Trends in Cognitive Sciences

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Review

The role of the locus coeruleus in shaping adaptive cortical melodies

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Neural dynamics are shaped and constrained by the projections of a small nucleus in the pons: the noradrenergic locus coeruleus (LC). Much like a bow to the brain's violin, activity in the LC lacks content specificity, but instead dynamically shapes the excitability and receptivity of neurons across the brain. In this review, we explain how the style of the bowing technique, which is analogous to different firing modes in the LC, affects distinct activity patterns in the rest of the brain. Through this analogical lens, we provide intuitive insights into how the complex activity of the LC acts to coordinate adaptive neural dynamics.

Highlights

The locus coeruleus (LC) is a small collection of cells in the pons that sends widespread, neuromodulatory projects to the rest of the brain.

The LC works analogously to the manner in which a bow is needed to express musical notes from a violin.

Different styles of bowing have distinct effects on the musicality of the notes expressed by the violin, and the same can be said for the different modes of LC activity.

Dysfunctional bowing (LC activity patterns) can be linked to different abnormal brain states.

The role of the LC in shaping whole-brain dynamics

The neural activity that emerges from the cerebral cortex is highly structured [1,2], yet also dynamic [3–5] and context specific [6,7]. While many structures influence whole-brain dynamics, in recent years, the LC, a key hub within the ascending noradrenergic system, has received prominent attention for its role in shaping the brain network dynamics that support cognitive function [8–13]. Through wide-ranging, yet unmyelinated fibres that innervate almost every region of the brain [14,15], the LC releases a neuromodulatory ligand known as noradrenaline (NA)/norepinephrine. Rather than directly transmitting an action potential to the target cell, NA instead changes the receptivity and excitability of target cells [16]. The interactions between LC fibres, local cellular ion channels, intrinsic calcium dynamics, and local glutamatergic processing have been argued to facilitate complex, adaptive behaviour [17,18]; however, we are only beginning to scratch the surface of the many and varied modes inherent to this complex system [10,11,15,18,19].

The impact of the LC on the rest of the brain has previously been likened to rotating a volume dial on a radio: activity in the LC can be turned up or down to alter the gain of a targeted neuron (Figure 1), after which the cell can be modulated to become more (or less) receptive to ongoing inputs, or respond more strongly when it crosses its firing threshold [9,16]. This analogy nicely captures the fact that the LC does not generate the specific glutamatergic signalling between regions (what we might call 'neural melodies' [20,21]), but rather allows the particular melodies to either be heard above (or dampened down into) the evolving neural 'pandemonium' [22]. However, this analogy can only be stretched so far. First, radios are passive devices, whereas the brain (including the LC) is an active, dynamic organ [12,23]. In addition, the gain analogy is difficult to extrapolate over time, yet we know that the LC shapes complex brain dynamics across multiple temporal scales [10,11,24,25]. Finally, the gain analogy is typically unidimensional, whereas the response properties of LC neurons, which were once thought to exist in an 'all-or-none' fashion, are now being shown to display subtleties that undermine a unidimensional perspective [15,26].

For these reasons, we propose a new analogy: that of a bow to the brain's violin. While the fingers on the strings of a violin designate the specific notes to be played (i.e., the cortical melody), a bow is required to move across the strings in order to extract a note from the instrument. This in turn elicits sound from the instrument and, hence, allows for the expression of a particular melody. This

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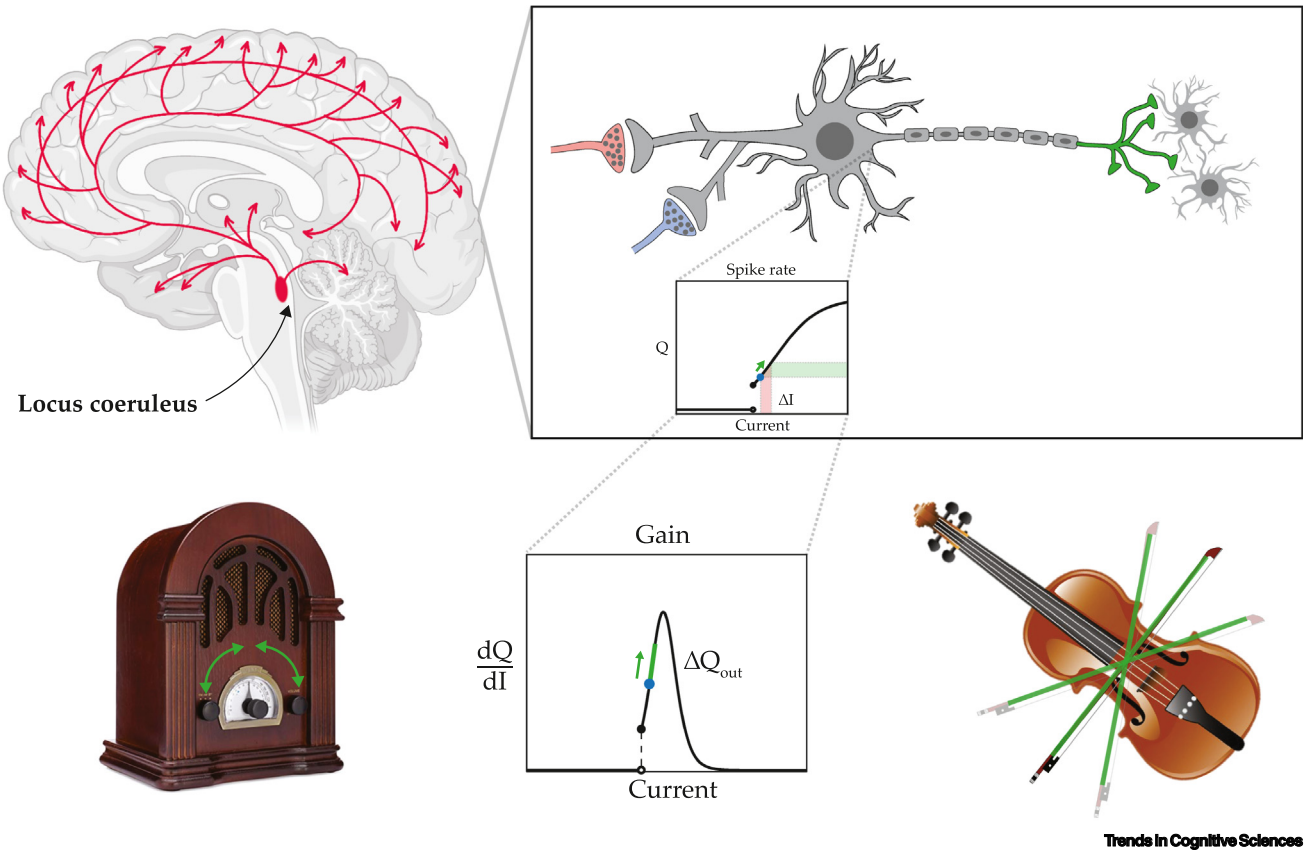

Figure 1. Functional neuroanatomy of the locus coeruleus (LC). Upper left: the LC is a small collection of catecholaminergic neurons in the rostral pons that sends diffuse, unmyelinated projections to regions throughout the central nervous system. Upper right: at target sites, the LC releases the neurochemical noradrenaline (NA). Rather than triggering an action potential, NA causes changes in the internal milieu of cells (e.g., by releasing stored Ca^{2+} or modifying ligand-gated ion channels); that is, it increases (or decreases) the neural gain (green) of local neurons (bottom middle inset). Bottom: although these changes in gain have traditionally been likened to changing a volume dial on a radio (left), here we argue that a more parsimonious analogy that captures key features of the spatiotemporal impacts of the LC on the brain is the effect that a bow has on the strings of a violin; that is, the LC changes the way that particular notes are expressed (e.g., the dynamics of the music), without effecting the specific string of notes per se, but in a dynamic manner that facilitates the expression of complex neuronal melodies.

analogy not only captures the original 'gain control' concept (e.g., bowing can be either soft or loud), but can also be extended to make contact with other crucial features of the LC, and its impact on the rest of the brain. For instance, in much the same way that different styles of bowing can elicit a variety of styles that can drastically change the volume, complexity, and 'musicality' (i.e., the tone quality or 'colour') of cortical melodies, we argue that heterogeneous activity within the LC is capable of mediating complex, adaptive dynamics throughout the central nervous system.

