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Noradrenergic modulation of rhythmic neural activity shapes selective attention

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During moments involving selective attention, the thalamus orchestrates the preferential processing of prioritized information by coordinating rhythmic neural activity within a distributed frontoparietal network. The timed release of neuromodulators from subcortical structures dynamically sculpts neural synchronization in thalamocortical networks to meet current attentional demands. In particular, noradrenaline modulates the balance of cortical excitation and inhibition, as reflected by thalamocortical alpha synchronization (~8–12 Hz). These neuromodulatory adjustments facilitate the selective processing of prioritized information. Thus, by disrupting effective rhythmic coordination in attention networks, age-related locus coeruleus (LC) degeneration can impair higher levels of neural processing. In sum, findings across different levels of analysis and modalities shed light on how the noradrenergic modulation of neural synchronization helps to shape selective attention.

Neuromodulation sculpts neural synchronization in attention networks

Daily life confronts us with a multitude of sensations that far exceeds neural processing resources. It thus poses a complex computational problem: What aspects of the environment are most relevant for current and future goal-directed actions and how can these be selected for further analysis [1]? A distributed network, including frontal and parietal cortical structures, supports the preferential processing of relevant information [2]. The thalamus orchestrates communication within this network via a transient synchronization of its **rhythmic neural activity** (see Glossary) [3,4], while **neuromodulators** tune synchronization in thalamocortical networks to correspond with current demands [5–11]. However, while evidence about the roles of neuromodulation and neural synchronization in the selective processing of prioritized information is accumulating, their interactions are often overlooked. Bridging levels of analysis, in this article we synthesize animal and human research indicating that neuromodulation supports **selective attention** by dynamically sculpting patterns of thalamocortical synchronization.

Rhythmic neural activity coordinates information processing in distributed cortical networks [2–4]. A thalamic pathway mediates frontoparietal modulations of **alpha activity** (~8–12 Hz) [12] that promote flexible information gating by temporarily disengaging task-irrelevant brain regions [13,14]. Note that functional equivalents of the primate alpha rhythm may manifest at lower frequencies in rodents [15,16]. Selective information processing in frontoparietal networks moreover depends on the timed release of neuromodulators from subcortical structures [8,17–21]. This opinion article focuses specifically on noradrenergic neuromodulation based on recent methodological advancements that open the door for noninvasive assessments (Box 1). A transient activation of the noradrenergic system increases the signal-to-noise ratio of currently relevant representations and biases the competition for processing resources across levels of the cortical hierarchy [22,23]. Recent studies indicate that activation within the **locus**

Highlights

Neural synchronization, particularly in the alpha frequency band (~8–12 Hz), supports routing prioritized information through thalamocortical attention networks.

The noradrenergic locus coeruleus (LC) has long been regarded as the nexus of a global arousal system, unable to innervate attention-relevant specific cortical networks. Recent evidence reveals a more specialized neuromodulatory system, which biases processing in thalamocortical circuits according to attentional demands.

Transient LC activations facilitate the selective processing of relevant information by flexibly adjusting local cortical excitability via thalamocortical alpha synchronization.

However, with advancing age, the LC harbors toxins and Alzheimer's-related tau precursors, making it susceptible to neurodegeneration, which may disrupt synchronization in the aging brain.

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coeruleus–noradrenaline (LC–NA) system translates into dynamic changes in alpha synchronization on a neural network level, presumably mediated via a thalamic mechanism [5–7,9,10,24,25] (Figure 1, Key figure). Thus, noradrenergic neuromodulation may act as a dynamic switch to modulate the sensitivity of cortical networks for processing high-priority inputs. In the following, we first summarize recent research on noradrenergic neuromodulation and neural synchronization before proposing how the noradrenergic modulation of rhythmic neural activity shapes attention.

Noradrenergic neuromodulation supports selective attention

In humans, noradrenergic cells cluster in distinct, pigmented nuclei in the brainstem. The largest of these is the LC, with a length of about 15 mm located adjacent to the fourth ventricle [26]. The LC receives afferent input from several subcortical structures and, crucially, the prefrontal cortex [27–29]. The LC thus integrates information from evolutionarily conserved regions controlling autonomic functions and arousal as well as phylogenetically younger areas implicated in higher-order cognition [30]. Via an ascending pathway, the LC in turn provides noradrenergic innervation for the thalamus and almost all areas of neocortex [25,29–31]. This connectivity pattern grants prefrontal regions a top-down regulatory influence on noradrenergic neuromodulation with its pronounced effect on thalamic and forebrain functioning [9,10,27,28,32].

A new look at the blue spot: more than diffuse arousal

Researchers had characterized the LC as a homogenous structure that uniformly broadcasts noradrenaline throughout the entire cortex via diffuse and highly arborized projections [33]. Importantly, such an arrangement would argue against a noradrenergic role in selective attention, which requires a spatially highly specific innervation of cortical networks [21] as well as differential innervation of representations that are the focus of attention versus those that should be ignored [22]. However, recent evidence indicates a more differentiated structural and functional organization of the LC [17,28,29,34–36]. For instance, a recent study [34] demonstrated that functionally distinct LC populations with connections to the amygdala and prefrontal cortex are involved in the acquisition and extinction of fear memories, respectively (see [17] for similar observations regarding attention). In addition, contrary to earlier assumptions of a synchronous activation of all LC cells [32], multiple distinct LC ensembles (i.e., subsets of synchronized LC neurons) were identified with the potential for a more targeted noradrenergic modulation [35]. Together with reports of a direct noradrenergic modulation of thalamic processing [31,37], these findings suggest an anatomically and functionally specialized neuromodulatory system that may be ideally suited to bias processing in thalamocortical networks corresponding to attentional demands [31,33].

