Arousal, Oscillations, and Cognition: Thalamus and the Yerkes-Dodson Law

C-Paper Submission

Joshua A. Cain

University of California, Los Angeles, 2020

Introduction:

It has become clear what the Thalamus is not: it is not the passive sensory relay system it was once characterized as; recent multimodal data continues to support the notion of the thalamus as a necessary partner for the cortex in a so-called thalamocortical system with a capacity for cognitive functioning (e.g., working memory, attention, etc.) apparently exceeding the sum of its parts. What remains unclear is what precise mechanisms underlie thalamic influence in cognition. Neuronal oscillations have been proposed to mediate the multi-scale spatio-temporal binding necessary for the large networks thought to be involved in cognitive functioning[1–4]. The thalamus has been proposed to play both a generating and modulatory role on cortical rhythms; yet, the former is controversial[5], and the latter remains far from fully characterized. It remains even less understood how the now apparent role of the thalamus and its oscillations in cognition relates to arousal. Since the formation of the Yerkes Dodson law in 1908[6], an interaction between arousal and cognitive functioning has been apparent, where arousal states brought on by environmental stimulation[6], stimulant drug administration[7], and deep brain stimulation[8] follow an inverted U-shaped curve where cognitive functioning is enhanced by increasing arousal to some maxima where, from that point, increasing arousal then begins to impair cognitive functioning. Increasingly numerous studies implicate the thalamus, with an emphasis on its central nuclei, in the maintenance of arousal[8–11]; though, these findings are not without controversy[12–14]. The thalamus's apparent dual role in cognitive functioning and arousal positions it at the cross-roads of this debate and provides an avenue to better pursue the neurodynamical substrate of these constructs as well as the depth of their interrelation.

Defining Arousal

In common language, arousal may seem like a straightforward concept—the absence of fatigue, the quality of being alerted (e.g., to stimuli), having bountiful energy. However, arousal as a scientific construct has often avoided satisfactory characterization, especially at the neural level. The term has been used synonymously with other vague concepts such as "mental activity"[15,16], "energy mobilization"[17], "metabolic activity"[17,18], "mental effort"[19], and "wakefulness"[18]. Arousal has encompassed measures of neural as well as physiological arousal including increased heart rate, pupil dilation, and muscle tension[19]. While these measures often do correlate, they often do not. Physiological measures of arousal do not correlate well with each other[17]; nor, do they uniformly covary with arousal's influence on cognitive functioning[19]. While "arousal" clearly encapsulates many concepts, a common thread through colloquial and scientific definitions of arousal may be that it relates to heightened states (e.g., of energy, heart rate, muscle tension, metabolic activity). In the context of neural dynamics, then, arousal is perhaps best characterized by, simply, a heightened rate of neural activity—action potentials—especially in cells whose activity is likely to bring about continued excitation (e.g., glutamatergic instead of GABAergic neurons). This is how the term will be applied here. This definition of arousal is thus nearly synonymous with the low-level neural properties likely to bring about action potentials such as excitability and depolarization[20]. In this view, arousal is not equivalent to[21] but highly related to metabolic activity in neural tissues, as often measured using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Indeed, state-changes from low-arousal states

to higher arousal states are, in general, marked by an increase in cerebral neural activity. Increases in cortical metabolism[18] as well as the firing rate of thalamic and cortical neurons readily predicts transitions from states associated with low arousal including sleep[22], anesthesia[18,23], and coma[18] to the high-arousal state of wakefulness. Note that this definition is distinct from arousal as the "level of consciousness"[24], as it is also sometimes defined. For instance, the tonic phase of a tonic-clonic seizure can result in the loss of consciousness but high neural activity. By the definition used here, this represents high arousal, despite the absence of consciousness.

While "Arousal" is perhaps most commonly used to denote long-lasting whole-brain states (e.g., sleep), our use of arousal here can be thought as the degree of excitability or neural activity along a continuum of spatial and temporal scales of understanding, from small brain regions to whole-brain states. This view of arousal is more akin to its use in contemporary neuroscience[20,25–27] and provides greater flexibility than more dated conceptions of arousal[19] which *only* describe slow, whole-brain, state changes. Instead, specific circuits or brain regions can be "aroused" while others are dormant (e.g., as often observed after severe brain damage[28,29]). Vigilance, moreover, is a highly related concept that can be thought of as arousal as it relates to a specific cognitive function (e.g., visual attention), during which the specific circuits/regions underlying that function are likely to be particularly active. While a full analysis is beyond the scope of this work, efforts should be made to further dissect the various interrelated concepts associated with "arousal".

Arousal and Cognitive Functioning: Interrelated Concepts

The classic inverted U-shaped interaction between arousal and cognitive performance suggests the intimate interdependence of these two constructs. As pointed out by Koch and Crick[30], arousal is necessary for cognition but not sufficient for it. Indeed, cognitive functioning appears to be a fragile phenomenon requiring a thin window of background arousal to occur optimally.

At the far low-end of arousal, coma and deep anesthesia reside. Indeed, these states are characterized by lowered cortical metabolism[18] and, often-times, burst suppression, characterized by quiescent cortical activity which may persist for up to 10-20 seconds followed by rapid "bursts" in activity[2,31]. While subjects awaken from even deep sleep may report some experience[32], subjects under deep anesthesia commonly report a feeling of no time having passed[33], perhaps indicative of a total absence of experience and of complex cognitive functioning. At the far high-end of arousal, the storm of depolarization that occurs with the tonic phase of tonic-clonic seizures and which co-occurs with loss of consciousness[29] represents an extreme high state of cortical activity[29,34], and thus arousal, where again, minimal or no cognitive functioning appears possible. In less extreme examples, both drowsiness (low arousal) and periods of high stress (an imperfect proxy for high arousal) may impair cognitive performance in healthy brains[6,35,36].

While this ("U" Shaped) relationship has become canon in cognitive science, it may be underappreciated how fluctuations in arousal may not only impair cognitive functioning (e.g., in coma, seizures), but may be necessary for it. In other words, purposeful "regulation" of arousal/neural activity[9] over both time and space may be used to dynamically reallocate cognitive resources in response to changing demands. This regulation may be conducted, in part, via neural oscillations, which represent temporally and spatially dynamic fluctuations in arousal—where the

"up" phase of oscillations result in increased excitability of neurons[37,38], resulting in increased firing rates[39,40]. Similarly, "down" phase will be used here to refer to the period of low excitability in oscillating tissues. Moreover, it may not be fully appreciated how rich the full spectrum of fluctuations in arousal/excitability are—again, both in space and in time. This is perhaps best exemplified by the "1/frequency(f)" trend in cortical oscillations. It is a feature of neural oscillations that more rapid oscillations (gamma, 40Hz – 100Hz) may be highly local while slower oscillations (e.g., delta, 1-4Hz) tend to recruit far more neurons over larger spatial extents, thought to result from the preclusion of high-frequency synchronization between distant neural populations due to axon delays. This has the effect of increasing the power of low frequencies and is evident in the 1/f trend in power-spectrum plotting of neural data[2].

Importantly, different regions of this spectrum are likely to interact with each other. The phenomenon of phase amplitude coupling (PAC) is a prime example of this—where slow (and generally spatially expansive) oscillations (e.g., delta waves) can modulate the amplitude of faster (more local) oscillations (e.g., gamma waves). Such interactions may be a necessary component of cognitive functioning. Indeed, interactions between fast local oscillations and more global slow oscillations may maximize information processing by allowing differentiated local processing (mediated by microcircuits that independently oscillate at high speeds) while simultaneously allowing for global integration (mediated by broad synchronization by slower oscillations), a balance thought necessary for efficient information processing in neural systems[41,42]. Naturally, the organization of neural rhythms is highly associated with cognitive functioning; synchrony in slower cortical oscillations are thought to bind local cortical processing into transient large-scale cortical assemblies capable of coordinating executive control mechanisms with multimodal processing units as a task may require[2,37,43].

Again, in trying to answer the question, "how does arousal interact with oscillations in cognition?", one is met with the challenge of separating "arousal" from faster fluctuations in excitability along what is perhaps more properly thought of as a continuum. Indeed, one can interpret the circadian rhythm as an ultra-slow and ultra-expansive (indeed, whole brain) oscillation[2]. Just like in PAC between faster and slower oscillations more commonly measured by scalp EEG, the circadian rhythm, and the arousal states (sleep/wakefulness/drowsiness) that it mediates, are likely to interact with higher frequency oscillations (e.g., delta-gamma). When arousal and oscillations are both characterized as fluctuations in excitability at different scales, their interaction appears inevitable. This paper will investigate that premise in the context of the oscillations that pervade the thalamocortical system.

Thalamus

The thalamus is well-positioned by its anatomy in the regulation of both cognitive functioning and arousal. The thalamus receives massive input from brainstem and basal forebrain arousal regulating systems[44]. Moreover, as thalamic tissues are located in the center of the brain and thus roughly equidistant from all points of the cortical mantel, thalamic tissues may be particularly well-positioned to coordinate the clocking of oscillations in cognition without accounting for variable axon-potential delays between cortical targets[2]. The purpose of this paper is to leverage recent experimental evidence and related theory to update the placement of the thalamus in the

interaction between arousal and cognition with an emphasis on the contribution of thalamocortical rhythms to these qualities. Here, we interrogate means by which the impact of arousal on thalamocortical interactions may, in-part, underlie the Yerkes-Dodson law. Broadly, we suggest that arousal represents the baseline level of arousal/excitability on which more rapid arousal/excitability fluctuations act as a form of gain control in cognition. This arousal "baseline" is likely to interact with oscillatory and non-oscillatory (e.g., center-surround architecture, neuromodulation) gain control mechanisms. As we shall see, these mechanisms converge on the thalamocortical system.

Thalamus in Arousal

Anatomical Context:

From its conception, the notion of an ascending reticular activating system (ARAS) has been thought to intimately involve thalamic mediation[45] on its way to cortex. Today, it remains clear that the arousal of the thalamocortical system necessitates the various nuclei associated with the ARAS. Transection of the caudal end of the medulla, just below the pons, results in normal sleep-wake cycles and a generally maintained thalamocortical arousal while destruction of the pons or midbrain or their disconnection from the thalamocortical system results in an acute coma-like state in cats[2,46] and humans[47]. Thus, arousal in the thalamocortical system cannot be maintained by sensory input alone but relies on control by brainstem nuclei beginning in the rostral pons.

Modern refinement of the interacts between the ARAS and thalamocortical system emphasize a "many to many" model characterized by a web of bidirectional connections. Thalamus sits as a major conduit of ascending arousal inputs, but, importantly, substantial extra-thalamic pathways also exist. Afferents of the monoaminergic nuclei (secreting serotonin, dopamine, and norepinephrine) has historically been highly implicated in arousal regulation and find their way to the thalamus while also widely innervating the cortex and basal forebrain directly[48]. The basal forebrain sends glutamatergic, gabergic, and cholinergic inputs to cortex[49] directly as well as cholinergic inputs to the thalamus[20,50]. Importantly, interconnections between these mesopontine nuclei, the basal forebrain, the thalamus, and cortex are highly recurrent with, for instance, cortex modulating brainstem output directly[49], adding complexity to the debate of exactly "where" arousal originates. The intralaminar nuclei (IL) of the central thalamus receive a disproportionate quantity of the cholinergic and glutamatergic input arriving to the thalamus from the brainstem as well as the basal forebrain[9,50,51]; moreover, they receive a bulk of the noradrenergic and serotonergic inputs stemming from the brainstem[20]. Like all "high-order" thalamic nuclei, IL nuclei connect most strongly to cortical association areas, though more diffusely than some other high-order thalamic nuclei such as the pulvinar and mediodorsal nucleus (MD), whose connections more closely reflect specific functional roles[49], as discussed more below. While these factors suggest the IL may be particularly implicated in broad arousal regulation, these nuclei are not the only conduits of arousal signals through the thalamus; for instance, particularly dense noradrenergic inputs also find their way to the pulvinar and lateral genicular nuclei, perhaps related to the allocation of attentional resources[52]. Cholinergic inputs have been thought to hyperpolarize gabaergic thalamic reticular nucleus (TRN) neurons, relieving thalamic relay cells of

inhibition[20,53,54]; however, recent studies have challenged this view, demonstrating cholinergic and noradrenergic secretion onto the TRN is positively associated with the induction of slow-wave sleep[55] and the maintenance of anesthetic-induced anesthesia[56], respectively. As discussed in more detail later, the complex effects of acetylcholine and norepinephrine may be best characterized as "neuromodulatory" rather than purely excitatory[52,57].

Indeed, while many of the nuclei inhabiting the rostral pons and midbrain are compellingly associated with the phenomenon of arousal, it remains debated which of these nuclei and what neural populations within them are most important for this phenomenon. Historically, cholinergic and noradrenergic secreting neurons of the ascending arousal system have received a bulk of the attention in the study of arousal; their firing rates *do* covary with wakefulness[52,53]. Cholinergic agonists injected systemically[58] as well as into the thalamus itself[59] (but perhaps not onto the TRN[55,56]) can induce recovery of consciousness under anesthesia. However, in one study[12], global disruption of the cholinergic system did not impact arousal state while disruption of the noradrenergic system indeed did lead to the slow high-amplitude oscillations in cortically activity characteristic of sleep and anesthesia. Strikingly, selective cell-body lesions of noradreneregic and cholinergic components of this system (e.g., the cholinergic neurons of the PPN, the cholinergic neurons of the BF, and the noradrenergic cells of the LC) has little effect on sleep-wake cycles[44]. This stands in contrast to the coma-like states caused by electrolytic lesions destroying cell-bodies and nearby fibers of passage (axons) in these nuclei (e.g., following cell body destruction throughout the basal forebrain nuclei[13]). Consequently, novel models take an integrative approach and suggest this system produces arousal through the collective activity of their various cell types and outputs (which includes the monoaminergic neurotransmitters as well as GABAergic and glutamatergic interactions); for a review, see Saper and Fuller[44].

While the connection of brainstem nuclei associated with arousal is characterized by broad divergence and many of their axons are unmyelinated[60], resulting in long communication delays, they remain dynamic systems that react to behavioral contexts, in part a result of feedback from higher-order systems (e.g., cortex)[49,52]. For instance, LC activity has been proposed to play a role in both long-term and short term modulation of arousal, responding in the order of 100ms to target presentation[52]; thus, some of the dynamic nature of thalamic activity in arousal may be driven by its brain-stem inputs. In sum, the influences of the brainstem nuclei associated with the ARAS on telencephalon function are not fully captured under the monolithic umbrella of cerebral "arousal"[52,57], while their collective activity appears absolutely necessary for it.

Experimental Evidence:

The interconnectivity of the thalamus with upstream arousal regulating systems, emphasizing its central components, position it to modulate cerebral arousal. On these grounds, Schiff, 2008[20] and many other works by the same author propose that the functional centrality of the thalamus in managing distributed cerebral circuits alongside its input from ARAS positions it to play a role in arousal regulation. That is, that the central aspects of the thalamus (including the intralaminar nuclei and the paralaminar aspects of other higher-order thalamic nuclei) may play a role in arousal by either **1)** maintaining broad cortical arousal, **2)** conducting broad cortical gain control and/or **3)** distributing arousal throughout the cerebrum unevenly so as to bias processing as demanded by

cognitive needs[20]. However, on the grounds that changes in the firing rate of thalamic cells in transitions from wake to sleep trail behind increased firing in the brainstem cholinergic system[20,61], the thalamus is not believed to initiate the shift from sleep to wakefulness. More recent literature continues to locate the thalamus within these bounds set by Schiff.

The activity and structural integrity of the thalamus and its cortical connections are unambiguously correlated with states of arousal, on different temporal scales. This includes state changes in arousal characterized by long-lasting shifts in activity within large-scale brain networks. For instance, the firing rate of thalamic neurons decreases in sleep as cells enter a state of rhythmic bursting[2,31], paralleled by decreased blood flow to the region[62,63]. Like sleep, a principal neural correlate of the loss of consciousness during anesthesia is reduced thalamic activity, assessed via regional metabolism and blood flow in humans[23] while thalamo-cortical connectivity also appears reduced and dynamically altered in anesthesia[64,65].

Similarly, damage to the thalamus and its connections with cortex have been widely associated with the symptoms of disorders of consciousness (DOC; e.g., coma, vegetative state, minimally-conscious state) following severe brain damage—which are in part characterized by low arousal[28]. Famously, infarct of the central thalamus is associated with a loss of consciousness in some patients[66]. Damage to the thalamus has been characterized as a principle neural correlate of the persistent vegetative state[67]; while some arousal in VS remains—particularly in primary cortex—cortical metabolism broadly decreases to sleep-like levels in most VS patients[18]. A meta-analysis of 13 fMRI studies in DOC patients reported reduced activity in the mediodorsal nucleus of the thalamus, the paralaminar portion of which is considered part of the "central thalamus"[68] in DOC patients. Furthermore, atrophy of the thalamus itself predicts the degree of symptoms in DOC (e.g., reduced arousal, reduced ability to respond to commands)[69] as well as future recovery[70,71] while DOC symptoms are further predicted by thalamocortical functional[72–74] and structural[75] connectivity as well as disturbances in intrathalamic network properties[74].

Moreover, central thalamic activity appears correlated with short term fluctuations in arousal. The firing rate of central thalamic neurons increases during the delay period of simple reaction time "vigilance" tasks[76]. Activity in the central thalamus has been shown to increase with increasing vigilance during attention tasks using PET[77] and fMRI[78] over a periods of seconds[77,79,80] to minutes[78]. Supporting the involvement of a dynamic brainstem input to thalamus in its role in arousal, increase in thalamic activity was paralleled by increased activity in the pons and midbrain in some[77,78] of these imaging studies. Short term enhancement of activity[77] as well as gamma power[76] in central thalamic nuclei may reflect task-dependent modulations of cortical arousal.

Though, the above correlational research of course contains many caveats which prevent a clear causal relation of the thalamus to arousal. For instance, DOC symptoms, as they are measured behaviorally (e.g., through response to verbal commands), involve the ability of patients to both be aroused and possess the cognitive functioning required to appropriately respond. Thalamic correlates of DOC symptoms may reflect impairment in the latter and not the former. Moreover, non-selective lesions (e.g., in DOC) are confounded by damage to fibers of passage alongside the nuclei they directly impact. Similarly, measures of performance in cognitive tests (e.g., attention tasks) are hard to relate to broad arousal alone and may require other parameters necessary for

cognitive functioning. Changes in thalamic activity or behavior as classically shown during sleep and anesthesia may be secondary to arousal regulation occurring elsewhere. A more discriminating look at the literature paints a more nuanced picture of thalamic involvement in arousal.

