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Thalamic pathways underlying prefrontal cortex–medial temporal lobe oscillatory interactions

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As focus shifts to large-scale network interactions involved in memory, it is becoming increasingly clear that oscillatory dynamics are critically involved. A number of studies have shown a negative correlation between memory retrieval in alpha and beta power, and a positive correlation between retrieval and theta power. In this opinion article, we suggest three thalamic sub-regions responsible for the coordination of oscillatory activity and the facilitation of memory processes. Specifically, the medial dorsal nucleus is related to changes in beta synchrony, the pulvinar is responsible for alpha synchrony, and the anterior thalamus is related to theta synchrony. These pathways may be modulated via frontal control, and changes in oscillations could be used to track the engagement of underlying memory systems.

Memory and thalamo–cortical networks

Although everyone acknowledges that memory encoding and retrieval are not isolated functions of any one brain area [1,2], there are many challenges in moving beyond the traditional studies focusing on individual regions (e.g., concentrating on the prominent role of the hippocampus) to obtain insight into the nature of network-level dynamics. Fortunately, recent studies increasingly support the idea that oscillatory dynamics in multiple brain regions are associated with different aspects of memory encoding and retrieval [3–5], thus providing an important tool for further investigating these network-level dynamics (see Glossary). These studies have generally found a consistent relationship between several frequency bands and successful encoding or retrieval of experiences: namely, that oscillatory power within the alpha (8–12 Hz) and beta (13–30 Hz) frequency bands generally decrease with these memory processes, while theta (3–8 Hz) and gamma (30–100+ Hz) bands increase in the regions directly involved in the memory operations. The critical next step is to understand why these relationships exist, and what they tell us about the larger functional organization of memory systems in the brain.

The central hypothesis advanced here is that different nuclei in the thalamus play a critical role in coordinating processing across different brain areas, and that these different thalamic circuits have characteristic oscillatory dynamics [6–10]. First order thalamic nuclei serve as a relay for sensory information into the neocortex, while higher order thalamic regions might serve a modulatory role in sensory processing. These nuclei receive extensive feedback projections from cortex-forming thalamo–cortical circuits. In this article, we show how a range of data on neural oscillations correlating with task performance can be explained in terms of the unique functional contributions of three different thalamically-defined circuits, with corresponding oscillatory signatures (in the alpha, beta, and theta bands). Furthermore, these thalamic networks provide different channels by which task-driven top–down control signals from the prefrontal cortex (PFC) can potentially shape memory processes [11–14].

Based on our previous work in this domain [15–17], two memory systems have informed our Three Circuit Model (Figure 1). The straightforward mapping of our theory based on lesion studies, neuroimaging, and thalamic connectivity would suggest that familiarity-based processing in the extra-hippocampal medial temporal lobe (MTL)

Glossary

Cross-frequency coupling: modulations of characteristics (e.g., power, phase) of oscillations in one frequency range that vary as a function of another frequency. For example spectral power in the gamma range is often seen to correlate with the phase of slow oscillations.
Frequency bands: groupings of neural oscillations witnessed in EEG, MEG, or local field potentials. These bands, both clinically and functionally defined, show correlations between behavior and changes in oscillatory power within a given frequency band. A common definition of these bands are: delta – 1–4 Hz, theta – 4–8 Hz, alpha – 8–12 Hz, beta – 12–30 Hz, and gamma 30–100+ Hz.
Neural oscillation: rhythmic synaptic activity of neuronal ensembles that is generated by intrinsic neural mechanisms of excitation and inhibition. Oscillations discussed in the current text are often originating from the influence of pacemaker like brain regions which have an architecture able to support these dynamics, and are measured in intracranial local field potentials and surface EEG/MEG.
Power: is the square of the amplitude (i.e., deviation from zero) of the activity in a given frequency band. In the Fourier transform of a time varying signal, power in a given frequency range reflects the overall contribution of those oscillations to the total signal averaged over time.
Synchronization: Quantified using various metrics (e.g., coherence, phase lag index, etc.), is generally used here as a measure derived from the Fourier transform of a given pair of time varying signals, which mainly reflects the frequency-dependent consistency of the phase angle between those signals. In short, power can provide a coarse measure of magnitude and temporal consistency of neuronal firing within a given region, while synchronization considers the interaction of two or more regions [72].

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Box 1. Medial temporal lobe memory systems

Extensive research has been done investigating the role of the MTL in the recall or recognition of previously studied items. The memory interval involves at least several minutes between study and test. Results from these paradigms provide evidence of two separable memory systems: recollective memory (recall of numerous, vivid supporting details that are bound together), supported by the hippocampus; and familiarity-based memory (fast recognition of items, without recall of supporting details, e.g., just knowing); supported by the entorhinal, perirhinal, and parahippocampal cortices [15,27]. The subtleties of this dichotomy, however, suggest that the two systems are not independent from each other: that the perirhinal and parahippocampal cortices aide the hippocampus in the retrieval required for episodic memories, and the hippocampus can also support familiarity based recognition [73]. Similarly, it has been suggested that interaction with frontal cortex allows for the executive guidance of memory processes, such that PFC can trigger cues in the MTL cortex, which allows the hippocampus to provide pattern completion and the recall of particular episodes.

cortex is supported by beta oscillations, while the recollective memory in the hippocampus is supported by theta oscillations. This mapping can likely provide traction for designing new empirical studies to test this relationship between neural oscillations and memory systems, as well as tracking the interaction with PFC regions. However, this simple dichotomy of recollection versus familiarity is only a first approximation of the complex interaction assumed in natural behavior. Building from this simple model, it may be possible to investigate the interaction of these two systems across multiple brain regions where the neural oscillations provide a signature for which memory system is driving which areas.