Noradrenaline biases processing towards prioritized representations

Noradrenergic neuromodulation influences selective attention via several mechanisms: first, LC activity is associated with the transition to, and the maintenance of, a vigilant behavioral state [23,38] that allows for the optimal processing of sensory information [39]. More specifically, transient (**phasic**) LC activations – in response to salient stimuli or recruited via top-down mechanisms [27,32] – are associated with rapid attention allocation and are essential for the signaling of sensory inputs [8,10,19]. Reliable phasic LC responses are observed against the backdrop of an ongoing (**tonic**) firing rhythm, whereby too low or high tonic LC firing is linked to drowsiness and stress, respectively (i.e., an inverted U-shaped association [38,40,41]). Second, in the prefrontal cortex, noradrenaline acts on α_{2A} -**adrenoceptors** to boost activity in attention networks [17,42,43]. Specifically, noradrenaline increases persistent firing in prefrontal circuits that code task-relevant information in the absence of external stimulation, a neural correlate of attention and working memory [42]. In line with this, α_{2A} -**agonists** have been applied to ameliorate senescent attention deficits in aged monkeys, hinting at noradrenergic neurodegeneration with

Glossary

Adrenoceptor: binding site for noradrenaline and noradrenergic drugs. The pre- and postsynaptically located α_2 -receptors mediate inhibition, whereas the postsynaptic α_1 - and β -adrenoceptors typically have excitatory effects.

Affinity: a receptor's affinity indicates what concentration of the ligand (e.g., noradrenaline) is sufficient to trigger a physiological response. α_2 -Adrenoceptors have the highest affinity for noradrenaline, followed by moderate-affinity α_1 - and low-affinity β -adrenoceptors.

Agonist: chemical that imitates the action of noradrenaline at adrenoceptors.

Alpha activity: rhythmic neural activity between 8 and 12 Hz, constitutes the dominant rhythm in the waking state that can noninvasively be recorded using electroencephalography (EEG) and magnetoencephalography.

Antagonist: chemical that blocks the action of noradrenaline at adrenoceptors.

Ascending neuromodulatory system: (ascending reticular activating system); a group of subcortical neuromodulatory nuclei that sends ascending tracts to the thalamus and cortex and has an activating influence on behavioral and cortical states.

Burst activity: when thalamic cells fire in a burst mode, the cortical EEG is synchronized. Neuromodulators like noradrenaline can shift thalamic cells to a single-spike, or transfer, mode of neuronal firing, which is associated with a desynchronized EEG.

Contralateral: on the opposite side. The left visual field, for instance, is processed in the contralateral, right, hemisphere.

Ipsilateral: on the same side (also see contralateral).

Locus coeruleus–noradrenaline (LC–NA) system: the locus coeruleus, Latin for the blue spot, is the largest cluster of noradrenergic cells in the human brain. In the locus coeruleus, noradrenaline is synthesized from dopamine (by dopamine beta-hydroxylase) and then released via widespread axons throughout the brain.

Neuromodulator: the main neuromodulators (serotonin, acetylcholine, dopamine, and noradrenaline) are released via diffuse projections from subcortical cell clusters

(nuclei). In target neurons, neuromodulators modify cellular properties and the effectiveness of their synaptic transmission.

Phasic: brief, burst-like firing pattern of noradrenergic neurons elicited in response to salient (e.g., aversive) stimuli or recruited internally via top-down mechanisms to support processing in the forebrain.

Rhythmic neural activity: also called neural oscillations or brainwaves, reflects the spatial summation (i.e., ensemble activity) of rhythmic postsynaptic potentials originating from apical dendrites.

Selective attention: the preferential processing of relevant information by enhancing the neural processing of prioritized stimuli while at the same time suppressing irrelevant stimuli.

Tonic: locus coeruleus cells fire in a state-dependent, slow (0.5–5 Hz) rhythm with the highest discharge during active wakefulness, followed by drowsy, inattentive states, slow-wave sleep, and, finally, minimal activity during rapid-eye-movement sleep.

advancing age (Box 2) [43] (but see [44]). Third, in sensory cortices, noradrenaline enhances the selective processing of currently relevant representations, probably in interaction with local glutamate levels [22,45]. Seminal work in monkeys found that noradrenaline application to the auditory cortex preceding sensory stimulation decreased the rate of spontaneous firing while mostly sparing stimulus-evoked responses (i.e., increased signal-to-noise ratios [46]). More recently, LC activation paired with auditory stimulation in rats was shown to induce long-lasting increases in tone-evoked neural responses [47]. In addition, in the same study LC activation led to stimulus-evoked activity in previously unresponsive auditory cortex neurons and improved perceptual detection abilities [47]. Crucially, recent evidence indicates that a noradrenergic modulation of thalamic information transmission may play a prominent role in the LC amplification of sensory processing [31,37]. Finally, on a network level, phasic LC activity has been conceptualized as a circuit breaker that interrupts ongoing processing in the dorsal attention network and supports the reorienting of attention, mediated via activation of the ventral attention network [48,49].

These lines of evidence indicate that noradrenergic neuromodulation biases neural information processing towards prioritized representations at multiple brain sites, including the thalamus and cortical regions. Although its effect varies across release and binding sites as well as LC firing modes (i.e., tonic or phasic), noradrenaline generally increases signal-to-noise ratios of salient or prioritized stimuli and thereby supports attention [21–23,50]. On a neural ensemble level, noradrenaline release is closely linked to changes in neural activity [5,10,24,25] within frequency bands that play a prominent role in selective attention.

Modulations of alpha-oscillatory activity support selective attention

Neural synchronization provides a mechanism for routing prioritized information through thalamocortical networks [3,4]. A long line of research implicates the most prominent oscillation in the waking state, the alpha rhythm, in attention [13,14]. Lesion studies suggest the thalamus as a pacemaker of the alpha rhythm [15,51,52]. However, intracranial recordings in primates also point to cortical generators in the parietal and occipital lobes [53–55]. Most likely, the alpha rhythm constitutes a complex product of thalamic and cortical generators, regions that are densely linked via reciprocal connections [4,15,51,55].

Alpha desynchronization: a domain-general attentional selection mechanism

Functionally, alpha oscillations are conceptualized as frontoparietal-mediated inhibition that temporarily disengages task-irrelevant brain regions and thus distributes processing resources to support selective attention [2,52,56]. This interpretation is based on the observation that shifts of attention – for instance, to a cued location of a visual display in a spatial orientation task – reliably decrease alpha activity in regions processing the attended space. By contrast, brain areas that code for the visual space occupied by distractors typically exhibit increased alpha-rhythmic activity [57,58]. Such attention-related, spatially targeted patterns of alpha modulation have commonly been investigated in the visual domain. However, they are also evident in somatosensory and auditory paradigms, suggesting a domain-general selection mechanism [59,60]. Please note that our discussions mainly concern within-region alpha modulations, for a discussion of inter-regional alpha dynamics, see [61].

