thalamic variability
Functional integration ('common drive')
e
Brain score Total power
r = −0.84
PCA dimensionality
f
Coverage of thalamic parcel by longitudinally sensitive voxels (%)
BSR
Prefrontal
Primary motor
Posterior parietal
Temporal
Sensory
Occipital
Premotor

widespread impairment in executive, memory and language-related functions[97]. Critically, this anterior-to-medial dorsal thalamic pattern also exhibits a strong connector hub property, and lesions to thalamic regions with weaker hub properties have a more limited impact on behaviour.

Given these findings, thalamic hubs are probably not (completely) functionally specialized for specific cognitive and behavioural functions but, rather, provide more domain-general contributions to brain functions. One hypothesis is that thalamic hubs coordinate the topological organization of cortical networks, and a focal lesion in a critical thalamic nucleus could have widespread and distal effects on cortical functions ('diaschisis'). In support of this, focal thalamic lesions disrupt the modular organization of cortical functional networks in humans[87]. Furthermore, thalamic regions whose lesions are associated with behavioural deficits across multiple domains also contain higher densities of the diffusely projecting matrix thalamocortical cells. These findings thus provide causal support of both the network and the behavioural significance of thalamic hubs.

A natural question to ask is whether there are inherent relationships between thalamic architecture and the well-established low-dimensional patterns (such as resting-state networks[89] and gradients in spatiotemporal organization[98]) observed in cortico-cortical functional connectivity[98]. Low-dimensional organization indicates that the number of variables required to explain a large amount of variance in distributed neural activity is far lower than the total number of variables in the data[99]. Indeed, these simple descriptions of the basic patterns of covariance observed in whole-brain neuroimaging data spatially coincide with regions that strongly correlate with either core or matrix thalamic populations during the resting state in humans[100]. In this study, the authors used high-resolution 7 T resting-state fMRI data and the relative amount of two calcium-binding proteins, parvalbumin and calbindin, to infer the relative distribution of core and matrix (respectively) nuclei within thalamic voxels. Tracking the time series within these voxels and comparing them with time series extracted from the cerebral cortex, it was shown that differences in thalamocortical functional connectivity recapitulated functional connectivity patterns within the cerebral cortex[100]. These same patterns have previously been shown to explain substantial amounts of variance across resting-state functional connectivity studies in humans, and also to relate to distinct cognitive capacities, as estimated using large-scale, automated meta-analyses of the cognitive neuroscience literature[98]. The striking correspondence between the thalamocortical and cortico-cortical functional connectivity patterns provides further evidence for the importance of thalamic organization in shaping whole-brain functional connectivity patterns.

The patterns identified in the previous analysis[100] are themselves relatively low-dimensional. There is also evidence to suggest a link between thalamic activity and the low-dimensional network patterns engaged during cognitive task performance[82] (Fig. 2c). One potential explanation for these low-dimensional patterns is that thalamic activity broadcasts gamma-frequency 'up' states in the cerebral cortex[36], but then uses the inhibitory blanket of the RTN to protect the cortical state from otherwise distracting thalamic input[101]. These results suggest that the thalamus facilitates integration by providing low-dimensional constraints over network-level dynamics in the cerebral cortex, but also simultaneously ensures that the resultant patterns are relatively segregated as well[82]. This interpretation is consistent with previous work investigating network dimensionality and temporal variability using resting-state fMRI[102].

Variability and integration

Brain activity exhibits remarkable variability from moment to moment, fluctuating across multiple spatial (neurons to networks) and temporal (milliseconds to days) scales[103,104]. Although the source of this variability is still unknown, it is thought that dynamic neural activity at the regional level may reflect summed synaptic inputs[105], directly linking local dynamics to communication between regions. This suggests that a greater number of functional inputs to any local brain region may increase the variability of its output (Fig. 2d). Consistent with this notion, computational modelling of the visual cortex has shown that the majority of 'noise variation' is shared across neurons that share tuning properties[106], suggesting a plausible general phenomenon that more temporal variability at the regional level may be characterized by a more integrated (that is, lower dimensional) network structure. As the thalamus is thought to dynamically relay and modulate information flow throughout the entire brain[25,95], thalamic variability may provide a key temporal signature of how functional network integration emerges overall.