Three circuit model of thalamic role in memory related oscillations

The first thalmo–cortical circuit involves the hippocampus and its associated subcortical network, including the anterior thalamus and medial septum, which are essential in the maintenance of theta oscillations (4–8 Hz) [18]. Theta oscillations have been shown to be critically involved in the successful encoding and retrieval of episodic-like memories in both humans and animals, as briefly described in Box 1 [3,19,20], and it is believed to be primarily driven by the pacemaker cells within the medial septum. The anterior thalamus, however, provides the connectivity for the hippocampus to potentially modulate communication with the medial and orbital PFC through theta synchronization [21,22]. Therefore, we think of the theta circuit as important for the core functioning of the hippocampus during

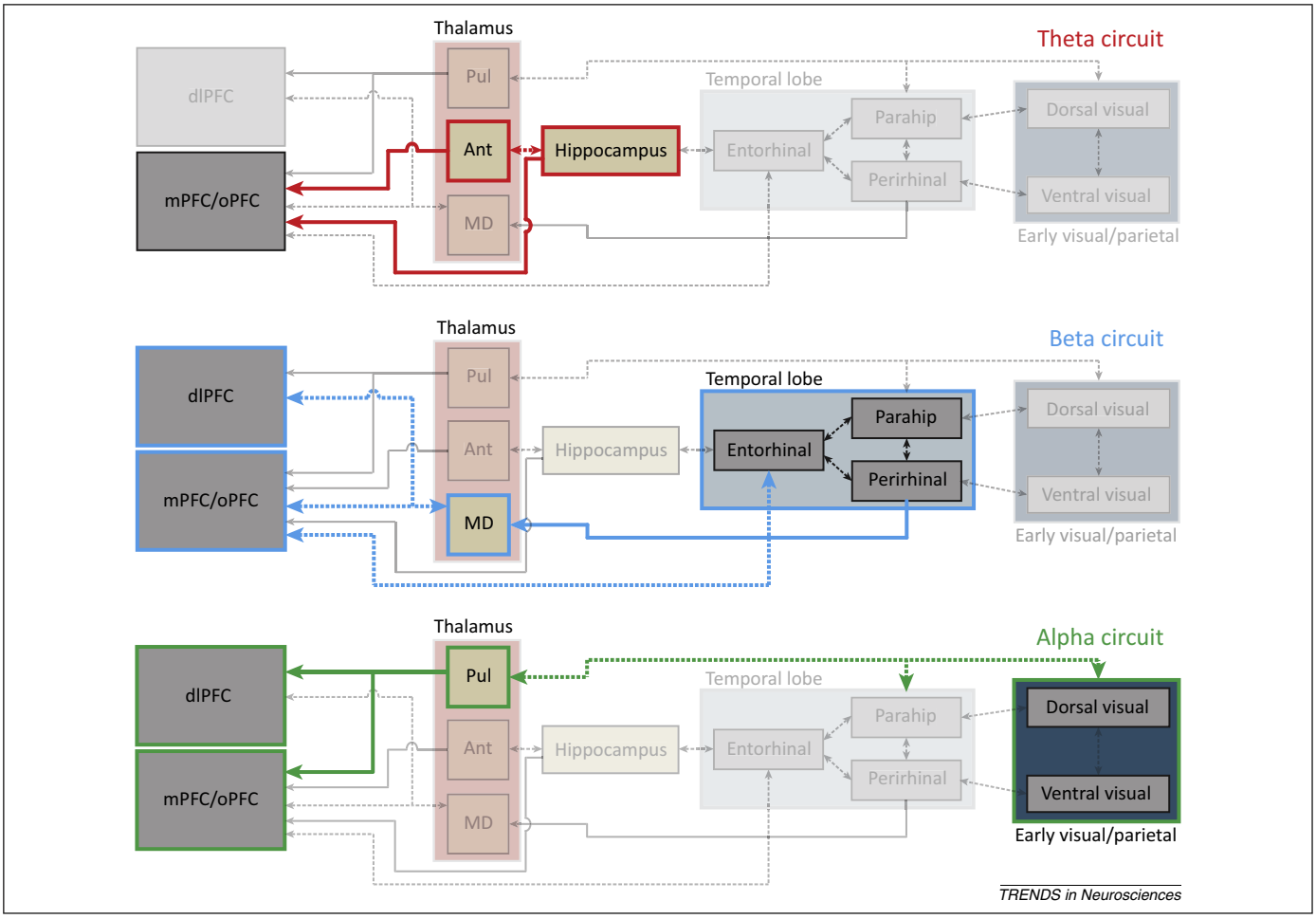

Figure 1. Three circuit model of neural oscillations in memory processes. Connectivity is shown between the prefrontal cortex (PFC) and various posterior cortical and subcortical regions, and the frequency bands proposed to be associated with those circuits. This models suggests that theta is dependent on the hippocampus and anterior (Ant) thalamus, beta is dependent upon the parahippocampal/rhinal cortex and the medial dorsal (MD) thalamus, and alpha is dependent on early visual/parietal cortex and the pulvinar (Pul). Gamma oscillations are believed to reflect local cortical processing and is modulated by these lower frequency bands through cross-frequency coupling. Unbroken lines show feedforward connections, and broken lines show bi-directional connections.

encoding and retrieval, and interactions with PFC regions during those processes.