In this article, we use the violin bow analogy to summarise the impact of the noradrenergic LC on the systems-level organisation of the brain. After briefly reviewing the functional neuroanatomy of the LC and its connections with key features of the nervous system, we highlight multimodal evidence for several distinct roles that the LC has in the nervous system, akin to stroke of the bow on the cortical strings. In the final section, we highlight how pathology within the LC (akin to playing the violin with poor technique or using a damaged bow) can negatively impact the diversity and expression of complex, adaptive, and dynamic brain states. Through this process, we offer an approachable overview of a rapidly evolving field and further identify places where new experiments are required to make solid conclusions regarding the role of the LC in shaping whole-brain dynamics.

The functional neuroanatomy of the noradrenergic LC

The LC is a small group (~2000–3000 in mice; ~50 000–60 000 in humans) of predominantly noradrenergic neurons located in the rostral pons [12]. Most of the axons from the LC travel long distances [14], sending widespread noradrenergic projections to the rest of the brain (Figure 1). The projections of the LC are relatively diffuse [14]: each noradrenergic neuron gives rise to collaterals that spread out to innervate many disparate regions [15]. The LC is also a premotor autonomic system nucleus, regulating sympathetic system activity via projections to the intermediolateral nucleus in the medulla, among other nuclei [14]. It is via these projections that the LC has an influence over the dilation of the pupil [27–31], which is an outcome measure often used to indirectly infer LC firing (Box 1).

The spiking activity of LC neurons is typically grouped into three distinct categories: off/silent [during rapid eye movement (REM) sleep], tonic, and phasic [9,32]. Tonic activity is characterised as a low-frequency, sparse spiking activity, which accounts for the baseline level of noradrenergic activity that covaries strongly with arousal level and brain state [8–11]. By contrast, the phasic mode is characterised by rapid and relatively global activation of LC neurons [9,25,32]. At their target sites, LC axons release NA, which acts as a ligand on three types of post- and presynaptic adrenergic receptor (i.e., α1, α2, and β [33]). The functional effects of each of these receptors depend on their differential sensitivities to NA (affinities for the ligand differ across receptors: α2 > α1 > β) and the different intracellular cascades linked to each class of G protein-coupled receptor [16,34–36]. Ultimately, these cascades modulate the opening (and closing) of voltage-gated ion channels, liberate intracellular Ca^{2+} levels from local stores, or inhibit neurotransmitter release [16,36]. Each of these mechanisms has the effect of modifying neuronal dynamics (i.e., changing the stroke of the bow) without altering the precise pattern of neural spikes that carries the information related to specific sequences of neural activity (i.e., not changing the melody). Both neural mass modelling approaches [16,24,37] (Box 2) and empirical studies [10,11,38] have demonstrated that these microscopic effects can have qualitative impacts on how the macroscopic networks of the brain (e.g., those we measure with techniques such as EEG and fMRI) interact over time.

One of the main computational roles of noradrenergic modulation is to change neural gain (Figure 1), that is, to alter the excitability of the target population, making the system more reactive to incoming signals [16]. However the mechanisms responsible for shaping population-level activity relate to more than just the intensity of LC firing; for instance, the location of specific

Box 1. Indirectly inferring locus coeruleus (LC) activity from the diameter of the pupil

In recent years, the diameter of the pupil has been used as an indirect readout of LC activity. While the pupil is well known to respond to ambient light levels, as well as the distance to a peripheral visual target, its diameter is also related to activity in the LC [115], which sends projections to both sympathetic and parasympathetic nuclei that both dilate (via the superior cervical ganglion) and constrict (via the ciliary ganglion) the diameter of the pupil, respectively [27]. There is now ample causal evidence linking LC spiking activity to pupil dilation [9,10,27,29].

Despite these causal links, the LC is not the only brain region where the activity covaries with the diameter of the pupil. For instance, there is evidence linking pupil diameter with activity in other subcortical nuclei, such as the superior and inferior colliculi, as well as the anterior cingulate cortex [28,71,115]. The pupil has also been shown to dilate with other neuromodulatory ligands, such as those of the serotonergic [116] system.

Although these results make the interpretation of the pupil diameter potentially more challenging, it is important to note that pupil diameter is still strongly (and causally) related to the LC [27,28]. Given the known anatomical projections of the LC, this suggests that the LC acts as a critical hub for controlling the intersection between the peripheral and central nervous systems, perhaps through the coordination of other neuromodulatory systems. In keeping with this, the LC has known direct, excitatory projections to the cholinergic basal forebrain [117] and serotonergic dorsal raphe [14]. Future research that uses exciting new neuroimaging technologies [118] across a range of behavioural states will help to refine our understanding of the links between the LC and pupil dilation.

Box 2. Using neural mass models to appreciate the systems-level impact of neuromodulation

The mammalian brain is organised across multiple scales, from the microscopic (e.g., precise synaptic connections between specific neural populations [15]) to the macroscopic (e.g., the highly reproducible temporal patterns of coordination in BOLD activity between regions of the cerebral cortex [2]). Unsurprisingly, it can be challenging to infer the macroscopic effects of changes at the microscopic level (and vice versa).

Fortunately, neural mass modelling affords a sensitive and principled means for crossing these scales [119]. Using insights from statistical physics and the study of complex, dynamical systems, differential equations can be used to create realistic (yet still highly abstract) models of neuronal interactions. An experimenter can then manipulate a key variable of interest (e.g., the anatomical connectivity between 'regions', or the baseline discharge rate, etc.) and then, following a principled transformation from the microscale to the macroscale, observe whether the manipulated variable can be read out from the emergent, macroscale dynamics (using similar techniques to those used in standard neuroimaging experiments).

Using this approach has led to advances in how we understand the impacts of the LC on macroscopic brain dynamics. For instance, increasing the slope of the gain (input–output) function that determines the responsiveness of individual neural populations to their synaptic inputs (a putative computational impact of NA [16]) was shown to mediate an increase in network-level integration between simulated BOLD time series [37], thus confirming a hypothesis that arose from the analysis of task-based fMRI data in humans [19]. Information theoretic algorithms applied to 'neural' data from the same model further confirmed a transition between information storage and transfer with heightened neural gain [120]. Together, both these models support the notion of LC-mediated reconfigurations in brain network dynamics across scales. We anticipate that future modelling studies, particularly those that incorporate known neuroanatomical details of receptor subtype expression and dynamic modes of population-level LC spiking activity across brain states, will catalyse major insights into the effects of the LC on whole-brain dynamics.

adrenergic receptors (e.g., pre- or postsynaptic), neuronal type (i.e., excitatory or inhibitory neurons), regional location (e.g., cerebral cortex vs. thalamus), and cellular location (i.e., pre- or postsynaptic receptors) can all have crucial effects on the way in which LC activity is translated into downstream outputs. For instance, the recruitment of excitatory noradrenergic receptors (such as the G*q*-mediated α1 receptor) can increase neuronal sensitivity; however, there are numerous other mechanisms through which NA can alter neuronal excitability [35,36,39,40]. A prime example occurs in the LC itself, where the α2 receptor is known to act as the primary presynaptic inhibitory receptor: it typically causes cells to become more inhibited with increasing concentrations of NA [8]. Indeed, dexmedetomidine, a potent sedative agent, is a selective α2 receptor agonist that inhibits the LC and essentially renders the recipient unconscious [41]. However, when located in the dendrites of thick, bi-tufted cortical pyramidal neurons, activation of the same receptor can facilitate coupling between the dendrites and cell body by closing ionic HCN *Ih* leak channels [36,40]. This latter mechanism has an important hypothetical role in both working memory and perception, either through the maintenance of recurrent excitatory signals [36] or via an apical amplification process [40] in different classes of cortical pyramidal neuron.