Underlining their functional relevance, event-related increases (synchronization) and decreases (desynchronization) of alpha-rhythmic activity in distractor- and target-coding brain regions have been associated with attention performance on a single-trial level [62,63]. Moreover, several studies suggest that attention-related modulations of alpha rhythms may provide a causal mechanism for the flexible selection of relevant information [64–66] (reviewed in [56]). For instance, using rhythmic transcranial magnetic stimulation to alter synchronization in the visual

Key figure

Locus coeruleus–noradrenergic neuromodulation shapes patterns of thalamocortical synchronization during attention

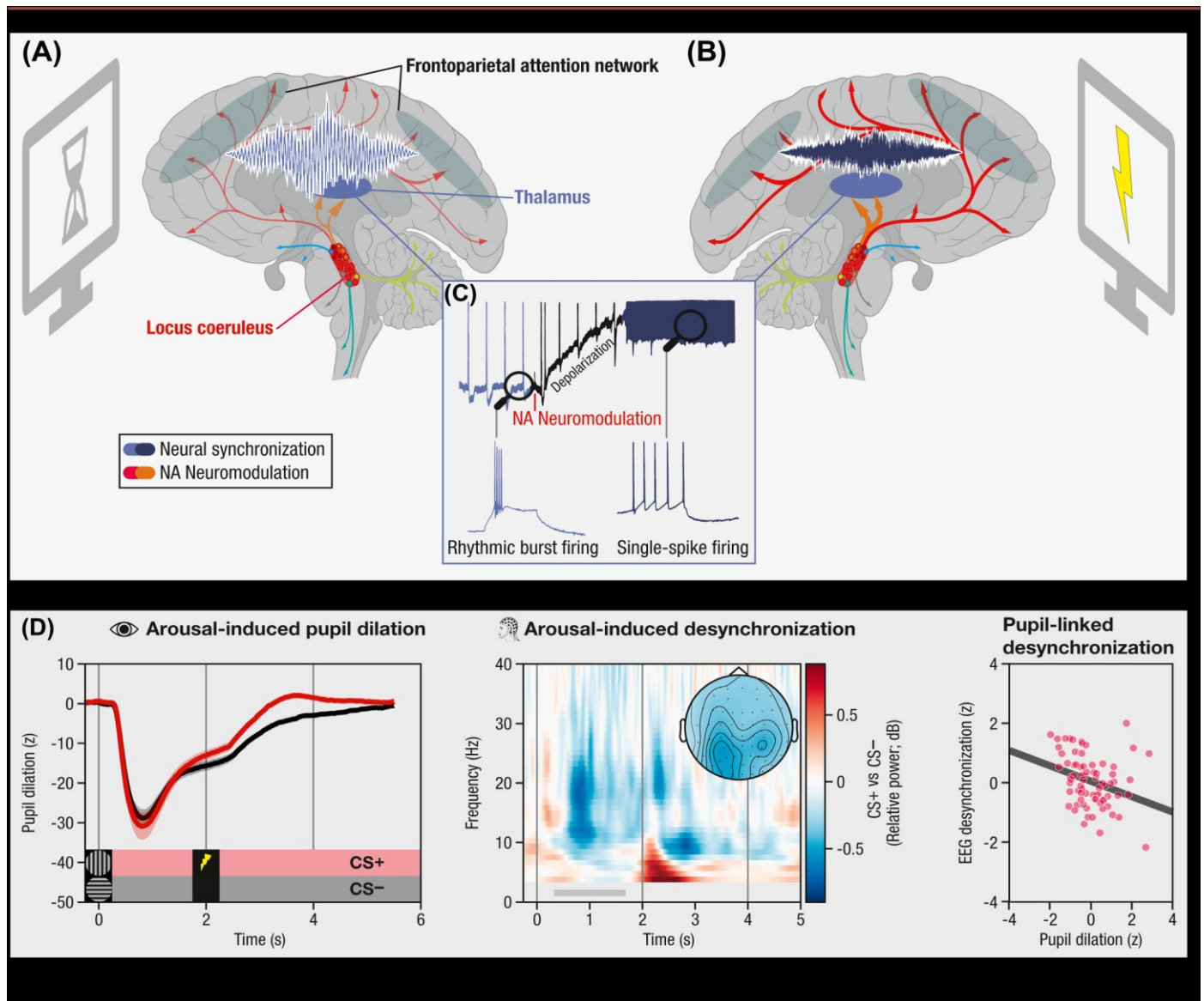
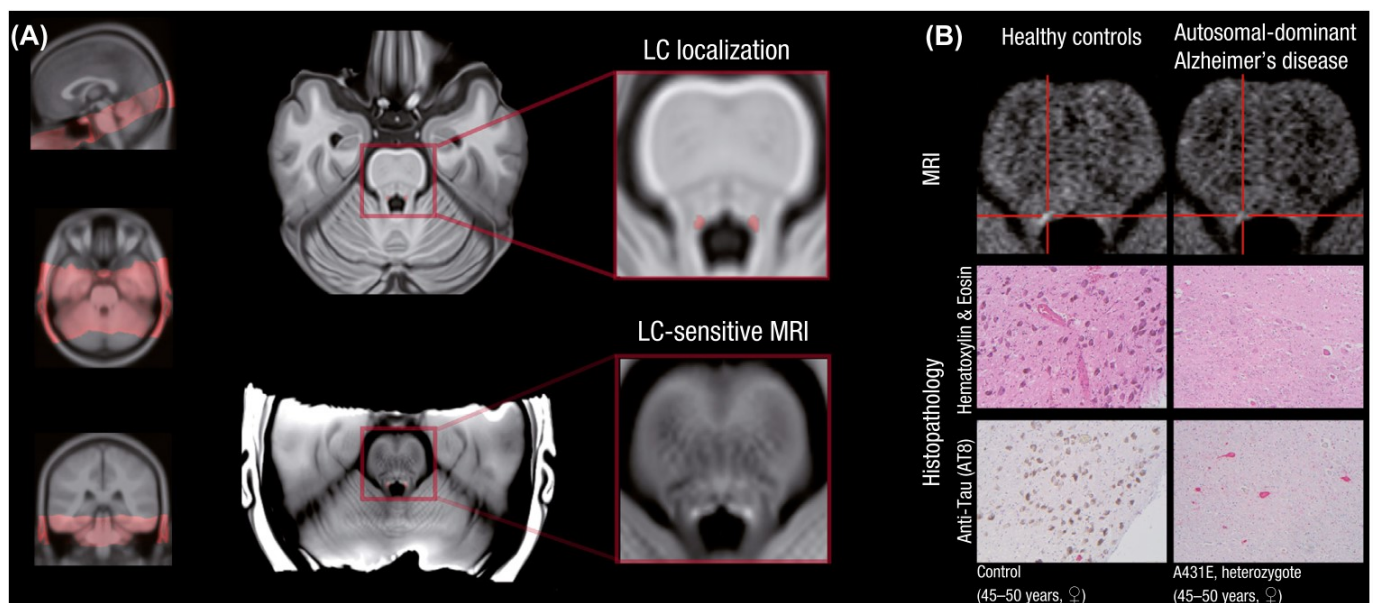