The anticholinergic properties of some anesthetics[81] have been used to implicate cholinergic projections to the thalamus in its particular disruption by anesthesia and role in arousal maintenance[23,58]. Seemingly supporting this mechanism, stimulation of cholinergic PPT innervating the thalamus and basal forebrain results in tonic depolarization of thalamic cells as well as their cortical targets. However, cortical activation by PPT stimulation survives cell-body lesions to either the thalamus or nucleus basalis, suggesting dual cholinergic-activating pathways through these nuclei[82–84]. Thus, acetylcholine's impact on cortical arousal does not necessitate thalamic involvement. Seemingly dispelling the notion that thalamus deactivation during anesthesia represents an "off-switch" in forebrain arousal by any mechanism, the effect of anesthesia on thalamus appears secondary to reduced cortical activity. Indeed, the transition of thalamic cells into rhythmic bursting as well as their reduced metabolic activity under anesthesia disappears when cortico-thalamic connections are severed[23]. Moreover, altered electrophysiological properties of the cortex begin at the moment of lost consciousness under anesthesia while altered thalamic activity trails this by roughly 10 minutes[23]. Indeed, causal modelling of altered network properties in anesthesia support the notion that pallidocortical instead of thalamofugal effective connectivity was related to loss of consciousness under propofol anesthesia[85].

Work to separate the arousal and cognitive symptoms of DOC more compellingly implicates extra-thalamic mechanisms of arousal than thalamic ones. While thalamic damage, assessed by MRI, predicts DOC symptoms broadly, it does not appear to predict the arousal sub-score in neuropsychiatric tests of DOC symptoms, rather predicting complex motor-responsivity which is more closely associated with cognitive functioning. Instead, aspects of the globus pallidus have been associated with the arousal sub-score. It should be noted that the intralaminar nuclei are too small to be parcellated and analyzed alone here while basal forebrain damage also did not correlate with the arousal sub-score[69]. Supporting a pallidal arousal mechanism, cell body lesions of globus pallidus pars externa produce increased delta power[86], a classical correlate of low-arousal states such as sleep. While traditional models of basal ganglia connectivity implicate basal-ganglia-thalamo-cortical pathways in mediating pallidal influence on cortex, direct pallido-cortical pathways have recently been identified and associated with the maintenance of electrocortical arousal[75,87,88]. The pallidum may maintain arousal independent of thalamic involvement.

Though, some work more compellingly draws a link between thalamus and arousal. For instance, cell-specific (calretin-containing) activation of mediodorsal neurons awakens rats from REM and nREM sleep[89]. Similarly, muscimol deactivation of the pulvinar can cause dramatic reduction in visual cortex excitability in response to visual stimuli[90,91] while MD lesions[92] and optogenetic inhibition in mice[93] can lead to prefrontal hypoactivity, the later coinciding with working memory impairments. However, perhaps the most compelling association between the thalamus and arousal has been in direct stimulation of the central thalamus, where the anterior intralaminar nuclei comprised of the central medial (CM), central lateral (CL), and paracentral nucleus (PC) have been

emphasized. Famously, a single minimally-conscious DOC patient regained some functioning following deep brain stimulation of the CL nucleus, including in the arousal sub-score[94]. Recent work in macaques seem to confirm this effect where electrical CL stimulation can induce wakefulness from sleep and anesthesia[11,95], producing eye-opening and increasing responsivity. Arousal produced through CL stimulation appears to interact with cognition as anticipated, producing increased performance in visual attention tasks requiring long-term vigilance[26] and an inverted U-shaped curve interaction between stimulation and cognitive performance when stimulating the anterior intralaminar nuclei either electrically or with GABA antagonists in rodents[8]. An important caveat of these studies is that stimulation may produce firing rates or patterns not observed in normal waking. Another is that electrical stimulation is not specific to CL cell bodies; however, cell-body specific stimulation via optogenetics[25,96] and from chemical[8,59] and anti-antibody[97] injections into the CL and CM nuclei (but see discussion of CM specificity in Honjoh et al.[25]) has produced similar effects. Together, these findings compellingly suggest that the thalamus can generate arousal both within state[8,26,90] and initiate state changes from sleep or anesthesia.

The cellular mechanisms of these transitions are beginning to be uncovered. As discussed in more detail below, cells in the IL nuclei can be subdivided into precisely-projecting core neurons, and the more broadly-projecting matrix cells, the latter of which are thought to possess a broad modulatory role and so may be particularly implicated in arousal modulation. The broad matrix cell projections to cortical layer I is thought to act as a coincidence detection mechanism with relay cell projection to deeper layers, which may facilitate gamma coherence and the biasing of processing in particular regions of cortex[98]. Indeed, increased gamma coherence within superficial layers, where matrix cells project, increased for effective (i.e., arousal-inducing) more than ineffective (i.e., non-arousal inducing) electrical stimulations of the CL in macaques as did broadband coherence between superficial and deep layers[11]. However, the spike rate of deep cortical layers (where core neurons primarily project) was more associated with arousal. Yet, the specific origin (e.g., matrix vs. core cells) of these effects are unclear in electrical stimulation. Specific activation of the matrix cells of the VM nucleus in rodents induces wakefulness from sleep and anesthesia as well as increased high-gamma power in the most superficial as well as deep cortical layers[25]. While the effect of VM matrix cells on cortical dynamics remain far from fully characterized, in part due to conflicting findings (see discussion of Cruikshank et al., 2012[99]), they appear to alter cortical dynamics for longer periods of time than core neurons, suggesting the potential for modulation of long-lasting changes in arousal[25,99]. Stimulation of core ventral-posteromedial thalamic neurons resulted in a transient impact on EEG which saw a quick return of slow-waves with no impact on arousal, seemingly confirming a long-held emphasis on matrix cells in long-term modulation of cortical dynamics. A classical finding is that roughly alpha-range (~10Hz) stimulation of the both higher-order[100] and lower-order[101] nuclei results in a cortical "augmenting" response, where successive stimuli result in increasingly large cortical depolarizations that may be accompanied by broad cortical synchrony[101]; this effect is less strong when stimulating cortical neurons directly. As suggested in Saalman, 2014[102], the broad slow-wave synchrony of sleep may transition to more local synchrony in high-arousal states, as mediated in part by thalamocortical modulation of cortical dynamics. Cortical Gamma-band synchronization in recent thalamic stimulation studies supports this notion and localizes this effect to the thalamic

matrix cells long theorized to mediate broad modulations of cortical activity due to their diffuse projections[103].

Despite this evidence, the thalamus is not likely to maintain arousal alone. Indeed, cell-body specific ablations of the thalamus suggest, strikingly, that the thalamus may not be necessary for the maintenance of wakefulness at all. Destruction of cell bodies in nearly the entire thalamus has been shown to produce little effect on sleep-wake cycles or on electrophysiological-correlates of arousal[13,14] while elimination of all thalamic afferents to a cortical region again does not lead to the bursting characteristic of sleep and anesthesia[12]. These results stand in stark contrast to the immediate coma-like state caused by similarly vast cell-body lesions created in the basal forebrain[13]. While suppression of the paraventricular thalamic nucleus does appear to induce sleep[104], these results are difficult to reconcile with the null effects of lesion studies. Inconsistencies between lesion and stimulation studies may be explained by compensatory activity by other brain regions following lesions of the thalamus, obscuring its contribution to arousal; yet, compensation by other brain regions is clearly not sufficient to maintain arousal following basal forebrain[13] or broad mesopontine lesions[2,46].

Conclusions

In sum, it remains clear that thalamic activity is highly related to arousal, as supported by a vast literature correlating its activity to short term, long term, state, and intrastate fluctuations in arousal; moreover, the compelling modulation of arousal and state changes following thalamic stimulation electrically [10,11,95] , optogenetically[96], and chemically[59] strongly supports the ability of thalamic tissues to dramatically enhance arousal in these preparations. Yet, it is much less clear that the thalamus maintains the waking state, where brainstem projections to cortex, directly or via the nuclei of the basal forebrain and basal ganglia (e.g., GP, Striatum)[75,85,87,88], may be more relevant to this function. Far from precluding thalamus from a role in arousal modulation, these findings only color it. Thalamus as “modulator” instead of “origin” of cerebral arousal is better supported by the literature. Thalamic filtering of projections from basal forebrain, midbrain, and brainstem nuclei may allow thalamic control of cortical dynamics via the dynamic reallocation of arousal. Given that optimal cognitive functioning exists in a narrow band of arousal states[6,8], thalamus-mediated reallocation of cortical arousal may not require the massive modulation of baseline excitatory tone necessary to bring about state-changes in arousal. Rather, thalamic contributions to arousal may exist as more subtle perturbations on top of baseline or “state” arousal levels more mediated by other structures. As the thalamus has long been associated with the reallocation of cortical resources in accord with rapidly changing cognitive demands, these arousal states may be localized and transient, closely interacting with the alterations in oscillatory dynamics we can more confidently say the thalamus certainly participates in.

Thalamus in Cognition

Anatomical Context:

We must forgive historical impressions of the thalamus as a passive sensory relay; it indeed fulfills this function, acting as the lone source of primary sensory input to the cerebral cortex with the

exception of olfactory information. Moreover, the rather simplistic loops that thalamic neurons form with the cortex and the general lack of connectivity thalamic neurons share with each other (save, within the thalamic reticular nucleus) do not readily suggest a system possessing the computational firepower nor the pluripotency necessary to underlie the dynamical processes presumably necessitated by cognition. Indeed, thalamic anatomy does not suggest its nuclei operate in cognition alone but, rather, in an obligatory interaction with cortex. Thalamic neurons, without tonic excitation through reciprocal cortical communication, cannot maintain sustained activity[2]. Interestingly, despite the cortical dependence of the thalamus, the relative size of thalamus has not grown to match its cortical partner throughout primate evolution, suggesting an abstracted role in cognition for the thalamus; with cortico-thalamic projections originating from every cortical region, a vast convergence of inputs is found on thalamocortical neurons that is matched by a vast divergence of their reciprocal thalamocortical projections[105]. While thalamic anatomy in the primate thalamus supports more multi-modal connectivity than in lower species, its small increase in size (relative to cortex) despite an explosion of cognitive faculties suggests that most low level computation—the ones and zeros of cognition—lies outside its borders while increasing the convergence of cortical signals onto thalamus can be seen as not a limitation but perhaps even a boon to its function in cognition[2]. Convergence of signals from virtually all sensory modalities has been suggested to play a role in the binding of modal-specific information[98,105–107]. Some[105] have gone as far as to postulate this convergence onto the thalamaus as *the* principle bottleneck through which cortical processing passes before emerging into the integrated and unitary[108] global workspace[43] of conscious experience.

The cellular architecture of thalamo-cortico-thalamic circuits is perhaps best characterized along the axis of specificity and divergence, where thalamo-cortico-thalamic communication seems both poised to maintain specific topographical relationships (e.g., the parallel somatotopic mappings between the somatosensory thalamic nuclei and the primary somatosensory cortex to which they send projections) as well as more diffuse interactions. Respectively, these properties may underlie the potential for sensory relay through thalamic nuclei as well as a broader, modulatory role of thalamus on disparate cortical regions; broad cortical influence seems necessary for a role in cross-modal cognitive functioning and in the modulation of broad electrocortical arousal. Immediately belying conceptions of thalamus as passive sensory relay alone, a large proportion of all thalamic inputs are cortical with some nuclei receiving the majority of their inputs from cortex instead of lower sensory areas[109]. Nuclei receiving most afferents from sensory nuclei are deemed “lower order”. These thalamic nuclei can be defined more readily by their sensory afferents and include, for example, the somatosensory ventral-lateral nucleus and the ventral posterior nuclei which contain topographical mappings of somatosensory information mirroring those in the primary somatosensory cortex with which it directly communicates. Higher order nuclei, while projecting more broadly throughout the cortex, can still be generally defined by the topography of their cortical afferents and the functions in which they participate[109]. These include, for example, the large mediodorsal (MD) and pulvinar nuclei (Pulv) as well as the intralaminar nuclei (IL), a grouping of small nuclei nestled within the white matter tracts of the internal medullary lamina coursing through the center of each thalami, but see Rovo et al., 2012[110] and Jones, 2012[103] . As discussed in detail below, these nuclei connect most prominently with the association cortex of the parietal and frontal lobes[102,111]. Though technically a higher-order thalamic nuclei, the thin shell

of neurons surrounding the anterior and lateral portions of the thalamus known as the thalamic reticular nucleus (TRN), serves both clear higher-order and lower-order functions. The TRN represents a somatotopic map parallel to that in the lower-order nuclei of the ventral thalamus and is theorized to play a role in maintaining cortico-thalamic oscillations thought necessary for proper high-level functions[112]. This nucleus provides the majority of inhibitory input into the thalamus across mammalian species and, in rodents, is the sole source of inhibitory control within the thalamus itself[98]. As a consequence, the TRN plays a massive role in modulating the background excitatory tone of the thalamocortical system. Single gabaergic TRN neurons project to many glutamatergic thalamic cells in both higher and lower order nuclei, providing broad inhibitory control. Much unlike the rest of the thalamus, TRN neurons form lateral interconnections which may allow for synchrony between parallel thalamic circuits to form[2], while, given that some TRN neurons send collaterals between functionally-related but disparate thalamic nuclei[20], also provide for integration within the thalamus itself[113]. The higher-order, lower-order distinction has retained its significance in lieu of recent discoveries in the structure-function relationships between thalamic nuclei and their influence on cortical dynamics; as suggested by their more intimate relationship with association cortex, the higher-order nuclei indeed appear to disproportionately mediate thalamic contributions to high-level cognitive functions[114].

However, this dichotomy does not fully capture the multifaceted nature of each thalamic nuclei; indeed, all thalamic nuclei receive sensory inputs and all form reciprocal connections with cortex[98,103]. The cellular architecture of the thalamo-cortical system is perhaps more suggestive of how the thalamus may act to both seed cortex with information and impact the down-stream processing of that information. The thalamus consists of two major cells types at opposite ends of the divergence/specificity spectrum[98,103,115]. In all thalamic nuclei, a sparse “matrix” of cells exists; in some nuclei, punctate groupings or “cores” of larger neurons form a “lattice” over this matrix. While the topographical connectivity of these cells varies widely between thalamic nuclei, core cells project to highly localized cortical regions while matrix cells project more diffusely throughout the cortex. In comparison to core cells, matrix cells have much less well-defined receptive fields and stimulus-response properties, a characteristic feature of cells within modules at a high stage in computational order[116]. Complicating the higher-order, lower-order distinction, a lattice of core cells permeating smaller matrix cells appears in both the lower-order relay nuclei as well as in higher-order nuclei including the intralaminar nuclei. While there are species differences in the staining of both subtypes, the presence of both widely-projecting (matrix-type) and narrowly-projecting (core-type) cells throughout the thalamus appears evolutionarily conserved[115], adding credence to the translational studies cited below.

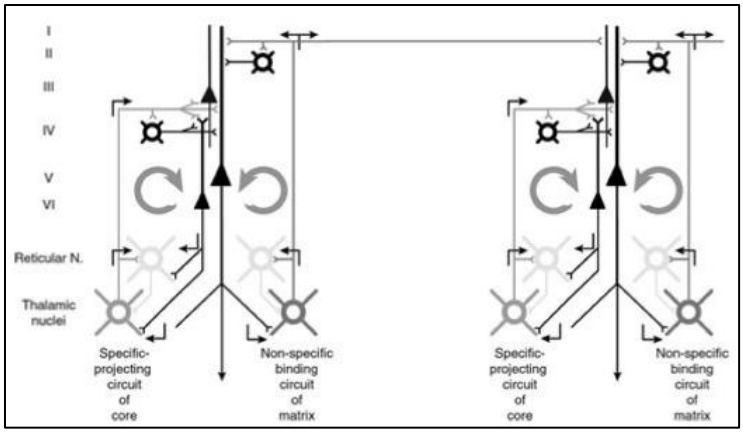


Figure 1: Adopted from Jones, 2009. A depiction of a classical model of corticothalamic and thalamocortical anatomical connectivity, complete with major gabaergic modulation from cortical and thalamic reticular neurons.

Furthermore, corticothalamic projections can be subdivided by the properties of layer IV and layer VI neurons. Layer IV neurons project to thalamus and thalamus only, synapsing on thalamic core neurons in relatively localized regions and do not form collaterals before exiting the cortical mantel, suggesting that these neurons are more relevant to local thalamocortical circuits. However, layer VI neurons often project to thalamic core neurons which do not then project back to the cortical region it is located in and layer VI neurons form collaterals to the TRN, providing an avenue for broader influence. Layer V, contrarily, project to more broad regions of the thalamus while also sending collaterals to diffuse cortical regions. These neurons do not synapse on the TRN, suggesting that their activity is well situated to promote general excitation in the thalamocortical system; interestingly, it is especially common for collaterals of Layer V neurons to synapse on the IL and Pulv nuclei[98], which are particularly implicated in arousal[8,10,117], as we will see. Completing this circuit, both matrix and core thalamic neurons form reciprocal connections with the TRN before core neurons terminate in largely middle cortical layers (III and IV) while matrix neurons terminate largely in superficial layers (I II and III). It has been proposed that this enables a coincidence detection mechanism[98] and that such a mechanism would further enhance the synchronous activity rife throughout the thalamocortical system[2].

Connectivity of Select Higher Order Thalamic Nuclei and Suggested Functions:

The gross anatomy of thalamic tissues is highly suggestive of their apparent role in cognitive functioning, where a reverberation of information up the computational order may flow through lower order thalamic nuclei to primary cortex, back to higher order thalamic nuclei, and finally association cortex[118], with shortcuts and feedback occurring at every step. Specific and divergent thalamocortical and corticothalamic inputs form an integrative structural skeleton spanning both within and between modal-specific networks while resting state fMRI data suggests a comparably integrative functional architecture in higher-order thalamocortical networks[119,120]. Yet, the connection densities of higher order nuclei still suggest functional specificity. For instance, the large mediodorsal thalamus is highly interconnected with the prefrontal cortex and is widely associated with high-order executive functioning. Damage to the MD, as well as reversible modulation[121], in humans is linked to deficits usually associated with "prefrontal syndromes" such as in working memory (WM) and cognitive flexibility[122] while many studies in animals demonstrate similar deficits (for a reviews see Mitchell and Chakraborty[122] and Pergola et al.[123]). The Pulvinar nucleus has diffuse projection networks throughout the frontal, parietal, and occipital lobes, but with its ventral portion connecting most strongly with occipital and inferior temporal

cortex and its dorsal portion, frontal, parietal, and superior temporal networks. This connectivity seems primed to mediate both higher and lower-order portions of classical visual attention networks integrating, for instance, frontal eye fields (FEF), lateral intraparietal (LIP) regions, and visual cortex[117,124]. Indeed, deactivation/lesion of the pulvinar often results in profound behavioral deficits in visual attention[91,125,126], that are matched by a highly-perturbed occipital power-spectrum[91]. The anterior intralaminar nuclei, on the other hand, project even more diffusely than other higher-order thalamic nuclei, but especially throughout frontal and parietal association cortex, suggesting their potential role in broader cortical modulation, such as arousal[49].

Thalamus as a Generator of Cortical Rhythms?