Given the anatomical and physiological properties of the brain, it is perhaps surprising that such a small nucleus can facilitate large-scale coordinated effects upon NA discharges. However, the global reach and physiological impact of the LC can have a demonstrative effect on whole-brain dynamics. For instance, phasic discharges of NA have been proposed as a mechanism for 'resetting' the state of the brain [13], which is a crucial way to ensure that the current state of the brain is maximally adaptive at any given point in time. From a functional point of view, it has been proposed that the ascending noradrenergic inputs to the cerebral cortex serve as an integrative signal to coordinate and facilitate communication between otherwise segregated systems [19,42]. By broadcasting a relatively low-dimensional signal to the rest of the brain that increases the receptivity and excitability of target regions, activity patterns in the LC can (somewhat counter-intuitively) promote the formation of a quasi-critical regime [24]. The effect is deceptively simple: by boosting activity patterns in a widespread fashion, those regions with an intermediate level of activity can now cross a nonlinear barrier that drastically increases their firing rate (known as a 'bifurcation' in dynamical systems theory [43]).

In other words, neurons that are already partially active (i.e., processing glutamatergic inputs) can now 'stand out' from the background activity [44] and, hence, have an impact on the evolving spatiotemporal brain state that controls a diverse set of brain states, including cognitive function [45,46], memory encoding [47,48], perceptual learning [49,50], motor performance [51], and perceptual awareness [38,52,53]. There is now empirical evidence to support this relatively global effect of the LC on whole-brain dynamics in both rodents [10] and humans [18,19,38,54–57]. However, further research that can either measure (or stimulate) the LC while simultaneously tracking the local release and impact of NA [26,58] in more than one region (particularly during distinct behavioural contexts) is required to confirm the biological mechanism of NA-induced alterations in large-scale network topology.

The style of the bowing affects systems-level neural dynamics

Different bowing techniques are necessary to express the full dynamic range of the violin: to change volume, create different accents, and imbue a melody with a highly syncopated rhythm. Extending our analogy, we propose that the ascending arousal system dynamically impacts the rest of the brain with much of the same dynamic range as the bow to the violin string. To demonstrate these effects, here we review numerous recent influential systems neuroscience results through this lens.

During sleep, the LC is in a low firing or silent state (during slow-wave sleep and REM sleep, respectively) [59]. Obviously, without a bow coursing across the strings, a violin will not resonate and, hence, no sound will be produced (Figure 2A). Neurons in the cerebral cortex do of course

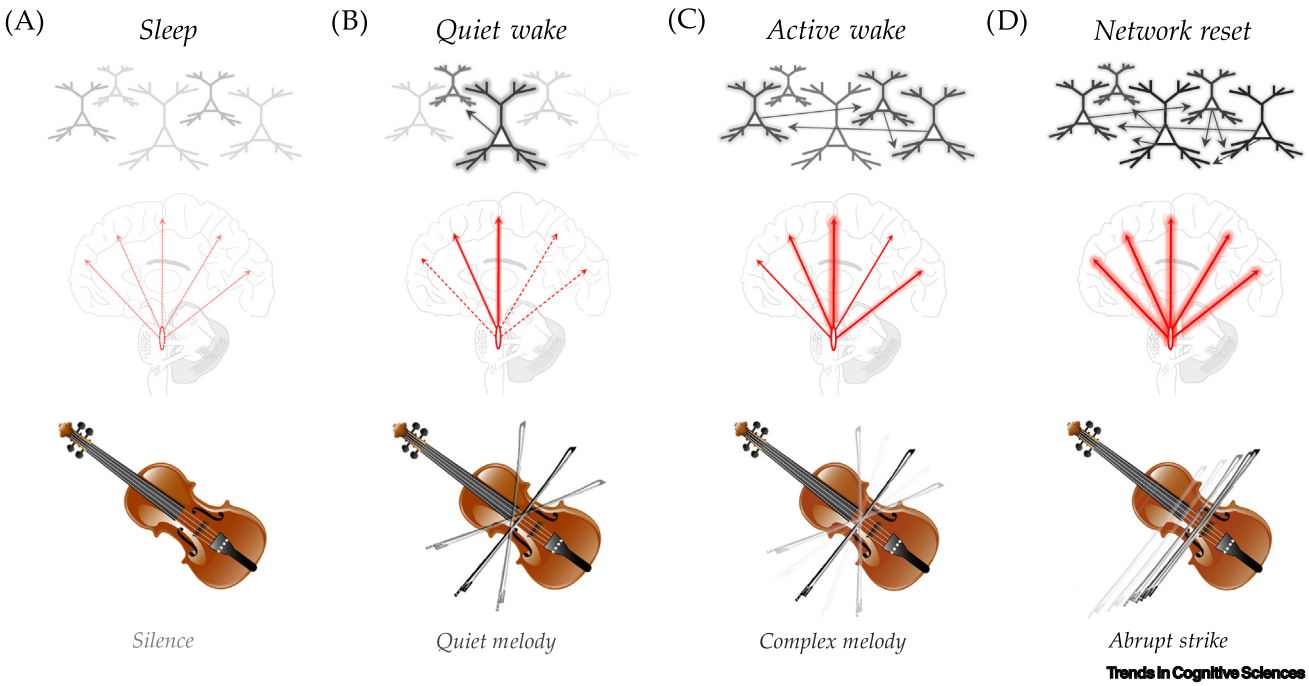

Figure 2. Different modes of locus coeruleus (LC) activity and their analogy to bowing styles. (A) Dreamless sleep is analogous to not having the bow touch the strings: without sufficient noradrenergic tone, neurons in the brain are not capable of becoming active or interacting with one another (i.e., there is relative silence); (B) during quiet wakefulness (e.g., low arousal states), subtle activity in the LC is hypothesised to promote unique coalitions of active neurons in the brain, which is akin to the execution of a subtle, quiet melody; (C) at higher levels of arousal (e.g., active wake), more vigorous and complex patterns of bowing are hypothesised to facilitate more complex, multilayered melodies, perhaps played at higher volume; (D) coordinated bursts of LC firing are putatively associated with a 'Network Reset' theory [67], in which multiple neurons are contacted simultaneously in a manner analogous to a sharp, abrupt strike across multiple strings.

spike during sleep, but these dynamics are thought to emerge from features intrinsic to neurons and their distributed anatomical connections [60,61]. In addition, LC neurons do have some spiking activity during different sleep states [62], and other neuromodulatory systems remain active during both slow-wave and REM sleep stages (primarily the pontine and forebrain cholinergic systems [63]). Importantly, the noradrenergic system is causally associated with arousal states and the transitions between them [64]. For instance, the probability of a sound-evoked transition from sleep to an awake state is heightened during periods of higher tonic LC activity, and increasing tonic LC tone through optogenetic stimulation has been shown to increase the probability of transitioning between different arousal states [65]. These effects are probably mediated by the widespread projections of the LC, a conclusion that is borne out by neural mass modelling of the ascending arousal system [24,66] (Box 2).

