The locus coeruleus and noradrenergic modulation of cognition

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Abstract | Mood, attention and motivation co-vary with activity in the neuromodulatory systems of the brain to influence behaviour. These psychological states, mediated by neuromodulators, have a profound influence on the cognitive processes of attention, perception and, particularly, our ability to retrieve memories from the past and make new ones. Moreover, many psychiatric and neurodegenerative disorders are related to dysfunction of these neuromodulatory systems. Neurons of the brainstem nucleus locus coeruleus are the sole source of noradrenaline, a neuromodulator that has a key role in all of these forebrain activities. Elucidating the factors that control the activity of these neurons and the effect of noradrenaline in target regions is key to understanding how the brain allocates attention and apprehends the environment to select, store and retrieve information for generating adaptive behaviour.

Volume transmission
Non-synaptic chemical signalling between neurons. It involves the diffusion into the extracellular space of a compound that has the ability to affect neurons several micrometres away during several hundred milliseconds.

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doi:10.1038/nrn2573
Published online
4 February 2009

Neuromodulators are released by neurons to alter the cellular properties of target neurons and the efficacy of their synaptic transmission. The main neuromodulators in the brain include serotonin and acetylcholine, as well as the catecholamines — dopamine and noradrenaline. The cell bodies of neuromodulatory neurons are grouped in specific nuclei in the brainstem, the midbrain and the basal forebrain, and through their widespread projections they influence many brain regions and functions. Moreover, volume transmission is characteristic of neuromodulator-releasing (neuromodulatory) neurons, allowing neuromodulators a broad spatiotemporal influence on the excitability and synaptic plasticity of cells in the region of release. Dopamine neurons are grouped in the midbrain ventral tegmental area (VTA) and substantia nigra (SN), and cholinergic neurons are grouped in the basal forebrain. The brainstem raphe nuclei and the locus coeruleus (LC) cluster serotonergic neurons and noradrenergic neurons, respectively. These neuromodulators have multiple effects in target regions that depend largely on the distribution of receptor types. The differential impact of these systems on cognitive function results largely from the differential innervation of the forebrain (FIG. 1) and from the afferent control of activity in the respective nuclei (see REF. 1 for an anatomical overview). However, any attempt to delineate the relative or specific roles of these systems in behaviour and cognition must take into account the reciprocal connections among all of these nuclei, as well as their common regulation through a descending projection from the prefrontal cortex (see REF. 2 for further discussion).

Serotonergic and noradrenergic innervation have similar density and distribution, are extremely widespread and are largely overlapping[1]. Moreover, a recent review has emphasized that serotonin and noradrenaline have similar effects on sensory neurons of all modalities, particularly in altering their receptive field properties[3]. Cholinergic neurons also have widespread forebrain projections, but with less axonal co-lateralization innervating restricted cortical fields, suggesting a more limited range of influence[4]. Dopamine neurons densely innervate the striatum and the frontal cortex, and there are some dopaminergic terminals in the perirhinal cortex and the hippocampus (although only ~15% of neurons in the VTA and in the SN that project to the hippocampus are dopaminergic)[5]. The rest of the cortical innervation by dopamine, if any, is sparse according to anatomical studies[6]. It has been suggested that the small amount of dopamine that has been detected in other cortical areas by microdialysis studies is released from LC terminals[7]. This could account for major discrepancies in the literature concerning the nature of the stimuli and the cognitive contexts that elicit activation of the dopaminergic system. Electrophysiological recordings of dopaminergic neurons suggest that these cells respond only to rewards or stimuli that predict rewards[8], whereas microdialysis studies show that dopamine is released in forebrain regions after both reward and punishment[9]. As LC neurons are activated by stimuli of both valences[10],

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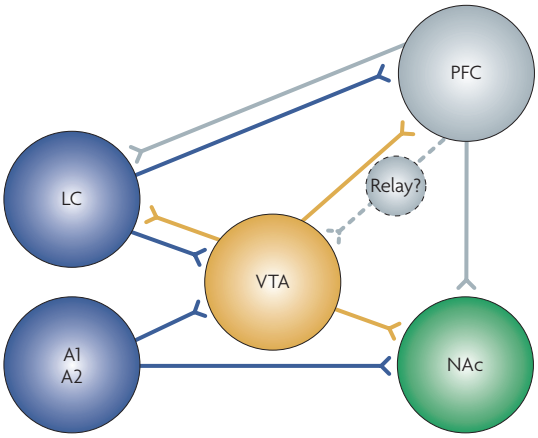

Figure 1 | **Anatomical connections that underlie interactions between the noradrenergic and dopaminergic systems.** Locus coeruleus (LC) activation elicits burst firing in the ventral tegmental area (VTA), resulting in dopamine release in the nucleus accumbens (NAc). LC activation also affects neurons in the prefrontal cortex (PFC) that project indirectly to the VTA (relay). Release of glutamate in the VTA results in increased excitability and more dopamine release in the NAc. The VTA projects to the LC[119], as does the PFC[120]. A1 and A2 are brainstem noradrenergic cell groups. Termini shown in blue release noradrenaline; termini shown in grey release glutamate; termini shown in yellow release dopamine. Figure is modified, with permission, from REF. 104 © (2007) Macmillan Publishers Ltd. All rights reserved.

the dopamine that was measured in the forebrain by microdialysis after negative stimuli might have been released from LC terminals.

The LC noradrenergic nucleus was the first neuromodulatory system to be delineated anatomically (see REF. 11 for historical background) and specified neurochemically[12]. As a result it is the most intensely investigated of these systems. The tiny nucleus LC, comprised of only 1,500 neurons in the rat, is situated deep in the pons and sends projections to most brain regions, including the brainstem, the cerebellum, the diencephalon and the paleo- and neocortex[13]. This noradrenergic projection from the LC to virtually all brain regions (with the notable exception of the basal ganglia) is the sole source of noradrenaline in the forebrain, and a single neuron can innervate diverse regions (see REF. 1 for a review). This unusual anatomical arrangement in itself sparked much of the early interest and speculation about the role of this system in cognitive processes (see REFS 14,15 for early reviews).