The second thalamic circuit essential to declarative memory involves the MTL beyond the hippocampus, which includes entorhinal, parahippocampal, and perirhinal cortices, connected via the medial dorsal nucleus of the thalamus to the medial, orbital, and lateral PFC [22–24]. Current evidence suggests this thalamo–cortical circuit may synchronize within the beta frequency range [25,26]. The extra-hippocampal MTL cortex is known to be involved in recognition or familiarity-based memory [15,24,27]. Therefore, one would predict that beta synchronization should correlate with familiarity-based recognition memory processes. However, simple dichotomies of recollection versus familiarity are only starting points: the rhinal cortex and parahippocampal areas also serve as the primary input and output for the hippocampus. Thus, the top–down control over these areas via associated PFC regions can provide an important means of manipulating the content that is encoded into the hippocampus, and the nature of the retrieval cues that are driving the hippocampal output. In this way, its speculated that the beta circuit may play a complimentary role providing executive control over the theta circuit.

Finally, the third thalamic circuit involves parietal and visual cortex interconnected via the pulvinar, which provides synchronization within the alpha (8–12 Hz) band between these posterior regions and the medial, orbital, and lateral PFC [10,28,29]. This circuit is important for bottom–up stimulus-driven encoding processes in memory [30], but it can also inhibit contradictory or interfering information during internally guided retrieval [31]. Therefore, its overall contribution to memory can be mixed, and depends on the nature of the task and on what kinds of memory processing are required.

Neural mechanisms of oscillations

Thalamic neurons have been shown to exhibit intrinsic oscillatory firing patterns, acting like a pacemaker system [6,10,32–35]. Neural recordings show that rhythmic firing in other areas interconnected with the thalamus can occur through common input pathways from these thalamic pacemaker neurons. These oscillations in firing patterns are further supported by interactions between excitatory principal cells and inhibitory interneurons within a local cortical cell assembly as well as between cortical and subcortical areas [9]. Several simulation studies have investigated the potential generation and synchronization of oscillations via thalamo–cortical circuits, as shown in Figure 2A [33,36–38]. Specifically, these models focus on the cycle of feedforward activation from the thalamus and feedback from the cortex, leading to oscillations of neural firing where the frequency and amplitude is dependent upon the particular properties of this circuit (e.g., the relative change in amplitude or phase of the feedforward, thalamo–cortico–thalamic, and intracortical components of the circuit can enhance or disrupt the circuit's ongoing oscillation).

Thalamic gating model

Thalamic circuits may play a functional role in selectively gating communication between cortical regions by synchronizing them in various frequency bands. This coordinating role can potentially operate independently of the PFC, while also providing a mechanism for top–down PFC-mediated control. Therefore, these gating mechanisms