Thalamus may participate in cortical rhythm generation by **1)** generating rhythms within thalamic tissues alone, or **2)** through interactions with cortex. As we shall see, both phenomena seem probable and likely work in tandem, contrary to earlier notions of thalamus as *the* oscillatory clock. The classic observation that the thalamus produces intrinsic delta oscillations immediately suggests its role in the origin of cortical rhythms. When released of excitation, thalamic relay cells enter a state of indefinite rhythmic bursting in frequencies within the delta range (.5-4Hz), a behavior observed in periods of low arousal such as slow wave sleep (SWS)[2]. Here, rapid bursts of thalamic activity, with firing rates similar to that when awake[22], permeate periods of quiescence, a behavior thought to inhibit trans-thalamic sensory processing[127]. The lateral connectivity provided by the TRN provides an avenue for synchrony among independent thalamic cells[98]. However, removal of the cortex leads to asynchronous delta oscillations in parallel thalamic circuits[128]. Despite the well-defined ability of single thalamic cells to generate intrinsic delta oscillations, the evidence suggests the thalamus should not be thought of as the lone delta pacemaker. Consistent with this observation, Jones[98] suggests that thalamo-cortico-thalamic reverberations maintain synchronous oscillations, proposing that core thalamic cell projection to deep layers form a coincident detection mechanism with matrix cell projections to superficial layers, reinforcing synchrony. From there, synchronous activity is spread topographically through the diffuse thalamocotical projections of matrix cells and the diffuse projections of Layer V corticothalamic cells. A trend of multiple generators—cortical as well as thalamic—and interdependent cortico-thalamic interactions pervades the literature across frequency bands.

For instance, alpha range thalamocortical influence has been heavily associated with the thalamic pulvinar nucleus[111,117], lateral geniculate nuclei[129,130], and the TRN[117,131] while alpha is also thought to be generated in deep cortical microcircuits driven by cortical layer 5 cells[132,133] (but see Halgren et al., 2019[134] for a discussion of caveats in layer-specific interactions). The discoverer of alpha rhythms, Hans Berger, originally proposed the notion of a thalamic alpha generator in in the 1930s[135]. Since, a number of mechanisms for thalamic alpha generation have been proposed[135–137]. Similar to proposed mechanisms for thalamic delta-range oscillations, alpha-range (7-14Hz) oscillations can also be produced through interactions between TRN and thalamic relay nuclei, where rebound depolarization elicits alpha oscillations following the rhythmic inhibition imposed by TRN spike-bursts[137,138]. Such a mechanism is thought to underlie the thalamically-generated alpha-range "spindles" present in stage-2 sleep and under barbiturate sedation[137,138]. Yet, it should be noted that spindles, which are unambiguously related to the thalamic activity, do not share the

topographical and temporal properties of waking alpha[138]. Other models do not implicate the TRN and rather have suggested that subsets of relays cells alone are able to generate thalamic alpha[135] intrinsically. Yet, a host of other models also highlight the potential for interactions between cortex and thalamus in both creating as well as determining the frequency of corticothalamic oscillations[139–141].

The diversity of theories in alpha generation is paralleled by incongruencies in the experimental evidence. Several studies have found increased alpha-band influence from the pulvinar on cortical activity during attention[111,142,143] (but see contradictions in Zhou et al.[91]). However, muscimol deactivation of the pulvinar in-fact increases occipital alpha amplitude[91] (though, alongside all low-frequency bands from .5Hz to 20Hz, consistent with general cortical quiescence). Despite its long-proposed role in mediating cortical alpha, activity of the pulvinar nucleus appears inversely correlated with occipital alpha power[91,144]. Compellingly, during quiet rest, human ECOG data suggests that alpha flows from the parietal cortex to the pulvinar thalamus[134].

As suggested in Halgren et al.[134], incongruencies between the latter finding and those during attention may be explained by state-dependent shifts in alpha-range influence between task and rest. Supporting this view, a recent study in macaques reports that alpha power (granger-causal) influence on classical frontoparietal modules of the visual attention system increases during periods when behavioral performance is higher on visual attention tasks compared to periods of lower performance[124]. The state-dependence of thalamocortical alpha-range interactions may be extended to other bands such as beta. In one study[93], MD-to-prefrontal beta-range connectivity appears to play a role in the maintenance period of working memory while prefrontal-to-MD beta-range connectivity takes over during the response period[93] (described in more detail below). The directionality of influence to and from the thalamus may depend on behavioral demands where periods of tasks requiring the maintenance or preparedness for sensory processing require particular thalamic influence. So, despite the ability of the thalamus to generate intrinsic rhythms in several frequency bands, it increasingly appears less like the global pacemaker of oscillatory frequencies it was once thought to be and more as an important component of networks which collectively generate oscillations via competing generators which shift dominance over time. The dynamic nature of oscillatory generation and propagation may support on-going reallocation of computational resources during cognitive functioning.

Functional Significance of Thalamocortical Oscillations

A vast literature explores the role of thalamocortical oscillations and their correlates. To make sense of it, we first focus on thalamocortical oscillations as temporally-varying phenomena and, next, as spatially varying phenomena.

Thalamic Selection in Time:

Phase Synchrony

Underlying much of high-level cognitive functioning (e.g., selective attention, working memory) may be the selective facilitation of representations of specific features, objects, bits of information etc. over competing information—often known as “gating” or “selection”. Sensorimotor gating

may be accomplished through neuronal phase synchronization[117]. Information held by distal neural populations demonstrating phasic firing may be bound together by synchronizing the arrival of their action potentials on shared post-synaptic boutons. Binding may be further enhanced by synchronizing phasic (sub)threshold moments of enhanced excitability in post-synaptic neurons with pre-synaptic action potentials[145,146]. In this way, minute changes in the phase of distal oscillators may be a mechanism by which low-order sensory information is selected for higher-order processing[117]. Moreover, similar mechanisms may underlie selection and integration of large-scale cortical ensembles, incorporating, for instance, multimodal information with top-down goals during cognition[118]. A feature of oscillatory binding between neural ensembles is that third parties, through the regulation of oscillatory synchrony, may alter the flow of information without themselves holding that information. The thalamus, centrally located and, thus, with similar action potential delays to all cortical regions[2], receiving converging inputs from virtually all of cortex but apparently lacking the vast processing power of its cortical partner[98], has been proposed as an ideal third-party—a conductor behind the symphony of continuously reshaping cortical oscillatory ensembles[2,98,106].

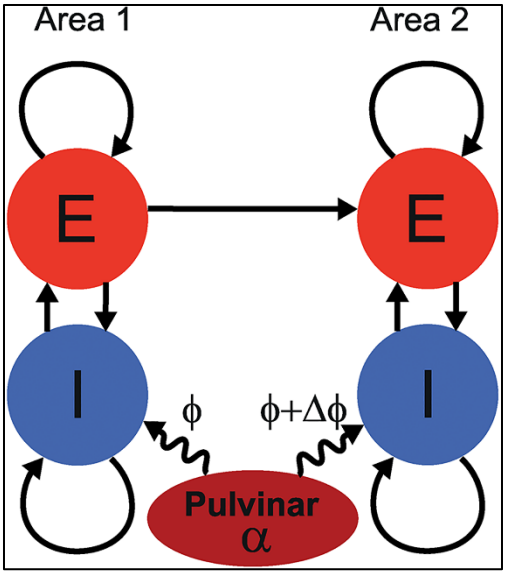


Figure 2: Adopted from Quax et al., 2017. In this simplified model, pulvinar introduces alpha-range oscillatory influence at phase Φ on inhibitory cortical interneurons (I), which acts to generate intercortical gamma-range synchrony between excitatory cells (E). Pulvinar may selectively gate this synchrony by modulating the relative phase of its alpha-range oscillators (Φ + Δ Φ).

For instance, as demonstrated by Saalman et al.[111], during attention, not only does alpha-range influence from the pulvinar to two regions of the visual cortex increase, so too does influence between these regions in the alpha and gamma bands[111]. These findings have been used to suggest that the pulvinar, and by extension, higher-order thalamic nuclei more broadly[102], actively generate temporary cortico-cortical ensembles in accord with behavioral demands[102] through imposing altered oscillatory dynamics. A recent computational model[147] describes how thalamic mediation of cortico-cortical information exchange may occur in the visual system. Here, two cortical nodes are modeled with excitatory pyramidal cells (E) and inhibitory interneurons (I). Spontaneous gamma-range oscillations are generated by cyclic interactions between E and I. Phasic alpha influence modulates inhibitory cortical interneurons within two interconnected cortical nodes; as discussed below, occipital alpha-band power is generally associated with inhibition[148]. Cyclic alpha-range influence from the pulvinar onto inhibitory interneurons entrains each node; decreasing the phase-shift between alpha-range influence to each node leads to increased gamma synchrony and information exchange between cortical pyramidal cells. Thus, zero-phase lagged alpha (consistent Φ) influence from pulvinar to disparate cortical regions may enhance intercommunication, as suggested by Saalman et al.[111], while pulvinar could also mediate information exchange via modulating the phase lag of its alpha-range inputs between cortical regions (Φ + Δ Φ). By selectively synchronizing occipital neurons, pulvinar may be able to

selectively gate bottom-up sensory information, a mechanism thought to underlie top-down modulations by attention[117], a process known to be impaired following damage to the pulvinar[91,125,126].

A recent series of studies in rodents expand on these in the pulvinar to incorporate the MD. Similar to the putative role of the pulvinar in commanding cortical alpha-range synchrony during attention, they suggest that mediodorsal beta-range influence may contribute to the maintenance of cortical ensembles in working memory.

In rats performing a WM task, MD spiking synchronized with prefrontal cortex (PFC) local field potentials (LFP's) in the beta range where MD spiking lead the PFC beta phase. Compellingly, subtly decreasing MD activity using designer receptors (DREADDs) reduced MD-prefrontal spike-phase coherence and increased working memory errors; these were correlated[149]. A more recent study in mice expanded on these findings using optogenetics to inhibit MD terminals on medial pre-frontal (mPFC) neurons briefly during differing periods of a spatial working memory task[93]. Here, performance was not impacted by MD terminal activity during the sampling phase of the working memory task. However, when applied in the delay phase, MD terminal excitation increased performance while MD inhibition decreased performance, suggesting that MD-mPFC interactions are less involved in the seeding of PFC with information but rather its maintenance, consistent with the canonical "modulatory" instead of "relay" role of higher-order thalamic nuclei. These effects were found only during long (60s) delays, suggesting that MD is necessary to actively maintain PFC information over long periods of time. The delay-period-related role of MD was paralleled in the directionality of beta-range influence, where MD beta drove PFC beta during the delay while PFC beta drove MD during the execution of the task. Consistent with the notion that working memory necessitates periods of increased activation to maintain information[93], this study demonstrated increased PFC activity during the delay period, which gradually decreased over the delay and that this sustained activity was negated by MD deactivation. Thus, MD influence may promote mPFC arousal alongside beta-range synchronization, sustaining representations in working memory.

Another recent study compelling suggests that MD helps maintain specific representations over others by decoding rule representations in the firing rates of PFC neurons. Recording from the PFC during the performance of an audio-visual two-alternative forced choice (2AFC) task, Schmitt et al.[150] discovered distinct neural populations tuned to each rule (e.g., rule 1, attend to vision or, rule 2, attend to audition). Rule-tuned cells showed temporal firing correlations, suggesting participation in a network encoding their respective rule. Suppression of the MD resulted in impaired performance. Again, MD suppression effects were specific to the delay period and were particularly impactful over long delay periods. In contrast with the PFC, MD spiking was not rule-specific, suggesting that MD actively modulates the expression of PFC rule representation without itself coding for them, in line with notions of thalamus as a third-party conductor of cortical information processing.

Together, the above finding concerning the MD suggest that it may facilitate the selection of specific cortical ensembles through oscillatory binding in the beta range. These findings are consistent with past finding in macaques, which find that frontal representations of "dominant"

rules oscillate in the beta range while "non-dominant" rules oscillate in the alpha-range[151]. It is further hinted at by these findings in rodents that the maintenance of rules may rely on excitation. If this is the case, the macaque findings are doubly interesting, as alpha-range oscillations are generally associated with inhibition while higher frequencies are generally associated with increased excitation, as discussed more below. A general role of cortical phase synchrony by the thalamus may be the selection of cortical ensembles, which mediate specific representations. Moreover, this process may interact with or result from imposed changes in excitation / inhibition within cortical tissues, an idea that will be further supported and unpacked below.

Cross-Frequency-Coupling

Within-frequency phase synchronization provides a mechanism by which the thalamus may coordinate cortical activity, especially within a modality. The selection of signals via a single frequency at the exclusion of others is a necessity in sensory selection where interactions from competing signals may impair attention to or maintenance of the selected signal. Given that different oscillations are thought to conduct different functions, distinct signals may facilitate parallel processing. For instance, bottom-up feed-forward mechanisms are thought to oscillate in the gamma range[152,153] while feed-back or top-down input is thought to ride on slower frequencies, such as in the beta and alpha range[111,154,155]. Likewise, this is apparent in functional distinctions between thalamocortical circuits with alpha-range oscillations generally dominating visual thalamic interactions, beta-range interactions generally dominating mediodorsal-frontal interactions in e.g., working memory, and theta-range interactions of focus in anterior thalamic nuclei interactions in long term memory encoding[118]. While parallelism may enhance the information processing capacity of a cognitive system and avoid signal mixing, effective cognitive functioning must also integrate sensory processing with those in other modalities, top-down signals, and, eventually, motor execution. Interactions between oscillations at different frequencies and across spatial scales may provide a mechanism where fast oscillations, thought to synchronize local cortical ensembles, are integrated across greater topographical extents by slower oscillations, perhaps even emanating from third-parties[156,157]. Several forms of this Cross-Frequency-Coupling (CFC) have been proposed[42].

Cross-Frequency Synchronization

Cross-Frequency Synchronization (CFS) is thought to integrate frequencies of ratios n:m, where n equals the frequency of the slow oscillation and m equals n*some integer multiple[157]. In other words, m must be a harmonic of n so that peaks of both oscillations coincide at some regular interval where the binding of these signals is thought to occur. For instance, in theta(~5hz)-beta(~20Hz) CFS where the n = 1 and m = 4, a moment of integration arrives when peaks align every four beta cycles. The harmonic structure of the frequency bands, for example where mean-alpha (10Hz) is roughly twice the frequency of mean-theta (~5Hz) and half that of mean-beta (20Hz) is thought to support this capacity[148]. Evidencing this general principle, Hawellek et al[158]. found that neural spiking, thought here to encode choice information, was simultaneously phase-locked to both beta and gamma phases.

Experimental demonstration of CFS, in stark contrast with simple within-frequency synchrony, is somewhat novel and somewhat rare. Indeed, the first demonstration of CFS in humans occurred in a 2005 MEG study where a three-level alpha(~10Hz)-beta(~20Hz)-gamma(~30-40Hz) CFS was observed during working memory task[159], while subsequent studies have further associated cortical CFS relationships in WM[160–162] and throughout behavioral contexts including visual attention[111], rest[163–165], and movement[166], but see Palva and Palva[157] for a 2018 review. Direct evidence of thalamo-cortical CFS is almost diminishingly rare. One study did find resting-state theta-gamma CFS in rats and that this was decreased in a group exposed to high stress[166]. While much work needs to be done in order to better characterize the role of CFS in direct thalamocortical interactions, it appears that thalamo-cortical oscillations exist in an environment where cortical and subcortical (e.g., hippocampus[162,167]) CFS is present and appears functionally significant in cognition. Cortico-cortical CFS, which necessitates precise frequency ratios, is thus likely impacted by thalamic influence on cortical oscillatory frequency, even if only indirectly.

Phase-Amplitude Coupling

Phase-Amplitude Coupling (PAC) describes the altered amplitude of rapid frequencies (e.g., gamma) during the increases and decreases in excitability that follow the phase of a slower frequency (e.g., theta). For instance, hippocampal CA1 theta phase appears to determine the amplitude of different gamma oscillations where the peak of CA1 theta enhances slow gamma power (30-80Hz) and the trough, fast gamma power (80-200Hz)[168]. As discussed, different oscillations are thought to reflect different functions. In this way, the phase of slow oscillations may chunk neural processing into discrete temporal units where peaks involved high amplitude high frequency activity and comprise one function, and troughs, which lack much high frequency activity, comprise another. For instance, Lisman and Idiart[169] propose that the ratio of gamma to theta-alpha (4-12Hz) oscillatory frequency (roughly 7:1) may underlie the 7+-2 limit of working memory where the "up" theta phase maintains working memory via a moment of cortical excitability on which roughly 7 gamma cycles vacillate between different discrete contents. Indeed, theta-gamma PAC is a common feature of working memory performance[170] and the gamma:theta cycle ratio was, strikingly, later shown to predict working memory capacity between individuals[171]. Suggesting that PAC is not a simple epiphenomena, theta-gamma PAC during a learning task is enhanced gradually over trials following training as performance increases[172].

PAC, like CFS, is a form of cross-frequency-coupling; however, they likely reflect different functions. Indeed, CFS and PAC appear to characterize different aspects of visual working memory[161]. PAC, unlike CFS, is indifferent to the phase of the high-frequency partner and thus is less likely to mediate the large-scale integration through coincidence detection putatively achieved via CFS[157]. In contrast with the relative paucity of direct evidence for CFS, PAC has been better characterized throughout cognitive domains; for a review see Canolty & Knight[156]. While theta-gamma PAC, is perhaps the most abundant form of PAC in the brain[156], this phenomenon pervades other frequency pairs and has been proposed to orchestrate activity during working memory, memory consolidation, sensorimotor processing, and attention[4,37,154,173].

The thalamus, which has been implicated in all of these processes, may accordingly utilize PAC to enact rapid modulations of cortical activity during cognition. For example, the aforementioned

cortico-cortical communication during attention revealed by Saalman et al.[111] coincided with alpha-gamma thalamocortical PAC, suggesting a role for PAC in thalamic orchestration of cortical activity. Recent ECOG and thalamic recording electrodes have seemingly confirmed the once theoretical notion of thalamocortical PAC in humans[165,174–176]. Thalamocortical PAC has been demonstrated across broad frequency band pairs when recording from the central median nucleus (of the anterior intralaminar nuclear group) and frontal cortex in humans at rest[165]. Moreover, stimulus-locked Mediodorsal-frontal cortical Beta-Gamma PAC has been found during the performance of recognition memory in humans[176]; moreover, the degree of PAC positively predicted correct responses, suggesting a functional relevance. Malekmohammadi[175] et al. explore a rare data-set with many thalamic and cortical contacts, and are thus better able to characterize the full breadth of human thalamocortical PAC at rest. They found broad theta-beta thalamo-cortical PAC between a breadth of thalamic and cortical electrodes; however, PAC waned and waxed over time in complex spatial patterns over thalamic and cortical contacts. These findings suggest the simple identification of paired frequency relationships in thalamocortical PAC is a limited window into a combinatorial explosion of complexity across temporal and spatial dimensions. The thalamus may partake in large-scale networks involving many interacting nodes with temporally-varying oscillatory interactions. A growing body of work on rhythmic visual sampling provides a glimpse of this complexity and its potential functional role in the context of the relatively well-defined circuits of visual attention.