In the past decade there has been a shift in focus, with a proliferation of studies addressing the role of the dopaminergic system in cognitive processes. This interest was stimulated by demonstrations of the engagement of midbrain dopaminergic neurons in reporting reward in the monkey. These studies have greatly contributed to the emerging field of neuroeconomics[8,16] and have reinforced the view that drugs of abuse activate dopamine transmission and thereby cause 'abnormal motivational learning', which is the basis for craving and addictive behaviour (see BOX 1)[17]. In addition, there is mounting evidence that schizophrenia and its associated cognitive deficits are mediated by deficient dopamine action in the frontal cortex[18,19]. One of the purposes of this Review is to show that dopamine is not the only neuromodulator that mediates these functions: the noradrenergic system also has a key role. In fact, when one considers the reciprocal connections between the two systems, and the systems' mutual connections to the prefrontal cortex, it is clear that they are highly interdependent (FIG. 1). Moreover, there are striking similarities between the factors that govern the activity of dopaminergic and noradrenergic neurons, suggesting that dopamine and noradrenaline are released simultaneously. The effects of these neurotransmitters on target neurons can also be similar, so differences in the functional roles of the two systems are likely to lie in the anatomical organization of their projection regions, where there are important divergences. The two systems may, however, work in concert in the regions of common projection. Both systems strongly innervate the frontal cortical regions, where concerted activity has been suggested by several investigators[2]. Importantly, other cortical regions and

Box 1 | **The noradrenergic system in drug addiction**

The basis for craving and addictive behaviour in relation to drugs of abuse has been the subject of intensive research for half a century[17]. There was early interest in the noradrenergic system, mainly because of its role in mediating the rewarding effects of intracranial self-stimulation (see REF. 103 for a review). In the 1970s interest was diverted to the dopaminergic system because of growing evidence that antagonists of dopamine receptors but not of noradrenaline receptors blocked self-administration of most drugs of abuse. Many subsequent studies corroborated this evidence, showing a drug-related increase in the release of dopamine in the ventral striatum for virtually all drugs of abuse (see REF. 104 for a review).

Craving and addiction were thought to develop through 'abnormal motivational learning', dependent on substances acting on this dopamine reward system[17]. However, there is recent evidence that the noradrenergic system is involved in both the rewarding properties of psychostimulants and opiates and the behavioural responses to them. Genetically modified mice with no α1b-adrenergic receptors fail to show the increased locomotor activity that is typical after administration of amphetamine and cocaine and furthermore show no oral preference for cocaine[105]. This is not surprising given the reciprocal interactions between the noradrenergic and dopaminergic systems. In addition, a recent series of studies showed that although the mesolimbic dopamine system is involved in mediating reward, it is under the control of the noradrenergic projections to the prefrontal cortex[106]. The anatomical connections that underlie this control are shown in FIG. 1.

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Long-term potentiation (LTP). A form of synaptic plasticity that results in a long-lasting increase in the strength of synaptic transmission.

thalamic sensory relay nuclei do not receive input from the dopaminergic system (FIG. 2).

A large body of literature implicates noradrenaline in cellular excitability, synaptic plasticity and long-term potentiation (LTP) (for reviews see REFS 20,21). An equally large number of studies have demonstrated the role of noradrenaline in gating and tuning sensory signals in the thalamus and the cortex; this work has been comprehensively reviewed[22]. Pharmacological studies have provided evidence that noradrenaline, interacting with other neuromodulators and hormones, modulates memory formation, mainly through actions in the amygdala and the hippocampus (see REF. 23 for a review). Other pharmacological approaches have revealed a noradrenergic influence in frontal cortical regions that are engaged in attention and working memory functions (reviewed most recently in REFS 24,25). In addition, electrophysiological studies in behaving primates and rodents have shown a clear relationship between activity in LC neurons and cognitive behaviours[26–28]. What is missing, however, is the link between the well-established actions of noradrenaline on target cells and networks and its putative role in cognitive functions, proposed from recordings of LC neurons in animals performing cognitive tasks. This Review will attempt to make this link, by focusing on some key experiments and re-evaluating their results from this perspective.

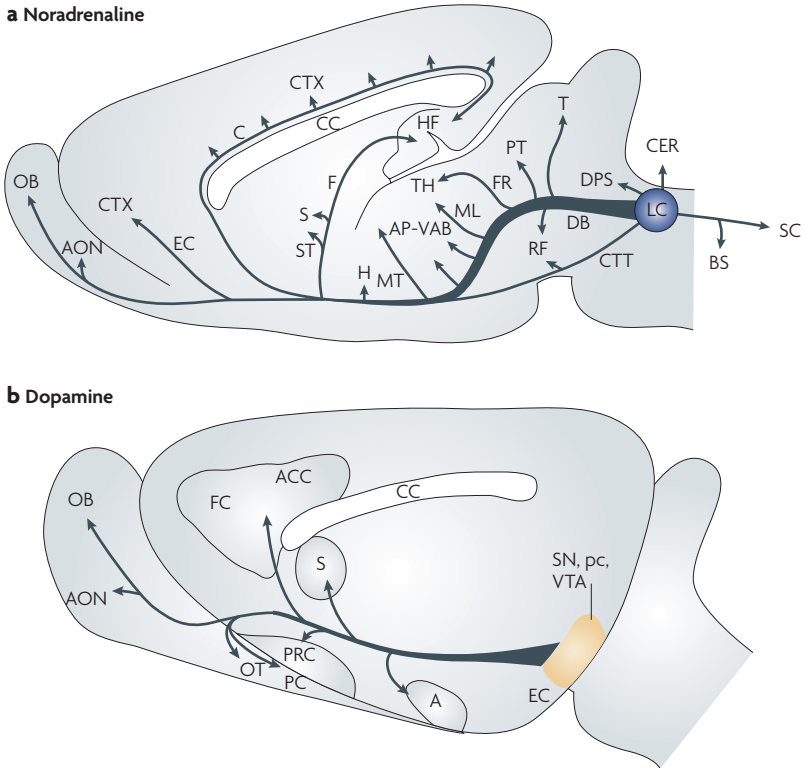

Figure 2 | **Comparative anatomy of the distribution of noradrenergic and dopaminergic projections in the rat brain. a** | Noradrenergic nuclei, including the locus coeruleus (LC), which contains ~1,500 cells that project mainly to the ipsilateral forebrain. Through extensive axonal branching, a single cell can have terminals in diverse remote brain regions, including the forebrain, the brainstem and the cerebellum. The entire cerebral cortex, including the frontal cortex and all sensory regions, receives input from the LC. The LC also sends projections to thalamic nuclei and limbic structures, including the amygdala (A), the hippocampus and the septum (S). The only major region that does not receive input from the LC is the area that contains the basal ganglia. **b** | Dopaminergic nuclei, including the ventral tegmental area (VTA), which is the main cortical input of the dopaminergic system, and the substantia nigra (SN), which projects to the striatum. Note that the cortical inputs are limited to the frontal regions — the entorhinal cortex (EC) and the piriform cortex (PC). ACC, anterior cingulate cortex; AON, anterior olfactory nucleus; AP-VAB, ansa peduncularis–ventral amygdaloid bundle system; BS, brainstem nuclei; C, cingulum; CC, corpus callosum; CER, cerebellum; CTT, central tegmental tract; CTX, cortex; DB, dorsal bundle; DPS, dorsal periventricular system; F, fornix; FC, frontal cortex; FR, fasciculus retroflexus; H, hypothalamus; HF, hippocampal formation; ML, medial lemiscus; MT, mamillothalamic tract; OB, olfactory bulb; OT, olfactory tract; pc, pars compacta; PC, piriform cortex; PRC, perirhinal cortex; PT, pretectal area; RF, reticular formation; S, septum; SC, spinal cord; ST, stria terminalis; T, tectum;TH, thalamus. Part **a** is modified, with permission, from REF. 121 © (1979) Annual Reviews, inc. Part **b** is modified, with permission, from REF. 122 © (1978) Annual Reviews, inc.