Evidence in humans is now building that this is indeed the case. For example, in resting-state fMRI data, elevated moment-to-moment variability in thalamic activity was the strongest marker of heightened functional integration (that is, lower dimensionality) across the brain[102] (Fig. 2e). In addition, individual differences in the temporal variability from the thalamus to its structurally connected cortical targets predicted lower network dimensionality (higher functional integration) over and above local variability in the thalamus alone[102], a result that echoes similar findings in macaque[106] and cat visual cortices[107]. These findings thus suggest that greater local temporal variability in the thalamus and heightened upregulation of variability from the thalamus to the cortex provide strong and unique signatures of how the whole-brain systems functionally integrate.

Beyond individual differences, it has been unclear whether thalamic variability is also associated with functional integration at the within-person level, and if so, whether such changes are cognitively relevant. In a recent longitudinal resting-state fMRI study, individuals who exhibited loss of moment-to-moment variability in thalamic activity also expressed a loss of functional network integration and a concomitant loss of cognitive function (fluid and crystallized intelligence, and perceptual speed) over the course of 2.5 years[108]. Crucially, the observed changes in thalamic variability co-occurred with changes in variability across much of the prefrontal cortex and striatum, implicating the larger fronto-striato-thalamic system in behaviourally relevant longitudinal changes in neuronal variability. Thalamic effects were most expressed within subregions with structural connections to the prefrontal cortex (Fig. 2f), as well as thalamic nuclei known to primarily project to the prefrontal cortex and receive striatal input (that is, mediodorsal and ventral anterior nuclei). These results highlight thalamic variability as a primary target in future longitudinal work in ageing populations.

Which mechanisms may allow an individual to exhibit higher temporal variability in thalamic activity? Although understudied to date, higher variability – which often correlates with optimal cognitive performance[104,109–112] – may be a direct reflection of pooling over more differentiated inputs[106]. Given that the fMRI signal in an individual voxel is thought to reflect activity distributed across millions of 'local' neurons, the more these neurons differ in their level and form of temporal variability, the higher that voxel-level temporal variation should be. Greater thalamic variability (perhaps from the diffuse projections of higher-order, matrix-type thalamic nuclei[14,22]) may then mediate

both an increase in functional integration over differing sets of axonal inputs as well as patterns of cellular differentiation that contribute to diversity in the observed local (ensemble) dynamics within more integrated brains[102].

Another plausible mechanism underlying elevated variability in the thalamus is fluctuations in neural gain — that is, variability in the transfer of input to output due to neuromodulatory influences[113]. For example, noradrenaline-mediated elevations in neural gain can lead to a more integrated whole-brain network structure[5,11,114], a topological feature that may relate to the effects of noradrenaline on oscillatory bursting and single spike firing modes in the thalamus[115]. Furthermore, previous studies on the relationship between dopamine, brain signal variability and cognitive performance[111,116] support theories of how dopaminergic neural gain[117] influences thalamic variability for modulating functional integration (but see ref. 118). Indeed, dopaminergic neurons naturally exhibit dominant low-frequency tonic firing patterns along with intermittent phasic bursts[119]. Mouse data highlight that dopamine-deficient animals display a complete lack of phasic bursting activity in the thalamus, but that dynamic bursting can be restored via dopaminergic agonism[119]. In addition, trial-to-trial variability in dopamine release appears to increase with increasing task proficiency[120]. Crucially, although the nature and direction of relations between dopaminergic and noradrenergic neurons can be highly complex, these systems are almost certainly coupled[121] and should serve as key targets for future research on the association between thalamic dynamics and functional integration.