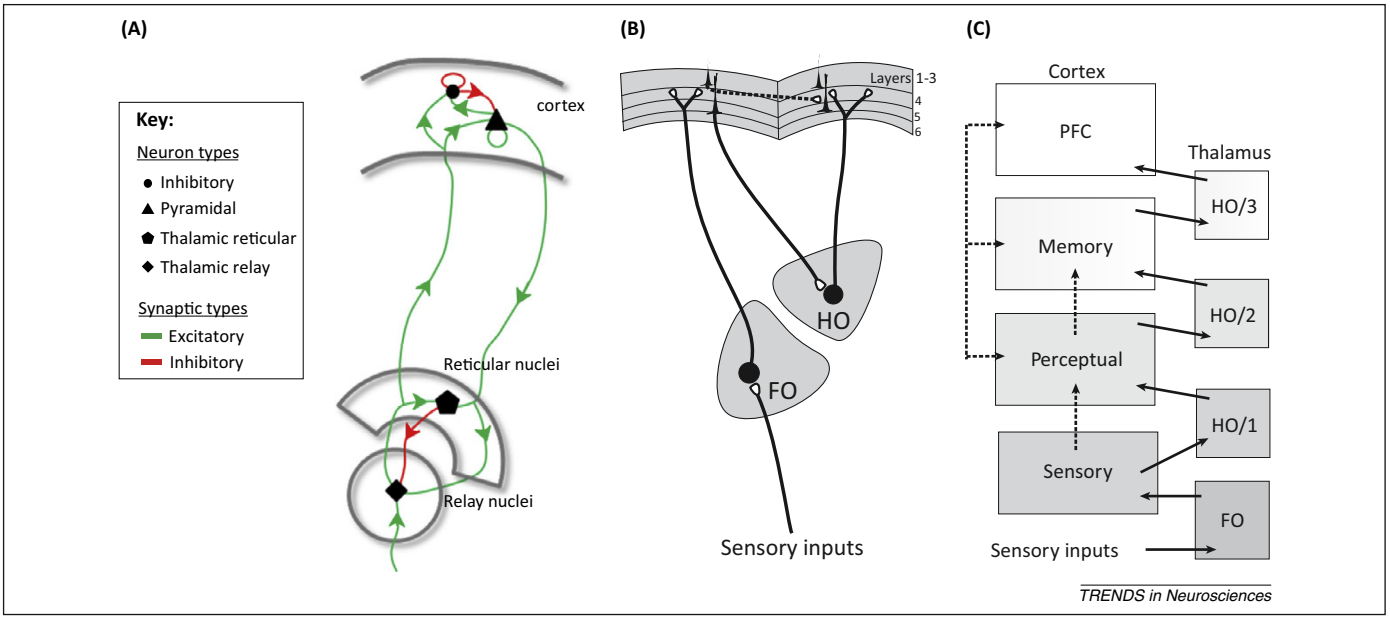

Figure 2. The role of thalamic nuclei in the cascading of information through the cortex (adapted, with permission, from [6,33]). **(A)** The excitatory and inhibitory architecture within a single thalamo–cortical loop that leads to intrinsic oscillations. Input feeds forward to both the thalamic reticular nucleus and the cortical region of interest. Here, GABAergic inhibitory interneurons within the reticular nucleus feedback onto the relay nucleus to stop thalamic firing, while in the cortex, the same inhibition process hinders the pyramidal cells' firing. This cortical inhibition, however, happens after a feedback signal returns to the thalamus from the cortical pyramidal cells, which reinitiates the feedforward process from the thalamic relay nuclei. **(B)** Thalamic nuclei connectivity with cortex, where sensory information first impacts first order (FO) nuclei, which then starts the cascade of relays through higher order (HO) nuclei involving both cortical–cortical connections (shown in broken lines projecting from superficial layers 2/3), and thalamo–cortical connections (shown in unbroken lines projecting from thalamus layer 4, and from the cortex via layers 5/6). **(C)** Schematic of how this cascade proceeds up the cortical hierarchy and the extension of this cascade model into the prefrontal cortex (PFC)-mediated loops of higher level cognitive systems, such as memory. **(A)** Reproduced, with permission, from [33]. **(B)** and **(C)** Reproduced, with permission, from [6].

implemented by oscillatory synchronization are central to the overall framework, ultimately affecting cognitive behavior, such as memory encoding and retrieval.

The mechanisms by which the thalamus plays this coordinating role have been articulated in the context of functional gating models in the visual thalamus [6,7]. Figure 2B (adapted from [6]) shows the relaying of first order (FO) sensory information from the sense organs through the FO thalamic region, such as the lateral geniculate nucleus, and onto the cortex. This FO cortical region sends this information, after some local processing, back to both the FO relay area of the thalamus, and to a higher order (HO) thalamic region, such as the pulvinar, which in turn drives HO cortical regions. The proposed role of these HO nuclei is to give a 'wake up call' to downstream cortical regions alerting them to send task-relevant information via cortico–cortical pathways between the lower and higher order cortex [6,8].

Figure 2C shows this same idea generalized to a schematic of how multiple cortical systems can be coordinated (adapted from [6]). Information is transmitted via the cortico–cortical connections to the next cortical region or regions, while the HO thalamic nuclei selectively activate the appropriate downstream cortical area that will be engaged in the next level of processing. Building from the perceptual level, this process of thalamic gating or selection can be extended to higher-level cognitive phenomena [7]. Furthermore, Figure 2C shows how thalmo–cortical circuits involving the PFC can provide top–down goal directed feedback onto these circuits.

An important consequence of the selection of particular cortical regions for subsequent processing is that other areas are implicitly selected to not be involved in subsequent processing. Emerging evidence in the domain of cognitive control suggests there may be distinct oscillatory signatures supporting volitional suppression of task-interfering cortical regions [31,39,40].

It is also crucial to realize that the model described above is specific to thalamic interactions with the neocortex (i.e., six-layer). How this model fits with subcortical structures, such as the hippocampus, which don't necessarily follow the laminar structure of the neocortex, is an open question. Indeed, there is substantial evidence that theta oscillations are dependent on many other structures besides the thalamus, including the medial septum [18]. It is interesting to note that power changes in the alpha and beta bands are negatively correlated with successful memory processes, while theta power is positively correlated. The fact that alpha and beta are proposed to be driven by six-layer cortico–thalamic interactions while theta is not, might provide fertile ground for resolving this functional dichotomy.

In summary, we argue that these same thalamic selection mechanisms described by Sherman and Guillery [6] and Saalmann and Kastner [7], operating on the three different thalamic circuits outlined above, can provide the gating of cortical processes relevant to particular memory functions. Furthermore, the particular oscillatory dynamics engaged by this selection process may provide indicators of which system-scale neural circuits are coordinating together to facilitate that particular form of memory processing.

Models of thalamic interaction with memory

Next, we attempt to reconcile the above framework with a set of existing models regarding the roles of different thalamic circuits in various declarative memory processes [21,22,24,41]. In particular, these models propose that the anterior nucleus of the thalamus is critically involved in memory encoding and retrieval, and the medial dorsal nucleus is involved in executive aspects of declarative memory including familiarity based recognition. These theories are based primarily on lesion work in animals, and human patient populations. For example, in rodents, lesions in either the medial dorsal nucleus or the PFC appear to disrupt the guidance of selecting the appropriate information to be retrieved along with general executive function [24], while lesions to the anterior nuclei hinders memory performance, but leaves executive function relatively unimpaired [21]. It is suggested that the anterior and medial dorsal nuclei assist in the creation and selection of content within declarative memory.

Thalamic anatomical connectivity also supports these theories. Both the anterior and medial dorsal nuclei project to various PFC regions; however, the medial dorsal nucleus is more strongly and diversely connected to multiple PFC regions [23,24,42]. Similarly, the anterior thalamic nuclei receive extensive inputs from the hippocampus, while the medial dorsal nucleus receives few, if any. In contrast, the medial dorsal nucleus receives direct inputs from the MTL cortical regions, such as the entorhinal, parahippocampal, and perirhinal cortices. These differences are potentially important, because both the MTL cortex and the hippocampus are key sites within the MTL for declarative memory, but there is also widespread evidence that these sites make qualitatively different contributions [22,24,27]. Much of this evidence indicates that the parahippocampal and perirhinal cortex are vital for familiarity based processes, while the hippocampus is required for recollection based processes. There is also the strong potential for these two memory systems to interact via shared PFC connectivity and the direct inputs of the MTL cortex into the hippocampus.