Figure 1. (A) Anatomically and functionally defined locus coeruleus ensembles innervate different cortical and subcortical targets [see colored cells/projections (circles/arrows)], including the thalamus and frontoparietal network (blue; gray). During inattentiveness, low noradrenaline (NA) levels are linked to rhythmic burst firing in thalamic alpha generators (see C). Alpha-rhythmic activity (~8–12 Hz) in thalamocortical attention networks indicates a state of relative inhibition [see high-amplitude, low-frequency oscillation (light blue)]. (B) Behaviorally relevant events elicit a transient increase in locus coeruleus activity. Elevated NA levels modulate cortical synchronization by shifting thalamic pacemakers from a rhythmic firing pattern to a mode of activity that allows for reliable information transfer (single-spike firing; see C). Neural activity in thalamocortical attention networks is desynchronized (dark blue), supporting the processing of attended stimuli. (C) NA depolarizes thalamic neurons and abolishes the rhythmic burst firing that is linked to thalamocortical alpha rhythms (reproduced, with permission, from [9]). (D) Pupil-indexed noradrenergic neuromodulation is related to cortical low-frequency desynchronization. (Left) Compared with perceptually matched control stimuli (CS–), fear-conditioned stimuli (CS+) elicit a transient pupil dilation, a marker of locus coeruleus activity (Box 1). (Middle) Concurrent electroencephalography recordings reveal an arousal-related alpha-beta desynchronization at posterior electrodes [topography shows averaged activity between 0.5–1.5 s and 8–20 Hz (gray horizontal bar)]. (Right) Larger pupil dilation is associated with more alpha-beta desynchronization (i.e., more negative values), indicating an association between proxies of noradrenergic neuromodulation and cortical synchronization (reproduced, with permission, from [7]). Credits: sagittal brain section, adapted from Patrick J. Lynch under a Creative Commons Attribution 2.5 License 2006.

Box 1. Novel noninvasive proxies reflecting noradrenergic neuromodulation

Technical challenges in reliably targeting the small brainstem nucleus have long impeded in-vivo research exploring LC's effects on attention in humans [105,106]. However, using recently developed magnetic resonance (MR) sequences [107–111], an elevated signal or hyperintensity can be observed bordering the fourth ventricle (Figure I). Applying a combination of MRI and histology of human postmortem samples, a recent study investigated whether this hyperintensity is an indicator for LC integrity (i.e., a proxy for cell density) [107]. Excitingly, the hyperintensities detected on LC-MRI scans indeed closely matched the location of noradrenergic cells that contained neuromelanin, as confirmed by subsequent histology [107] (cf. [112]). The dark, insoluble pigment neuromelanin is a by-product of catecholamine synthesis and thus accumulates in the LC across the lifespan [113]. Within LC cells, neuromelanin scavenges metals and, as a compound, produces paramagnetic effects [114]. Therefore, neuromelanin–metal compounds may serve as endogenous contrast agent that allows the noninvasive assessment of LC integrity using MRI [114]. Nevertheless, unraveling the precise contrast mechanisms underlying LC-MRI is an active area of research [109,111]. Recent findings of elevated MR contrast in rodents naturally lacking neuromelanin suggest LC's high water content and abundance of metal ions as sources of the hyperintensity [110]. Irrespective of the precise contrast mechanisms, transgenic mice with a ~70% reduction of noradrenergic neurons lack the elevated LC-MRI signal evident in wild-type mice, indicating noradrenergic cells as a source of the hyperintensity [110]. Lower LC-MRI contrast has consistently been reported in diseases associated with noradrenergic neurodegeneration, like Alzheimer's [109,111,115].

In addition to structural measures, studies in rodents and primates established luminance-independent pupil changes as a proxy for noradrenergic activity [28,40,41,98,116–118]. Pupil dilation reflects the interaction of two opposing muscles: the dilator and sphincter pupillae, innervated by the sympathetic and parasympathetic nervous systems, respectively. Critically, the LC functions as a premotor nucleus for both, by stimulating/inhibiting sympathetic and parasympathetic preganglionic neurons, respectively [119]. Indeed, optogenetic activation of the LC caused the pupil to dilate, whereas inhibition reliably constricted the pupil [28,41]. In combination with studies that demonstrated LC spiking and noradrenergic axon activity before pupil dilations [98,116], this suggests that pupil dilation may serve as a moment-to-moment index of noradrenergic activity [117]. However, cholinergic and serotonergic influences on pupil dilation have also been reported [98,120] and further research is needed to disentangle their relative contributions. Taken together, LC-MRI and pupil dilation are valuable noninvasive tools to advance our understanding of the noradrenergic system across species.



Trends in Cognitive Sciences

Figure I. Locus coeruleus magnetic resonance imaging (LC-MRI) in healthy aging and neurodegenerative disease.