If sleep states are analogous to a lack of bowing, then waking up from sleep is akin to the application of a tonic, slow-moving bow to the strings of the violin (Figure 2B). Indeed, optogenetic [11] and chemogenetic [10] stimulation of the LC has been shown to alter typical patterns of cross-regional interaction characteristic of anaesthesia by increasing the strength of functional interactions between otherwise disconnected regions [5,10]. However, styles of bowing are more nuanced than being simply either 'on' or 'off'. In much the same way, the mode of spiking in the LC differs substantially across different arousal states [62]. Moderate levels of tonic spiking are associated with sustained arousal that facilitates the precise encoding of sensory information [9,25]. These changes facilitate an improvement in attentional performance, which we hypothesise likely acts by coordinating phasic LC discharges with the rest of the attentional system (i.e., rapid bow strikes), ultimately providing the brain with the means to liberate the precise neural coalitions required to track an attentionally relevant target, while effectively leaving the rest of the system unperturbed. By contrast, higher levels of tonic spiking are linked to a more frantic, frazzled cognitive mode [68] associated with highly stressed or panic attack states, which we propose relates to heightened interactions between neural coalitions that ultimately interfere with the selective activity patterns required for the mediation of precise behavioural outputs [24].

Based on these links, it has been suggested that the dynamical changes between LC firing modes help to adaptatively shift the brain between states that promote unique behaviours and cognitive functions. For instance, if an animal is focussed on a particular feature of their surrounding environment (e.g., hunting or eating a well-earned meal) and either a particular resource is exhausted or a new salient stimulus appears (e.g., a rustle in the bushes, potentially reflecting a hungry predator), a phasic burst in the LC could activate a larger number of α1 receptors around the brain and, hence, render the brain susceptible to processing of the novel stimulus. This process has been termed a 'network reset' [67]. In keeping with this hypothesis, there is evidence that phasic increases in pupil diameter accompany changes in perceptual interpretation [69]. Through our analogy, this mechanism might be best represented as a sharp blast across multiple strings, after which a novel melody can be played on the instrument (Figure 2D).

A variety of musical forms can be played on a violin. Additionally, within a particular piece of music, there are many different sections with their own dynamics, from a quiet, emotive section to a passionate high-volume section filled with rapid flurries of notes. Mirroring this variety, there is emerging evidence that the dynamic coordinated activity of the cells within the LC may be more subtle than originally hypothesised (Figure 2C). The 'all-or-none' notion of LC dynamics was based on the results of the original experiments, in which the LC of anaesthetised animals was titrated against aversive stimulation of the limb, in part because this intervention triggers a robust increase in LC activity [70]. Using trial-averaged data (to increase signal-to-noise ratios), there are typically clear increases in firing rate across all cells within the LC following forepaw stimulation [27,70,71].

The single-trial patterns are often more sparse, suggesting that the LC has more subtle responses to individual stimuli that only look as though they are *en masse* when averaged together. However, aversive stimuli do activate neurons across the LC [26], suggesting that the nucleus is capable of multiple distinct modes of coordinated spiking activity. This has led to the suggestion that the LC acts in a more differentiated and subtle manner (i.e., multiple bows for different subsystems [15]), depending on the specific behavioural context, although this hypothesis has been difficult to test directly due to challenges associated with imaging the LC in awake animals [15].

Outside of the experimental challenges, there are good reasons to assume that the LC is capable of differentiated dynamical regimes. A key characteristic of expertise in playing the violin is the capacity to demonstrate a flexible technique and substantial dynamic range (i.e., knowing when and where to deploy different accents, rhythms, and volume changes) (Figure 2C). By way of analogy, this suggests that switching between different cognitive processes (melodies), such as working memory manipulation and attentional focus, is akin to a dynamically evolving, complex piece of music. Over the course of a day, the neural dynamics required to support our varied behaviours are substantial: we switch back and forth to different attentional foci, become absorbed in a range of different tasks, and sometimes get bored before a particular activity ends. There is emerging theoretical and empirical support for this notion: a recent neural mass model (Box 2) suggests that the diffuse projections of the LC are capable of supporting multiple, unique processing modes in the brain [24], and the complexity of neural signals following brain stimulation is maximal in intermediate arousal states [72]. This of course makes sense from the point of view of an animal, because the capacity to explore and learn about a new environment (e.g., to look for resources) is driven by several cortical and subcortical brain systems [22,73], and systems that can facilitate their sophisticated interaction will undoubtedly amplify adaptive behaviour and, hence, act as crucial substrates for natural selection.

Bowing the violin with poor technique

Numerous disorders of the brain are associated with pathological involvement of the LC; however, these syndromes are, at first glance, distinct. For instance, abnormal LC dynamics have been linked to neurodegenerative (such as dementia [74]), neurodevelopmental [such as attention deficit and hyperactivity disorder (ADHD) [75]], and neuropsychiatric disorders (such as anxiety [76] and post-traumatic stress disorder [77]), each of which have strikingly distinct symptom profiles. A benefit of our approach is that we can extend our analogy to characterise each of these disorders within the same framework. For instance, all three disorders share impairments in context sensitivity [e.g., firing (or not) at the wrong times], which is akin to striking (or not) the bow along the strings of the violin at an inappropriate moment, but differ widely in terms of their strength and temporal dynamics (Figure 3): the context-insensitive melodies might be played at a volume that is either too high (anxiety [76]; red in Figure 3) or too low (dementia [74]; green in Figure 3), or in a manner that can fluctuate substantially over time (ADHD; blue in Figure 3).

Numerous neurodegenerative syndromes [76], most notably, Alzheimer's disease [74,78,79] and Parkinson's disease [80,81], are associated with the accumulation of abnormally folded proteins (and ultimately, cell death [82]) in the LC [83]. However, most studies investigating dementia-related pathologies at the whole-brain level have focussed on patterns observed in the cerebral cortex [84,85]. This is perhaps not surprising; indeed, if we hear a melody that wavers in intensity or plays loudly in the wrong context, we often first imagine that there must be a problem with the tuning of the strings. However, a decline in LC activity is capable of recreating many of the features of dementia at the systems level (Figure 3; green); by placing the brain into a suboptimal mode, it is more difficult to ignite the formation and engagement of the effective neuronal coalitions required to mediate effective cognitive performance [24] or to form [86] and recall [87] specific memories in a context-dependent fashion. Alternatively, the bow might 'slip' from time to