Similarly, the pulvinar has been shown to be functionally related to early visual and parietal cortex through the synchronization of these cortical regions within the alpha band [43]. A pattern of reduced alpha power and simultaneous increase in gamma power is generally found in attention and perception studies of the visual cortex [44]; however, these same alpha dynamics have been widely observed in memory studies [4,5,39,40]. New evidence in declarative memory show that alpha oscillations play an active role in gating perceptual information to downstream processes such as those involved in memory encoding and retrieval [31].

These ideas can be summarized to suggest that the pulvinar is involved in the gating of perceptual information, the medial dorsal thalamus is involved in the retrieval of familiarity based memories, and the anterior

Box 2. Human versus animal models of oscillations

A critical issue for the empirical evidence reviewed in this article is the potential overlap or disconnect between animal and human memory models – we are proposing a model of human memory, but much of the supporting theories and data originated from animal models. For example, in studies of theta oscillations, single cell and intercranial methods are only possible in animals, and have provided a wealth of data supporting theories founded on spatial navigation. These theories are based on rodent hippocampal place cells, that is, CA3 and CA1 neurons that consistently fire when the animal is in a particular spatial location [74]. These place cells precess in theta phase as the animal runs through a learned environment, so that place cells for upcoming locations first fire at the peak of the on-going theta oscillation, and as the animal approaches that cell's corresponding spatial location, the cell fires at more and more advanced phase positions until it reaches the trough of the theta oscillation [75,76]. This phase precession of place cells suggests that the hippocampus is doing a form of cued recall, where the current spatial location cues the firing of the next spatial location and so on, binding each of the place cells together into a coherent trace of past experience [77]. This was bolstered by the fact that these sequences of cells were seen to fire during both sleep and awake states in the same order as they were experienced, dubbed hippocampal replay, and that memory for these sequences is strengthened through this replay [78].

This exciting work was incorporated into human hippocampal research founded on the cognitive neuroscience constructs of episodic memory, and recollection/familiarity (see Box 1 for further discussion). These theories suggest that the hippocampus encodes the contextual (i.e., spatial and temporal) information of experiences for later retrieval, and that the mechanisms derived from animal models provide explanatory power for how this might occur in humans. Empirical studies testing the animal models of spatial navigation against human behavior have found correlational support for the role of theta in human episodic memory [3,79], although it is difficult to test episodic recall without verbal report and memory related human theta oscillations may be centered at a lower frequency (~3 Hz) as compared to rodents (~8 Hz) [80,81]. Similarly, the human homolog to place cells is still debated [82–84]. Anatomical comparisons between human and rodents (namely thalamic connectivity, and PFC regions) must also be approached cautiously when considering how data from one model can inform cross-species theories. How closely animal theories of spatial navigation align with human models of episodic memory is still being probed by current research. What is clear, however, is that the interplay between human and animal models has been beneficial in moving both fields forward, and that it is necessary to carefully test the theories of one domain against the other.

thalamus is involved in the creation and retrieval of episodic/recollection based memories. Our three pathway model integrates these ideas to propose a theory of how thalamic nuclei can be used to explain the various frequency related effects seen in memory studies. We argue that recollection and familiarity may show the coordination of different frequency bands, with theta being more related to recollective/episodic processes, beta being more related to familiarity and executive control over memory processes, and alpha providing task dependent gating of sensory information into higher order systems.

Evaluating the three pathway model

We now review several recent studies that focus on the role of beta, theta, and alpha oscillations in memory dynamics and thalamic interactions to highlight where predictions of the above framework are consistent with recent data.

Theta and anterior thalamus

Are the anterior thalamus and the theta rhythm specifically associated with hippocampally-mediated encoding and recall? Several studies, in both humans [3,13,45–48] and rodents [14,19,49,50] have shown increased power and synchronization between the hippocampus and neocortex that positively correlates with behavior requiring recollective memory. These studies suggest that the hippocampus couples to the frontal cortex by means of theta oscillations, and this coupling facilitates the transfer of information between these two regions, as described in Box 3. Results relating hippocampal encoding and retrieval to thalamic nuclei also have a long history in both animal [21,23,24,51] and human [52,53] literature, with evidence suggesting that theta oscillations are dependent upon several subcortical areas, including the thalamus and the medial septum [51]. Similarly, lesions to the anterior thalamus in rodents [22,24] have been shown to be disruptive of episodic-like associative memory. A couple of recent studies which support this connection between behavior, oscillations, and the thalamus are worth noting here. Fuentemilla *et al.* [20] recently published magnetoencephalography (MEG) results from humans showing increased theta synchronization between the medial PFC and hippocampus for autobiographical memory recall compared to semantic recall; critically, in this same comparison, they found increased theta power localized in an unidentified thalamic region. Similarly, Pergola *et al.* [54] found increased blood oxygen level-dependent (BOLD) response in the anterior nuclei of the thalamus during the retrieval of paired associates in a recognition memory paradigm. How BOLD response relates to MEG/electroencephalography (EEG) measures of oscillations in memory paradigms is not well understood (although see [55]); however, the co-occurrence of these structures in similar experimental paradigms at least provides evidence for their relevance in the required cognitive processes.