Theories of LC noradrenergic system function

The LC is part of what used to be known as the 'ascending reticular activating system' (REFS 29,30), and so it is not surprising that early theories of the function of this system focused on vigilance and sleep–wake cycles[31,32] (TIMELINE). During quiet wakefulness, LC neurons fire at a regular slow rate (~1 Hz), whereas they show bursts of firing in response to arousing stimuli and fire at a diminished rate during drowsiness and slow-wave sleep (SWS)[33]. These neurons are completely silent during rapid eye movement (REM) sleep, when the cortical electroencephalogram has a high arousal profile[31]. Although there is unequivocal evidence for this role in vigilance, the LC has been assigned a putative role in many other important functions, including attention, sensory processing, synaptic plasticity, network resetting, memory formation, memory retrieval, decision making and performance facilitation (TIMELINE). A strong theoretical framework was initially proposed by attributing a dual role to the noradrenergic activation that accompanied the aroused state. Noradrenaline was claimed to "...affect synapses throughout the CNS, suppressing most, but permitting or even accentuating activity in those that are transmitting novel or significant stimuli" (REF. 34), suggesting that noradrenaline has complex excitatory and inhibitory effects in target regions. Furthermore, as the aroused state "...favours the development of persistent facilitatory changes in all synapses that are currently in a state of excitation" (REF. 34), S. Kety predicted a role for noradrenaline in LTP, even though the discovery of LTP was only published the following year[35] and little was known about the effects of noradrenaline on cell membrane potentials, excitability and intracellular signalling pathways. These hypotheses inspired further investigations of the effects of the LC in the forebrain that, as described below, have had important implications for furthering our understanding of how the brain selects, stores and retrieves information to permit adaptive behaviour.

Electrophysiological studies in behaving primates and rodents reveal a clear relationship between neuronal activity in the LC and behaviour, inspiring much theorizing about the function of the system. Recording from LC neurons in rats performing a differential conditioning task showed that LC neurons respond to reward and punishment, and later to stimuli in any modality that are

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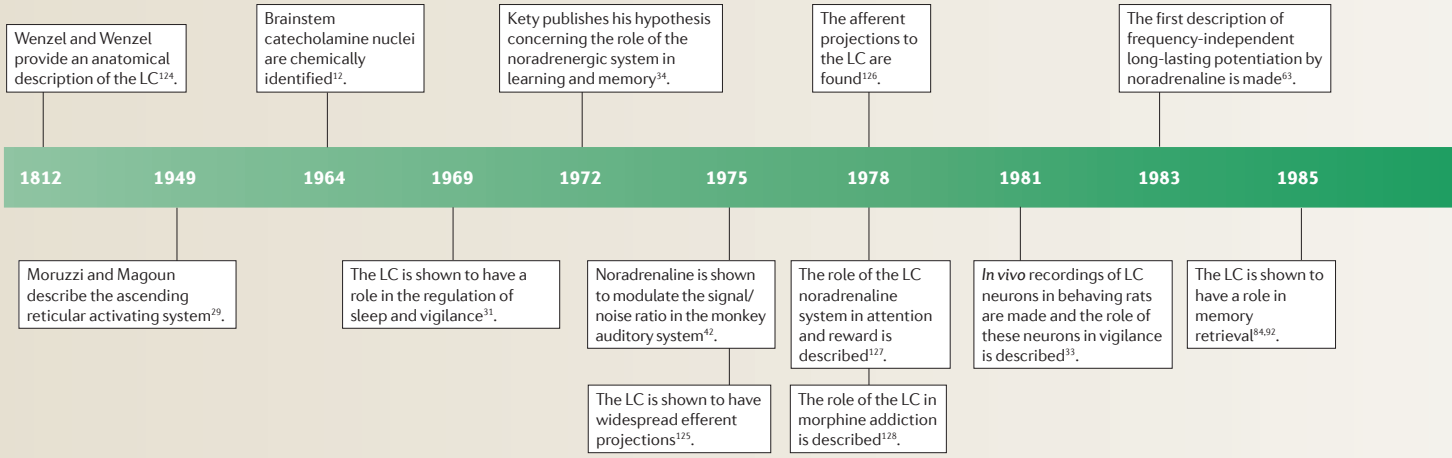
Timeline | **Milestones in research on the LC noradrenergic system**



associated with reinforcement[10,36]. LC neurons respond most vigorously to any changes in stimulus-reinforcement contingencies (for example, during extinction or reversal). In monkeys, LC neurons show similar phasic responses to stimuli that are associated with reward in a signal-detection task and rapidly shift responses during reversal[37]. Importantly, adjustment of LC responses to changes in stimulus-reinforcement contingencies precedes changes in behavioural responses in both rats and monkeys[10,36,37]. Taken together, these observations led several investigators to suggest that the LC noradrenaline system facilitates attentional and cognitive shifts and behavioural adaptation to changes in environmental imperatives[10,27,28,36,38]. In this light, Aston-Jones and Cohen suggested that the LC noradrenaline system "...facilitates behavioural responses to the outcome of task-specific decision processes" (REF. 26).

Noradrenaline effects on target neurons

Noradrenaline has multiple effects on target neurons' membrane potentials, cellular excitability, intracellular cascades and synaptic plasticity. Noradrenergic signalling occurs through three major categories of receptors, α1, α2 and β, with subtypes in each group that each elicit different cellular responses. Noradrenaline affects cellular excitability by blocking a Ca^{2+}-dependent K^+ current, resulting in a marked reduction in afterhyperpolarization. This in turn allows an increase in evoked neuronal firing. A cyclic AMP-dependent increase in GABA (γ-aminobutyric acid)-induced inhibition of cerebellar Purkinje cells has also been reported[22]. Both of these cAMP-mediated actions are β-receptor dependent (FIG. 3). Noradrenaline can enhance or block excitatory responses to glutamate, depending on its concentration, with enhancement and blockade being mediated by α1- and β-receptors, respectively[1]. This type of action of noradrenaline was referred to as early as 1979 as 'enabling', because the release of noradrenaline promoted more effective signal transmission in cells converging on the same target neurons[39].

These *in vitro* studies suggest that the effect of noradrenaline release in any brain region will be complex and will depend on the intracellular concentration of noradrenaline and the availability and affinity of receptor subtypes in the target region. This point has been elaborated in relation to the effects of noradrenaline on synaptic plasticity in the hippocampus[40], where it promotes LTP in the dentate gyrus through action at β-receptors[21], and in the prefrontal cortex, where it facilitates working memory in aged primates through α-receptors[41].