A seminal study by Fiebelkorn et al.[177] demonstrated that, in humans, response accuracy to cues presented on an attended-to object, vs. an unattended object was reweighted in the theta phase, such that the "good" theta phase corresponded to increased accuracy to cues on the attended-to object and decreased accuracy to unattended objects. The "poor" theta phase had the opposite results. This has been used to argue that phasic reweighting allows for a flexibility in cognitive networks[37], where the "poor" phase allows for a period of lighter focus, where attention may be easily broken if necessitated by shifting environmental needs. Two parallel studies have investigated the neural correlates of this phenomenon by recording from the human frontal and parietal cortex using ECOG[38] and recording single unit/LFP activity in the FEF, LIP, and dorsal pulvinar in macaques[124,178]. The results of both studies suggest that theta-phasic behavioral

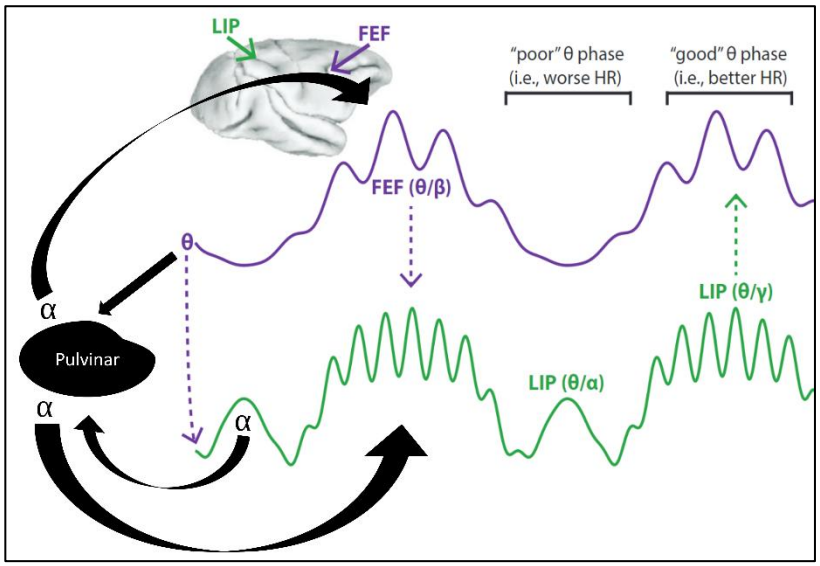


Figure 3: Adopted from Fiebelkorn et al., 2018, and modified. A depiction of cortical and thalamic interactions during attention where oscillatory dynamics of frontoparietal and thalamic nodes of the classic visual attention system are modulated by theta phase. Arrows represent the directionality of influence, which changes based on the theta phase. Frequency bands are denoted by their Greek letters.

performance indeed correlates with theta phase in visual attention networks, including the FEF, LIP, and dorsal pulvinar, where the "good" theta phase corresponded to increased cortical excitability. This effect was specific to neurons that responded to cues, which also formed a spatial pattern[38]. This dynamic theta-phase reweighting of attention corresponded to a reorganization of communication between the recorded nodes. During the "good" theta phase, gamma power increased in the LIP while beta power increased in the FEF, driving each other in their corresponding dominant frequencies. In the "poor" theta phase, alpha dominated the LIP and drove pulvinar alpha while in the "good" theta phase, pulvinar drove LIP and FEF alpha[124](see figure 3). From the perspective of the "good" theta phase as an attentive state with the "poor" theta phase as an inattentive state, the state-dependent bidirectional flow of alpha-range influence is consistent with earlier findings of pulvinar driving alpha in attention[111] while parietal cortex drives pulvinar alpha at rest[134]. Here is a framework that compellingly connects oscillatory synchrony, presumably the function of oscillatory influence from each region on another[111], with the dynamic reweighting of excitability occurring during PAC, a concrete example of the multi-level interactions of thalamocortical oscillations often presumed but rarely so compellingly demonstrated. The specificity of theta-rhythmicity to cells with receptive fields overlapping with cues suggests one more relevant dimension: space.

Thalamic Selection in Space

The frequency of neural oscillations within cortical tissues may alter cortical dynamics to facilitate or impede local cortical processing as a selection mechanism in cognitive functioning[38,148,179,180]. As different frequency bands are thought to support different functions, the topographical redistribution of oscillatory power (between say, alpha vs. gamma) throughout the cortex may be a selection process for specific task-relevant networks in cognition[148,181]. As previously alluded to, this may result from thalamus-driven shifts in E/I balance.

Alpha-Gating:

Despite its apparent task-relevance[111,154], increases in alpha power are generally associated with a cortical off-period[148]. Occipital alpha power famously increases when one close's their eyes. Though, this effect is not only contingent on the absence of visual stimuli; opening one's eyes in a totally darkened room[182] as well as mentally searching with eyes closed reduces occipital alpha[183]. Thus, occipital alpha desynchronization appears impacted by top-down modulations of attention and may reflect a preparedness for sensory processing. Increases in alpha power have been associated with the blocking of competing stimuli in both working memory and attention[179,181,184,185] while spontaneous increases in occipital alpha-power lead to a decreased response from cortex by transcranial magnetic (TMS) and sensory [186] perturbation. Rather than a slow waning and waxing of attentional allocation, alpha modulation may reallocate cortical resources on the millisecond scale, as evidenced by the phenomenon of alpha event-related desynchronization (ERD) and event-related synchronization (ERS). When a cue appears, occipital cortex representing its location exhibits alpha ERD[181] and is replaced by an increase in gamma-range oscillations[91,187]. Fitting with alpha-blocking, this is thought to reflect the release of inhibition and a consequent shift into active processing[181]. On the other hand, alpha ERS is associated with the suppression of competing or irrelevant cortical regions, for instance, in the

hemisphere ipsilateral to a cue in a visual attention task in visual attention[188] as well as short term visual working memory tasks[179,189]. In its most spatially-precise presentation, ERS/ERD form center/surround architectures over visual cortex during spatial attention, thought to emphasize a stimulus within a portion of the visual field[190].

Furthermore, alpha-blocking may be phasic such that its inhibitory influence on cortical processing wanes and waxes with its phase[155]. A simple example is the classic attentional blink paradigm, where noticing a brief (e.g., for 15ms-long) stimulus decreases the chance of noticing the next stimulus. The observation that the attention blink requires a stimulus-presentation frequency of roughly 10Hz suggests that occipital alpha phase becomes driven by the 10Hz images and the up and down phases of occipital alpha correspond to moments of increased and decreased stimulus detection[148,191]. This hypothesis has been all-but confirmed by experimental relation of alpha phase to behavioral results[192,193].

However, it is immediately difficult to reconcile alpha as simply an inhibitory mechanism with its apparent associations with active processing during task[111,124,154], for instance the increased thalamocortical alpha-range influence during attention[111,124,142,143]. A theory proposed by Klimesch[148] attempts to reconcile these apparent contradictions and explain how activity in a single frequency band may facilitate communication while generally suppressing activity. Starting with the assumption that alpha power generally constitutes inhibition, increasing alpha amplitude (from a low level, see "case 1" in figure 4) in a cortical tissue could deactivate tonically-active cortical neurons in a phasic way. If the down-phase of alpha surpasses some threshold, the neurons that it effects will cease to fire for some extent of that phase, and so too with other neurons affected by the same alpha oscillator and with similar action-potential thresholds. Thus, the periodic inhibition and excitation that occurs with each complete alpha phase produces synchronized activity between cortical neurons (see "case 2a" in figure 4). Synchronized activity, it is widely suggested, through temporal summation, increases the chance that their common targets will be activated, perhaps binding individual neurons or local assemblies into larger networks[3]. However, further increasing the amplitude of alpha waves does not lead to the inhibition desired in competing networks; rather, a baseline shift in the inhibitory tone of modulating alpha waves is necessary to silence some (see

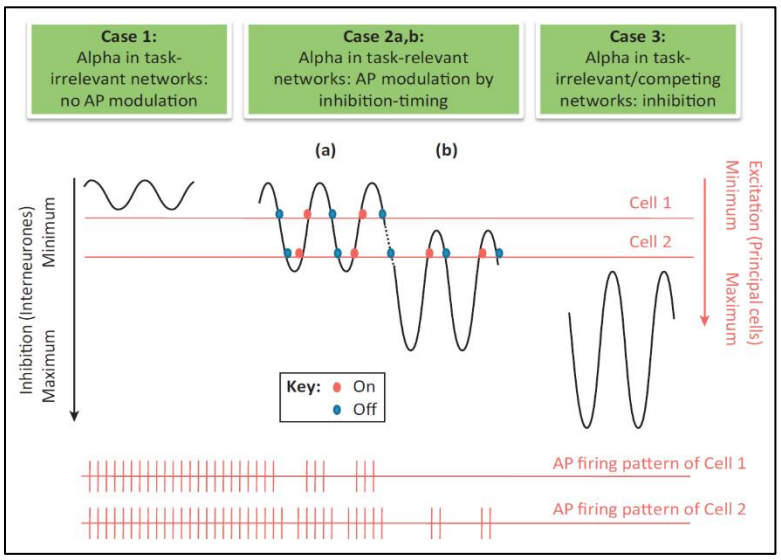


Figure 4: Adopted from Klimesch, 2012. Figure describes four cases of differential alpha baseline inhibition and alpha amplitude. In case 1, alpha baseline inhibition and amplitude is low and so it has a minimal effect on cortical dynamics, allowing for tonic excitation of cortical pyramidal neurons. In case 2a, amplitude has increased to tonically deactivate both cell 1 and cell 2 while, in case 2b, a baseline shift tonically deactivates cell 1. A final baseline shift in Case 3 results in tonic deactivation of both cells.

"case 2b" in figure 4) or all (see "case 3" in figure 4) of the neurons of possible competing assemblies.

We can apply this model to thalamocortical interactions by assuming the thalamus is the source of alpha-range modulations (the oscillations of Figure 4) while the modulated cells (cell 1 and cell 2) are cortical. In this framework, the synchrony of Case 2a may be the function of heightened thalamocortical alpha-range influence[111,124,142,143] during task. Thalamus may also play a role in the cortical inhibition of Case 2b, 3 by modifying cortical excitability. As expanded on in Saalman and Kastner, 2009[117], visual thalamus (LGN, Pulvinar), in coordination with TRN, may play a role in modulating the responsivity of visual cortex. Influence of the TRN, which is known to contain topographical maps[98] and change its activity during attention[194], is proposed to mediate visual gating via the modulation of visual thalamic and, by extension, occipital cortical gain[117,190,195,196]. For instance, activity of the (GABAergic) visual TRN (visTRN) has been shown to increase during an audio-visual divided attention task in mice when mice must attend to auditory cues and decrease when mice must attend visually, suggesting a role for the visTRN in modal-specific feed-forward inhibition[195]. Heightened inhibition in the LGN was found during "attend to auditory" trials while optogenetic visTRN inhibition reduced this difference, supporting a TRN-thalamocortical axis in sensory gating. As interactions between the TRN and the cortically-projecting thalamic relay neurons are theorized to generate alpha rhythms[131], TRN interactions provide an avenue through which alpha oscillations are applied to baseline shifts in excitability. Receiving massive converging inputs from executive and visual areas, the TRN may impose center-surround architecture on visual thalamic regions (which also display topographically specific activations to attention) and their downstream cortical targets[117]. In other words, the visual thalamus may be a source of baseline shifts[117] and, together with the visual thalamus(e.g., pulvinar), the alpha-frequency coupling that occurs on top of them[111] as illustrated by the Klimesch[148] model.

Synthesis: Arousal and Cognition in Thalamocortical Oscillations

An interaction between arousal and the oscillations presumed to underlie several aspects of cognition becomes unavoidable in the view that both represent fluctuations in neuronal excitability. Here, we cover three mechanisms by which arousal states may impact thalamocortical oscillations in cognition and form an inverted-U: **1)** arousal impacts oscillatory frequencies, **2)** arousal states act as a global baseline shift in excitability, and **3)** arousal states covary with neuromodulation emanating from the ARAS. As elaborated below, the thalamocortical system may be particularly susceptible to arousal fluctuations because its two halves, thalamus and cortex, may fluctuate in arousal somewhat independently, particularly impairing their cooperation. Indeed, each half possesses different cellular architectures, oscillatory generators, and inputs, which could facilitate different responses to changing arousal levels.

Arousal and Oscillatory Frequency

Arousal appears to alter oscillatory frequencies—with high arousal generally increasing them—which may impact within-frequency and cross-frequency interactions during cognitive functioning. For instance, a near-ubiquitous neural correlate of transitions from higher to lower arousal states is the trading of asynchronous higher frequencies (gamma, beta) to synchronous

lower (e.g., delta) frequencies. Examples include sleep[22], anesthesia[23,197], and disorders of consciousness, where the severity in the later can be effectively stratified by the ratio of high and low frequencies[198]. This trend may even be amenable to simple mathematical formulation, where the slope of the 1/f power-law or "spectral slope" reflects E/I balance (where a more negative slope suggests increased inhibition) in computational studies[199–201] as well as human ECOG data[27]. Some exceptions do exist where the high amplitude delta waves characteristic of slow-wave sleep exist in the waking state, including Angelman Syndrome, a neurodevelopmental disorder characterized by cognitive deficits but retained consciousness[202] and thus apparent arousal. Similarly, in anesthesia, global delta synchrony may be lower than in waking (despite high local delta synchrony)[203,204]. Despite these possible counterexamples, a positive correlation between cortical oscillatory frequency and neural depolarization retains heuristic value.

This holds true in the thalamus. Across many mechanisms, proposed thalamic generators of rhythms are dependent on the level of depolarization[98,135,137,139,141,205]. Not only are specific windows of depolarization of neurons necessary, but some models suggest the precise frequency of generated oscillations smoothly increase as depolarization increases[135,137]. For instance, a subset of thalamic neurons that intrinsically oscillate in the delta-to-alpha range are thought to seamlessly change their oscillating frequency between 2 and 13 Hz following increasing depolarization[135]. Thus, even subtle changes in arousal may elicit impactful changes in oscillatory frequency, maintaining the relevance of small shifts in arousal on thalamocortical oscillations even within normal waking, in the absence of state changes (e.g., sleep), and in healthy individuals. Because different oscillators likely have different, and likely non-linear, functions describing the relationship between arousal and frequency, alterations in arousal are likely to bias the oscillatory frequency between distinct structures (e.g., thalamus, cortex) into different relative ratios, even if both frequencies increase and decrease monotonically alongside arousal. Again, the effect is doubly significant if changes in arousal were to diverge between regions or impact only one of them. These effects may be particularly impactful in corticothalamic relationships, as opposed to cortico-cortical relationships, as thalamus and cortex possess highly distinct cell types and, likely, oscillatory generators.

Disruption of the ratio of oscillatory frequencies could have a dramatic effect on cross-frequency coupling. This is particularly the case in CFS, which necessitates precise integer frequency ratios (harmonics), where the peaks of harmonics meet, potentially facilitating cross-frequency integration, and non-harmonics rarely meet, leaving isolated signals. As the temporal resolution of CFS is determined by the higher frequency within a pair[157], even subtle biases in oscillatory frequency between coupled oscillators could induce a functionally-significant ratio-shift. A potential example of this mechanism, 10Hz rTMS has been shown to enhance alpha-gamma CFS, which correlates with performance on a visual WM task[206]. This is thought to result from a modulation of excitability (and not entrainment[206,207]).

Though, in the extreme, jumping frequency bands, for instance from alpha to theta due to slowing may lead to more dramatic effects on cognition; for instance, excessive theta could cause unwanted signal mixing between different modalities[208] normally segregated by oscillatory frequency and excessive theta-high-frequency PAC. One can imagine this effect as a transient phenomenon due

to the dysregulation of arousal or more persistent, due to a longer lasting downregulation of (e.g., thalamic) arousal. A form of persistent thalamic slowing, in particular, where alpha-range oscillations dip into the theta range, has been associated with "thalamomcortical dysrhythmia" (TCD), a condition used to explain symptoms in a host of psychiatric conditions, including but not limited to neurogenic pain[209], tinnitus[210], Parkinson's disease[211], and depression[208,212]. Seeming to confirm that theta in TCD patients shares the same generator as alpha in healthy individuals, in some patients with apparent TCD, in the place of the alpha peak characteristic of healthy EEG, a theta peak exists which, like healthy alpha, is suppressed during eye opening[209]. Specifically, hyperpolarization of the thalamus is thought to result in excessive theta-to-alpha-range signal mixing, increased gamma power, and theta-gamma cross-frequency coupling, leading to interference due to excessive intermodal communication and positive pathological symptoms due to the excessive "active processing" associated with gamma-band oscillations[208,210]. While perhaps immediately counterintuitive, in light of reduced thalamic arousal, excessive gamma activity is thought to reflect an "edge effect" resultant from the boundary between excessive low-frequency oscillations and generators of normal oscillatory frequency[208]. While TCD has largely been discussed as a persistent pathology, a more subtle or more transient form of these effects may explain deficits in cognition that accompany very high and low arousal states. One can imagine that suboptimal arousal regulation at aberrant levels of arousal (e.g., acute stress) may lead to discordant arousal levels in thalamus and cortex, leading to a momentary TCD-like state, a possible mechanism behind cognitive impairment at very high or low levels of arousal.

In the context of PAC specifically, as in TCD, heightened PAC between the excessively dominant low and high frequency oscillations may occur, perhaps simply due to their increased prevalence[208]. For instance, excessive PAC of this kind may result in the symptoms of neuropsychiatric disorders when occupying relevant cortical regions—for instance Parkinson's Disease[213,214], when impacting the motor cortex, and tinnitus, when impacting the auditory cortex[210,214] . Moreover, divergent frequency ratios between lower and higher frequency pairs could alter the cycles obtained by the higher frequency every low-frequency cycle. For instance, if thalamic oscillatory frequency suddenly jumped ahead of its cortical partner, gamma frequencies generated during the "up" phase of a thalamus-generated theta rhythm would complete fewer cycles before evaporating during the down phase. If, as has been suggested in the context of working memory[169], each gamma cycles defines a unique moment of information processing (e.g., the processing of a single item in working memory), this ratio-shift would lead to impaired cognition (e.g., working memory capacity).