In rats, O'Neill *et al.* [56] found increased theta synchrony between medial PFC and ventral hippocampus during a T maze task. Interestingly, beta synchrony was also found during this task in the medial dorsal thalamus, suggesting that these oscillations may coordinate in some way [25,56]. Indeed, Cholvin *et al.* [57] have recently found that inactivating the reuniens and rhomboid thalamic nuclei of the midline thalamus, which provide major reciprocal connections from frontal cortex back to the hippocampus, prevents animals from shifting from learned escape strategies in an adapted Morris water maze task. How these results obtained in rats can be directly related to the human homologue of episodic memory remains a challenge (see Box 2), but several studies have shown a correlation between theta oscillations and episodic like memories in the rat [58–60].

In summary, there is MEG evidence that theta synchronization between the PFC and the hippocampus can facilitate recollective memory processes in humans [20]. There is some indirect MEG and BOLD evidence that the thalamus plays a role in this synchronization process [20,54],

Box 3. Functional role of neuronal oscillations

- **Theta oscillations:** it has been demonstrated that the rat hippocampus synchronizes with other regions such as the PFC and the striatum in situations where the exchange of memory related information is relevant [19,20,50,85]. When rats are navigating a spatial environment, hippocampal theta oscillations modulate neuronal firing in a phasic manner. Specifically, hippocampal place cells have been identified to code for the rat's position [74]. As the rat advances through a place field, the theta phase-of-firing of the respective place field changes systematically as the rat advances [76]. This demonstrates a scheme in which neuronal information related to memory is represented by phase coding (Box 2). In order for another region to utilize this code, for example, the PFC, this region also needs information about the hippocampal theta phase. As such, the phase synchronization between regions could reflect the exchange of phase coded information [86].
- **Alpha oscillations:** two ideas have been proposed for how alpha activity is involved in the routing of information. The first is 'routing by inhibition' in which the alpha power is strong in task-irrelevant regions and low in task relevant regions [40]. Given the inhibitory nature of the alpha activity [87], this allows the task-relevant regions to communicate, as illustrated in Figure 3 in main text. A second perspective posits that alpha phase-synchronization reflects inter-regional communication. For example, it has been demonstrated through intracranial monkey recordings that ventral regions in the temporal lobe are synchronizing in the alpha band when spatial attention is allocated [44]. Note that the 'routing by inhibition' and phase-synchronization hypothesis are not contradictory. Possibly the alpha activity partly inhibits a given area allowing only the most excitable neuronal representations to activate; the neuronal representations are then exchanged by means of inter-regional phase synchronization [88]. Both the power and phase of the alpha activity must be coordinated to allow for these schemes to operate. The pulvinar could play a crucial role in this coordination [43,44].
- **Beta oscillations:** it has been proposed that beta phase-synchronization reflects top–down processing. For example, prefrontal regions can serve to coordinate the processing in earlier sensory regions during the allocation of attention [89,90]. This has resulted in the 'information via desynchronization hypothesis', similar to what might be going in the alpha band [4]. The basic claim is that beta desynchronization reduces the phasic modulation allowing for a richer neuronal code to emerge, as shown in Figure 3 in main text. We propose that the medial dorsal thalamus is involved in coordinating rhinal with neocortical regions during memory processing via beta oscillations.
- **Gamma activity phase-locked to low frequency oscillations:** both animal and human recordings have demonstrated that power in the gamma band is coupled to the phase of theta, alpha, and beta oscillations [26,54,91–93]. It has been suggested that the inter-regional phase synchronization allows for the exchange of information via cortical–cortical projects reflected in the gamma band being

which is bolstered by the known connectivity between the hippocampus and the PFC through the anterior thalamus from rodents [22,24]. Our model connects these ideas, suggesting recollective memory works through the anterior thalamus via theta synchronization; however, to date, there is no strong evidence supporting this claim in humans.

Beta and medial dorsal thalamus

Does the medial dorsal (MD) nucleus of the thalamus, and beta band oscillations, indicate the use of familiarity-based memory processing in the MTL, and PFC-mediated control over memory by manipulating MTL representations? A recent study used mice to investigate the role of MD in an alternating choice T-maze task [25]. Recordings from PFC and the MD showed increased synchronization between these two regions in the beta (13–30 Hz) frequency range for control mice, and that pharmacologically deactivating the MD not only lead to decreased PFC–MD synchronization, but also decreased acquisition and later performance on the T-maze compared to controls. Cross *et al.* [61] targeted similar regions in the rat by lesioning the MD or the medial PFC. They assessed single item recognition (i.e., novelty of a given item), associative recognition (i.e., object recognition in a particular place), and recency discrimination (i.e., identifying the most recently seen object). Results showed that the MD was critical for associative memory and recency memory, but not for item novelty. This pattern of results generally support Aggleton *et al.*'s [22] model of recognition memory, and suggest that the MD may be partially involved in recollection based memories. These results are also in line with Van der Werf *et al.*'s [21] characterization of MD mediating executive aspects of memory, where MD engagement may be synchronizing frontal control over medial temporal lobe input to the hippocampus. These ideas are further discussed in the Concluding remarks section.