(A) Orientation of a typical LC-sensitive sequence covering the brainstem (left). The localization of the LC, bordering the fourth ventricle, is highlighted in red on an axial slice of standard anatomical scan (middle, upper panel). In LC-MRI, the LC can be detected as a cluster of bright, hyperintense voxels (middle, lower panel) (reproduced, with permission, from [122]). (B) In neurodegenerative diseases, noradrenergic cells decline. Lower in-vivo LC-MRI contrast in autosomal-dominant Alzheimer's disease (upper panel) corresponds to noradrenergic neurodegeneration in participants who died with the same disease-causing mutation (A431E). In particular, hematoxylin and eosin (H&E) staining reveals LC depigmentation (i.e., absence of the dark, granular neuromelanin). In addition, immunostained slides with anti-tau (AT8) show neurofibrillary tangles within noradrenergic neurons, as well as the presence of tau positive threads (red) (reproduced, with permission, from [115,122]).

cortex revealed a frequency- and spatially-specific modulation of perception [64]. Stimulation within the alpha, but not other control frequencies, impaired performance **contralateral** to the stimulated hemisphere, while increasing **ipsilateral** target detection. Hence, artificially increasing synchronization of alpha-rhythmic activity biased attention away from the visual space processed by the stimulated brain site [1,64]. In a recent neurofeedback training study, participants learned

Box 2. Age-related changes in noradrenergic neuromodulation

Recent cross-sectional investigations of large lifespan samples report a decline in LC-MRI signal, a proxy for noradrenergic cell density, starting around 60 years of age [121–123]. For instance, in over 600 participants (18–88 years), a negative quadratic relationship between age and LC-MRI contrast was detected, compatible with a loss of noradrenergic cells in later life [121]. Additionally, in-vivo positron emission tomography (PET) imaging revealed a lower availability of the noradrenergic transporter in later life, prominently in the thalamus [106]. Taken together, the available evidence suggests that aging impairs the noradrenergic system at multiple points (i.e., LC cell bodies, LC terminal regions) resulting in less reliable noradrenergic neuromodulation in later life (but see [124] for a discussion).

Recent theories of cognitive aging posit a high susceptibility of LC neurons to neurodegeneration, presumably resulting from their exposure to natural stressors [124,125]. For instance, the anatomical location of the LC adjacent to the ventricular system and its widespread, unmyelinated axons expose it to toxins from cerebrospinal fluid and blood circulation [124–126]. Neuromelanin accumulating in the LC may become toxic. While neuromelanin initially traps free metals and thus counters their toxicity, when a cell dies it releases its accumulated neuromelanin, potentially accelerating neuronal decline [113]. Further, the LC's constant, tonic firing rhythm produces a high bioenergetic demand associated with an increased risk of oxidative stress and subsequent cell damage [124–126]. Analyses of postmortem samples moreover identified the LC as one of the first brain sites in which abnormally phosphorylated tau proteins accumulate, a hallmark of age-related neurodegenerative diseases, like Alzheimer's [127,128]. Tau burden in the LC linearly increases with Alzheimer's disease progression and is associated with LC shrinkage, already at presymptomatic stages of the disease [111,128]. Besides its influence on cognitive processing [23,50], noradrenergic neuromodulation subserves critical neuroprotective functions (e.g., anti-inflammatory effects mediated via action on β -adrenoceptors on microglia) [124,126] and thus a loss of LC cells may exacerbate the progression of age-related neurodegenerative diseases [124].

In sum, due to its exposure to various physiological stressors (e.g., toxins, oxidative stress, and aberrant tau) the LC shows a high vulnerability for age-related neurodegeneration with probably deleterious consequences for late-life cognitive abilities. Following this notion, a growing number of in-vivo [122,129–132] and postmortem [133] studies demonstrate the importance of LC integrity for the maintenance of cognitive performance in aging.

to manipulate alpha synchronization in left relative to right parietal areas [65]. The training-induced shift in alpha rhythms led to a corresponding alteration in visually evoked responses during the training as well as a change in alpha asymmetry after training. Importantly, interindividual differences in alpha asymmetry were associated with a sustained modulation of attention [65], underlining the functional relevance of alpha rhythms [65,67]. Notably, artificially reinstating alpha synchronization in distractor-processing brain regions may aid older adults in overcoming their attentional deficits [66] (Box 3).

However, several recent studies indicate that attention-related alpha modulations may not be associated with markers of early sensory gain control [68–70]. This suggests that early sensory gain control and alpha-rhythmic inhibition may represent complementary mechanisms of selective attention [70,71]. Subsequent localizations of cortical alpha activity close to the parietal lobe suggest that, upstream of early sensory processing, alpha synchronization may help gate information flow through thalamocortical networks [13,56,71].

Taken together, while alpha activity likely constitutes one among several mechanisms, attention-related alpha modulation consistently emerges as a domain-general, behaviorally relevant mechanism for the selective processing of relevant information. But how do alpha modulations help shape attention?

Routing prioritized information via alpha-mediated inhibition

First, desynchronization of alpha-rhythmic activity may facilitate the firing of neuronal ensembles coding selected stimuli by releasing these ensembles from inhibition [13,60]. Thereby, decreases in alpha activity dynamically regulate the windows for processing and facilitate the timed expression of a neural code necessary for the representation of prioritized information [72]. In particular, within an alpha oscillation, inhibitory and excitatory phases alternate in a cyclic succession indicated by the peaks and troughs of the oscillation [13,14]. Local increases in alpha amplitude

Box 3. Noradrenergic neurodegeneration may disrupt rhythmic coordination within the aging brain

With age, brain structure and function change, resulting in declining attention [70,104]. Such cases of non-optimal performance can shed light on the dynamics of complex systems [134]. In particular, changes in neuromodulation have been identified as crucial determinants of aging cognition [124,135]. However, age differences in the modulation of neural rhythms are also linked to cognitive decline.

With advancing age, alpha rhythms occur less often and, when they do, have diminished amplitudes and lower peak frequencies [103,136]. In addition, older adults show differential alpha modulations during attention tasks [62,137–140]. For example, older compared with younger adults show a delayed and diminished alpha synchronization for task-irrelevant stimuli, which suggests a less reliable attentional filter [62,141,142]. Accumulating evidence links age-related changes in alpha dynamics and cognitive decline [62,138–140,143]. However, a recent study showed comparable attentional alpha modulations in middle-aged and older adults, which did not influence behavior [70]. Taken together, inhibitory processes, as expressed by alpha modulations, may operate less reliably in older adults, at least at high levels of task difficulty [143,144].

Integrating neuromodulatory and oscillatory changes, in this opinion article we propose a hypothetical link bridging levels of analysis [135]: noradrenergic neurodegeneration (Box 2) may lead to age-related neuronal loss in the LC [121,122]. As a consequence, older adults may be less able to recruit noradrenergic neuromodulation to bias information processing according to current goals [21,22]. Neural synchronization in thalamocortical networks is dynamically modulated via noradrenergic inputs [9,10,24,31]. Hence, age-related impairments in modulating alpha synchronization to selectively gate relevant information may partly reflect diminishing noradrenergic drive [5–7].