Arousal as a Baseline Shift

Given that arousal is generally associated with long lasting up-shifts in neural excitability (e.g., wakefulness, vigilance), arousal can be viewed as a baseline level of excitability on which faster changes of excitability (e.g., oscillations, center surround architecture) fluctuate in a (generally) more spatially and temporally precise manner. While it remains inconclusive if the thalamus is necessary to maintain wakefulness, higher-order thalamic nuclei do appear necessary for maintaining behaviorally-relevant forebrain arousal to some degree. This is evidenced by the lost arousal in anatomically-connected cortical regions following MD and Pulvinar thalamic damage

or deactivation[90–93] and the cognitive deficits that follow[90,91,93]. The topographic specificity of this effect suggests that thalamus-mediated arousal, at least from these higher-order nuclei, is not a global dial of arousal but may support specific modal functions. Thus, thalamus may be responsible for the institution of localized baseline-shifts during cognition in the support of local cognitive functions, an "arousal regulation"[20]. Thalamus-mediated arousal may sustain representations and promote select cortical processes over long periods of time during, for instance, working memory[93,150] and vigilant attention[26,77,78]. This view is consistent with classical notions of arousal as limited mental energy that may be distributed throughout the brain in accord with behavioral needs[19]. In this view, in the absence of ample "energy" (i.e., arousal/excitability), mental processes cannot occur and cognition is impaired—representations fall out of working memory and vigilance diminishes. However, this conception only explains half the Yerkes Dodson law and does not describe how states of high arousal may also impair cognition. Application of a global baseline shift in excitability to the mechanisms of more spatially-specific arousal regulation described above reveals a fragility to very low as well as very high levels of arousal.

Arousal as a Baseline Shift in the More Local Reweighting of E/I Balance

Klimesch[148] outlines how baseline shifts in excitation may enable the selection of cortical ensembles (see figure 4). The model can be extended to include arousal by adding an additional parameter: a global baseline level of cortico-thalamic excitation on which more temporary baseline shifts in excitation (e.g., the shift from case 2a to 2b in figure 4) occur during cognition. For example, if cortical and/or thalamic excitation is lower than optimal, case 2b (in figure 4/5) may occur when 2a was appropriate for an ensemble of cortical cells, leading to a disordered selection of cortico-cortical communication and impaired cognition. Furthermore, case 3, characterized by high alpha amplitude and high inhibition (as in the case of alpha ERS) may occur excessively while alpha ERD would occur less effectively. In this case, an inability to highlight task-relevant networks would occur. In this way, both the selection of cortical ensembles and the suppression of task-irrelevant networks, such as in the center-surround architecture of ERD/ERS, could be impaired by hypo-arousal, leading to a general decrease in signal to noise (SNR) ratio across these two mechanisms. In the case of low arousal, SNR is decreased because the processing of both task-relevant and non-task relevant signals do not readily escape inhibition.

A real-world example of this phenomenon in humans may be ADHD, which is proposed to result from forebrain hypoarousal[215,216]. Supporting this notion, a heightened ratio of theta:beta power, and thus a shift towards lower frequency oscillations, is a classical correlate of ADHD symptomatology[217,218]. While the theta:beta ratio effect may be driven by only a subset of ADHD patients[181], hypo-arousal remains a plausible underpinning of ADHD in, at least, some cases. Congruent with this notion, reduced alpha ERD is seen in ADHD[179], possibly reflecting excessive inhibition. Interestingly, ERD reduction in ADHD (compared to controls) is greater in less difficult tasks[179], mirroring the classic observation that low arousal generally impairs cognition to a greater extent in less difficult tasks[19]. On the other hand, reduced surround ERS, another possible source of deficits in attention, is, perhaps counterintuitively, less clearly associated with ADHD[181]. Moreover, exaggeration of the closely related somatosensory MU wave (7.5–12.5Hz) has been reported in response to distracting stimuli in ADHD[219], suggesting no clear deficit in and perhaps

even excessive stimulus suppression in ADHD, also congruent with excess inhibition. Thalamus has previously been discussed in the context of arousal and alpha-mediated attention selection in ADHD[181]. Indeed, morphological differences in the pulvinar as well as its task-related functional connectivity with cortical connections have been linked to ADHD[220]. A modified Klimesch model[148], with the thalamus (esp. the pulvinar) as the source of alpha-rhythmic influence and center-surround architecture with the addition of a global baseline shift down in arousal may provide a framework with which to understand these findings in ADHD. In other words, some ADHD symptoms may result from a biasing toward the right side of Figure 5.

On the other hand, a global baseline shift up in arousal (i.e., increased excitation) would facilitate ERD. Interestingly, using emotionally-arousing images[221,222] or pain[223] as stimuli facilitates alpha ERD in comparison to less arousing stimuli. This, too, may introduce cognitive impairments through reduced SNR. Excess excitation, in the Klimesch[148] model may lead to Case 2a (effective cortical communication) when Case 2b (ineffective cortico-cortical communication) is desired and thus an inability to suppress task-irrelevant networks. Moreover, excessive arousal may lead to Case 1 instead of Case 2a/b, where networks avoid selection through alpha-range synchrony entirely but none-the-less retain activity that could interfere with task-relevant processing. In other words, a reduction in SNR is produced at high arousal levels because the processing of both task-relevant and non-task-relevant stimuli are elevated above the level of alpha-blocking and may readily compete. Such a mechanism may explain the decreased performance seen during periods of high arousal in tasks involving the preservation of specific stimuli above distractors[224,225], such as in divided attention and working memory[226–228] (see figure 7).

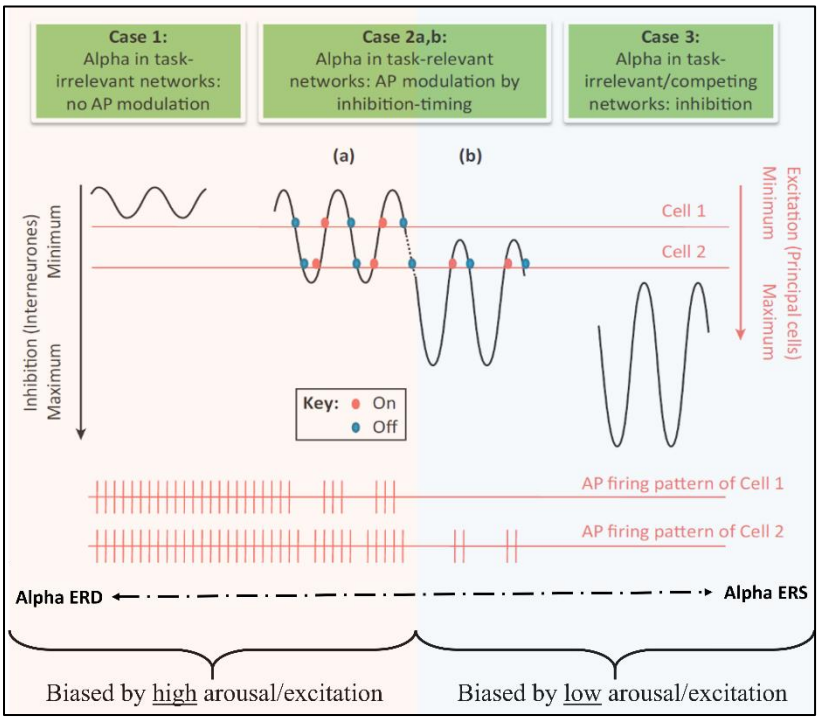


Figure 5: Adopted from Klimesch, 2012, and modified. Note that, in theory, all conditions represented here (Case 1-3), are needed for the proper selection of signals, where select cortical ensembles are selected via both local baseline shifts and oscillatory binding on top of them as contrast mechanisms. Shifts in arousal may impair this contrast and shift which ensembles find themselves selected or find themselves unselected. Here, conditions that are biased by low arousal are overlaid in a light blue while conditions that are biased by high arousal are overlaid in a light orange.

Thus, a precise intermediate level of arousal optimizes corticothalamic interactions in this model. Deviation from the optimal relative baseline level of arousal inevitably leads to an inverted U.

Importantly, not only broad corticothalamic arousal but relative cortical and thalamic arousal may be highly important as deviations of cortex and thalamus in opposing directions (see figure 5) away from an optimal arousal baseline would be twice as detrimental to their interactions as a collective upswing or downswing in arousal.

A Baseline Shift in Phase Amplitude Coupling, Rhythmic Attention

Increased high-frequency amplitude during the "up" phase of a lower frequency characterized by high excitability, known as PAC, may reflect the natural response of neural tissues exposed to moments of increased excitability[156]. Thus, just as a baseline shift in arousal may impact the spatial contrast established in e.g., center-surround architecture, so too might it impact the contrast established temporally between the shifting neural dynamics which define PAC. For instance, the occipital alpha-gamma PAC theorized to underlie pulvinar control of occipital information flow[111,147] necessitates the crossing of some threshold of excitation with each alpha phase, so as to elicit differential gamma power. In the extreme, a baseline shift down in arousal could theoretically ensure that the "up" alpha phase characterized by higher arousal no longer surpasses this threshold where no gamma power is elicited.

Though, more subtle changes in arousal may also be impactful. Small changes in arousal could bias oscillatory phenomena towards the characteristics of either the up or down phase, contracting or expanding the phase window in which an oscillatory phenomena (e.g., heightened gamma power) may exist without fully eliminating PAC. For instance, in theta-gamma PAC, if successive gamma cycles encode different items in working memory, as has been suggested[169], a restriction of the period during the "up" phase where arousal is high enough to support these gamma oscillations would reduce the number of items held in working memory, assuming that relative oscillatory frequencies of theta and gamma are held constant. Given that a functional significance is often attributed to both the up and down phases during PAC[124,156], there is likely some ideal threshold between up and down phases for a given form of PAC. Deviation from this ideal, via a baseline shift in arousal, is likely to impair cognition regardless of its valence, providing cognitive impairment in cases of excessively low and high arousal and, again, an inverted U. By this mechanism, relative thalamic and cortical excitability may have implications for thalamocortical PAC and thus the cognitive functions it is presumed to underlie across several cognitive modalities[111,124,176].

This follows, for example, in the context of rhythmic sampling, where a complex reordering of the activity of a fronto-thalamo-parietal network follows the theta phase[124]. Here, the "up" theta phase coincides with increased attention and increased fronto-parietal high-frequency power (see Figure 6). Thus, a baseline shift down in arousal may disallow for rhythmic excitation in the theta range to promote high-frequency fronto-parietal activity and their corresponding intercommunication to take place, impairing the attentional processes this intercommunication is presumed to conduct.

Similarly, too-high arousal may bias the "up" theta phase and its many properties, while too-low arousal may bias the "down" theta phase and the properties supported by it. The interaction of global arousal with this temporal reallocation of excitability mirrors that with the spatial reallocations of excitability described above (i.e., in the Klimesch model). Namely, contrast between the up and down phase is reduced in both cases, where, in low arousal, more of the usual up-phase resembles that of the down phase (e.g., more alpha power) as thresholds of excitability necessary to facilitate the up-phase dynamics are not exceeded. This could impair processing of stimuli in the focus of attention. Moreover, in high arousal, the down phase may begin to resemble the up-phase, where high-frequency power and the signal processing it conducts may be more present in the down-phase, leading to heightened competition by stimuli outside the focus of attention. Decreased SNR, in this context, leads to a behaviorally testable prediction—that the amplitude of theta-rhythmic shifts in performance on this type of divided attention task forms an inverted U-shaped relationship with arousal states.

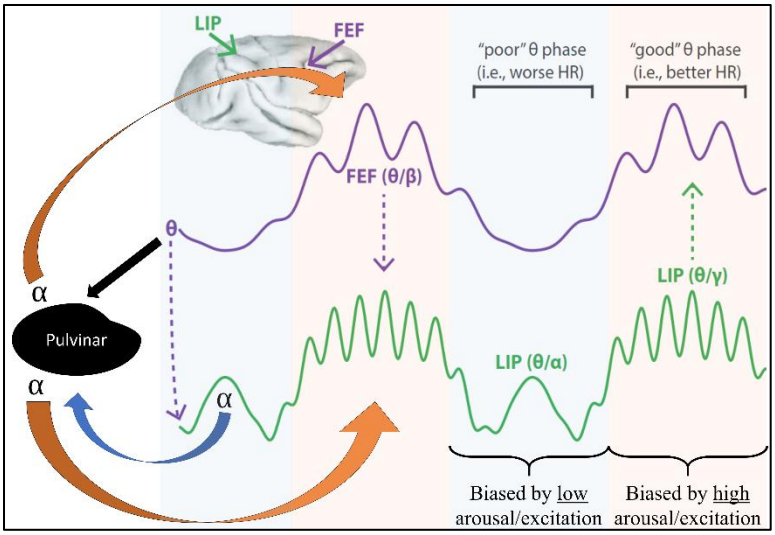


Figure 6: Adopted from Fiebelkorn et al., 2018, and modified. Here, conditions that are biased by low arousal are overlaid in a light blue while conditions that are biased by high arousal are overlaid in a light orange. The same color scheme denotes how the directionality of alpha-range influence to and from the pulvinar is biased by arousal.

In regards to thalamo-cortical relationships specifically, thalamic alpha-range influence may remain low in the lengthened down-state brought on by low arousal and so too, the cortico-cortical communication it is thought to facilitate[111]. Similarly, thalamo-cortical alpha-range influence would excessively dominate in high-arousal, which may reflect a broader trend. It is an interesting tendency in the literature reviewed here that thalamocortical influence appears to dominate during periods of heightened task engagement and/or heightened performance[111,124,142,143] while corticothalamic influence appears to dominate at rest or reduced task engagement[124,134], at least in the alpha and beta bands. In addition to the alpha-range interactions of rhythmic sampling, beta-range thalamocortical influence appears to positively covary with maintained cortical excitability during working memory while corticothalamic influence dominants once the maintenance period ends and a response is given[149]. A fascinating possibility is that directionality may be driven by shifting levels of arousal. Congruent with this notion, Stitt et al.[229] found that, remarkably, *thalamocortical* influence increased during periods of high arousal (as inferred by pupillary diameter) while *corticothalamic* influence increased during periods of low arousal, albeit in different frequency bands (theta vs. alpha). Pupil diameter is thought to covary primarily with NE secretion, which itself, is thought to covary with arousal as discussed below.

Different Tasks, Different Thresholds?

A classical Yerkes-Dodson era finding is that different types of tasks have different arousal-performance curves where "easier" tasks have more monotonic increases in performance following increased arousal while more "difficult" tasks display the typical inverted "U"[6]. In the original Yerkes Dodson experiments, this trend was found in rats trained to discriminate the brightness of two light sources. When a difference in brightness was very high, arousal only improved performance while more subtle discriminations displayed the inverted "U"[6]. Thus, the "difficult"/ "simple" distinction may stem from the degree of contrast between competing stimuli and target stimuli found within a task, as determined by their relevance to that task[224]. For instance, vigilant attention tasks generally require attention to one type of stimuli, and thus may readily produce a context of extreme contrast between that stimuli and others. If a subject is made to only attend to the appearance of a black "X" in the center of the visual field, other possible stimuli (e.g., a high-pitched sound happening behind her) need not be expected and thus their processing need not be facilitated. Accordingly, performance in these tasks scale monotonically with increased arousal. In accord with the presented theory, a baseline shift increase in arousal would heighten both target-related activity and non-target-related activity. However, due to the high intrinsic contrast of this type of task, heightened arousal only amplifies/speeds the processing of target stimuli.

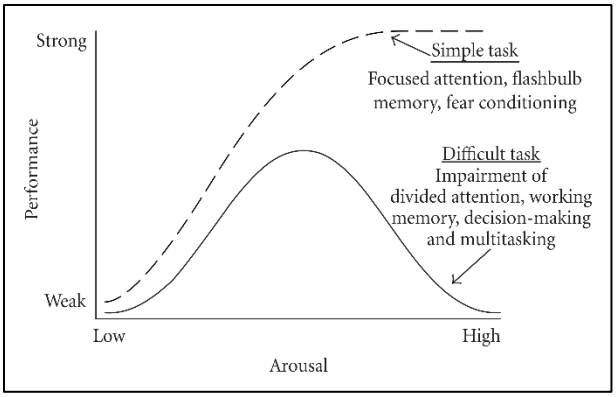


Figure 7: Adopted from Diamond et al., 2007. Depiction of the impact of task type/difficulty on the interaction between arousal and task performance. Easy tasks monotonically increase in performance as arousal increases. More "complex" tasks, involving many competing stimuli (divided attention, working memory), are impaired by high arousal.

On the other hand, "complex" tasks, such as divided attention, cognitive flexibility, and working memory, naturally require subtle contrasts between many competing stimuli so as to rapidly update and shift between processing of these stimuli[224]. Here a decrease in contrast (SNR) due to high levels of arousal could instead impair performance by enhancing the processing of distracting stimuli. This could be applied, for instance, to working memory, where E/I balance regulation, putatively involving the MD thalamus[149,230,230–233], maintains selected representations against competition (e.g., incoming sensory stimuli). This notion is supported by findings that suggest high levels of stress, which may be an imperfect stand-in for high arousal[19], impairs working memory via a decrease of focus on task-relevant stimuli[226–228]. This paradigm could be feasibly extended to the also MD-related domain of cognitive flexibility, where, similarly, select representations/rules/stimuli are selected against competing stimuli. Complicating matters, however, cognitive flexibility tasks also require the rapid shift to competing stimuli, a capacity that could be conceivably facilitated by the lowered SNR brought on by high arousal. Despite this, cognitive flexibility is thought to generally decrease with increasing arousal[234–237]. As discussed below, the impact of neuromodulation may help explain this apparent contradiction.

Neuromodulation, SNR, and ARAS

Until this point, we have largely viewed the ascending inputs to thalamus, such as those from the LC, as a source of broad excitatory and inhibitory tone, which they undoubtably are. However, this ignores the fact that the serotonin and catecholamine systems of the deep brain have an impact themselves on information processing and cognition that is more complex than simply imposing a linear modification on excitation. Alterations in neuromodulator secretion have been associated with, for instance, cognitive deficits in ADHD[238], schizophrenia [239], and aging[57,240]. Indeed, neuromodulators, by nature, modulate the impact of other neurotransmitters (e.g., GABA and glutamate)[52,57] instead of directly impacting the polarization of post-synaptic neurons, and so may have effects on cognition that are not best characterized as the generation of arousal states. However, their modulatory influence is likely to covary, but not without exceptions, with arousal.

For instance, the LC increases its activity as arousal increases during waking, decreases its activity in drowsiness, and further decreases its activity during deep sleep[52]. Interestingly, NE secretion is nearly absent during REM sleep, during which time acetylcholine increases secretion (from low levels during deep sleep) to surpass waking levels, suggesting a somewhat non-linear interplay between neuromodulator systems and arousal-modulation[241]. NE secretion is thought to conduct a form of non-linear gain control where, in general, NE secretion acts to enhance the contrast between lowly-excited tissue and highly-excited tissues, enhancing the SNR of selection processes[52] (see figure 8). The interaction of this mechanism with arousal has, itself, been able to explain the Yerkes-Dodson law. Here, low NE secretion relates to a state of low arousal, low SNR and, naturally, low cognitive performance. However, moderate (phasic) NE secretion corresponds to moderate arousal and, by enhancing SNR, leads to a state of maximized focused attention. Finally, high (tonic) NE secretion corresponding to acute stress and high arousal, leads to the enhancement of task-relevant and non-task relevant stimuli, perhaps maximizing cognitive flexibility at the expense of focused attention[52,242] at some very high level of arousal. Neuromodulation, through its covariance with arousal, is likely to interact with the other arousal-related mechanisms discussed here. For instance, the gain control mechanism proposed for NE secretion would interact with center-surround architectures by further enhancing the contrast between the relatively excited center and inhibited surround. Moreover, this interaction may even explain some apparent contradictions.