Effects of noradrenaline on sensory pathways

Neuromodulators act in concert with other afferents to change or 'modulate' the activity of target cells or networks. The modulatory effect of noradrenaline on cellular responses has been examined in awake monkeys that were presented with a series of conspecific vocalizations that elicited an evoked response in the auditory cortex[42]. If noradrenaline was applied to the auditory neuron by iontophoresis before the stimulus was presented, it induced a decrease in spontaneous activity but spared the evoked response to the auditory signal. Subsequent studies confirmed the 'enabling' effect of noradrenaline in the cerebral cortex, in association with somatosensory stimuli[43]; in the cerebellum, in conjunction with application of the inhibitory transmitter GABA[44]; and in the hippocampus, after stimulation of the afferent pathway from the cortex[45]. This work was extended to investigate the effects of noradrenaline on responses to afferent sensory input in cortical and thalamic regions in anaesthetized and awake animals. Most of these studies showed that increasing extracellular noradrenaline by stimulating the LC, or by pharmacological means, inhibited spontaneous activity while sparing the evoked response to sensory stimulation in auditory, visual and somatosensory pathways. In some cases non-responsive neurons could be shifted to a responsive mode by increasing extracellular noradrenaline, a phenomenon that has been referred to as sensory gating. This extensive early work was reviewed by Foote and Morrison[1], who concluded that

Iontophoresis
The introduction of a substance into a cell by ion transfer, using electrodes to apply an electrical potential to the membrane.

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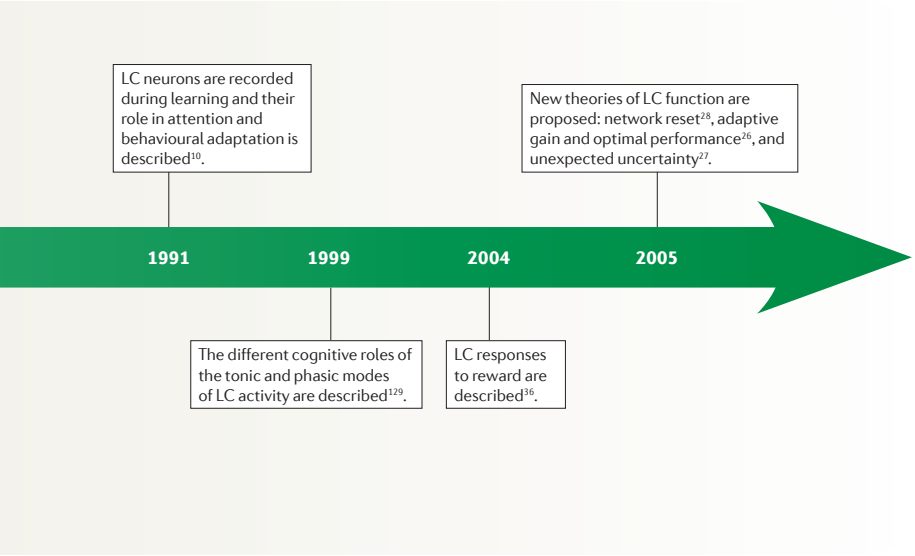

"...adequate characterization of the functional properties of the noradrenergic system requires that its impact be considered with regard to other neural systems projecting on the same target neurons." Later studies unequivocally support this conclusion (for a review see REF. 22).

In addition to the improvement of signal/background noise ratio and gating, several recent studies have shown other interesting effects of noradrenaline on sensory processing. Repeated measurement of the firing of one neuron (a single unit) in the auditory cortex found that the neuron responded preferentially to tones of specific frequencies and to a lesser degree to neighbouring frequencies. The cells are said to be tuned to their 'best frequency'. Noradrenaline sharpens this tuning by inhibiting responses to neighbouring frequencies while selectively sparing responses evoked by the best frequency[46]. This suggests that in the presence of increased arousal the auditory system is more selective or more finely tuned. Similar tuning effects in the rat visual cortex have also been reported[3].

Improvements of spike timing and rhythmicity in neuronal responses to sensory stimuli after stimulation of the LC have been reported for somatosensory and olfactory modalities. Tactile stimulation of the rat paw elicits a biphasic response in some neurons of the somatosensory cortex. Priming stimulation of the LC, 200 ms before the paw stimulation, inhibits spontaneous activity of the neuron while significantly modifying the evoked response. The latency is shorter and the trial-to-trial jitter in latency is reduced. The effect of priming stimulation on spike timing is most striking: it increases the synchronous precision of consecutive spikes in the submillisecond range[47]. Similar effects have been described in the piriform cortex, which is the primary olfactory region in the brain. A single unit can be activated by a range of odours and subsequently emit a single short phasic burst, a multiphasic response or an inhibitory response. Priming stimulation of the LC inhibits spontaneous activity of the neuron and has multiple effects on odour-evoked responses, depending on the characteristics of the initial response. In some neurons the latency and jitter are reduced and the number of spikes in the response is increased. A response can be induced in a non-responding neuron after LC stimulation, suggesting that there is a lowering of the firing threshold, an enhancement along the afferent pathway or an 'unmasking' of the response by selective inhibition of spontaneous activity. Most interestingly, for some cells spike timing is modified, with the stimulus enhancing the synchronicity of the spikes[48] (FIG. 4).

According to many investigators and computational models, precise and reliable spike timing in sensory pathways should provide a basis for stimulus encoding[49–51]. There is a large body of evidence for this across invertebrate and vertebrate species[52–54]. Thus, it follows that gating, tuning and enhancement of spike synchrony by LC activation should facilitate perceptual acuity. Nevertheless, there has been scant investigation of this prediction. Ideally, experiments would entail recording from a sensory pathway in an awake, behaving animal while the animal is engaged in a psychophysical evaluation of the perceptual modality in question, with some trials primed with electrical stimulation of the LC. To our knowledge, no such experiments have been attempted.

The effect of noradrenaline on perceptual acuity has been addressed by a few pharmacological experiments, mainly in the olfactory system, which is heavily innervated by neurons from the LC. Blockade of both α- and β-receptors in the olfactory bulb in awake, behaving adult rats impaired the animals' ability to discriminate between closely related odours, without impairing learning or memory of odour–reward association[55]. Given the need to block both types of receptors, this is likely to be accomplished by a combination of effects on local inhibitory neurons and principal cells, resulting in modification of the rhythmic firing of local ensembles that encode the odour 'object' (REF. 55). In humans, increasing noradrenaline by treating with a reuptake blocker dramatically reduced thresholds for the detection of both sour and bitter tastes[56]. These pharmacological data support the notion that the LC noradrenergic modulation of the response properties of sensory neurons enhances perceptual acuity. Nevertheless, there is no control for the actual effects of the pharmacological manipulation of the neuronal reactivity to the stimulus in the sensory pathway involved. Ideally, any pharmacologically induced changes would be correlated with the perceptual acuity demonstrated in behavioural performance. This remains to be demonstrated.

The noradrenergic system and attention

Manipulation of the noradrenergic system through pharmacology or neurotoxic lesions in rodents, monkeys and humans has provided substantial evidence for the modulatory influence of noradrenaline on cognitive functions that depend on the frontal cortex. In behavioural paradigms designed to measure attention, rats with lesions to the ascending noradrenergic projection showed marked cognitive deficits[57], particularly under conditions

Biphasic response
A neuronal response composed of an initial excitation, inhibition and then a second excitatory response.

Jitter
The trial-to-trial variability in the latency of a neuronal response to a specific stimulus.

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Perforant pathway
The bundle of fibres that contains the axons of neurons that project from the entorhinal cortex to the hippocampus.