In humans, a recent analysis of stroke patients with thalamic lesions found reduced cued recall accuracy of studied picture pairs correlated with reduced volume in the MD [62]. Another study done by the same group used functional magnetic resonance imaging (fMRI) to target these structures in healthy individuals. Inside an MRI scanner, participants encoded a set of paired associates, then performed a recognition test for a single item from each of those pairs, and finally, outside the scanner, participants were given a cued recall test for the associated items. Their results showed increased BOLD response in the MD and in the dorsal lateral PFC during encoding and retrieval for items that had both successful recognition and cued recall, compared to items which showed correct recognition but incorrect cued recall [54]. Similarly, epilepsy patients with electrodes implanted in various thalamic nuclei showed increased beta (20 Hz) synchrony between depth electrodes in the MD and surface electrodes over the PFC for correctly remembered items compared to lure items during a recognition memory test. This beta oscillation also showed cross frequency coupling with a modulation of gamma power (55–80 Hz) on the surface electrode [26].

In summary, there is strong evidence supporting the involvement of MD thalamus in PFC BOLD response and beta oscillations during recognition memory processes [26,54]. There are also well established human models suggesting that the extra hippocampal MTL cortex is critical for familiarity based recognition [27]. What has yet to be shown is the direct connection between humans models of familiarity and beta synchronization within the MTL cortex. Similarly, there is preliminary evidence from rodents that theta and beta oscillations may simultaneously contribute to these memory processes [54,61,62], but it is unclear how or in what capacity they interact.

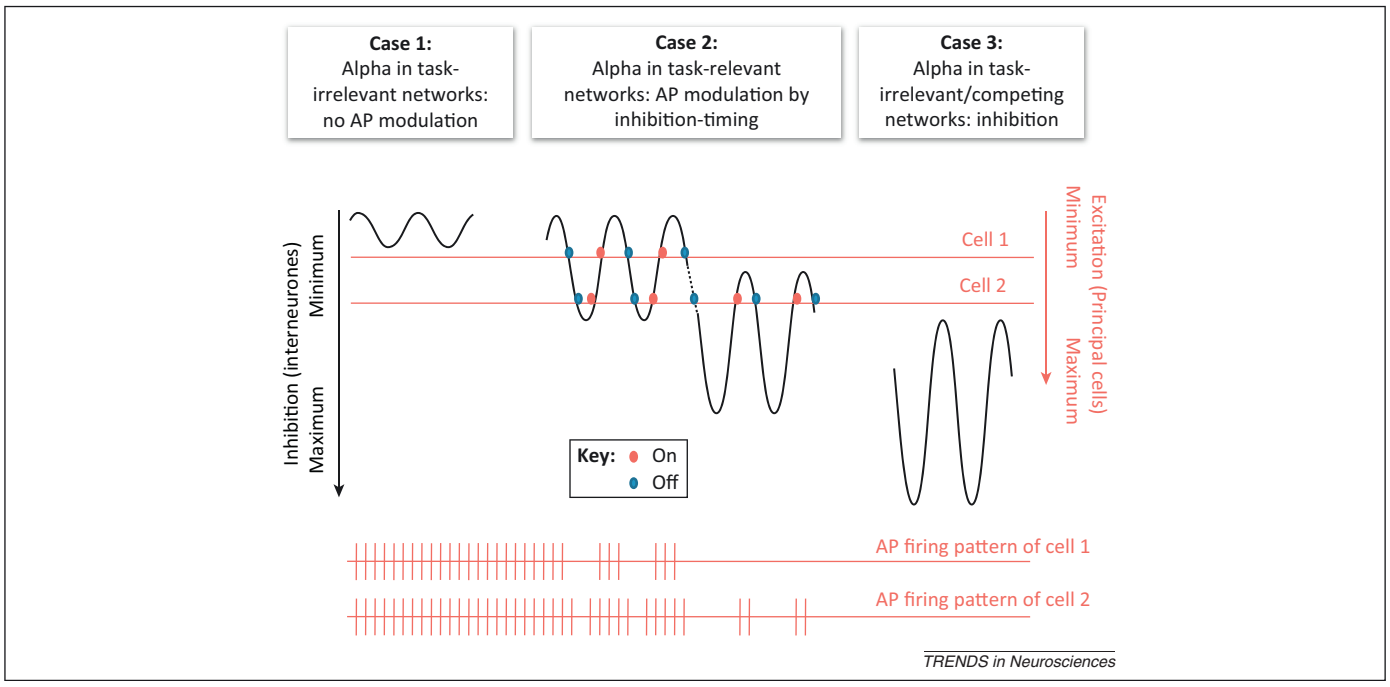

Figure 3. Three cases of how oscillations can influence cortex. **Case 1:** In task-irrelevant networks, the amplitude is small and has no impact on cell firing rate, which is symbolized by vertical lines representing action potentials (APs) in the lower panel. **Case 2:** In task-relevant networks, the amplitude increases and starts to inhibit the generation of APs in target cells during the inhibitory phase of the oscillation. Depending on the excitation level of target cells, the impact of the inhibitory oscillation is different (e.g., cell 1 and 2). With an increase in amplitudes, the inhibitory baseline increases, which means that inhibition increases not only during the phases with maximal inhibition (plotted here as troughs), but also during those with minimal inhibition (plotted here as peaks). **Case 3:** If inhibition increases further, all target cells are silenced. This case is assumed for neuronal structures that are potentially competing relative to the processing of a task. A good example is the inhibition of potentially competing regions in the ipsilateral hemisphere. Figure and caption reproduced, with permission, from [5].

Alpha and pulvinar

Is alpha power modulation associated with the gating and modulation of sensory information during memory encoding? Alpha has prominently been studied in the context of directed attention, and generally shows a decrease in power in a given receptive field when attention is directed to that field [63] (although see [64] for more discussion). This is supported by studies showing synchronization between the neocortical regions in the alpha band coordinated by the pulvinar [7,8,43,44]. These results support theories of how alpha can be seen as either inhibiting cortical function, or indicative of nonactive cortex [5,40]. Klimesch [5] suggests that this inhibition operates in two different active ways, as shown in Figure 3 and discussed in Box 3.