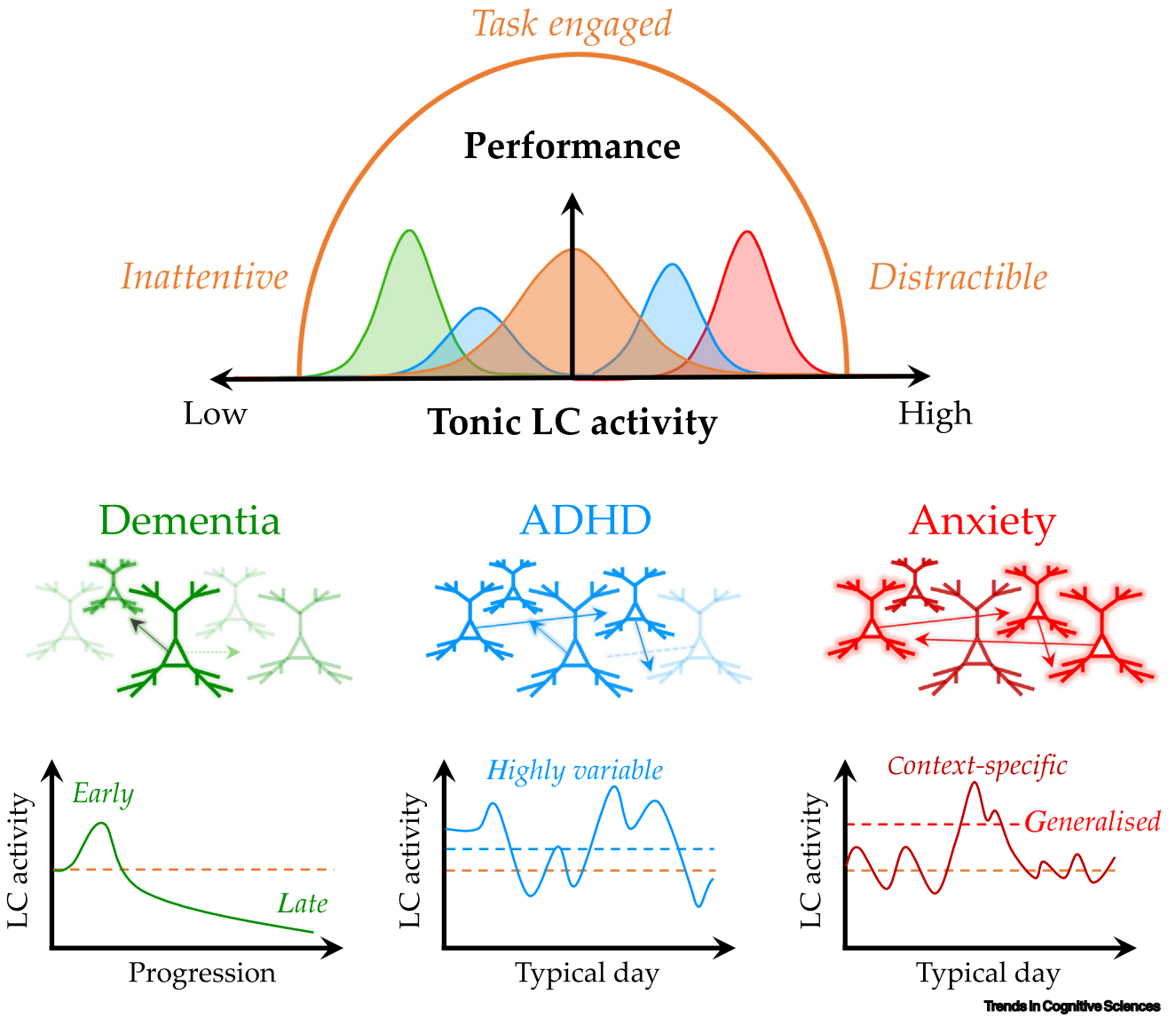

Figure 3. Different disorders and how they relate to abnormal locus coeruleus (LC) activity and bowing. The bowing analogy is extended here to characterise three seemingly unrelated neurodegenerative, neurodevelopmental, and neuropsychiatric disorders according to the well-known, inverted U-shaped Yerkes–Dodson relationship (orange) between arousal (denoted as tonic LC activity [9]; *x*-axis) and cognitive performance (*y*-axis): low LC activity corresponds to inattentiveness, high LC activity corresponds to distractibility, whereas intermediate levels facilitate a task-engaged state [9]. The orange curve on the plot designates a hypothetical distribution of firing rates during the awake state. LC pathology in advanced dementia is hypothesised to lead to lower frequency LC activity (green peak), which impairs recruitment of the cortical coalitions required for effective cognitive function. However, there is also evidence for heightened LC activity early in the condition [i.e., above normal levels (orange broken line)]; abnormal LC dynamics in attention deficit and hyperactivity disorder (ADHD) cover a broad range, and abrupt attention shifts are reminiscent of the loud, rapid, and erratic dynamics of the 'Network Reset' theory [67] (right blue peak). However, individuals with ADHD can not only focus intensely on topics of interest, but also have periods of relative cognitive inertia (left blue peak); that is, LC dynamics are hypothesised to be highly variable over the course of a typical day; in anxiety, heightened LC tone drives rapid activity patterns that are often poorly aligned with the overall context (red peak) and can be either generalised (light-red broken line) or context specific (dark-red line). Distributions are exaggerated for effect.

time, particularly as the difficulty of the music increases, for example, as the cognitive challenges outweigh the capacity of the LC to coordinate the appropriate networks required to solve the task at hand and, thus, manifest some of the more paroxysmal symptoms of neurodegenerative disease [88–91]. For instance, abnormal LC firing can worsen symptoms of Parkinson's disease (e.g., the amplitude of resting tremor [90] or freezing [92]). There is also evidence that LC activity

becomes heightened early during the course of the disease [93] (Figure 3). Importantly, a renewed focus on LC pathology within dementia syndromes may help to create novel opportunities for pharmacological treatment of dementia symptoms [76,94,95], which have traditionally focussed on renormalising levels of acetylcholine in the brain [96].

Viewed through the lens of our musical analogy, disorders such as ADHD can be viewed as switching rapidly between different styles, albeit with a relative shift toward heightened LC tone (the right- and left-shifted blue peaks in Figure 3). Consistent with this perspective, there is strong evidence that individuals with ADHD have catecholaminergic (i.e., noradrenergic and dopaminergic) dysregulation. Specifically, individuals with ADHD are proposed to reside in a suboptimal [i.e., heightened (right peak) or diminished (left peak)] LC state that could either augment (or diminish) the sensitivity to distracting stimuli. Crucially, both states would increase the need for heightened executive control [97] normally used to attend to behaviourally relevant phasic responses [75], hence leading to substantial attentional distraction. This suggests a novel hypothesis: that individuals with ADHD likely have more variable LC dynamics that cause rapid shifting and refocussing across a range of cognitive tasks (Figure 3). Interestingly, the mainline treatment for ADHD increases the level of both dopamine and NA in the presynaptic space [98]. While this might seem counter-intuitive, it is important to recall that intrinsic levels of NA can cause compensatory reductions in the tonic level of LC firing (i.e., a decrease in general intensity of bowing [99,100]) while increasing the catecholaminergic levels in the prefrontal cortex to improve executive control, perhaps via top-down modulation of neuromodulatory activity [12]. Consistent with this idea, a recent study used pupillometry (Box 1) during a challenging working memory task to show that methylphenidate increased the size of evoked pupil dilations (suggestive of elevated phasic LC activity) and task performance in individuals with ADHD [101]. However, others have argued that attentional abnormalities may also arise from lower levels of NA [102]. Either way, convergent results provide evidence linking LC dysregulation to the pathophysiology of ADHD.