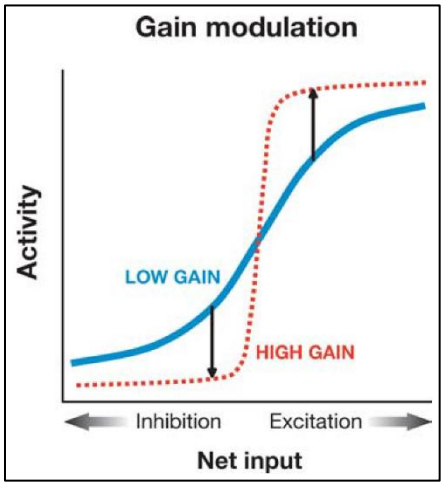


Figure 8. Adopted from Aston-Jones et all., 1999. A depiction of the type of non-linear gain control thought to be imposed by NE secretion. Here, high secretion of NE (corresponding to high gain) heightens the activity of highly excited neurons and reduces that of lowly excited neurons.

For instance, the global baseline-shift model prediction of increased interference from non-target stimuli at high arousal levels may be seen as contradicted by a compelling literature associating high arousal with reduced cognitive flexibility[234–237]. A baseline shift up in excitability/arousal may maintain competition by non-target stimuli and could be thought to facilitate cognitive flexibility, which requires readily shifting to them. However, the literature generally disagrees. A possible explanation for this discrepancy is the enhancement of SNR[52] by NE secretion, and thus

the reduction in cognitive flexibility through the suppression of competing stimuli at high levels of arousal and thus high NE secretion. This view is consistent with the observation that β-adrenergic receptor antagonists may protect against stress-induced impairments in cognitive flexibility[236].

A fascinating possibility is that the interaction of NE secretion and broad neural excitability during arousal produces interacting non-linear effects on cognition that may summate to a flatter inverted U-shaped curve, attenuating the negative effects of arousal on cognition produced by both mechanisms. In other words, if the "focused, inflexible" period of NE secretion occurs at higher arousal levels than the flexibility produced by a global baseline shift up in excitability, NE secretion could counteract the augmenting effect of a baseline shift on cognitive flexibility.

Differential expression of these dual effects on different cognitive domains could then explain the apparent contradiction in impaired cognitive flexibility (requiring rapid shifts to competing stimuli) and impaired working memory (requiring the elevation of some select stimuli above competing stimuli) at high levels of arousal. This may underlie the inability of β-adrenergic receptor antagonists to protect against stress-induced impairment of working memory[35,36], in contrast with its effects on behavioral flexibility[236]—where a baseline shift impairs selection in the former and NE-related SNR enhancement reduces flexibility in the later. While this particular example is firmly in the realm of speculation, the highly nonlinear interaction of arousal with cognitive functioning is likely resultant from the no-doubt complex interaction of neuromodulator and excitatory (e.g., center / surround) selection mechanisms.

Like many neural systems, the parallel thalamocortical cells that comprise the bulk of the thalamus may be viewed as a weight matrix with values that fluctuate over time and which apply their values to their projections. As discussed here, this thalamic weight matrix is likely to contain features such as center-surround architecture imposed by the TRN, and rhythmic fluctuations in time. It is this dynamic weight matrix that the arousal modulation and neuromodulation of the ARAS meet when impacting the thalamus, and thus the merger is likely to result in a thalamocortical system that responds to the firing rate of ARAS neurons, but with a specificity far exceeding that of the small nuclei comprising the ARAS alone (e.g., ~32,000 neurons exist in the human LC[52]). Of course, the ARAS contains direct cortical projections[49] where specificity may be obtained. However, the thalamus, containing a trace of recent cortical activity as well as upstream sensory information, may contain a more ideal weight matrix with which to multiply the gain control functions defined by the glutamatergic/GABAergic activity of ARAS as well as those defined by

its neuromodulatory components (see figure 9). Furthermore, there may be value in providing parallel inputs from ARAS to cortex as well as thalamus, as discussed more below.

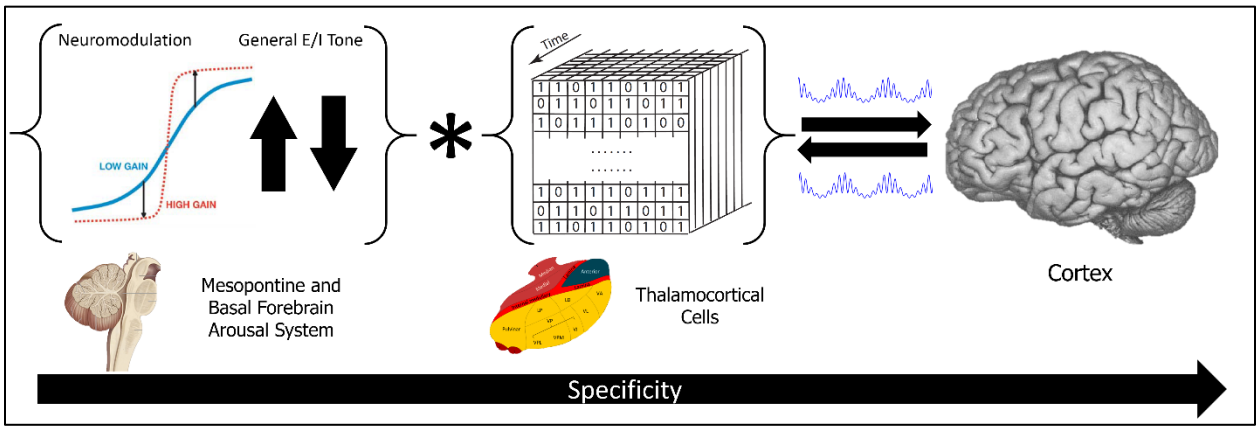


Figure 9. A depiction of the interaction between mesopontine and basal forebrain arousal systems and thalamus. Here, neuromodulator and excitatory influence from these structures synapse on the more distributed thalamus, depicted here as a weight matrix. All of the thalamic selection mechanisms discussed in this paper may be represented as altered weights in this weight matrix. The application of inputs from lower-level ARAS systems to each cell of this weight matrix could modify thalamic selection mechanisms while imbuing specificity to upstream ARAS efferents on their way to cortex.

Conclusions: Thalamus as a Simple Recipient of Arousal Fluctuations or Mediator of Them?

Despite our best attempts to characterize it here, the role of the thalamus in arousal and its impacts on cognition avoid monolithic description. In recursive networks, of which the thalamocortical system is a prime example, it is difficult to characterize "where" a phenomenon begins. Thus, the role of the thalamus in arousal regulation is necessarily both as a modulator of cortical arousal, congruent with classical views of thalamus as a node in the ARAS[44], but also a recipient of arousal as one half of a collective "thalamocortex" necessitating a limited window of arousal levels to optimize cognitive functioning.

Conductor of Arousal Regulation

Thalamic selection mechanisms appear to conduct dynamic reweighting of cortical processes in cognition. Viewing thalamocortical interactions as a reweighting of arousal, with both excitatory and inhibitory influence, and not as a simple aspect of the ARAS that linearly moves arousal up and down, may explain the relatively subtle alterations in arousal following thalamic damage or deactivation[90–93] (e.g., reduced excitability in visual cortex following pulvinar deactivation[90,91]) and the maintenance of wakefulness that often follows[12–14]. The thalamus may leverage its ability to conduct arousal regulation at many scales. Large-scale reallocation of arousal between large cortical networks could bias processing within certain cortical network or reflect the need for different arousal levels in distinct cognitive domains (level 2 from the bottom in the "arousal regulation pyramid" in figure 10). Of focus here, the thalamus may also participate in more spatially and temporally precise reweighting laid on top of this (levels 3,4 in figure 10).

Recipient of Arousal Regulation

Thalamic selection in cognition, oscillatory and otherwise, appears to depend on precise resting levels of excitability in both cortex and thalamus. If one or both structures moves from this optima, thalamocortical synchrony and cross-band interactions may suffer alongside the cognitive functions they conduct. While the thalamus has traditionally been considered a component of the ARAS, this history has been reevaluated in recent years[12,13,48]. A new history may emphasize the bifurcation of the ascending arousal pathway into cortical and thalamic targets which could facilitate the maintenance of stable relative arousal/neuromodulation between the two structures while global arousal shifts up and down in accord with behavioral needs. In this view, thalamus is another recipient of upstream arousal and not a participant in it.

Overview

As with most debates, a balance between competing views is likely the best characterization. The thalamus both receives subcortical arousal / neuromodulator input and transmits it to cortex following some degree of modification. Based on the reviewed literature, we may deemphasize the role of the thalamus in setting whole-brain arousal, which the pons/midbrain/basal forebrain/globus pallidus may be more implicated in. Rather, the role of the thalamus may be best characterized as the reweighting and gifting of specificity to upstream arousal and neuromodulatory signals. Furthermore, its role appears to be as a conductor of the low-level operations of cognition occurring primarily in the cortex. So, the thalamus lies at some middle level of specificity, nonetheless mediating several interacting levels of arousal regulation (see Figure 10). These levels, including global arousal, baseline shifts, oscillations etc. can be viewed as components of a multi-scale and hierarchical structure of dynamic regulation in arousal/excitability (see Figure 10), where lower levels (generally slower and more spatially expansive) interact with higher levels (generally faster and more spatially specific). As we have seen, interactions between scales of arousal regulation (global arousal and oscillations) may produce the curious U-shaped curve of the Yerkes Dodson law. The thalamus, at the heart of these inter-scale interactions, may be particularly implicated in this effect. The interrelation of cognitive mechanisms (e.g., oscillations) with arousal suggested here in the context of thalamic function should compel the further integration between parallel lines of thalamic research in arousal and cognition.

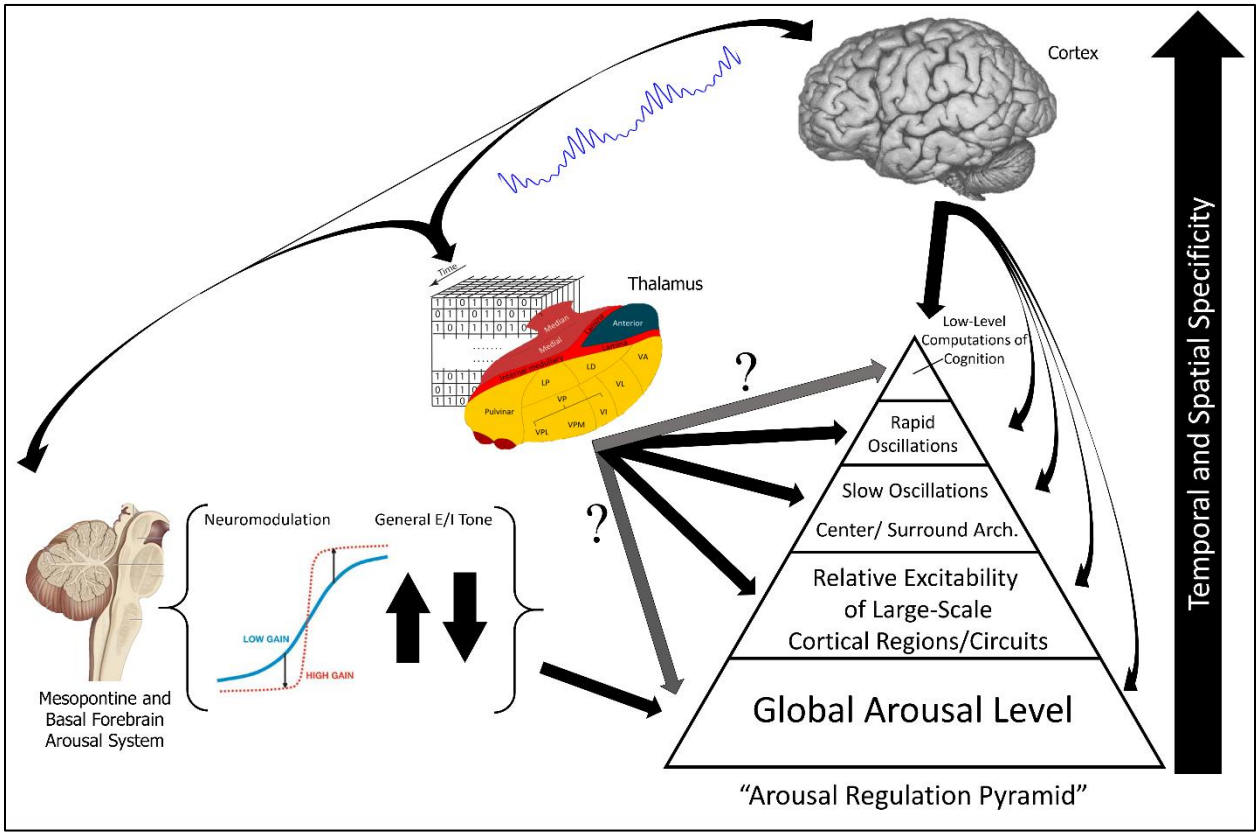


Figure 10. A depiction of the hierarchy of arousal regulation and the place of the thalamus within it. Mesopontine and Basal forebrain structures project to thalamus and cortex, obtaining specificity through each pathway. Thalamus, as discussed here, apparently coordinates many processes in the middle of our hierarchy, such as slow oscillations (delta – alpha). However, it is less clear to what degree it mediates baseline arousal state, especially state changes in arousal. Moreover, it is less clear to what degree the thalamus mediates the low-level computations of cognitive functioning or, more simply, acts to modulate them, putatively via modulation of cortex where they are more certain to reside. Queston makes denote this uncertainty. Items here generally progress towards spatial and temporal specificity when moving upward and to the right; however, some exceptions exist including some forms of activity of the lower ARAS, which can respond to stimuli with high temporal (though low spatial) precision – within milliseconds in some cases.

References

1. VanRullen, R. & Koch, C. Is perception discrete or continuous? Trends in Cognitive Sciences 7, 207–213 (2003).
2. Buzsáki, G. Rhythms of the Brain. (Oxford University Press, 2006). doi:10.1093/acprof:oso/9780195301069.001.0001.
3. Varela, F., Lachaux, J. P., Rodriguez, E. & Martinerie, J. The brainweb: phase synchronization and large-scale integration. Nat. Rev. Neurosci. 2, 229–239 (2001).
4. Fries, P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends in Cognitive Sciences 9, 474–480 (2005).
5. Halgren, M. et al. The Generation and Propagation of the Human Alpha Rhythm. bioRxiv https://doi.org/10.1101/202564 (2018) doi:10.1101/202564.
6. Yerkes, R. M. & Dodson, J. D. The relation of strength of stimulus to rapidity of habit-formation. Journal of Comparative Neurology and Psychology 18, 459–482 (1908).
7. Andrzejewski, M. E. & Holder, N. Chapter 11 - Amphetamine and Signal Detection. in Neuropathology of Drug Addictions and Substance Misuse (ed. Preedy, V. R.) 117–125 (Academic Press, San Diego, 2016). doi:10.1016/B978-0-12-800212-4.00011-X.
8. Mair, R. G., Onos, K. D. & Hembrook, J. R. Cognitive Activation by Central Thalamic Stimulation: The Yerkes-Dodson Law Revisited. Dose-Response 9, dose-response.10-017.Mair (2011).
9. Schiff, N. D. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci 33, 1–9 (2010).
10. Schiff, N. D. Chapter 24 - Central thalamic deep brain stimulation for support of forebrain arousal regulation in the minimally conscious state. in Handbook of Clinical Neurology (eds Lozano, A. M. & Hallett, M.) vol. 116 295–306 (Elsevier, 2013).
11. Redinbaugh, M. J. et al. Central thalamus modulates consciousness by controlling layer-specific cortical interactions. bioRxiv 776591 (2019) doi:10.1101/776591.
12. Constantinople, C. M. & Bruno, R. M. Effects and mechanisms of wakefulness on local cortical networks. Neuron 69, 1061–1068 (2011).
13. Fuller, P. M., Sherman, D., Pedersen, N. P., Saper, C. B. & Lu, J. Reassessment of the structural basis of the ascending arousal system. J Comp Neurol 519, 933–956 (2011).
14. Vanderwolf, C. H. & Stewart, D. J. Thalamic control of neocortical activation: A critical re-evaluation. Brain Research Bulletin 20, 529–538 (1988).
15. Einhauser, W., Koch, C. & Carter, O. Pupil dilation betrays the timing of decisions. Front. Hum. Neurosci. 4, (2010).
16. Kahneman, D. & Beatty, J. Pupil Diameter and Load on Memory. Science 154, 1583–1585 (1966).
17. Eysenck, M. Attention and Arousal: Cognition and Performance. (Springer Science & Business Media, 2012).
18. Laureys, S. The neural correlate of (un)awareness: lessons from the vegetative state. Trends in Cognitive Sciences 9, 556–559 (2005).
19. Kahneman, D. Attention and Effort. (Prentice-Hall, 1973).
20. Schiff, N. D. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann. N. Y. Acad. Sci. 1129, 105–118 (2008).
21. Vazquez, A. L., Fukuda, M. & Kim, S.-G. Inhibitory Neuron Activity Contributions to Hemodynamic Responses and Metabolic Load Examined Using an Inhibitory Optogenetic Mouse Model. Cereb Cortex 28, 4105–4119 (2018).
22. Steriade, M., Timofeev, I. & Grenier, F. Natural Waking and Sleep States: A View From Inside Neocortical Neurons. Journal of Neurophysiology 85, 1969–1985 (2001).
23. Alkire, M. T., Hudetz, A. G. & Tononi, G. Consciousness and anesthesia. Science 322, 876–880 (2008).
24. Di Perri, C. et al. Measuring consciousness in coma and related states. World J Radiol 6, 589–597 (2014).
25. Honjoh, S. et al. Regulation of cortical activity and arousal by the matrix cells of the ventromedial thalamic nucleus. Nat Commun 9, (2018).
26. Baker, J. L. et al. Robust modulation of arousal regulation, performance, and frontostriatal activity through central thalamic deep brain stimulation in healthy nonhuman primates. J. Neurophysiol. 116, 2383–2404 (2016).
27. Lendner, J. D. et al. An Electrophysiological Marker of Arousal Level in Humans. bioRxiv 625210 (2019) doi:10.1101/625210.
28. Brain Function and Responsiveness in Disorders of Consciousness. (Springer International Publishing, 2016).
29. Tononi, G., Boly, M., Gosseries, O. & Laureys, S. Chapter 25 - The Neurology of Consciousness: An Overview. in The Neurology of Conciousness (Second Edition) (eds Laureys, S., Gosseries, O. & Tononi, G.) 407–461 (Academic Press, San Diego, 2016). doi:10.1016/B978-0-12-800948-2.00025-X.
30. Crick, F. & Koch, C. Are we aware of neural activity in primary visual cortex? Nature 375, 121–123 (1995).
31. Steriade, M. & Timofeev, I. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 37, 563–576 (2003).
32. Windt, J. M., Nielsen, T. & Thompson, E. Does Consciousness Disappear in Dreamless Sleep? Trends Cogn. Sci. (Regul. Ed.) 20, 871–882 (2016).
33. Cheeseman, J. F. et al. General anesthesia alters time perception by phase shifting the circadian clock. Proc Natl Acad Sci U S A 109, 7061–7066 (2012).
34. DeSalvo, M. N. et al. Focal BOLD fMRI changes in bicuculline-induced tonic–clonic seizures in the rat. NeuroImage 50, 902–909 (2010).
35. Murphy, B. L., Arnsten, A. F. T., Jentsch, J. D. & Roth, R. H. Dopamine and Spatial Working Memory in Rats and Monkeys: Pharmacological Reversal of Stress-Induced Impairment. J. Neurosci. 16, 7768–7775 (1996).
36. Ernst, M., Lago, T., Davis, A. & Grillon, C. The effects of methylphenidate and propranolol on the interplay between induced-anxiety and working memory. Psychopharmacology 233, 3565–3574 (2016).
37. Fiebelkorn, I. C. & Kastner, S. A Rhythmic Theory of Attention. Trends in Cognitive Sciences 23, 87–101 (2019).
38. Helfrich, R. F. et al. Neural mechanisms of sustained attention are rhythmic. Neuron 99, 854-865.e5 (2018).
39. Nir, Y. et al. Regional Slow Waves and Spindles in Human Sleep. Neuron 70, 153–169 (2011).
40. Mazzoni, A., Whittingstall, K., Brunel, N., Logothetis, N. K. & Panzeri, S. Understanding the relationships between spike rate and delta/gamma frequency bands of LFPs and EEGs using a local cortical network model. NeuroImage 52, 956–972 (2010).
41. Koch, C., Massimini, M., Boly, M. & Tononi, G. Neural correlates of consciousness: progress and problems. Nat. Rev. Neurosci. 17, 307–321 (2016).
42. Jensen, O. & Colgin, L. L. Cross-frequency coupling between neuronal oscillations. Trends Cogn. Sci. (Regul. Ed.) 11, 267–269 (2007).
43. Cho, S. B., Baars, B. J. & Newman, J. A Neural Global Workspace Model for Conscious Attention. Neural Netw 10, 1195–1206 (1997).
44. Saper, C. B. & Fuller, P. M. Wake-Sleep Circuitry: An Overview. Curr Opin Neurobiol 44, 186–192 (2017).
45. Moruzzi, G. & Magoun, H. W. Brain stem reticular formation and activation of the EEG. Electroencephalography and Clinical Neurophysiology 1, 455–473 (1949).
46. Lindsley, D. B., Bowden, J. W. & Magoun, H. W. Effect upon the EEG of acute injury to the brain stem activating system. Electroencephalogr Clin Neurophysiol 1, 475–486 (1949).
47. Posner, J. B., Plum, F., Saper, C. B. & Schiff, N. Plum and Posner's Diagnosis of Stupor and Coma. (Oxford University Press, USA, 2007).
48. Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J. & Scammell, T. E. Sleep State Switching. Neuron 68, 1023–1042 (2010).