Arousal influences

Based on the functional repertoire reviewed above, the thalamus is probably not associated with one simple functional signature but, rather, is well positioned to modulate ongoing cortical activity, connectivity, topology and variability through various mechanisms. For example, the glutamatergic driver outputs from the thalamic nuclei can strongly drive cortical responses, and thalamocortical inputs have been shown to elicit stronger cortical-evoked activity than cortico-cortical inputs[122]. Thalamocortical inputs to cortical regions are adaptive, as they can be modulated by inhibitory influences from the basal ganglia and the RTN[24]. Thus, the combination of excitatory and inhibitory thalamocortical interactions can dynamically shape cortical activities across spatial scales, giving rise to a wide range of activity profiles that are related to a multitude of behavioural phenomena. Another key question then becomes: what other factors can modulate thalamic dynamics to shape the expression of the functional repertoire?

A major modulator of thalamic dynamics is the arousal state. Multiple studies have shown that altering excitation or inhibition in the thalamus from the ascending arousal system leads to altered spontaneous dynamics and arousal states within the cortex[123–125], suggesting that the thalamus acts as a key convergent pathway shaping arousal in cortical networks. Intriguingly, whereas inhibiting thalamic activity can drive slow-wave (that is, low-frequency) activity[123], lesioning or ablating the thalamus does not have the same effect[126,127], suggesting an active role for inhibitory thalamic circuits in generating the slow waves, rather than simply reflecting the absence of or reduction in thalamic input to the cortex.

In humans, the question of how large-scale thalamocortical networks shift their dynamics across arousal states has been studied via fMRI. These studies have demonstrated distinct thalamocortical dynamics across a spectrum of arousal states, with maintained cortical connectivity[128] but sharp suppression of thalamocortical connectivity at the onset of sleep[129]. More recent studies have distinguished distinct patterns of thalamocortical functional connectivity across arousal states[130]; specifically, thalamocortical connectivity selectively increased to sensorimotor networks during light sleep, and intra-thalamic connectivity increased broadly during the transition into sleep. Although changes in systemic physiology could also modulate functional connectivity across arousal states due to their direct effects on haemodynamics[131,132], the distinctive spatial patterning of these observations during sleep nonetheless suggests distinct neural activity changes across nuclei and networks.

Within low arousal states such as sleep, ongoing cognitive processes take place spontaneously, such as the memory consolidation that occurs during non-rapid eye movement sleep. These memory processes are associated with distinct EEG signatures with clear links to function — for instance, the slow waves characteristic of deep sleep have been linked to stabilization and consolidation of memory[133]. Electrophysiological studies have clearly established a key role for intrinsic thalamic oscillations in sleep slow waves, originally in foundational studies in animal models[35,134]. For instance, there is evidence that sleep spindles demonstrate coupled activity in the thalamus[135]. Invasive electrophysiological recording of a subset of thalamic nuclei in human patients[136] has now elucidated the temporal links between cortical and thalamic oscillations during sleep. These invasive recordings suggest that cortical excitation drives a thalamic up state, leading to thalamic coordination of sleep spindles and synchrony across the distributed network. Building on this already identified critical role for thalamocortical networks in synchronizing cortical oscillations linked to memory, further dissection of the thalamic correlates of sleep oscillations remains a key area for future work, especially with regards to how distinct thalamic nuclei may drive this phenomenon.

In addition to expressing distinct dynamics during different arousal states, the thalamus also appears to play a distinctive role in effecting the transition between arousal states (Fig. 3a). Rare direct recordings from the human thalamus demonstrated that changes in spontaneous thalamic activity preceded changes in cortical arousal by several minutes[137]. The precise nature and origin of these thalamic changes is not yet fully understood. Studies using simultaneous EEG and fMRI have identified transient increases in thalamic activity occurring at the transition between sleep and wakefulness[138], as well as at co-fluctuation with low and high arousal within the awake state[139] (Fig. 3b). Recently, a study using accelerated fMRI to detect sub-second thalamic activity identified a temporal sequence of activity across thalamic nuclei that precedes transitions in arousal states[140], with the intralaminar centromedian thalamus activating earlier than other thalamic nuclei, and preceding the behavioural signatures of arousal (Fig. 3a). These temporal sequencing results point to a key role for the thalamus in regulating transitions between states in humans, consistent with causal evidence from the animal literature, and moreover illustrate how specific nuclei play distinct roles relative to cortical network structure. In particular, a switch in oscillatory state in a single nucleus could potentially trigger a cascade throughout the cortical feedback loops leading to a widespread switch in thalamic and cortical activity states. Another possibility is that slow changes in release of neuromodulatory substances within the thalamus can produce such temporal sequences, owing to local differences in receptor densities across individual nuclei.