Hole board
A piece of apparatus used in rodent behavioural studies to measure exploratory activity and an animal's preference for or response to novelty.

of high arousal or high task demand (see REFS 58,59 for reviews of earlier work). In non-human primates, optimal levels of noradrenaline in the prefrontal cortex are necessary for selective attention and working-memory tasks. Low noradrenaline function, induced by local administration of clonidine (an α_2-receptor agonist) at presynaptic sites to inhibit the release of noradrenaline, impaired performance, but higher concentrations of the same drug at postsynaptic sites facilitated performance, particularly in aged monkeys[60,61]. However, it should be noted that, unlike other cortical regions, the frontal cortex receives substantial dopaminergic input, which has been implicated in the same cognitive processes. As mentioned above, noradrenergic and dopaminergic neurons respond to similar environmental stimuli, and so noradrenaline and dopamine should be released simultaneously in the frontal cortex, where they can act together to modulate network activity. The extensive and convincing evidence that dopamine, noradrenaline and other neuromodulators act in concert to mediate cognition in the prefrontal cortex has recently been reviewed[2].

In humans, positron emission tomography (PET) studies have suggested that clonidine acts on attentional processes by modulating the connectivity between brain regions, including the LC, that are part of a functional network that mediates attention. As in the monkey studies, the effects of clonidine were largely dependent on the level of arousal. While subjects were resting with their eyes closed, clonidine reduced the effective connectivity between various brain regions, as measured by correlations in activity over time. However, if clonidine was administered while the subject was engaged in a visual attention task, the effective connectivity between frontal and parietal regions was enhanced, as was the influence of the LC on these regions[62]. The important conclusion from this imaging study is that noradrenaline affects cognitive processes, in this case attention and working memory, by facilitating the functional integration of brain regions that have been implicated in these processes, rather than by exerting local effects in a discrete brain region.

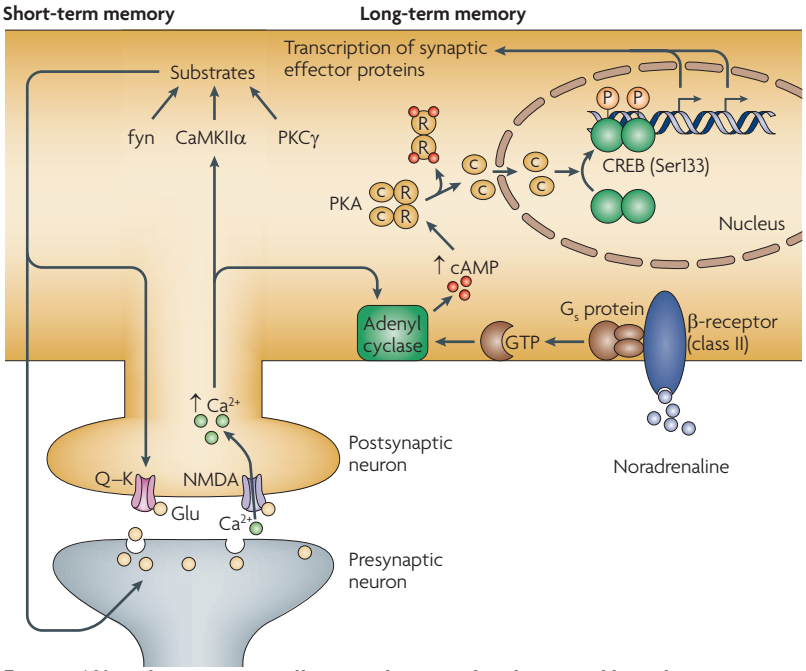

Figure 3 | **Noradrenergic signalling mechanisms for short- and long-lasting plasticity.** The intracellular cascades that are involved in short- and long-term plasticity, originally proposed for long-term potentiation. The short-term memory cascades are NMDAR (*N*-methyl-D-aspartate receptor) and Ca^{2+} dependent. Activation of the cyclic AMP cascade by adenyl cyclase leads to activation of the transcription factor cAMP-responsive element binding protein (CREB) and subsequently to gene expression. This can be achieved through the activation of a family of receptors that are coupled to G proteins, including noradrenergic β-receptors. Activation of any or all of the neuromodulatory systems will release ligands for these receptors, ultimately leading to transcription and protein synthesis, which promote long-term plasticity underlying memory formation. CaMKIIα, Calcium/calmodulin-dependent protein kinase IIα; PKA, protein kinase A; PKC, protein kinase C; Q–K, quisqualate–kainate glutamate receptor. Figure is modified, with permission, from REF. 123 © (1995) Current Biology.

LC noradrenaline system and synaptic plasticity

Harley[63] and others have provided a large body of evidence of a permissive role for noradrenaline in LTP, mediated by β-receptors, in all hippocampal subfields (for a review of early studies, see REF. 20). More recent investigations concerning the functional significance and behavioural control of the modulatory influence of the LC noradrenaline projection on synaptic plasticity in the hippocampus have yielded interesting results. Responses in the dentate gyrus to stimulation of the perforant pathway were markedly enhanced immediately after the rat encountered a novel object in a familiar hole board apparatus. This enhancement did not occur if the rat had been pretreated with the β-receptor antagonist propranolol[64]. In a later study that used a similar behavioural protocol, transient potentiation, induced by a weak tetanic stimulation of this pathway, was transformed into full LTP if the rats were allowed to explore the hole board before the weak tetanus was administered[65]. Again, pharmacological controls suggested the involvement of the noradrenergic system acting through β-receptors, as the enhancement was blocked by propranolol. Further support for the involvement of the LC noradrenaline system in this behavioural facilitation of synaptic plasticity and LTP comes from studies which showed that LC neurons fire in phasic bursts when the rat encounters a novel object in the same hole board[66,67]. This would result in an increase in extracellular noradrenaline in the hippocampus, promoting LTP.

LTP in the dentate gyrus is enhanced in thirsty rats if they receive water reinforcement after the high-frequency stimulation[68]. In a companion study, LTP could be reinforced by a footshock applied before the tetanus[68]. Presumably, the common feature of positive and negative reinforcement is arousal. The LC activation that is associated with arousal would result in the observed facilitation. Indeed, these behaviourally induced effects on synaptic plasticity were not present when the rats were pretreated with propranolol[69]. Electrophysiological studies in rats and monkeys indicate that LC neurons respond with phasic bursts to primary rewards in a conditioning situation[10,36] and to footshock[70], so it is likely that these noradrenergic neurons are activated by the presentation of the rewards and punishments in these experiments.