This proposal is compatible with the notion that a shortage of neuromodulators in aging and disease impairs thalamic alpha generation [103]. Initial empirical support comes from a study that recorded cortical electroencephalogram (EEG) activity during participants' lifetime and subsequent postmortem concentrations of neuromodulators in the thalamus of Alzheimer's patients and controls [145]. Compared with controls, Alzheimer's patients' specimens showed lower noradrenaline levels in the thalamus [145] (Box 2). Among patients, cortical alpha rhythms were linked to cognition and, importantly, thalamic noradrenaline levels, while other neuromodulators showed no reliable association [145]. Finally, another investigation in healthy older adults approximated noradrenergic responsiveness using pupil dilation and EEG desynchronization and revealed an association with attentional performance as well as a decline in later life [7]. While several questions remain to be answered, we propose that age-related noradrenergic decline disrupts the rhythmic coordination in thalamocortical networks necessary for attention.

during the inhibitory up-phases elevate neural response thresholds, resulting in a reduced likelihood of action potential initiation [60]. Massed neural firing is therefore more likely during release from inhibition during the down-phases of the corresponding alpha cycle [3,6,73,74]. With increasing alpha amplitude, the duty cycle for neuronal processing becomes shorter [13], whereas decreases in alpha activity allow for longer processing windows (i.e., wider troughs). On an information-theoretical level, synchronization of alpha rhythms increases the redundancy of neuronal firing and thereby reduces the information carried in the transmitted neural code [72]. Desynchronization of low-frequency activity, in turn, enhances the information-coding capacity of neural ensembles representing prioritized stimuli [72,75]. In sum, by adjusting excitation and inhibition in thalamocortical networks, dynamic modulations of alpha-oscillatory activity support the selective processing of attended stimuli.

While the previous sections separately outlined how noradrenergic and alpha-oscillatory mechanisms support selectivity, there are indications they interact [5–7]. Such interactions were envisioned by Steriade and colleagues [76] almost 30 years ago: 'Neuromodulatory systems are capable of shifting thalamocortical networks between different oscillatory states. Synchrony and other network properties could be exploited for controlling the flow of information between brain areas and for deciding where to store important information.' Excitingly, the tools to explore neuromodulatory influences on thalamocortical synchronization during attention have become increasingly available (Box 1).

Spontaneous alpha oscillations are under tonic noradrenergic control

The degree of cortical synchronization fluctuates across behavioral states. Strongly synchronized cortical regimes reflect reduced vigilance and slow-wave sleep [51], whereas desynchronized modes of activity reflect alert wakefulness [45]. Rhythmic firing in the LC shows an inverse,

state-dependent pattern with the rate of tonic discharge increasing from sleep to active wakefulness [38,41]. Importantly, these two patterns are linked, as activation of the LC (and related **ascending neuromodulatory systems**) abolishes rhythmic firing in the thalamus and thereby modulates cortical synchronization [9,25,31,76].

Seminal studies [77,78] investigated the effect of pharmacological noradrenaline blockade and selective lesions in the ascending noradrenergic tract on alpha-rhythmic activity in sensory cortices in awake cats. After suppressing noradrenergic neuromodulation, alpha activity showed a marked increase, suggesting an inhibitory effect of the LC on thalamocortical alpha generators [77,78]. Suppressing noradrenaline also made the cats stand motionless. Without the ability to modulate cortical synchronization their behavior had become detached from the environment [79]. Further investigations [25] extended these findings by revealing a dual effect of noradrenergic drugs on cortical synchronization in awake rats: while α_1 -**antagonists** and α_2 -agonists promoted synchronization at around 8 Hz in a dose-dependent manner, α_2 -antagonists reduced synchronization and were associated with increased behavioral activation. Whereas α_1 receptors are often excitatory, α_2 -agonists tend to be inhibitory. These observations, together with the fact that α_1 receptors require more noradrenaline to activate than do α_2 receptors [80], suggest that the release of large amounts of noradrenaline elicits cortical desynchronization, mediated via thalamic α_1 -adrenoceptors, and allows for reliable thalamocortical information transfer [9,76]. Low noradrenaline levels during states of inattentiveness in turn are presumed to promote synchronization via action on α_2 -adrenoceptors in line with their higher **affinity** for noradrenaline [25].

Mechanistically, via depolarization of the membrane potential, noradrenaline suppresses rhythmic **burst activity** in thalamic neurons and promotes a mode of neural activity that allows for more precise information transfer [9,76,81] (Figure 1). Note that rhythmic firing within the thalamus is crucially implicated in the generation of alpha rhythms [51,52]. Hence, tonic noradrenergic innervation of the thalamus promotes cortical desynchronization. Accordingly, in two recent studies in rats, tonic LC activation abolished thalamic burst firing [31,37] (also see [82]). This noradrenergic modulation enhanced the information transmitted in the thalamic firing and improved perceptual sensitivity. Control experiments revealed that noradrenaline's action on thalamic α_1 -adrenoceptors enhanced information transmission irrespective of sensory and cortical influences [31]. Taken together, initial invasive animal studies demonstrate a direct modulation of ongoing alpha oscillations by tonic changes in noradrenergic neuromodulatory drive.

Tonic noradrenergic neuromodulation shapes cortical and behavioral states: new animal studies of an old mechanism

Corroborating earlier observations, optogenetic LC activation in rodents reduced low-frequency electroencephalogram (EEG) synchronization (<10 Hz) and stimulated transitions towards more activated behavioral states (e.g., sleep-to-wake transitions, locomotion) [38,41,83]. Spontaneous fluctuations in pupil-indexed noradrenergic tone (Box 1) also covary with thalamic bursting [82] and cortical activity in awake mice [39]. Specifically, constricted pupils, as observed during periods of drowsiness or inattentiveness, were associated with increased bursting and cortical low-frequency (<10 Hz) fluctuations. By contrast, with greater pupil diameters, suggestive of stronger noradrenergic drive, there was a shift towards increased activity at higher frequencies (50–100 Hz; [39]). The mice in this study additionally completed a challenging auditory detection task. Optimal performance occurred at intermediate pupil dilation, in line with an inverted U-shaped relationship between tonic noradrenaline levels and performance [32,39] (for investigations in humans, see [84]). Intermediate noradrenaline levels thus appear to promote more reliable processing of sensory stimuli in thalamocortical circuits via low-frequency desynchronization [39].