Neuromodulatory circuits are known to be a primary controller of these arousal states in the thalamus, not just within sleep but also as arousal is dynamically modulated during wakefulness. Arousal is regulated by distributed circuits across the brainstem, hypothalamus and

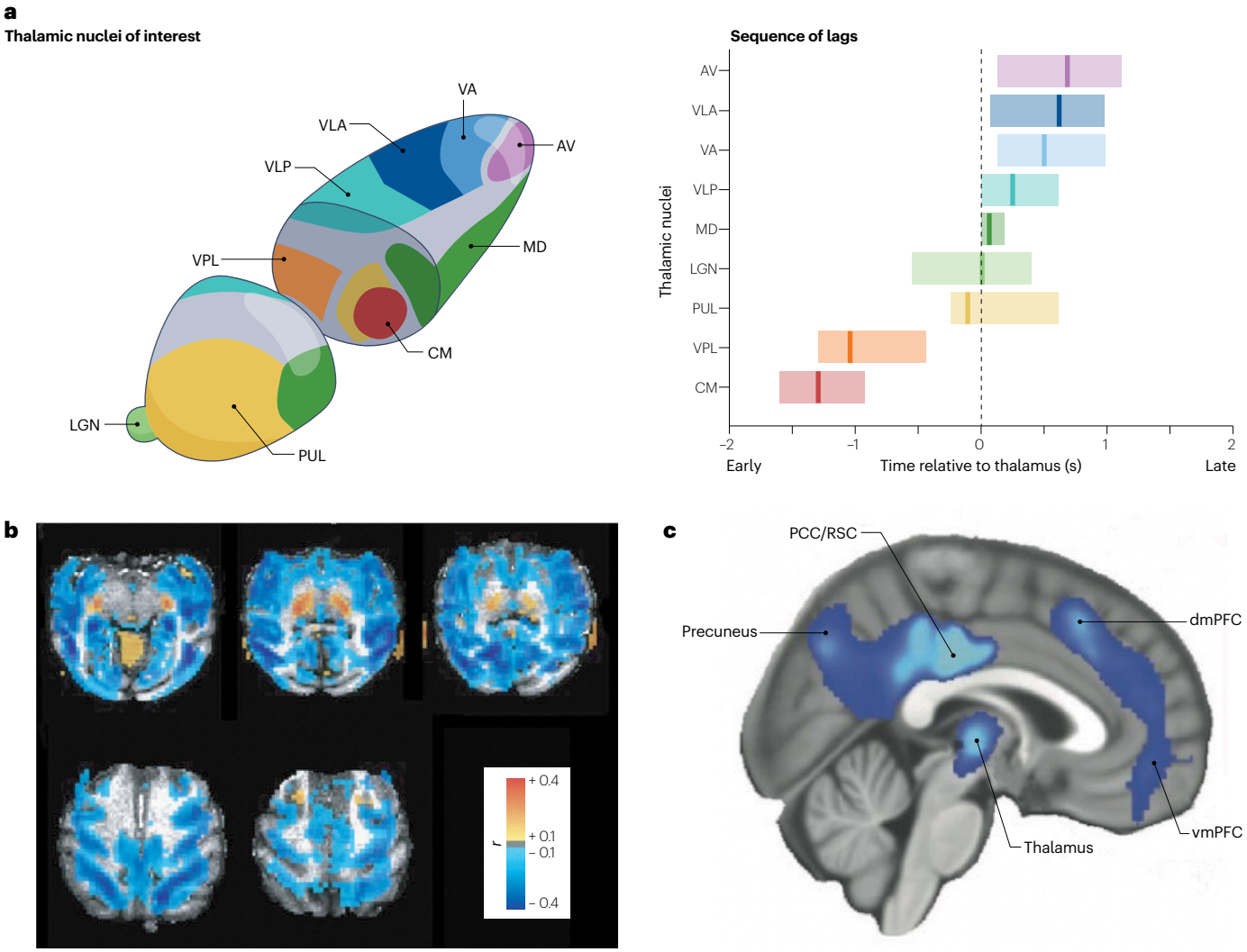


Fig. 3 | Arousal shapes thalamic activity and thalamocortical dynamics. a, Individual nuclei of the thalamus imaged with 7 T functional MRI (fMRI), locked to arousal state transitions. A temporal sequence of activity emerges across thalamic nuclei, preceding the moment of transition to higher arousal states. Shading shows 95% confidence interval for activity timing in each thalamic nucleus, locked to arousal. **b**, A spatial template of key fMRI predictors of arousal shows thalamic correlations with arousal state. The colour intensity shows the strength of each region's correlation with behavioural arousal measured via eye closures; the thalamus shows strong positive correlations. **c**, Inducing sedation with dexmedetomidine, a drug that induces decreased noradrenergic neuromodulatory tone, causes decreased thalamic glucose metabolism and connectivity. AV, anteroventral nucleus; CM, centromedian nucleus; dmPFC, dorsomedial prefrontal cortex; LGN, lateral geniculate nucleus; MD, mediodorsal nucleus; PCC, posterior cingulate cortex; PUL, pulvinar nucleus; RSC, retrosplenial cortex; VA, ventral anterior nucleus; VLA, ventral lateral anterior nucleus; VLP, ventral lateral posterior nucleus; vmPFC, ventromedial prefrontal cortex; VPL, ventral posterolateral nucleus. Part **a** adapted from ref. 140, Springer Nature Limited. Part **b** adapted with permission from ref. 139, PNAS. Part **c** adapted from ref. 144, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

basal forebrain[141], and the thalamus is a primary target on which these neuromodulatory circuits converge[16,141,142]. Dopaminergic, noradrenergic and cholinergic tone each influence the properties of spontaneous thalamic activity and thalamocortical dynamics[143], allowing the thalamus to differentially engage the functional repertoire described above (Fig. 1b). Neuromodulatory pathways exhibit distinct projections across different thalamic nuclei[15,16] and could form a control mechanism for dynamically shaping which aspects of the thalamic functional repertoire are engaged. These neuromodulatory effects on the