The ability to respond to stressful situations, often linked to the engagement of the sympathetic nervous system [27,103–107], is, in many instances, highly adaptive and has been shown to rely on increased firing in the LC. For instance, stressful contexts can elicit LC firing that ultimately mediates reconfiguration of the macroscale brain networks required to complete challenging tasks [103]. However, if the LC fires too rapidly in the wrong context, then the downstream neural dynamics can rapidly mediate maladaptive states, such as anxiety [104] and stress [105]. Consider how jarring it would be to hear the manic 'Flight of the Bumblebee' in the middle of a sombre orchestral arrangement (Figure 3; red). In much the same way, there is evidence that heightened LC activity mediates many of the symptoms of anxiety (such as rapid thoughts, subjective fear, and muscular fidgeting [104]); heightened tonic levels may correspond to trait anxiety, whereas more phasic patterns are reminiscent of context-specific anxiety, each of which likely have different downstream signatures at the whole-brain level [108]. The same can be said for post-traumatic stress disorder, in which exposure to a salient stimulus can boost noradrenergic tone following the presentation of a similar stimulus [109–111]. Interestingly, the predominant treatment for both conditions involves the diminution of the noradrenergic system [77,112]. It will be important to tease apart these subtle mechanisms in future work that tracks LC dynamics in ethologically relevant behavioural situations that mimic anxiety as it is experienced in the real world, rather than in more artificial laboratory settings [113].

Concluding remarks

In this review, we have motivated an instrumental analogy to help orient neuroscientists toward the numerous, exciting vistas contacted by systems neuroscience into the function of the LC. By viewing the LC as a bow with precise control of neural melodies, our perspective offers an intuitive

Outstanding questions

To what extent are higher-level cognitive processes, such as working memory, attentional focus, and response inhibition, dependent on the integrity and dynamics expression of distinct states of LC activity?

How complex are the dynamics of the LC? How do they vary as a function of different behavioural states?

Can the dynamic expression of LC states and their downstream effects on the coordinated activity within the cerebral cortex be used to sensitively and specifically identify individuals at risk of different neuropsychiatric disorders?

How can we use high-quality neuroimaging data, such as 7T fMRI data (for humans) and neuropixels and multi-electrode arrays (for other animal species), to improve our understanding of the role of the LC in shaping whole-brain dynamics?

Why are there correlations between central cholinergic tone and both pupil dilation during the waking state and constriction during REM sleep?

What are the state-dependent interactions between the different subcomponents of the ascending arousal system, and how do they relate to unique behavioural states?

Can we use ethological task designs (e.g., novel virtual reality tasks) to characterise how LC firing rates track with ethological behaviours?

analogy capable of capturing a particularly salient aspect of the noradrenergic system on the brain. Namely, that despite its small size and position within the brainstem, the LC is ideally positioned to coordinate a range of different dynamic modes of neural activity. Our hope is that this analogy can also be 'inverted' and, hence, used to generate novel hypotheses and insights across a range of different behavioural contexts and neurological disorders (see Outstanding questions).

For many good reasons, current research on the LC is often constrained to specific tasks and periods of time, which is akin to studying how a bow strokes an individual violin on a specific piece of music. From our perspective, it is crucial to integrate the insights gleaned from these targeted studies with an appreciation of the systems-level embedding of the LC: to track the melody from a violin within the context of the whole orchestra. By understanding the contextual dynamical changes of the LC during ethologically relevant tasks (such as reading a newspaper, watching a movie, or engaging in an active conversation), we foresee a future in which we appreciate how the different modes of LC activity (i.e., bowing techniques and dynamics) can be used to mediate different adaptive behaviours. In particular, deciphering the logic of the interactions between different arms of the ascending arousal system [114] or how the interconnections between the LC and the rest of the brain control its dynamics over time [12] are both crucial questions for understanding how, when combined with the inherent complexity of the brain, the LC is capable of coordinating a cognitive concerto.

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Declaration of interests

None declared by authors.

References

1. Biswal, B. *et al.* (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn. Reson. Med.* 34, 537–541
2. Smith, S.M. *et al.* (2013) Functional connectomics from resting-state fMRI. *Trends Cogn. Sci.* 17, 666–682
3. Lurie, D.J. *et al.* (2020) Questions and controversies in the study of time-varying functional connectivity in resting fMRI. *Netw. Neurosci.* 4, 30–69
4. Karahanoğlu, F.I. and Van De Ville, D. (2015) Transient brain activity disentangles fMRI resting-state dynamics in terms of spatially and temporally overlapping networks. *Nat. Commun.* 6, 7751
5. Shine, J.M. and Poldrack, R.A. (2017) Principles of dynamic network reconfiguration across diverse brain states. *NeuroImage* 180, 396–405
6. Barch, D.M. *et al.* (2013) Function in the human connectome: task-fMRI and individual differences in behavior. *NeuroImage* 80, 169–189
7. Smith, S.M. *et al.* (2009) Correspondence of the brain's functional architecture during activation and rest. *Proc. Natl. Acad. Sci. U. S. A.* 106, 13040–13045
8. Poe, G.R. *et al.* (2020) Locus coeruleus: a new look at the blue spot. *Nat. Rev. Neurosci.* 21, 644–659
9. Aston-Jones, G. and Cohen, J.D. (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.* 28, 403–450
10. Zerbi, V. *et al.* (2019) Rapid reconfiguration of the functional connectome after chemogenetic locus coeruleus activation. *Neuron* 103, 702–718
11. Carter, M.E. *et al.* (2010) Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nat. Neurosci.* 13, 1526–1533
12. Breton-Provencher, V. and Sur, M. (2019) Active control of arousal by a locus coeruleus GABAergic circuit. *Nat. Neurosci.* 22, 218–228
13. Sara, S.J. (2009) The locus coeruleus and noradrenergic modulation of cognition. *Nat. Rev. Neurosci.* 10, 211–223
14. Samuels, E.R. and Szabadi, E. (2008) Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. *Curr. Neuropharmacol.* 6, 254–285
15. Totah, N.K. *et al.* (2018) The locus coeruleus is a complex and differentiated neuromodulatory system. *Neuron* 99, 1055–1068
16. Shine, J.M. *et al.* (2021) Computational models link cellular mechanisms of neuromodulation to large-scale neural dynamics. *Nat. Neurosci.* 24, 765–776
17. Mather, M. *et al.* (2016) Norepinephrine ignites local hotspots of neuronal excitation: how arousal amplifies selectivity in perception and memory. *Behav. Brain Sci.* 39, e200
18. Wainstein, G. *et al.* (2021) The ascending arousal system promotes optimal performance through mesoscale network integration in a visuospatial attentional task. *Netw. Neurosci.* 5, 890–910
19. Shine, J.M. *et al.* (2016) The dynamics of functional brain networks: integrated network states during cognitive task performance. *Neuron* 92, 544–554
20. Peyrache, A. *et al.* (2012) Spatiotemporal dynamics of neocortical excitation and inhibition during human sleep. *Proc. Natl. Acad. Sci. U. S. A.* 109, 1731–1736
21. Buzsáki, G. (2004) Large-scale recording of neuronal ensembles. *Nat. Neurosci.* 7, 446–451
22. Shine, J.M. (2021) The thalamus integrates the macrosystems of the brain to facilitate complex, adaptive brain network dynamics. *Prog. Neurobiol.* 199, 101951
23. Friston, K.J. *et al.* (2018) Deep temporal models and active inference. *Neurosci. Biobehav. Rev.* 90, 486–501
24. Müller, E.J. *et al.* (2020) Diffuse neural coupling mediates complex network dynamics through the formation of quasi-critical brain states. *Nat. Commun.* 11, 6337