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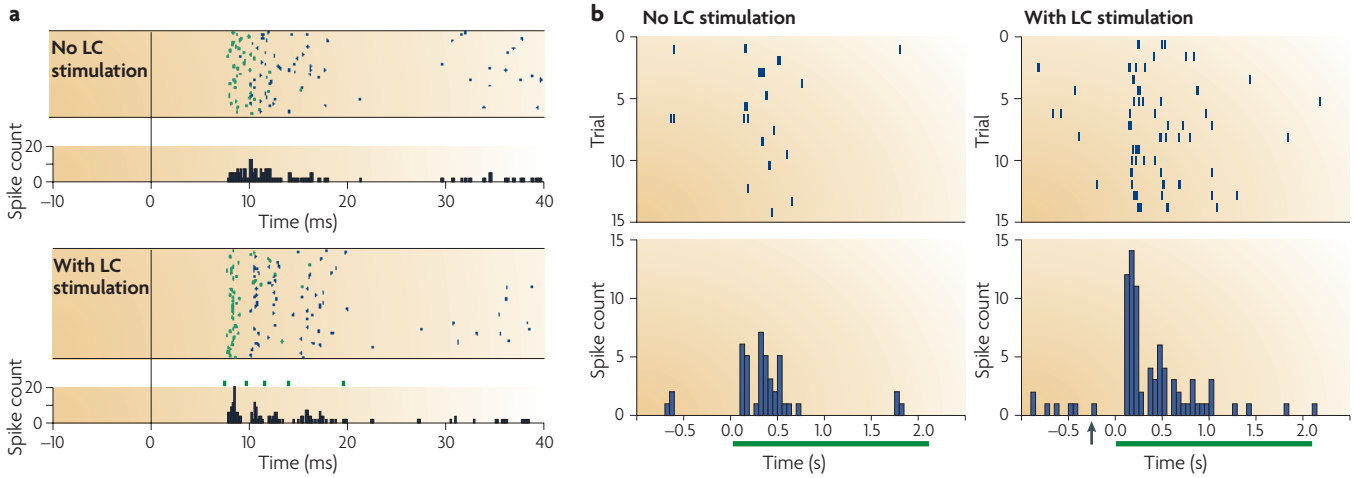

Figure 4 | **The influence of the LC on spike timing in two sensory systems. a** | The response of a single unit in the rat somatosensory cortex to a discrete tactile stimulation of the forepaw. In the raster displays, each dot represents an action potential (spike); each row shows the distribution of spikes over time before and after the tactile stimulation. The histograms show cumulative spike count in 100 μs bins. The top plots show trials without priming stimulation of the locus coeruleus (LC); the bottom plots show trials in which the LC was stimulated 200 ms before the tactile stimulation. Note the increased reliability of the response, the decreased jitter in the response latency and the improved spike timing in those trials preceded by the priming stimulation[47]. **b** | The response of a single unit in the piriform cortex to a 2-second olfactory stimulus (green line). The left-hand plots show trials without priming stimulation of the LC; the right-hand plots show trials in which the LC was stimulated 200 ms before the olfactory stimulation (arrow). Note the increased reliability of the response, the decreased jitter in the response latency and the improved spike timing in those trials preceded by the LC stimulation[48]. Part **a** is modified, with permission, from REF. 47 © (2004) Blackwell Science. Part **b** is modified, with permission, from REF. 48 © (2002) Blackwell Science.

Subsequent studies have shown, using a broad range of tasks, that enhancement of synaptic plasticity can be induced by behaviour alone[71]. A recent study that examined behavioural influences on synaptic plasticity in the CA1 region of the hippocampus showed that LTP and long-term depression (LTD) in Schaffer collaterals were differentially modulated according to the behavioural context. Induction of LTD was facilitated by exploration of an environment containing a novel arrangement of familiar objects, and LTP was facilitated by a novel context alone. Although they have opposite results (enhancement and depression), both long-term effects seem to be dependent on the noradrenergic system, as they were both blocked by β-receptor antagonists injected into the cerebral ventricles[71].

The LC noradrenaline system does not act alone, or solely in the hippocampus, in mediating the reinforcement of synaptic plasticity by behavioural factors. Noradrenaline acts in concert with other neuromodulators, especially acetylcholine, in a functional network that includes the basal lateral nucleus of the amygdala and the medial septum to reinforce LTP in the dentate gyrus[72]. Similarly, in the cortex, spike timing-dependent plasticity has been shown to be under the control of multiple neuromodulators, and it is the relative activation of neuromodulator receptors that controls the gating and polarity of cortical plasticity[73].

These investigations support the notion that behavioural arousal promotes synaptic plasticity. The fact that the effects of the behavioural manipulation are blocked by propranolol implicates the noradrenergic system, acting at β-receptors, in mediating the effects of this arousal in the brain. This is indeed a direct fulfilment of one of the Kety prophesies — that is, that arousal induced by behavioural engagement will promote "…facilitatory changes in all synapses that are currently in a state of excitation" (REF. 34). Furthermore, activation of the intracellular cAMP cascade, through β-noradrenergic receptors, facilitates LTP and long-term memory formation, proving him right again[74,75].

Long-term depression
A form of synaptic plasticity that results in a long-lasting decrease in the strength of synaptic transmission.

Noradrenaline and memory

Consolidation. Evidence for an influence of noradrenaline on memory processes (summarized in FIG. 5) comes mainly from pharmacological studies in which noradrenergic transmission is manipulated after memory acquisition — during the so-called consolidation period — and the animal is tested at a later time, when the effect of the drug has presumably dissipated. This approach has demonstrated that noradrenaline interacts with other transmitters, neuromodulators and stress hormones in the amygdala or the hippocampus to promote long-term memory formation (see REF. 76 for a comprehensive review). Pharmacological studies have also revealed a late stage of memory formation that is dependent on β-noradrenergic receptors: rats injected intracerebrally with a β-receptor antagonist 2 hours after learning showed amnesia when tested 48 hours later. If the injection was administered immediately after learning there was no effect, suggesting that there is a time window after a learning experience during which the noradrenergic system is activated to reinforce long-term memory processing[77,78]. Recent studies suggest that this late noradrenaline-dependent memory consolidation might

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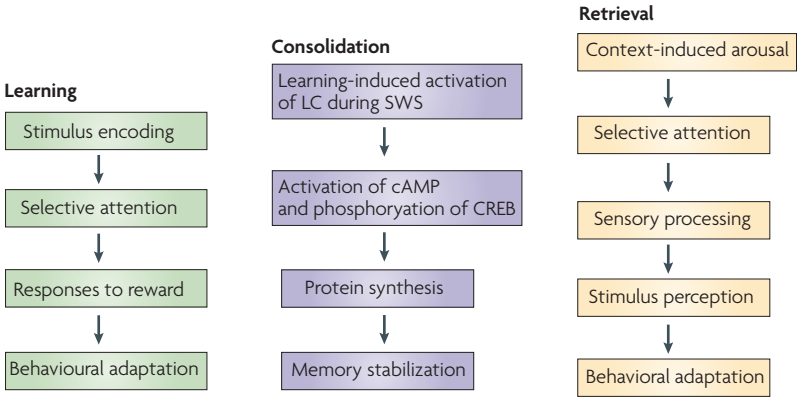

Figure 5 | **The influence of the LC on stages of memory.** Locus coeruleus (LC) neurons fire at critical periods during learning, during off-line memory consolidation and during retrieval, releasing noradrenaline in crucial forebrain regions that control attention and sensory processing (see main text for relevant references). CREB, cAMP-responsive element binding protein; SWS, slow-wave sleep.

occur during SWS. LC neurons, which are usually quiescent during sleep, show a transient increase in activity during SWS after an intensive learning experience[79].