thalamus are beginning to be studied through causal manipulations in humans as well. A unique study using a combined positron emission tomography–magnetic resonance approach to image the neural effects of a noradrenergic sedative (the α_2-adrenergic agonist, dexmedetomidine) showed that decreased noradrenergic signalling causes disruption of thalamocortical connectivity and decreased thalamic activity[144] (Fig. 3c). Interestingly, recent work has shown that noradrenergic receptors are heterogeneously expressed in the non-human primate thalamus, with a greater expression in intralaminar and midline structures[145], suggesting that neuromodulatory ligands[16] may afford precise control over the thalamocortical functional repertoire.

Finally, thalamic activity is not only a critical component of spontaneous shifts in arousal but also a key mechanism of general anaesthesia, consistent with the powerful role for the thalamus in shaping large-scale cortical dynamics. Although distinct anaesthetic agents act through a diversity of unique mechanisms, disruption of thalamocortical dynamics is generally observed across many of these medications. Propofol, one of the most widely used anaesthetics, is a GABAergic agonist that binds widely throughout the brain and causes a shift in EEG dynamics towards high-amplitude slow oscillations and frontal alpha oscillations[146–148]. Computational modelling has demonstrated a key role for thalamus in generating these frontal alpha oscillations, specifically with tonic inhibition slowing oscillations within the corticothalamic feedback loop, and synchronized inhibitory input from the RTN to multiple thalamic nuclei, producing high synchrony throughout the frontal cortex[149]. A recent study demonstrated that stimulation of the central lateral thalamus can drive awakening in anaesthetized animals[150], and suggested that this effect is mediated by restoring wake-like intracolumnar and intracortical functional connectivity. Similar effects have been observed in mice[151] and relate to clinical observations linking abnormal conscious arousal states to thalamic lesions[152]. Finally, it is notable that general anaesthetics typically induce qualitatively distinct brain states as compared with sleep[153], suggesting that a diverse range of thalamocortical state dynamics can be induced by non-naturalistic manipulations of neuromodulatory tone throughout the brain.