49. Laureys, S., Gosseries, O. & Tononi, G. The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology. (Academic Press, 2015).
50. Kolmac, C. & Mitrofanis, J. Organization of the basal forebrain projection to the thalamus in rats. Neurosci. Lett. 272, 151–154 (1999).
51. Parvizi, J. & Damasio, A. Consciousness and the brainstem. Cognition 79, 135–160 (2001).
52. Aston-Jones, G. & Cohen, J. D. AN INTEGRATIVE THEORY OF LOCUS COERULEUS-NOREPINEPHRINE FUNCTION: Adaptive Gain and Optimal Performance. Annu. Rev. Neurosci. 28, 403–450 (2005).
53. Steriade, M. Acetylcholine systems and rhythmic activities during the waking–sleep cycle. in Progress in Brain Research vol. 145 179–196 (Elsevier, 2004).
54. McCormick, D. A. & Prince, D. A. Acetylcholine induces burst firing in thalamic reticular neurones by activating a potassium conductance. Nature 319, 402–405 (1986).
55. Ni, K.-M. et al. Selectively driving cholinergic fibers optically in the thalamic reticular nucleus promotes sleep. eLife 5, e10382 (2016).
56. Zhang, Y. et al. Activation of noradrenergic terminals in the reticular thalamus delays arousal from propofol anesthesia in mice. The FASEB Journal 33, 7252–7260 (2019).
57. Li, S.-C. & Sikström, S. Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. Neuroscience & Biobehavioral Reviews 26, 795–808 (2002).
58. Xie, G. et al. Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study. Br J Anaesth 106, 548–557 (2011).
59. Alkire, M. T., McReynolds, J. R., Hahn, E. L. & Trivedi, A. N. Thalamic Microinjection of Nicotine Reverses Sevoflurane-induced Loss of Righting Reflex in the Rat. Anesthesiology 107, 264–272 (2007).
60. Edlow, B. L. et al. Neuroanatomic Connectivity of the Human Ascending Arousal System Critical to Consciousness and Its Disorders. J Neuropathol Exp Neurol 71, 531–546 (2012).
61. Steriade, M., Datta, S., Paré, D., Oakson, G. & Curró Dossi, R. C. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. J. Neurosci. 10, 2541–2559 (1990).
62. Kajimura, N. et al. Activity of Midbrain Reticular Formation and Neocortex during the Progression of Human Non-Rapid Eye Movement Sleep. J. Neurosci. 19, 10065–10073 (1999).
63. Hofle, N. et al. Regional Cerebral Blood Flow Changes as a Function of Delta and Spindle Activity during Slow Wave Sleep in Humans. J. Neurosci. 17, 4800–4808 (1997).
64. Guldenmund, J. P. et al. Thalamus, Brainstem and Salience Network Connectivity Changes During Propofol-Induced Sedation and Unconsciousness. Brain Connectivity 3, (2013).
65. Murphy, M. et al. Propofol Anesthesia and Sleep: A High-Density EEG Study. Sleep 34, 283–291 (2011).
66. Castaigne, P. et al. Paramedian thalamic and midbrain infarcts: Clinical and neuropathological study. Annals of Neurology 10, 127–148 (1981).
67. Monti, M. M., Laureys, S. & Owen, A. M. The vegetative state. BMJ 341, c3765 (2010).
68. Hannawi, Y., Lindquist, M. A., Caffo, B. S., Sair, H. I. & Stevens, R. D. Resting brain activity in disorders of consciousness: a systematic review and meta-analysis. Neurology 84, 1272–1280 (2015).
69. Lutkenhoff, E. S. et al. Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. Annals of Neurology 78, 68–76 (2015).
70. Lutkenhoff, E. S. et al. Thalamic atrophy in antero-medial and dorsal nuclei correlates with six-month outcome after severe brain injury. Neuroimage Clin 3, 396–404 (2013).
71. Lutkenhoff, E. S. et al. The thalamic basis of outcome and cognitive impairment in traumatic brain injury. bioRxiv 669390 (2019) doi:10.1101/669390.
72. Zhou, J. et al. Specific and Nonspecific Thalamocortical Functional Connectivity in Normal and Vegetative States. Conscious Cogn 20, 257–268 (2011).
73. Laureys, S. et al. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. The Lancet 355, 1790–1791 (2000).
74. Crone, J. S. et al. Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. NeuroImage: Clinical 4, 240–248 (2014).
75. Zheng, Z. S. & Monti, M. M. Thalamic and extra-thalamic connections of the Globus Pallidus in the human brain: The ultradirect pathway. bioRxiv 688283 (2019) doi:10.1101/688283.
76. Schiff, N. D. et al. Gating of attentional effort through the central thalamus. Journal of Neurophysiology 109, 1152–1163 (2012).
77. Kinomura, S., Larsson, J., Gulyás, B. & Roland, P. E. Activation by attention of the human reticular formation and thalamic intralaminar nuclei. Science 271, 512–515 (1996).
78. Paus, T. Functional anatomy of arousal and attention systems in the human brain. Prog. Brain Res. 126, 65–77 (2000).
79. Nagai, Y. et al. Brain activity relating to the contingent negative variation: an fMRI investigation. NeuroImage 21, 1232–1241 (2004).
80. Naito, E. et al. Fast reaction to different sensory modalities activates common fields in the motor areas, but the anterior cingulate cortex is involved in the speed of reaction. J. Neurophysiol. 83, 1701–1709 (2000).
81. Tassonyi, E., Charpantier, E., Muller, D., Dumont, L. & Bertrand, D. The role of nicotinic acetylcholine receptors in the mechanisms of anesthesia. Brain Research Bulletin 57, 133–150 (2002).
82. Steriade, M., McCormick, D. A. & Sejnowski, T. J. Thalamocortical oscillations in the sleeping and aroused brain. Science 262, 679–685 (1993).
83. Steriade, M., Amzica, F. & Nuñez, A. Cholinergic and noradrenergic modulation of the slow (approximately 0.3 Hz) oscillation in neocortical cells. J. Neurophysiol. 70, 1385–1400 (1993).
84. Steriade, M., Dossi, R. C. & Nuñez, A. Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: cortically induced synchronization and brainstem cholinergic suppression. J. Neurosci. 11, 3200–3217 (1991).
85. Crone, J. S., Lutkenhoff, E. S., Bio, B. J., Laureys, S. & Monti, M. M. Testing Proposed Neuronal Models of Effective Connectivity Within the Cortico-basal Ganglia-thalamo-cortical Loop During Loss of Consciousness. Cereb Cortex 27, 2727–2738 (2017).
86. Qiu, M.-H., Vetrivelan, R., Fuller, P. M. & Lu, J. Basal ganglia control of sleep-wake behavior and cortical activation. Eur. J. Neurosci. 31, 499–507 (2010).
87. Chen, M. C. et al. Identification of a direct GABAergic pallidocortical pathway in rodents. Eur J Neurosci 41, 748–759 (2015).
88. Saunders, A. et al. A direct GABAergic output from the basal ganglia to frontal cortex. Nature 521, 85–89 (2015).
89. Mátyás, F. et al. A highly collateralized thalamic cell type with arousal-predicting activity serves as a key hub for graded state transitions in the forebrain. Nature Neuroscience 21, 1551–1562 (2018).
90. Purushothaman, G., Marion, R., Li, K. & Casagrande, V. A. Gating and control of primary visual cortex by pulvinar. Nature Neuroscience 15, 905–912 (2012).
91. Zhou, H., Schafer, R. J. & Desimone, R. Pulvinar-Cortex Interactions in Vision and Attention. Neuron 89, 209–220 (2016).
92. Parker, A. & Gaffan, D. Interaction of frontal and perirhinal cortices in visual object recognition memory in monkeys. Eur. J. Neurosci. 10, 3044–3057 (1998).
93. Bolkan, S. S. et al. Thalamic projections sustain prefrontal activity during working memory maintenance. Nat Neurosci 20, 987–996 (2017).
94. Schiff, N. D. et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 448, 600–603 (2007).

95. Donoghue, J. A. et al. Neural Signatures of Loss of Consciousness and Its Recovery by Thalamic Stimulation. http://biorxiv.org/lookup/doi/10.1101/806687 (2019) doi:10.1101/806687.
96. Liu, J. et al. Frequency-selective control of cortical and subcortical networks by central thalamus. eLife 4, e09215 (2015).
97. Alkire, M. T., Asher, C. D., Franciscus, A. M. & Hahn, E. L. Thalamic microinfusion of antibody to a voltage-gated potassium channel restores consciousness during anesthesia. Anesthesiology 110, 766–773 (2009).
98. Jones, E. G. Synchrony in the Interconnected Circuitry of the Thalamus and Cerebral Cortex. Annals of the New York Academy of Sciences 1157, 10–23 (2009).
99. Cruikshank, S. J. et al. Thalamic Control of Layer 1 Circuits in Prefrontal Cortex. J Neurosci 32, 17813–17823 (2012).
100. Steriade, M., Timofeev, I., Grenier, F. & Dürmüller, N. Role of Thalamic and Cortical Neurons in Augmenting Responses and Self-Sustained Activity: Dual Intracellular Recordings In Vivo. J. Neurosci. 18, 6425–6443 (1998).
101. Castro-Alamancos, M. A. & Connors, B. W. Spatiotemporal properties of short-term plasticity sensorimotor thalamocortical pathways of the rat. J. Neurosci. 16, 2767–2779 (1996).
102. Saalmann, Y. B. Intralaminar and medial thalamic influence on cortical synchrony, information transmission and cognition. Front. Syst. Neurosci. 8, (2014).
103. Jones, E. G. The Thalamus. (Springer Science & Business Media, 2012).
104. Ren, S. et al. The paraventricular thalamus is a critical thalamic area for wakefulness. Science 362, 429–434 (2018).
105. Ward, L. M. The thalamic dynamic core theory of conscious experience. Consciousness and Cognition 20, 464–486 (2011).
106. Jerath, R. & Beveridge, C. Multimodal Integration and Phenomenal Spatiotemporal Binding: A Perspective From the Default Space Theory. Front Integr Neurosci 13, (2019).
107. Crick, F. Function of the thalamic reticular complex: the searchlight hypothesis. Proc Natl Acad Sci U S A 81, 4586–4590 (1984).
108. Edelman, G. M. & Tononi, G. A Universe of Consciousness: How Matter Becomes Imagination. xiii, 274 (Basic Books, New York, NY, US, 2000).
109. Sherman, S. M. & Guillery, R. W. The role of the thalamus in the flow of information to the cortex. Philos Trans R Soc Lond B Biol Sci 357, 1695–1708 (2002).
110. Rovó, Z., Ulbert, I. & Acsády, L. Drivers of the Primate Thalamus. J Neurosci 32, 17894–17908 (2012).
111. Saalmann, Y. B., Pinsk, M. A., Wang, L., Li, X. & Kastner, S. The Pulvinar Regulates Information Transmission Between Cortical Areas Based on Attention Demands. Science 337, 753–756 (2012).
112. Pinault, D. The thalamic reticular nucleus: structure, function and concept. Brain Research Reviews 46, 1–31 (2004).
113. Crabtree, J. W. Intrathalamic sensory connections mediated by the thalamic reticular nucleus. CMLS, Cell. Mol. Life Sci. 56, 683–700 (1999).
114. Wolff, M. & Vann, S. The Cognitive Thalamus as a Gateway to Mental Representations. Journal of Neuroscience 39, 3–14 (2019).
115. Jones, E. G. Viewpoint: the core and matrix of thalamic organization. Neuroscience 85, 331–345 (1998).
116. Smith, A. T., Singh, K. D., Williams, A. L. & Greenlee, M. W. Estimating Receptive Field Size from fMRI Data in Human Striate and Extrastriate Visual Cortex. Cereb Cortex 11, 1182–1190 (2001).
117. Saalmann, Y. B. & Kastner, S. Gain control in the visual thalamus during perception and cognition. Curr Opin Neurobiol 19, 408–414 (2009).
118. Ketz, N. A., Jensen, O. & O'Reilly, R. C. Thalamic pathways underlying prefrontal cortex–medial temporal lobe oscillatory interactions. Trends in Neurosciences 38, 3–12 (2015).
119. Hwang, K., Bertolero, M. A., Liu, W. B. & D'Esposito, M. The Human Thalamus Is an Integrative Hub for Functional Brain Networks. The Journal of Neuroscience 37, 5594–5607 (2017).
120. Tyll, S., Budinger, E. & Noesselt, T. Thalamic influences on multisensory integration. Communicative & Integrative Biology 4, 378–381 (2011).
121. Peräkylä, J. et al. Causal Evidence from Humans for the Role of Mediodorsal Nucleus of the Thalamus in Working Memory. J Cogn Neurosci 29, 2090–2102 (2017).
122. Mitchell, A. S. & Chakraborty, S. What does the mediodorsal thalamus do? Front. Syst. Neurosci. 7, (2013).
123. Pergola, G. et al. The Regulatory Role of the Human Mediodorsal Thalamus. Trends in Cognitive Sciences 22, 1011–1025 (2018).
124. Fiebelkorn, I. C., Pinsk, M. A. & Kastner, S. The mediodorsal pulvinar coordinates the macaque fronto-parietal network during rhythmic spatial attention. Nature Communications 10, 215 (2019).
125. Snow, J. C., Allen, H. A., Rafal, R. D. & Humphreys, G. W. Impaired attentional selection following lesions to human pulvinar: evidence for homology between human and monkey. Proc. Natl. Acad. Sci. U.S.A. 106, 4054–4059 (2009).
126. Petersen, S. E., Robinson, D. L. & Morris, J. D. Contributions of the pulvinar to visual spatial attention. Neuropsychologia 25, 97–105 (1987).
127. Franks, N. P. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nature Reviews Neuroscience 9, 370–386 (2008).
128. Timofeev, I. & Steriade, M. Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats. Journal of Neurophysiology 76, 4152–4168 (1996).
129. Hughes, S. W. et al. Thalamic Gap Junctions Control Local Neuronal Synchrony and Influence Macroscopic Oscillation Amplitude during EEG Alpha Rhythms. Front Psychol 2, (2011).
130. Lőrincz, M. L., Kékesi, K. A., Juhász, G., Crunelli, V. & Hughes, S. W. Temporal Framing of Thalamic Relay-Mode Firing by Phasic Inhibition during the Alpha Rhythm. Neuron 63, 683–696 (2009).
131. Steriade, M. & Deschenes, M. The thalamus as a neuronal oscillator. Brain Research Reviews 8, 1–63 (1984).
132. Silva, L. R., Amitai, Y. & Connors, B. W. Intrinsic oscillations of neocortex generated by layer 5 pyramidal neurons. Science 251, 432–435 (1991).
133. Mejias, J. F., Murray, J. D., Kennedy, H. & Wang, X.-J. Feedforward and feedback frequency-dependent interactions in a large-scale laminar network of the primate cortex. Science Advances 2, e1601335 (2016).
134. Halgren, M. et al. The generation and propagation of the human alpha rhythm. PNAS 116, 23772–23782 (2019).
135. Hughes, S. W. & Crunelli, V. Thalamic Mechanisms of EEG Alpha Rhythms and Their Pathological Implications. Neuroscientist 11, 357–372 (2005).
136. Soplata, A. E. et al. Thalamocortical control of propofol phase-amplitude coupling. PLOS Computational Biology 13, e1005879 (2017).
137. Wang, X.-J. Multiple dynamical modes of thalamic relay neurons: Rhythmic bursting and intermittent phase-locking. Neuroscience 59, 21–31 (1994).
138. De Gennaro, L. & Ferrara, M. Sleep spindles: an overview. Sleep Medicine Reviews 7, 423–440 (2003).
139. Hindriks, R. & van Putten, M. J. A. M. Thalamo-cortical mechanisms underlying changes in amplitude and frequency of human alpha oscillations. Neuroimage 70, 150–163 (2013).
140. Lee, J. H., Whittington, M. A. & Kopell, N. J. Top-Down Beta Rhythms Support Selective Attention via Interlaminar Interaction: A Model. PLOS Computational Biology 9, e1003164 (2013).
141. Robinson, P. A. et al. Prediction of electroencephalographic spectra from neurophysiology. Phys. Rev. E 63, 021903 (2001).