These studies, together with the data that indicate a clear role for the LC noradrenaline system in LTP (discussed above), leave little doubt that the system is important for long-term memory consolidation, as predicted over 30 years ago[34]. There is evidence that activation of the cAMP–protein kinase A cascade is necessary for the effects of the noradrenergic system (FIG. 3), as interruption of any step leading to protein kinase A activation prevented long-term memory formation or long-lasting LTP[80]. Nevertheless, determination of the molecular and cellular processes that are activated through noradrenaline receptors alone will not lead to a full understanding of the role of the LC noradrenaline system in memory. The biological and cognitive significance of a memory, expressed as adaptive behaviour, lies in the memory's retrieval, and this requires a systems level of analysis[81].

Retrieval. "...the only proof of there being retention is that recall actually takes place" REF. 82. Indeed, memory lends itself to study and evaluation through its retrieval and behavioural expression or, in the case of humans, through its verbal report. Retrieval occurs as a result of the integration of incoming environmental information with the memory network that is triggered by that information[83] and by the context in which an experience occurred in the past. If the experience had an emotional valence attached to it, this context can be a compelling retrieval trigger[84]. Despite the intuitive appeal of a retrieval perspective on memory, there have been relatively few animal studies of the neurobiological mechanisms of retrieval. The protocol for such studies requires an animal to be prepared with a weak memory — either by a post-training intervention known to induce amnesia (such as electroconvulsive shock, hypoxia, hypothermia or administration of inhibitors of protein synthesis or other drugs) or by an extended training-to-test interval (forgetting). In most of these situations, administering treatments that increase arousal just before the retention test will alleviate the amnesia, presumably by facilitating retrieval of the residual memory. Increasing the release of noradrenaline pharmacologically[85] or by electrical stimulation of the LC[86] has been shown to be a highly effective way of facilitating retrieval in rats that have forgotten a series of left–right turns in a maze. Complementary pharmacological studies implicate the β-noradrenergic receptor in mediating this noradrenaline-induced retrieval facilitation[87]. Arousal-inducing manipulations to facilitate retrieval are not limited to pharmacological agents or electrical stimulation: a brief exposure to the experimental context can have similar effects if this context has been associated with reinforcement. This contextual cue reminder effect is likely to be mediated by a conditioned activation of the arousal systems of the brain, including the LC[84,88,89].

Support for the notion that the noradrenergic system has a specific role in the retrieval aspect of memory comes from studies of mutant mice temporarily lacking dopamine β-hydroxylase, an enzyme that is essential for the synthesis of noradrenaline. These animals were able to learn a contextual fear-conditioning task but showed a deficit in retention 48 hours after training. Evidence for a retrieval deficit was provided by restoring noradrenaline function in the mutant mice between training and retention testing by injecting a noradrenaline precursor[90]. Furthermore, in rats injection of propranolol before the contextual fear-conditioning test or spatial learning impaired retrieval 24 hours after training but not 1 hour or 1 week after training. These results suggest that the noradrenergic system is necessary for the retrieval of recent memories but not remote memories[90].

Compelling new evidence for this explicit role of the LC noradrenaline system in memory retrieval comes from a functional MRI (fMRI) study in which human subjects were presented with neutral faces in emotional or neutral contexts. Their emotional response during the encoding phase was measured by pupil size and their brain was imaged during the retrieval phase. Activation of the LC region was observed during retrieval if and only if there had been an emotional response, as indexed by pupil dilation, during the encoding phase (FIG. 6). Moreover, this same LC region was more tightly connected to the amygdala when the correctly remembered faces had been encoded in an emotional context. No other brain region that was activated by the retrieval effort showed this increased functional connectivity with either the LC or the amygdala. The authors suggest that this coordinated action of the LC and the amygdala activates forebrain fronto-hippocampal networks that are essential for memory retrieval[91]. These results confirm the previously proposed role for LC neurons in mediating the effects of contextual cue reminders on forgetting and retrieval[84,92]. Moreover, the tight connection between the degree of emotional response during encoding and the engagement of the LC during subsequent retrieval, demonstrated by these imaging studies, encourages the pursuit of recent hypotheses concerning the role of the noradrenergic system in post traumatic stress disorder (see BOX 2).

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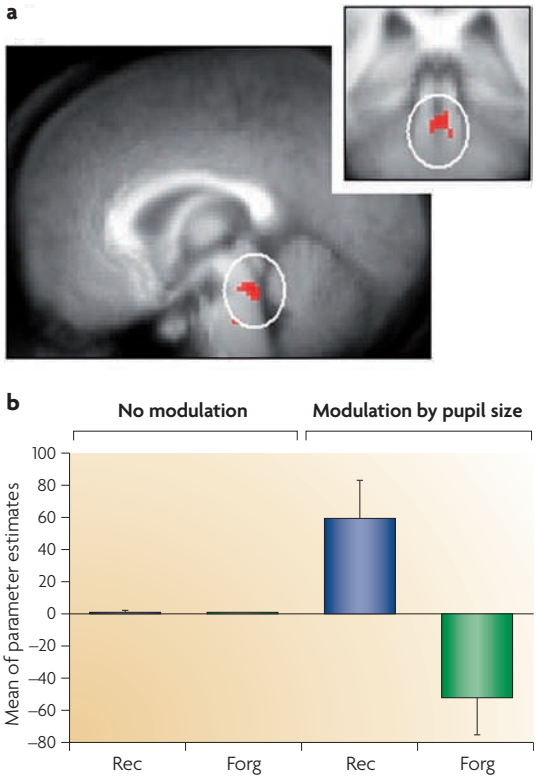

Figure 6 | **The human LC during memory retrieval.** During the encoding phase of memory formation, subjects were presented with stimuli embedded in neutral or negative emotional contexts. Emotional responses were measured during this phase as pupil dilation in response to the stimulus. **a** | Activation in the locus coeruleus (LC) displayed on the mean structural MRI image, normalized to the same stereotactic space (red). **b** | Parameter estimates of the responses in the LC to stimuli presented in a negative context versus a neutral context, modulated by the pupil size observed at encoding. The LC was the only brain region that was activated specifically by the emotional stimulus at successful retrieval if and only if the stimulus had elicited an emotional response at encoding. This demonstration of the role of the LC in memory retrieval corroborates earlier studies reporting that stimulation of the LC noradrenaline system facilitated memory retrieval in rats[85–87]. Forg, forgotten faces; rec, recognized faces. Figure is reproduced, with permission, from REF. 91 © (2006) Society for Neuroscience.

Behaviourally relevant stimuli
Signals from the environment that elicit a response from an animal, usually approach or avoidance. These can be either primary rewards or punishments, such as food or predators, or stimuli that have been associated with primary reward or punishment.

Perceptual rivalry
The spontaneous switching from one subjective percept to another in the presence of ambiguous stimuli; it occurs in all sensory modalities.