The thalamus shapes and constrains adaptive brain dynamics

In the preceding sections, we outlined the central role played by the thalamus in shaping evoked responses, functional connectivity, network topology and neuronal variability, often through its tight connections with the ascending arousal system (Fig. 1b). Note that each of these features is also specific to the empirical lens (for example, our emphasis is on human functional neuroimaging) through which they were investigated, and thus under different contexts these features could reflect different or similar underlying neural capacities. Henceforth, how might this functional repertoire work together to support cognitive functions? Although the role of the thalamus in sensory and motor processes is relatively easy to link to relatively concrete measures — such as the perception of a particular stimulus, or the movement of a particular effector — the same cannot be said for cognitive processes, which are often far more abstract in nature. However, in the cases where we can break down cognitive processes into smaller components, there are clear predictions that can be made regarding the role of the thalamus in cognition. For instance, if an item needs to be held over a delay in working memory, then thalamocortical normalization is of great importance, as evidenced in rodents[45]. Alternatively, if interactions in the cerebral cortex are required to support flexible decision-making, the diffuse projections of the higher-order or matrix thalamus could help ensure coordinated synchrony between relatively specialized pyramidal neurons in the cerebral cortex[6]. Similar integration is required for large-scale circuits of the brain, such as the cerebellum and basal ganglia, and there is ample evidence that the thalamus plays a crucial role in amalgamating these signals to maximize adaptive behaviour[14]. Finally, the evidence that diffusely projecting intralaminar nuclei of the thalamus are involved in the transition between sleep and wake[140,150] further highlights the importance of the thalamus for coordinating the global brain dynamic modes required for cognitive function[10].

To provide a concrete example of how these different computations may play out at the systems level, we highlight new work showing how the functional repertoire of the thalamus (that is, relating to activity, coupling/topology, variability and arousal) can aid decision-making under uncertainty[154]. When faced with a complex perceptual scene, the deliberate processing of specific, cognitively relevant perceptual features (likely requiring selective gain control) can cause certain features to 'pop out' of the noisy background. Such selective processing may be akin to sitting deep in a single attractor within a landscape of potential processing modes, a phenomenon linked to cortical alpha rhythms[155] that likely emerge from relatively selective thalamocortical loop interactions[156]. Conversely, when we are less certain about what to attend to in our environment, the brain may instead need to track multiple stimulus features at the same time[157,158]. Doing so may require a 'flatter' attractor landscape, within which the brain can more easily switch processing modes, a process likely requiring higher neural 'excitability' (that is, variability) and neuromodulatory arousal[159] via more distributed interactions between the thalamus and the cerebral cortex[14,62]. Due to various design-level challenges in past human work, testing whether and how the functional repertoire of the thalamus is engaged in these distinct cognitive challenges had been inherently difficult.