142. Molotchnikoff, S. & Shumikhina, S. The lateral posterior-pulvinar complex modulation of stimulus-dependent oscillations in the cat visual cortex. Vision Res. 36, 2037–2046 (1996).
143. Wróbel, A., Ghazaryan, A., Bekisz, M., Bogdan, W. & Kamiński, J. Two streams of attention-dependent beta activity in the striate recipient zone of cat's lateral posterior-pulvinar complex. J. Neurosci. 27, 2230–2240 (2007).
144. Liu, Z. et al. Finding thalamic BOLD correlates to posterior alpha EEG. Neuroimage 63, 1060–1069 (2012).
145. Fries, P. Rhythms For Cognition: Communication Through Coherence. Neuron 88, 220–235 (2015).
146. Singer, W. Neuronal synchrony: a versatile code for the definition of relations? Neuron 24, 49–65, 111–125 (1999).
147. Quax, S., Jensen, O. & Tiesinga, P. Top-down control of cortical gamma-band communication via pulvinar induced phase shifts in the alpha rhythm. PLOS Computational Biology 13, e1005519 (2017).
148. Klimesch, W. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 16, 606–617 (2012).
149. Parnaudeau, S. et al. Inhibition of Mediodorsal Thalamus Disrupts Thalamofrontal Connectivity and Cognition. Neuron 77, 1151–1162 (2013).
150. Schmitt, L. I. et al. Thalamic amplification of cortical connectivity sustains attentional control. Nature 545, 219–223 (2017).
151. Buschman, T. J., Denovellis, E. L., Diogo, C., Bullock, D. & Miller, E. K. Synchronous Oscillatory Neural Ensembles for Rules in the Prefrontal Cortex. Neuron 76, 838–846 (2012).
152. Singer, W. Distributed processing and temporal codes in neuronal networks. Cogn Neurodyn 3, 189–196 (2009).
153. Bosman, C. A. et al. Attentional stimulus selection through selective synchronization between monkey visual areas. Neuron 75, 875–888 (2012).
154. Palva, S. & Palva, J. M. New vistas for α-frequency band oscillations. Trends in Neurosciences 30, 150–158 (2007).
155. Klimesch, W., Sauseng, P. & Hanslmayr, S. EEG alpha oscillations: The inhibition–timing hypothesis. Brain Research Reviews 53, 63–88 (2007).
156. Canolty, R. T. & Knight, R. T. The functional role of cross-frequency coupling. Trends in Cognitive Sciences 14, 506–515 (2010).
157. Palva, J. M. & Palva, S. Functional integration across oscillation frequencies by cross-frequency phase synchronization. European Journal of Neuroscience 48, 2399–2406 (2018).
158. Hawellek, D. J., Wong, Y. T. & Pesaran, B. Temporal coding of reward-guided choice in the posterior parietal cortex. Proc. Natl. Acad. Sci. U.S.A. 113, 13492–13497 (2016).
159. Palva, J. M., Palva, S. & Kaila, K. Phase Synchrony among Neuronal Oscillations in the Human Cortex. J. Neurosci. 25, 3962–3972 (2005).
160. Akiyama, M., Tero, A., Kawasaki, M., Nishiura, Y. & Yamaguchi, Y. Theta-alpha EEG phase distributions in the frontal area for dissociation of visual and auditory working memory. Scientific Reports 7, 42776 (2017).
161. Siebenhühner, F., Wang, S. H., Palva, J. M. & Palva, S. Cross-frequency synchronization connects networks of fast and slow oscillations during visual working memory maintenance. eLife 5, e13451 (2016).
162. Chaieb, L. et al. Theta-gamma phase-phase coupling during working memory maintenance in the human hippocampus. Cognitive Neuroscience 6, 149–157 (2015).
163. Jirsa, V. & Müller, V. Cross-frequency coupling in real and virtual brain networks. Front. Comput. Neurosci. 7, (2013).
164. Siebenhühner, F. et al. Genuine cross-frequency coupling networks in human resting-state electrophysiological recordings. PLOS Biology 18, e3000685 (2020).
165. Fitzgerald, T. H. B., Valentin, A., Selway, R. & Richardson, M. P. Cross-frequency coupling within and between the human thalamus and neocortex. Front. Hum. Neurosci. 7, (2013).
166. Darvas, F., Miller, K. J., Rao, R. P. N. & Ojemann, J. G. Nonlinear phase-phase cross-frequency coupling mediates communication between distant sites in human neocortex. J. Neurosci. 29, 426–435 (2009).
167. Belluscio, M. A., Mizuseki, K., Schmidt, R., Kempter, R. & Buzsáki, G. Cross-Frequency Phase–Phase Coupling between Theta and Gamma Oscillations in the Hippocampus. J. Neurosci. 32, 423–435 (2012).
168. Colgin, L. L. et al. Frequency of gamma oscillations routes flow of information in the hippocampus. Nature 462, 353–357 (2009).
169. Lisman, J. E. & Idiart, M. A. Storage of 7 +/- 2 short-term memories in oscillatory subcycles. Science 267, 1512–1515 (1995).
170. Lisman, J. E. & Jensen, O. The Theta-Gamma Neural Code. Neuron 77, 1002–1016 (2013).
171. Kamiński, J., Brzezicka, A. & Wróbel, A. Short-term memory capacity (7±2) predicted by theta to gamma cycle length ratio. Neurobiology of Learning and Memory 95, 19–23 (2011).
172. Tort, A. B. L., Komorowski, R. W., Manns, J. R., Kopell, N. J. & Eichenbaum, H. Theta-gamma coupling increases during the learning of item-context associations. Proc. Natl. Acad. Sci. U.S.A. 106, 20942–20947 (2009).
173. Lakatos, P. et al. An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. J. Neurophysiol. 94, 1904–1911 (2005).
174. Magrassi, L. et al. Single unit activities recorded in the thalamus and the overlying parietal cortex of subjects affected by disorders of consciousness. PLOS ONE 13, e0205967 (2018).
175. Malekmohammadi, M., Elias, W. J. & Pouratian, N. Human Thalamus Regulates Cortical Activity via Spatially Specific and Structurally Constrained Phase-Amplitude Coupling. Cereb Cortex 25, 1618–1628 (2015).
176. Staudigl, T. et al. Memory signals from the thalamus: Early thalamocortical phase synchronization entrains gamma oscillations during long-term memory retrieval. Neuropsychologia 50, 3519–3527 (2012).
177. Fiebelkorn, I. C., Saalmann, Y. B. & Kastner, S. Rhythmic Sampling within and between Objects despite Sustained Attention at a Cued Location. Current Biology 23, 2553–2558 (2013).
178. Fiebelkorn, I. C., Pinsk, M. A. & Kastner, S. A Dynamic Interplay within the Frontoparietal Network Underlies Rhythmic Spatial Attention. Neuron 99, 842-853.e8 (2018).
179. Lenartowicz, A. et al. Electroencephalography Correlates of Spatial Working Memory Deficits in Attention-Deficit/Hyperactivity Disorder: Vigilance, Encoding, and Maintenance. J. Neurosci. 34, 1171–1182 (2014).
180. Miller, E. K. & Cohen, J. D. An Integrative Theory of Prefrontal Cortex Function. Annu. Rev. Neurosci. 24, 167–202 (2001).
181. Lenartowicz, A., Mazaheri, A., Jensen, O. & Loo, S. K. Aberrant Modulation of Brain Oscillatory Activity and Attentional Impairment in Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 3, 19–29 (2018).
182. Penfield, W. & Jasper, H. Epilepsy and the Functional Anatomy of the Human Brain. xv, 896 (Little, Brown & Co., Oxford, England, 1954).
183. Adrian, E. D. & Matthews, B. H. C. The interpretation of potential waves in the cortex. The Journal of Physiology 81, 440–471 (1934).

184. Händel, B. F., Haarmeier, T. & Jensen, O. Alpha Oscillations Correlate with the Successful Inhibition of Unattended Stimuli. Journal of Cognitive Neuroscience 23, 2494–2502 (2010).
185. Klimesch, W. EEG-alpha rhythms and memory processes. International Journal of Psychophysiology 26, 319–340 (1997).
186. Haider, B., Duque, A., Hasenstaub, A. R., Yu, Y. & McCormick, D. A. Enhancement of Visual Responsiveness by Spontaneous Local Network Activity In Vivo. Journal of Neurophysiology 97, 4186–4202 (2007).
187. Brookes, M. J. et al. GLM-beamformer method demonstrates stationary field, alpha ERD and gamma ERS co-localisation with fMRI BOLD response in visual cortex. NeuroImage 26, 302–308 (2005).
188. Medendorp, W. P. et al. Oscillatory activity in human parietal and occipital cortex shows hemispheric lateralization and memory effects in a delayed double-step saccade task. Cereb. Cortex 17, 2364–2374 (2007).
189. Sauseng, P. et al. Brain oscillatory substrates of visual short-term memory capacity. Curr. Biol. 19, 1846–1852 (2009).
190. Pfurtscheller, G. Induced Oscillations in the Alpha Band: Functional Meaning. Epilepsia 44, 2–8 (2003).
191. Hanslmayr, S., Gross, J., Klimesch, W. & Shapiro, K. L. The role of alpha oscillations in temporal attention. Brain Research Reviews 67, 331–343 (2011).
192. Zauner, A. et al. Alpha entrainment is responsible for the attentional blink phenomenon. NeuroImage 63, 674–686 (2012).
193. Busch, N. A., Dubois, J. & VanRullen, R. The Phase of Ongoing EEG Oscillations Predicts Visual Perception. J. Neurosci. 29, 7869–7876 (2009).
194. McAlonan, K., Cavanaugh, J. & Wurtz, R. H. Guarding the gateway to cortex with attention in visual thalamus. Nature 456, 391–394 (2008).
195. Wimmer, R. D. et al. Thalamic control of sensory selection in divided attention. Nature 526, 705–709 (2015).
196. Halassa, M. M. et al. State-Dependent Architecture of Thalamic Reticular Subnetworks. Cell 158, 808–821 (2014).
197. Purdon, P. L., Sampson, A., Pavone, K. J. & Brown, E. N. Clinical Electroencephalography for Anesthesiologists Part I: Background and Basic Signatures. Anesthesiology 123, 937–960 (2015).
198. Chennu, S. et al. Spectral Signatures of Reorganised Brain Networks in Disorders of Consciousness. PLOS Computational Biology 10, e1003887 (2014).
199. Miller, K. J., Sorensen, L. B., Ojemann, J. G. & Nijs, M. den. Power-Law Scaling in the Brain Surface Electric Potential. PLOS Computational Biology 5, e1000609 (2009).
200. Freeman, W. J. & Zhai, J. Simulated power spectral density (PSD) of background electrocorticogram (ECoG). Cogn Neurodyn 3, 97–103 (2009).
201. Gao, R., Peterson, E. J. & Voytek, B. Inferring synaptic excitation/inhibition balance from field potentials. Neuroimage 158, 70–78 (2017).
202. Frohlich, J. et al. Emergence of consciousness and complexity amidst diffuse delta rhythms: the paradox of Angelman syndrome. bioRxiv 697862 (2019) doi:10.1101/697862.
203. Wang, K., Steyn-Ross, M. L., Steyn-Ross, D. A., Wilson, M. T. & Sleigh, J. W. EEG slow-wave coherence changes in propofol-induced general anesthesia: experiment and theory. Front. Syst. Neurosci. 8, (2014).
204. Liang, Z. et al. A comparison of different synchronization measures in electroencephalogram during propofol anesthesia. J Clin Monit Comput 30, 451–466 (2016).
205. Llinás, R. R. & Steriade, M. Bursting of thalamic neurons and states of vigilance. J. Neurophysiol. 95, 3297–3308 (2006).
206. Hamidi, M., Slagter, H. A., Tononi, G. & Postle, B. R. Repetitive Transcranial Magnetic Stimulation Affects behavior by Biasing Endogenous Cortical Oscillations. Front Integr Neurosci 3, (2009).
207. Johnson, J. S., Hamidi, M. & Postle, B. R. Using EEG to explore how rTMS produces its effects on behavior. Brain Topogr 22, 281–293 (2010).
208. Llinás, R. R., Ribary, U., Jeanmonod, D., Kronberg, E. & Mitra, P. P. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. PNAS 96, 15222–15227 (1999).
209. Sarnthein, J. & Jeanmonod, D. High thalamocortical theta coherence in patients with neurogenic pain. NeuroImage 39, 1910–1917 (2008).
210. De Ridder, D., Vanneste, S., Langguth, B. & Llinas, R. Thalamocortical Dysrhythmia: A Theoretical Update in Tinnitus. Front. Neurol. 6, (2015).
211. Sarnthein, J. & Jeanmonod, D. High Thalamocortical Theta Coherence in Patients with Parkinson's Disease. J. Neurosci. 27, 124–131 (2007).
212. Llinás, R., Urbano, F. J., Leznik, E., Ramírez, R. R. & van Marle, H. J. F. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci. 28, 325–333 (2005).
213. Hemptinne, C. de et al. Exaggerated phase–amplitude coupling in the primary motor cortex in Parkinson disease. PNAS 110, 4780–4785 (2013).
214. Vanneste, S., Song, J.-J. & De Ridder, D. Thalamocortical dysrhythmia detected by machine learning. Nature Communications 9, 1103 (2018).
215. Sergeant, J. The cognitive-energetic model: an empirical approach to Attention-Deficit Hyperactivity Disorder. Neuroscience & Biobehavioral Reviews 24, 7–12 (2000).
216. Geissler, J., Romanos, M., Hegerl, U. & Hensch, T. Hyperactivity and sensation seeking as autoregulatory attempts to stabilize brain arousal in ADHD and mania? ADHD Atten Def Hyp Disord 6, 159–173 (2014).
217. Snyder, S. M. & Hall, J. R. A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. J Clin Neurophysiol 23, 440–455 (2006).
218. Snyder, S. M. et al. Blinded, multi-center validation of EEG and rating scales in identifying ADHD within a clinical sample. Psychiatry Res 159, 346–358 (2008).
219. Yordanova, J., Kolev, V. & Rothenberger, A. Chapter 18 - Event-related oscillations reflect functional asymmetry in children with attention deficit/hyperactivity disorder. in Supplements to Clinical Neurophysiology (eds Başar, E., Başar-Eroğlu, C., Özerdem, A., Rossini, P. M. & Yener, G. G.) vol. 62 289–301 (Elsevier, 2013).
220. Ivanov, I. et al. Morphological abnormalities of the thalamus in youths with attention deficit hyperactivity disorder. Am J Psychiatry 167, 397–408 (2010).
221. Cesarei, A. D. & Codispoti, M. Affective modulation of the LPP and α-ERD during picture viewing. Psychophysiology 48, 1397–1404 (2011).
222. Balconi, M. & Lucchiari, C. Consciousness and arousal effects on emotional face processing as revealed by brain oscillations. A gamma band analysis. International Journal of Psychophysiology 67, 41–46 (2008).
223. Peng, W., Babiloni, C., Mao, Y. & Hu, Y. Subjective pain perception mediated by alpha rhythms. Biological Psychology 109, 141–150 (2015).
224. Diamond, D. M. Cognitive, Endocrine and Mechanistic Perspectives on Non-Linear Relationships Between Arousal and Brain Function. Nonlinearity Biol Toxicol Med 3, 1–7 (2005).
225. Diamond, D. M., Campbell, A. M., Park, C. R., Halonen, J. & Zoladz, P. R. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson law. Neural Plast. 2007, 60803 (2007).
226. Coy, B., O'Brien, W. H., Tabaczynski, T., Northern, J. & Carels, R. Associations between evaluation anxiety, cognitive interference and performance on working memory tasks. Applied Cognitive Psychology 25, 823–832 (2011).
227. Eysenck, M. W., Derakshan, N., Santos, R. & Calvo, M. G. Anxiety and cognitive performance: Attentional control theory. Emotion 7, 336–353 (2007).
228. Sarason, I. G., Sarason, B. R., Keefe, D. E., Hayes, B. E. & Shearin, E. N. Cognitive interference: Situational determinants and traitlike characteristics. Journal of Personality and Social Psychology 51, 215–226 (1986).

229. Stitt, I., Zhou, Z. C., Radtke-Schuller, S. & Fröhlich, F. Arousal dependent modulation of thalamo-cortical functional interaction. Nat Commun 9, (2018).

230. Marton, T. F., Seifikar, H., Luongo, F. J., Lee, A. T. & Sohal, V. S. Roles of Prefrontal Cortex and Mediodorsal Thalamus in Task Engagement and Behavioral Flexibility. J Neurosci 38, 2569–2578 (2018).

231. Ferguson, B. R. & Gao, W.-J. Thalamic Control of Cognition and Social Behavior Via Regulation of Gamma-Aminobutyric Acidergic Signaling and Excitation/Inhibition Balance in the Medial Prefrontal Cortex. Biol. Psychiatry 83, 657–669 (2018).

232. Rikhye, R. V., Gilra, A. & Halassa, M. M. Thalamic regulation of switching between cortical representations enables cognitive flexibility. Nature Neuroscience 21, 1753–1763 (2018).

233. Parnaudeau, S. et al. Mediodorsal thalamus hypofunction impairs flexible goal-directed behavior. Biol. Psychiatry 77, 445–453 (2015).

234. Marko, M. & Riečanský, I. Sympathetic arousal, but not disturbed executive functioning, mediates the impairment of cognitive flexibility under stress. Cognition 174, 94–102 (2018).

235. Hillier, A., Alexander, J. K. & Beversdorf, D. Q. The Effect of Auditory Stressors on Cognitive Flexibility. Neurocase 12, 228–231 (2006).

236. Alexander, J. K., Hillier, A., Smith, R. M., Tivarus, M. E. & Beversdorf, D. Q. Beta-adrenergic Modulation of Cognitive Flexibility during Stress. Journal of Cognitive Neuroscience 19, 468–478 (2007).

237. Martindale, C. & Greenough, J. The Differential Effect of Increased Arousal on Creative and Intellectual Performance. The Journal of Genetic Psychology 123, 329–335 (1973).

238. Rubia, K. et al. Effects of Stimulants on Brain Function in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis. Biological Psychiatry 76, 616–628 (2014).

239. Brisch, R. et al. The Role of Dopamine in Schizophrenia from a Neurobiological and Evolutionary Perspective: Old Fashioned, but Still in Vogue. Front. Psychiatry 5, (2014).

240. Li, S.-C. & Rieckmann, A. Neuromodulation and aging: implications of aging neuronal gain control on cognition. Current Opinion in Neurobiology 29, 148–158 (2014).

241. Jasper, H. H. & Tessier, J. Acetylcholine Liberation from Cerebral Cortex during Paradoxical (REM) Sleep. Science 172, 601–602 (1971).

242. Aston-Jones, G., Rajkowski, J. & Cohen, J. Role of locus coeruleus in attention and behavioral flexibility. Biol. Psychiatry 46, 1309–1320 (1999).