25. Devilbiss, D.M. and Waterhouse, B.D. (2011) Phasic and tonic patterns of locus coeruleus output differentially modulate sensory network function in the awake rat. *J. Neurophysiol.* 105, 69–87
26. Breton-Provencher, V. *et al.* Spatiotemporal dynamics of norepinephrine during learned behavior. *Nature* (in press)
27. Liu, Y. *et al.* (2017) Dynamic lateralization of pupil dilation evoked by locus coeruleus activation results from sympathetic, not parasympathetic, contributions. *Cell Rep.* 20, 3099–3112
28. Joshi, S. and Gold, J.I. (2020) Pupil size as a window on neural substrates of cognition. *Trends Cogn. Sci.* 24, 466–480
29. Joshi, S. *et al.* (2016) Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. *Neuron* 89, 221–234
30. Reimer, J. *et al.* (2014) Pupil fluctuations track fast switching of cortical states during quiet wakefulness. *Neuron* 84, 355–362
31. McGinley, M.J. *et al.* (2015) Waking state: rapid variations modulate neural and behavioral responses. *Neuron* 87, 1143–1161
32. Safaai, H. *et al.* (2015) Modeling the effect of locus coeruleus firing on cortical state dynamics and single-trial sensory processing. *Proc. Natl. Acad. Sci. U. S. A.* 112, 12834–12839
33. Jones, B.E. (2020) Arousal and sleep circuits. *Neuropsychopharmacology* 45, 6–20
34. Armstrong, C.M. and Hille, B. (1998) Voltage-gated ion channels and electrical excitability. *Neuron* 20, 371–380
35. Ramos, B.P. and Arnsten, A.F.T. (2007) Adrenergic pharmacology and cognition: focus on the prefrontal cortex. *Pharmacol. Ther.* 113, 523–536
36. Wang, M. *et al.* (2007) α2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell* 129, 397–410
37. Shine, J.M. *et al.* (2018) The modulation of neural gain facilitates a transition between functional segregation and integration in the brain. *eLife* 7, e31130
38. Munn, B.R. *et al.* (2021) The ascending arousal system shapes neural dynamics to mediate awareness of cognitive states. *Nat. Commun.* 12, 6016
39. Phillips, W.A. *et al.* (2016) The effects of arousal on apical amplification and conscious state. *Neurosci. Conscious.* 2016, niw015
40. Labarrera, C. *et al.* (2018) Adrenergic modulation regulates the dendritic excitability of layer 5 pyramidal neurons in vivo. *Cell Rep.* 23, 1034–1044
41. Brown, E.N. *et al.* (2011) General anesthesia and altered states of arousal: a systems neuroscience analysis. *Annu. Rev. Neurosci.* 34, 601–628
42. Shine, J.M. (2019) Neuromodulatory influences on integration and segregation in the brain. *Trends Cogn. Sci.* 23, 572–583
43. Rabinovich, M.I. *et al.* (2015) Dynamical bridge between brain and mind. *Trends Cogn. Sci.* 19, 453–461
44. Mather, M. *et al.* (2016) GANEing traction: the broad applicability of NE hotspots to diverse cognitive and arousal phenomena. *Behav. Brain Sci.* 39, e228
45. Aston-Jones, G. *et al.* (2000) Locus coeruleus and regulation of behavioral flexibility and attention. *Prog. Brain Res.* 126, 165–182
46. Gilzenrat, M.S. *et al.* (2010) Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cogn. Affect. Behav. Neurosci.* 10, 252–269
47. Lemon, N. *et al.* (2009) Locus coeruleus activation facilitates memory encoding and induces hippocampal LTD that depends on β-adrenergic receptor activation. *Cereb. Cortex* 19, 2827–2837
48. Clewett, D. *et al.* (2014) Locus coeruleus neuromodulation of memories encoded during negative or unexpected action outcomes. *Neurobiol. Learn. Mem.* 111, 65–70
49. Martins, A.R.O. and Froemke, R.C. (2015) Coordinated forms of noradrenergic plasticity in the locus coeruleus and primary auditory cortex. *Nat. Neurosci.* 18, 1483–1492
50. Glennon, E. *et al.* (2019) Locus coeruleus activation accelerates perceptual learning. *Brain Res.* 1709, 39–49
51. Burgess, C.R. and Peever, J.H. (2013) A noradrenergic mechanism functions to couple motor behavior with arousal state. *Curr. Biol.* 23, 1719–1725
52. McBurney-Lin, J. *et al.* (2019) Locus coeruleus-norepinephrine modulation of sensory processing and perception: a focused review. *Neurosci. Biobehav. Rev.* 105, 190–199
53. Escanilla, O. *et al.* (2012) Noradrenergic but not cholinergic modulation of olfactory bulb during processing of near threshold concentration stimuli. *Behav. Neurosci.* 126, 720–728
54. Warren, C.M. *et al.* (2016) Catecholamine-mediated increases in gain enhance the precision of cortical representations. *J. Neurosci.* 36, 5699–5708
55. Shine, J.M. *et al.* (2018) Catecholaminergic effects on dynamic network topology are dependent upon behavioral state. *Netw. Neurosci.* 2, 381–396
56. Kosciessa, J.Q. *et al.* (2021) Thalamocortical excitability modulation guides human perception under uncertainty. *Nat. Commun.* 12, 2430
57. Jacobs, H.I. *et al.* (2020) Dynamic behavior of the locus coeruleus during arousal-related memory processing in a multi-modal 7T fMRI paradigm. *eLife* 9, e52059
58. Feng, J. *et al.* (2019) A genetically encoded fluorescent sensor for rapid and specific in vivo detection of norepinephrine. *Neuron* 102, 745–761
59. Swift, K.M. *et al.* (2018) Abnormal locus coeruleus sleep activity alters sleep signatures of memory consolidation and impairs place cell stability and spatial memory. *Curr. Biol.* 28, 3599–3609
60. Bonjean, M. *et al.* (2012) Interactions between core and matrix thalamocortical projections in human sleep spindle synchronization. *J. Neurosci.* 32, 5250–5263
61. Muller, L. *et al.* (2016) Rotating waves during human sleep spindles organize global patterns of activity that repeat precisely through the night. *eLife* 5, 1195
62. Aston-Jones, G. and Bloom, F. (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J. Neurosci.* 1, 876–886
63. Tsunematsu, T. *et al.* (2020) State-dependent brainstem ensemble dynamics and their interactions with hippocampus across sleep states. *eLife* 9, e52244
64. Pace-Schott, E.F. and Hobson, J.A. (2002) The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat. Rev. Neurosci.* 3, 591–605
65. Hayat, H. *et al.* (2020) Locus coeruleus norepinephrine activity mediates sensory-evoked awakenings from sleep. *Sci. Adv.* 6, eaaz4232
66. Dehaene, S. and Changeux, J.-P. (2005) Ongoing spontaneous activity controls access to consciousness: a neuronal model for inattentional blindness. *PLoS Biol.* 3, e141
67. Bouret, S. and Sara, S.J. (2005) Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. *Trends Neurosci.* 28, 574–582
68. Arnsten, A.F.T. (1998) The biology of being frazzled. *Science* 280, 1711–1712
69. Einhäuser, W. *et al.* (2008) Pupil dilation reflects perceptual selection and predicts subsequent stability in perceptual rivalry. *Proc. Natl. Acad. Sci. U. S. A.* 105, 1704–1709
70. Akaike, T. (1982) Periodic bursting activities of locus coeruleus neurons in the rat. *Brain Res.* 239, 629–633
71. Reimer, J. *et al.* (2016) Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. *Nat. Commun.* 7, 13289
72. Casali, A.G. *et al.* (2013) A theoretically based index of consciousness independent of sensory processing and behavior. *Sci. Transl. Med.* 5, 198ra105
73. Cisek, P. (2012) Making decisions through a distributed consensus. *Curr. Opin. Neurobiol.* 22, 927–936
74. Jacobs, H.I.L. *et al.* (2021) In vivo and neuropathology data support locus coeruleus integrity as indicator of Alzheimer's disease pathology and cognitive decline. *Sci. Transl. Med.* 13, eabj2511
75. del Campo, N. *et al.* (2011) The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 69, e145–e157
76. Holland, N. *et al.* (2021) The role of noradrenaline in cognition and cognitive disorders. *Brain* 144, 2243–2256