A multimodal EEG–fMRI experiment was devised to capture these various phenomena using fast cortical dynamics (EEG), slower cortical and subcortical activity (fMRI), and pupillometry (arousal) while participants performed the multi-attribute attention task[154] (Fig. 4). Briefly, participants were presented with stimuli comprising four unique dimensions present on every trial, and 'uncertainty' was manipulated by varying the number of dimensions that were task relevant. The results revealed that the brain indeed shifted into a more excitable (for example, more variable or entropic) and aroused cortical state with increasing uncertainty, effects dominantly associated with elevated activity in thalamic regions with frontoparietal projections (for example, the mediodorsal thalamus (MD) and the anterior pulvinar) (Fig. 4). Elevated mediodorsal activity is further consistent with recent findings reporting distinct MD neuronal populations in mice that resolve decision uncertainty from conflicting or low signal task inputs[160]. Crucially, the effects in the EEG–fMRI experiment were especially pronounced in those adults better able to perform the task (Fig. 4). It may thus be that processing uncertainty drives a topologically broad-scale 'thalamo-frontoparietal' system to permit dynamic target selection within high-dimensional contexts[161–163] in higher-performing adults. Indeed, findings from this study[154] highlight all core features of our proposed functional repertoire of the thalamus; the thalamus appears to influence local cortical activity at fast and slow temporal scales, reflect coupling or topology within the broader thalamo-frontoparietal system, drive moment-to-moment variability in cortical activity as well as reflect neuromodulatory arousal. In short, the capacity for deploying flexible, multi-demand attentional resources is critically dependent on the architecture of the thalamus and its interactions with the rest of the brain.

Future outlook and conclusions

Although previous generations of cognitive neuroscientists may have been dissuaded from incorporating the thalamus into their imaging protocols and experimental hypotheses (Box 2), we hope that the ideas conveyed in this Perspective will encourage others to further investigate this crucial structure nestled deep within the subcortex. We have argued that many key features of brain function, including