A recent animal study set out to explicitly test how pupil-indexed neuromodulation shapes patterns of thalamocortical communication [5]. In states of low noradrenergic tone, indicated by constricted pupils, synchronization between the thalamus and parietal cortex was governed by the alpha frequency. By contrast, pupil dilation was associated with alpha desynchronization and increased high-frequency oscillations (>30 Hz) [5]. On a behavioral level, in periods of thalamocortical alpha synchronization, animals engaged less with their environment, indicating that neuromodulatory inputs allow dynamic switching between behavioral states [3,5,9].

Noninvasive tools indicate tonic noradrenergic influences on alpha rhythms in humans

Direct investigations of noradrenergic influences on cortical and behavioral states in humans are scarce [84–89]. However, a noninvasive brain stimulation technique known to increase LC discharge (vagus nerve stimulation [90,91]) robustly increased pupil dilation and diminished alpha oscillations [87]. This complements a recent investigation in rats demonstrating that vagus nerve stimulation abolished rhythmic burst firing and improved information transmission in the thalamus [37]. Notably, vagus nerve stimulation-induced modulations of thalamic firing were similar to those induced by direct LC activation [31]. In another study, intake of a drug that enhances cortical noradrenaline levels increased pupil dilation, alpha desynchronization, and behavioral effects suggestive of cortical excitation [86,88]. Finally, during rest, periods of high pupil-indexed neuromodulation coincided with low-frequency desynchronization as well as high-frequency synchronization [89]. Interestingly, pupil dilation showed an inverted U-shaped relationship with alpha rhythms [89], as suggested by previous animal research [25]. Taken together, across species and measures, the level of tonic LC activity modulates the level of cortical synchronization, presumably mediated via a thalamocortical mechanism.

Phasic noradrenergic neuromodulation elicits transient alpha desynchronization

While acting on a more circumscribed spatial and temporal scale, the neural processes that mediate selective attention are similar to those underpinning global changes in cortical synchronization (i.e., cortical state) [11,45]. In particular, local cortical desynchronization, as observed during selective attention, has been suggested to arise as a result of phasic neuromodulation that gains spatial specificity by focused glutamatergic inputs [22,45].

Several animal studies have directly investigated the influence of phasic LC activation on circumscribed changes in cortical oscillatory dynamics. Specifically, naturally occurring [10] and artificially induced [24,83] phasic LC activity have been related to modulations of cortical excitability [36]. After pulsed trains of LC stimulation that mimicked naturalistic LC bursts, a transient decrease in low-frequency activity (<11 Hz) and a concomitant increase in high-frequency (>45 Hz) rhythms in the prefrontal cortex were observed [24]. A pharmacological noradrenaline blockade abolished these effects, confirming an underlying noradrenergic mechanism [24]. A follow-up study that investigated sensory-evoked phasic LC activity replicated and extended these findings [10]. Sensory stimulation produced robust phasic LC activity that preceded prefrontal low-frequency desynchronization (<15 Hz) and high-frequency synchronization (>30 Hz) by about 150–200 ms [10]. Importantly, these prefrontal changes linearly scaled with the amplitude of LC responses and were eliminated after a pharmacological disruption of LC discharge [10].

Taken together, phasic LC activation rapidly provokes localized cortical excitation. This encompasses transient desynchronization of low-frequency activity as well as the increased high-frequency synchronization that is essential for the selective processing of salient information [10,24,92]. These noradrenaline-induced changes in cortical synchronization are thought to

arise via a thalamic mechanism and a noradrenergic activation of cholinergic and GABAergic neurons in the basal forebrain [9,10,24,25,93].

Initial studies suggest phasic noradrenergic influences on neural desynchronization during attention in humans, as well [6,7,94] (Figure 1). For example, in one study [7], participants completed an arousal-manipulated attention task while pupil dilation and EEG were recorded concurrently. During the attention task, arousing or perceptually matched control stimuli were presented on a trial-by-trial basis to dynamically modulate arousal-related noradrenergic drive [18]. Crucially, larger pupil dilation in response to arousing stimuli was associated with a stronger transient alpha–beta desynchronization (9–30 Hz), indicating a common underlying dependence on phasic noradrenaline release [10]. On a behavioral level, noradrenergic responsiveness, as approximated by greater pupil dilation and EEG desynchronization, was linked to better attention across several tasks [7]. Similarly, attention-related pupil dilation has recently been linked to spatially circumscribed alpha desynchronization on a single-trial level [94]. Finally, in another study, larger pupil dilation and EEG desynchronization were associated with increasing difficulty in a parametric attention task [6]. Specifically, with increasing attentional demands, alpha activity desynchronized whereas theta and gamma rhythms increased [3,5]. Again, pupil-indexed neuromodulation tracked oscillatory changes. To probe a potential thalamic contribution to these attention-related effects, participants completed the task a second time during functional MRI. Importantly, multivariate analyses revealed that behaviorally relevant thalamic blood oxygen level-dependent (BOLD) modulations were indeed associated with both pupil dilation and EEG desynchronization [6]. Together, this supports a role of noradrenergic neuromodulation in attention-related cortical excitability adjustments, likely mediated via the thalamus.

To summarize, early investigations in animals linked tonic noradrenaline levels to the degree of spontaneous alpha synchronization [9,25,79], a marker of cortical excitability [64]. Specifically, they elucidated that noradrenaline modulates cortical synchronization by shifting thalamic neurons from a rhythmic firing pattern to a mode of activity that allows for reliable information transfer [9,31,81,82]. As rhythmic firing of thalamic pacemaker cells contributes to the generation of the cortical alpha rhythm [4,51,52], spontaneous alpha oscillations are under tonic noradrenergic control. More recent investigations, also in humans, extended these findings by revealing an association between ongoing, pupil-indexed noradrenergic activity and low-frequency synchronization in thalamocortical circuits [5,15,39,82,87,89]. Importantly, the processes mediating selective attention are thought to be similar to those underpinning such global changes in cortical synchronization [11,45]. Accordingly, transient bursts of LC activity have been shown to induce cortical desynchronization, likely again via a thalamic mechanism [10,24,31,83]. In summary, phasic LC activation may facilitate the selective processing of relevant stimuli by transiently modulating thalamocortical alpha synchronization, which in turn adjusts local cortical excitability [5–9,15,25].