77. Amos, T. *et al.* (2014) Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). *Cochrane Database Syst. Rev.* 7, CD006239
78. Kelly, S.C. *et al.* (2017) Locus coeruleus cellular and molecular pathology during the progression of Alzheimer's disease. *Acta Neuropathol. Commun.* 5, 8
79. Bondareff, W. *et al.* (1987) Neuronal degeneration in locus coeruleus and cortical correlates of Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 1, 256–262
80. Rommelfanger, K.S. and Weinshenker, D. (2007) Norepinephrine: the redheaded stepchild of Parkinson's disease. *Biochem. Pharmacol.* 74, 177–190
81. Sommerauer, M. *et al.* (2017) Evaluation of the noradrenergic system in Parkinson's disease: an 11C-MeNER PET and neuromelanin MRI study. *Brain* 64, 53
82. Surmeier, D.J. *et al.* (2017) Selective neuronal vulnerability in Parkinson disease. *Nat. Rev. Neurosci.* 18, 101–113
83. Betts, M.J. *et al.* (2019) Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. *Brain* 142, 2558–2571
84. Buckner, R.L. *et al.* (2008) The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38
85. Seeley, W.W. *et al.* (2009) Neurodegenerative diseases target large-scale human brain networks. *Neuron* 62, 42–52
86. Hammerschmidt, T. *et al.* (2013) Selective loss of noradrenaline exacerbates early cognitive dysfunction and synaptic deficits in APP/PS1 mice. *Biol. Psychiatry* 73, 454–463
87. Murchison, C.F. *et al.* (2004) A distinct role for norepinephrine in memory retrieval. *Cell* 117, 131–143
88. Brunnström, H. *et al.* (2011) Differential degeneration of the locus coeruleus in dementia subtypes. *Clin. Neuropathol.* 30, 104–110
89. Taylor, N.L. *et al.* (2020) Shaking with fear: the role of noradrenaline in modulating resting tremor. *Brain* 143, 1288–1291
90. Dirkx, M.F. *et al.* (2020) Cognitive load amplifies Parkinson's tremor through excitatory network influences onto the thalamus. *Brain* 143, 1498–1511
91. Oertel, W.H. *et al.* (2019) The locus coeruleus: another vulnerability target in Parkinson's disease. *Mov. Disord.* 34, 1423–1429
92. Taylor, N.L. *et al.* The contribution of noradrenergic activity to anxiety-induced freezing of gait. *Mov. Disord.* (in press)
93. Matchett, B.J. *et al.* (2021) The mechanistic link between selective vulnerability of the locus coeruleus and neurodegeneration in Alzheimer's disease. *Acta Neuropathol.* 141, 631–650
94. O'Callaghan, C. *et al.* (2021) Locus coeruleus integrity and the effect of atomoxetine on response inhibition in Parkinson's disease. *Brain* 144, 2513–2526
95. Levey, A.I. *et al.* (2021) A phase II study repurposing atomoxetine for neuroprotection in mild cognitive impairment. *Brain* Published online December 17, 2021. https://doi.org/10.1093/brain/awab452
96. Hampel, H. *et al.* (2018) The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain* 141, 1917–1933
97. Sonuga-Barke, E.J.S. and Castellanos, F.X. (2007) Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neurosci. Biobehav. Rev.* 31, 977–986
98. Gamo, N.J. *et al.* (2010) Methylphenidate and atomoxetine enhance prefrontal function through α2-adrenergic and dopamine D1 receptors. *J. Am. Acad. Child Adolesc. Psychiatry* 49, 1011–1023
99. Zhao, Z. *et al.* (2009) Association of changes in norepinephrine and serotonin transporter expression with the long-term behavioral effects of antidepressant drugs. *Neuropsychopharmacology* 34, 1467–1481
100. ter Huurne, N. *et al.* (2015) Methylphenidate alters selective attention by amplifying salience. *Psychopharmacology* 232, 4317–4323
101. Wainstein, G. *et al.* (2017) Pupil size tracks attentional performance in attention-deficit/hyperactivity disorder. *Sci. Rep.* 7, 8228
102. Spencer, R.C. *et al.* (2015) The cognition-enhancing effects of psychostimulants involve direct action in the prefrontal cortex. *Biol. Psychiatry* 77, 940–950
103. Hermans, E.J. *et al.* (2011) Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. *Science* 334, 1151–1153
104. Morris, L.S. *et al.* (2020) The role of the locus coeruleus in the generation of pathological anxiety. *Brain Neurosci. Adv.* 4, 1–18
105. Ross, J.A. and Van Bockstaele, E.J. (2021) The locus coeruleus- norepinephrine system in stress and arousal: unraveling historical, current, and future perspectives. *Front. Psychiatry* 11, 601519
106. Goddard, A.W. *et al.* (2010) Current perspectives of the roles of the central norepinephrine system in anxiety and depression. *Depress. Anxiety* 27, 339–350
107. McCall, J.G. *et al.* (2015) CRH engagement of the locus coeruleus noradrenergic system mediates stress-induced anxiety. *Neuron* 87, 605–620
108. Saviola, F. *et al.* (2020) Trait and state anxiety are mapped differently in the human brain. *Sci. Rep.* 10, 11112
109. Mckinnon, A.I. *et al.* (2020) Enhanced emotional response to both negative and positive images in post-traumatic stress disorder: evidence from pupillometry. *Biol. Psychol.* 154, 107922
110. Naegeli, C. *et al.* (2018) Locus coeruleus activity mediates hyperresponsiveness in posttraumatic stress disorder. *Biol. Psychiatry* 83, 254–262
111. Grueschow, M. *et al.* (2021) Real-world stress resilience is associated with the responsivity of the locus coeruleus. *Nat. Commun.* 12, 2275
112. Armstrong, C. and Kapolowicz, M.R. (2020) A preliminary investigation on the effects of atenolol for treating symptoms of anxiety. *Mil. Med.* 185, e1954–e1960
113. Rodgers, R.J. *et al.* (1997) Animal models of anxiety: an ethological perspective. *Braz. J. Med. Biol. Res.* 30, 289–304
114. Brezina, V. (2010) Beyond the wiring diagram: signalling through complex neuromodulator networks. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 365, 2363–2374
115. Szabadi, E. (2018) Functional organization of the sympathetic pathways controlling the pupil: light-inhibited and light-stimulated pathways. *Front. Neurol.* 9, 1069
116. Cazettes, F. *et al.* (2021) Phasic activation of dorsal raphe serotonergic neurons increases pupil size. *Curr. Biol.* 31, 192–197
117. España, R.A. and Berridge, C.W. (2006) Organization of noradrenergic efferents to arousal-related basal forebrain structures. *J. Comp. Neurol.* 496, 668–683
118. Jing, M. *et al.* (2020) An optimized acetylcholine sensor for monitoring in vivo cholinergic activity. *Nat. Methods* 17, 1139–1146
119. Breakspear, M. (2017) Dynamic models of large-scale brain activity. *Nat. Neurosci.* 20, 340–352
120. Li, M. *et al.* (2019) Transitions in information processing dynamics at the whole-brain network level are driven by alterations in neural gain. *PLoS Comput. Biol.* 15, e1006957