Generally among studies of memory, alpha shows a consistent decrease in power correlated with both recollective and familiarity based memory processes [4,5,65,66]. These power changes are usually found in the posterior cortex (early visual and parietal), and suggests that alpha is likely being used to inhibit incoming sensory information while these memory processes are engaged [5]. Direct support for this notion was found in a recent MEG study in which a cue indicated whether a subsequently presented picture should be encoded or not. An increase in alpha power for nonencoding cues predicted subsequent forgetting, but was also predictive of subject general memory performance for the to-be remembered items [31]. How this inhibition is regulated is unclear; however, two recent fMRI studies involving memory guided visual search have found that the pulvinar's connectivity with frontal cortex is modulated by task relevant versus irrelevant items presented in the visual field [67,68]. This suggests that frontal cortex may be modulating pulvinar activity, likely through the reticular thalamic nucleus, to influence alpha activity in early visual and temporal cortex.

These same ideas can be extended to include recent studies of active suppression of long term memory processes in which increased alpha power was found in potentially interfering cortical regions. A pair of recent studies manipulated the number of items required to be retrieved for successful execution of a given trial [48,69]. Results from this study, using EEG data recorded during memory testing, show that theta power was positively correlated and alpha power was negatively correlated with the number of successfully retrieved items. A similar study also showed that alpha/beta power decreased when trying to retrieve a target memory; however, the design was also able to show that alpha/beta power increased for items competing with the target memory [39]. It is not clear from these studies if alpha and beta power work through similar mechanisms, as described by Klimesch [5]; however, they likely have influence over different parts of cortex. In summary, the pulvinar has a well established role in coordinating alpha synchrony in animal models [7,8,10,43], and there is recent evidence in human models showing that alpha oscillations provide an active function of cortex suppression that would otherwise interfere with the memory retrieval [39,48,69]. There is also human fMRI evidence showing PFC modulation of the visual cortex through the pulvinar [67,68]. What has yet to be shown

Box 4. Outstanding questions

- Can combined EEG–fMRI measures verify the role of specific thalamic nuclei in cortical oscillations?
- Do changes in beta power reflect the same functional implications as changes in alpha power?
- Is beta synchronization between frontal and MTL cortex related to familiarity based memory processes?
- How do theta and beta oscillations interact during various memory process?
- Is synchronization within specific memory systems possible through deep brain stimulation of thalamic nuclei?

is the involvement of pulvinar in PFC synchronization with posterior cortex during memory processes, and that this circuit operates separately from beta oscillations (Boxes 3 and 4).

Concluding remarks

This review has focused on the potential thalamic mechanisms required for the synchronizing of various cortical regions during memory processes. The fundamental ideas of a thalamic gating mechanism were extended to support higher order cortical synchronization, and specific thalamic circuits were used to constrain which frequency bands are likely to occur with known memory systems.

How these oscillations relate to each other in terms of familiarity versus recollection based memories is a testable empirical question. There are several potentially observable scenarios where these two memory systems either operate independently or interact with each other. Without hippocampal input, beta oscillations may dominate frontal cortex and, therefore, promote MTL based familiarity memory retrieval. However, if the hippocampus becomes sufficiently engaged, theta power may dominate frontal cortex, reducing beta power, and thereby promoting recollective memory retrieval. Finally, these two oscillations may be able to coordinate together where frontal beta power would be modulated by hippocampal theta or vice versa, and the medial temporal cortex inputs to the hippocampus can provide a PFC guided signal over retrieval.

By contrast, based on a synchronization ratio theory [70], the alpha band is least likely to synchronize with either theta and beta, perhaps putting alpha in a particular functional role of deselecting cortical areas to be synchronized within these two memory systems. Our model provides the constructs and a theoretical scaffolding for designing experiments which can dissociate the current functional similarity between alpha and beta; namely that beta can synchronize the MTL cortex with PFC regions to guide behavior, and alpha can synchronize the PFC with posterior perceptual regions to select or de-select cortical regions involved in a given memory process.

The intended contribution of this review is to bridge models of thalamic mechanisms and the current state of memory related oscillation literature. Through this, it was suggested that theta and beta power may work through the frontal cortex towards the coordination of multiple memory systems. It may be possible to bias cortical function towards one of these memory systems by manipulating the underlying thalamic nuclei responsible for synchronization. Lee *et al.* [71] recently outlined the potential for deep brain stimulation in memory disorders, which focused predominately on gamma range stimulation of the medial temporal lobe system. Our review of the literature suggests that there are potentially fruitful thalamic nuclei that could be stimulated in lower frequency bands. Indeed, it was suggested in their review that memory effects were dependent on synchronization in lower frequency bands; our three pathway model suggests an approach which targets the manipulation of these bands directly through specific thalamic nuclei.

Future studies in this domain should focus on the synchronization of thalamic and cortical regions within the discussed frequency bands. The most direct approach to testing recollective versus familiarity based memories is within humans, and because of this, the most effective tool for the noninvasive testing of these ideas would be the conjunction of EEG and fMRI, or deep source localization in MEG. Here, changes in large scale scalp oscillations can be matched to changes in response for particular thalamic subregions. These methods can be used within well known paradigms of recollection and familiarity to test how these changes in oscillatory power relate to changes in BOLD activity in specific regions, or the synchronization of multiple regions.

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