Is there a specific noradrenergic modulation of alpha desynchronization?

Noradrenaline is one of multiple neuromodulators that influences attention [21] and state-dependent thalamocortical synchronization [11,45,76]. Especially cholinergic neuromodulation originating from the nucleus basalis contributes to attentional functions [20]. Stimulation [95] and lesion [93] studies revealed that acetylcholine abolishes rhythmic burst firing in the thalamus and desynchronizes the cortex. This cholinergic modulation of thalamic firing patterns [9] facilitates reliable thalamocortical information transfer [81]. Note that thalamic burst firing is implicated in the generation of the cortical alpha rhythm [51,52] (for cholinergic modulation of thalamic alpha-rhythms, see [96,97]). Hence, acetylcholine promotes cortical desynchronization, similar to the action of noradrenaline [9,11,31,83]. The overlapping and unique features of cholinergic and noradrenergic neuromodulation during attention are an area of active research [11,21,86,88].

Outstanding questions

How do different neuromodulatory systems (e.g., noradrenaline, acetylcholine) interact to shape cortical excitability according to attentional demands?

Can noradrenergic influences on low-frequency desynchronization be disentangled from their association with (concurrently observed) high-frequency synchronization? Does noradrenergic neuromodulation exert its effects on synchronization primarily indirectly via the thalamus or are there also direct effects in the cortex?

What is the relative contribution of noradrenergic and other neuromodulatory systems to luminance-independent changes in pupil diameter? Can we solve the inverse problem (inferring neural activity from pupil recordings)?

Can noninvasive stimulation techniques that influence noradrenergic neurotransmission (e.g., vagus nerve stimulation) be exploited to optimize cortical alpha synchronization during attention? Can we disentangle different neuromodulatory correlates of vagus nerve stimulation?

This endeavor is complicated by the fact that several noninvasive proxies of noradrenergic neuromodulation are also influenced by cholinergic activity (e.g., pupil dilation [98], vagus nerve stimulation [91,99]), likely reflecting dense and reciprocal connections between the nuclei [100]. Interestingly, however, a study exploring neuromodulatory determinants of state-dependent cortical synchronization revealed that noradrenergic but not cholinergic influences control the dynamics of cortical networks [101]. The neural processes underpinning cortical state changes are similar to those regulating attention [11,45]. Thus, noradrenergic influences on thalamocortical synchronization likely play a mechanistic role in attention [31,102], presumably in concert with other neuromodulators [100].

State and species differences may explain differences in frequency bands

Notably, several animal studies reviewed in the preceding sections report LC-dependent decreases in low-frequency activity that only partly overlap with the alpha frequency [10,24,39,83]. Species and state differences may explain these lower frequency effects. First, a cortical 3–5 Hz rhythm in rodents has been suggested as an evolutionary precursor and functional homolog of the primate alpha rhythm [15,16]. Second, the thalamocortical mechanisms underlying the alpha rhythm can also generate lower frequency rhythms, although in different behavioral states [103]. Several of the reported animal experiments were conducted during reduced vigilance states (anesthesia) [8,10,24] that are characterized by relative thalamocortical synchronization (i.e., dominated by slower rhythms [10,45,51]). In sum, recent findings demonstrate that LC activation abolishes rhythmic bursting in the thalamus [31,37,82] and thus shows a mechanistic relation to generators of the cortical alpha rhythm [15,51,52]. State (anesthesia vs. waking) and species (rodents vs. primates) differences may underlie the differences in frequency bands observed across studies.

Noradrenergic effects on low and high frequencies may act in concert

In addition to decreases in alpha rhythms, most LC-stimulation studies report a synchronization in high frequencies [10,24]. While alpha rhythms are generated by thalamocortical interactions [15,51], gamma oscillations are considered the product of cortical interneurons [52]. Recently, the ‘glutamate amplifies noradrenergic effects’ model [22] outlined how noradrenaline activates cortical interneurons and induces local gamma synchronization (cf. [101]). Alpha rhythms constrain the time windows for high-frequency activity [6,13,73]. Thus, noradrenaline’s alpha-desynchronizing action in the thalamus [25,31] and gamma-synchronizing action in the cortex [22] may act in concert to promote attention [13,92].

Concluding remarks

Rhythmic neural activity within a frontoparietal network interconnected by the thalamus supports the preferential processing of prioritized information needed for selective attention [3,48]. Prefrontal control over noradrenergic nuclei provides a powerful tool to bias processing in thalamocortical networks according to attentional demands [17,27,28]. While earlier conceptualizations considered the noradrenergic LC as a homogenous structure that uniformly broadcasts its output throughout the brain, recent evidence reveals a more targeted system suited for attention-related forebrain modulation [33]. Novel technological advances that enable noninvasive assessments of the LC–NA system contribute to this refined understanding (Box 1). Noradrenergic neuromodulation biases information processing towards prioritized representations across multiple brain sites, prominently including the thalamus [25,31]. On a neural ensemble level, fluctuations in noradrenergic neuromodulation translate into changes in rhythmic neural activity [9–11,76,83]. In particular, modulations of alpha-oscillatory activity, mediated via a thalamocortical circuit, temporarily disengage task-irrelevant brain areas and thus facilitate the flexible gating of information [3,5,13]. Hence, because the prefrontal cortex provides input to the LC [27,28], noradrenergic influences on thalamic pacemakers grant prefrontal–brainstem circuits control over cortical alpha

synchronization [5,9,25,87]. Prefrontal LC activation may thus subserve the selective processing of prioritized information by dynamically adjusting the balance of cortical excitation and inhibition via alpha synchronization [6–8,10].

With advancing age, our ability to filter out relevant pieces of information wanes [104]. We highlight evidence suggesting that age-related degeneration of the LC (Box 2) may impair thalamocortical alpha synchronization (Box 3) and contribute to attention deficits in later life [7]. While several questions remain to be answered (see Outstanding questions), the reviewed findings highlight how the noradrenergic modulation of neural synchronization shapes attention.

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Declaration of interests

No interests are declared.

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