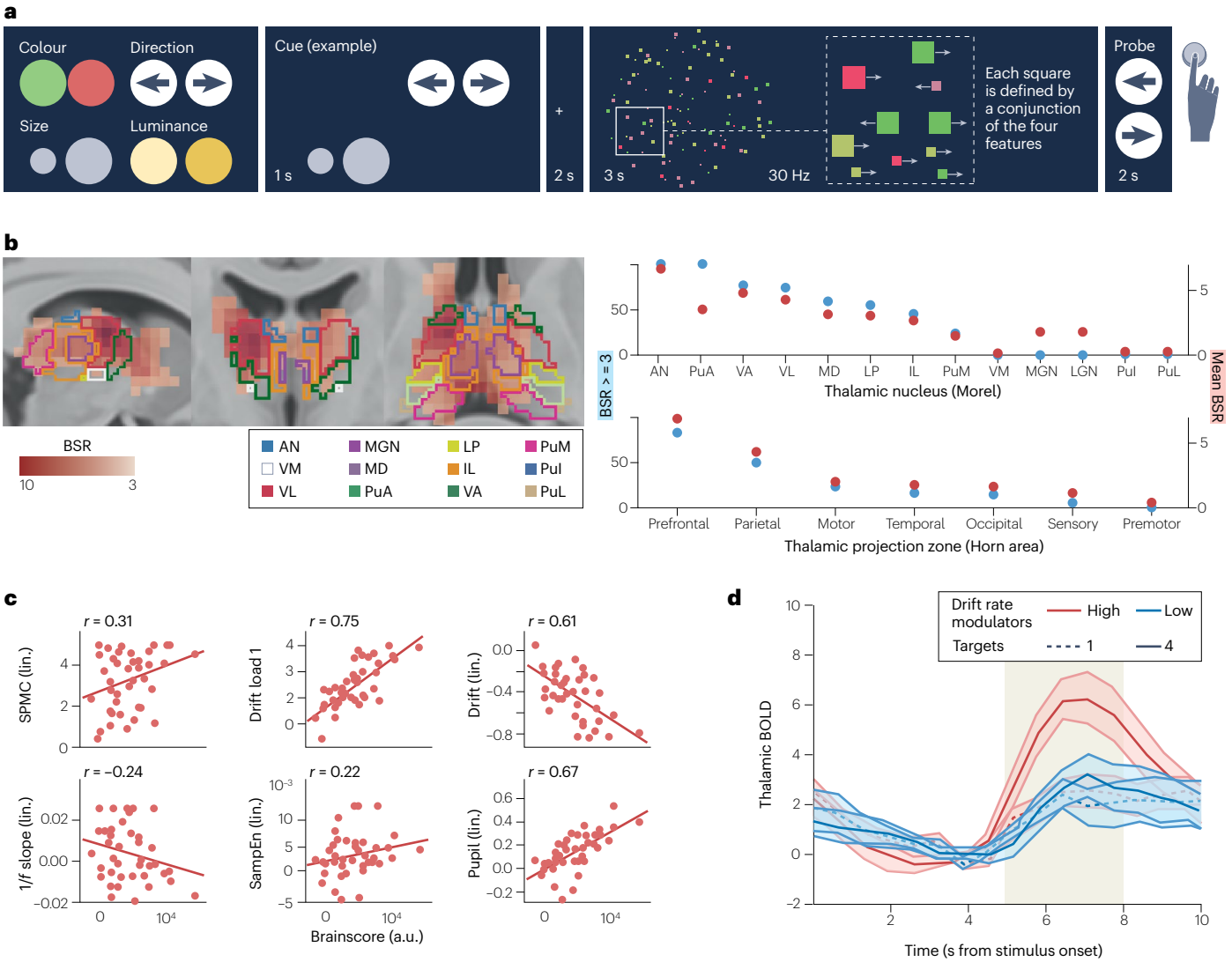


Fig. 4 | The functional repertoire of the thalamus serves decision-making under parametric uncertainty. a, In the multi-attribute attention task, participants were first cued with a set of potentially task-relevant stimulus features 1–4 (any set of colour, direction, size or luminance). They were then shown a stimulus that contains all four features and subsequently asked to make a decision about one feature. Participants underwent functional MRI (fMRI) and electroencephalography (EEG) during the task, in separate sessions. **b**,**c**, Results indicated that participants with larger parametric increases in thalamic blood oxygen level-dependent (BOLD) (especially in anteromedial nuclei that project to frontoparietal cortical targets) (panel **b**) were more likely to upregulate EEG-based 'excitability' (reduced alpha and increased gamma, expressed by a spectral power modulation component (SPMC)), have flatter 1/*f* spectral slopes, have higher sample entropy (SampEn), exhibit a higher drift rate and drift rate modulation and show heightened arousal (first derivative of pupil responses) (panel **c**). **d**, Those who expressed higher uncertainty-related modulation of behavioural drift rate expressed higher thalamic modulation particularly during stimulus presentation (yellow shading). AN, anterior nucleus; BSR, bootstrap ratio; IL, intra-laminar; LGN, lateral geniculate nucleus; LP, lateral-posterior; MD, mediodorsal; MGN, medial geniculate nucleus; PuA, anterior pulvinar; Pul, pulvinar proper; PuL, lateral pulvinar; PuM, medial pulvinar; VA, ventral anterior; VL, ventrolateral; VM, ventromedial. Figure reprinted ref. 154, Springer Nature Limited.

local activity, connectivity, network topology, variability and systems-level coordination, are crucially dependent on the integrity and influence of thalamic organization. Although the role of the thalamus in systems-level organization is becoming increasingly appreciated, there are numerous open questions that remain to be clarified. First, although the thalamus appears to act as a connector hub in the network organization of the brain[87,95], it is unclear whether this topological role is maintained across arousal states. Indeed, the precise relationship between different arms of the neuromodulatory arousal system and the distributed thalamocortical system remains to be effectively clarified in vivo. Second, more careful characterization of the involvement of different thalamic subregions across diverse cognitive contexts will also vastly improve our understanding of how distributed cortico-subcortical architectures dynamically reconfigure to facilitate complex, adaptive behaviour. We also foresee a major role for studies designed to integrate across species, delineating the

similarities and differences inherent within thalamic organization across phylogeny, and how these might underpin crucial cognitive idiosyncrasies across evolutionary time. Last, it will be important to determine precisely how the macroscopic features that cognitive neuroscientists measure (for example, the BOLD signal or event-related potentials) relate to (dys)function within the thalamus. Although this is undoubtedly a complex issue, we envisage that advances in neuronal recordings and the integration of neuronal signals with generative computational modelling approaches will further enhance the conclusions that can be made.

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