Noradrenaline and 'network reset'

A simplified overarching theory concerning the role of neuromodulatory systems in the mammalian brain that could account for the effects of the LC noradrenaline system on attention, sensory processes and memory retrieval has previously been proposed. In an analogy with the role of neuromodulators in the crustacean nervous system, it was suggested that release of neuromodulators in response to environmental imperatives serves to interrupt the activity of existing functional networks and facilitate their reorganization to promote rapid behavioural adaptation[93]. Since then, some further evidence for this view has been found in studies of attention, perception and memory retrieval.

Network reset in attention. A recent review delineates two functionally independent attention networks in the cortex: a dorsal frontoparietal network that drives attention towards stimuli based on 'internal goals or expectations' and links them to appropriate behaviour, and a ventral frontoparietal network that detects 'salient and behaviourally relevant stimuli' (REF. 94). Human fMRI studies support the view that the ventral network is driven only by environmental stimuli that have task relevance, and that output from this network to the dorsal network switches the focus of attention to those stimuli. The authors go on to speculate that "...when an important stimulus appears outside the current focus of attention, fast-latency signals from the ventral network initiate reorienting by sending a 'circuit-breaking' or 'interrupt' signal to dorsal regions, which change the locus of attention" (REF. 94). Moreover, they conclude that the functional relationship between the LC noradrenaline system and the ventral attention network suggests that LC neurons might drive activity in the latter. Reinforcing this conjecture, the salient and behaviourally relevant stimuli that seem to drive the network are the same type of stimuli that elicit phasic responses of LC neurons in behaving monkeys[95] and rats[10,36,66,96]. Recording studies in freely moving rats have indicated that LC cells fire in response to salient stimuli on the first few presentations but that the response rapidly disappears when there is no behavioural relevance, only to reappear when the stimulus is followed by reinforcement[10,96]. LC cells also fired when the exploring rat encountered unexpected novelty[96] and in an operant-discrimination task, further indicating that LC cells fire in response to stimuli that are behaviourally relevant[66].

In addition, noradrenaline has been shown to facilitate or promote adaptation to changes in the behavioural requirements of a task. When rats were required to change from a place strategy (for which they make a series of left–right turns) to a visual strategy (for which they follow vertical striped cue cards) to find a reward, they had to shift their attention from egocentric kinaesthetic or proprioceptive cues provided by the left–right turns to the allocentric visual cues located in the maze. Rats make this switch with difficulty; however, the new response repertoire was acquired much more quickly if they were injected before each daily session with a drug that increased the firing of LC neurons[38]. In another task that was designed explicitly to measure attentional shift, elevating noradrenergic activity at α1-receptors in the medial prefrontal cortex facilitated cognitive performance[97].

Network reset in perception. A recent study provided evidence for the influence of noradrenaline on a 'network reset' underlying a perceptual shift in human subjects. Psychophysical evaluation of perceptual switches induced by ambiguous stimuli was shown to be correlated with pupil dilation, and the magnitude of the dilation was associated with the duration of the subsequent perceptual stability. The phenomenon occurred in both visual and auditory perceptual rivalry protocols[98]. As there is strong pharmacological evidence that pupil

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Box 2 | **Noradrenaline, reconsolidation and post traumatic stress disorder**

Memories exist in active and inactive states[107]. The noradrenergic system is engaged during the retrieval processes that activate memories — especially memories with a strong emotional valence[91] (see main text). Active memories are then susceptible to modification or reorganization as a function of ongoing cognitive activity. Presumably this reorganization involves changes in neuronal network substrates of memory and their underlying synaptic connectivity. Here again the noradrenergic system is a key player: it initiates cellular processes that lead to the new protein synthesis that is necessary for long-term synaptic plasticity (FIG. 4). There is now extensive evidence that new protein synthesis is necessary for maintaining a memory after it has been reactivated[108,109]. This post-retrieval memory processing has been termed 'reconsolidation' (REFS 110,111).

Hypermnesic processes related to reconsolidation might underlie a severe anxiety syndrome known as post traumatic stress disorder (PTSD). This disorder can appear after an individual experiences a terrifying event and involves persistent re-enactment of the event in the form of flashbacks or nightmares. First identified and studied in war veterans, PTSD is now recognized as a widespread syndrome that affects victims of crimes and witnesses to horrific accidents or other traumatic events. Like most anxiety disorders, PTSD is highly resistant to psychotherapeutic intervention. Basal levels of noradrenaline are abnormally high in the cerebrospinal fluid of these patients, indicating dysfunction in the central noradrenergic system. Drugs such as prazosin or clonidine, which act at noradrenergic receptors, have been used to relieve symptoms in some patients[112].

We know that the re-enactment of episodes by the patient is accompanied by a massive release of noradrenaline[112], which could reinforce the memory for the event (see the section in the main text on noradrenaline and memory). Reconsolidation is highly dependent on the noradrenergic system. This has been demonstrated by injecting a β-receptor antagonist systemically[113], intracerebroventricularly[114] or *in situ* in the prelimbic region of the prefrontal cortex[115] or the amygdala[116] of the rat. The release of noradrenaline that is associated with the retrieval of the traumatic episode and the well-documented involvement of the noradrenergic system in reconsolidation processes have led to the proposal of a pharmacotherapy based on the blockade of β-receptors[113,116,117]. Propranolol administration in conjunction with psychotherapy, involving a controlled reactivation of the memory, could be an effective treatment for PTSD. Recent clinical trials using such a protocol have reported promising results[118].

dilation is controlled through α2-receptors, by the release of noradrenaline from the LC, pupil dilation should be a reliable measure of LC activity, especially under low light conditions[99]. Based on this evidence, the investigators suggest that "...noradrenaline released from the LC plays a critical role in perceptual rivalry" (REF. 99). This interpretation of these striking results remains to be confirmed by recording from the LC in such a perceptual task in primates or by fMRI studies in humans. The feasibility of such a study has been confirmed in a recent publication of the activation of the "LC region" in humans[91].

Network reset in memory retrieval. It has been argued that there is no clear demarcation between perception and memory retrieval, but rather a dynamic interaction between them. Tulving emphasized the view that "...remembering is the joint product of information stored in the past and information present in the immediate cognitive environment of the rememberer" (REF. 83). He argued that remembering is an activity similar to perceiving, in the sense that it involves the apprehension and the comprehension of contemporary stimuli in the light of past experience. This is strongly reminiscent of William James's general law of perception: "Whilst part of what we perceive comes through our senses from the object before us, another part (and it may be the larger part) always comes out of our own head" (REF. 82). This dynamic interactive view of perception emphasizes that the individual creates the perceptual experience from the physical stimulus itself and from past knowledge about all aspects of the stimulus in its context. On the other hand, the memory network that is activated by contemporary stimuli organizes and provides meaning to the present perceptual experience.

It is clear that memory retrieval requires a shift in attention in order to select stimuli in the current environment that are related to the target memory. Memory retrieval could thus be promoted by 'network resets' that would underlie rapid reorganization of the perceptual/cognitive field. Of course, the part that comes out of our own head in organizing the perceptual field is itself a result of a retrieval operation. The imaging studies discussed in the preceding sections clearly implicate the LC noradrenaline system in these operations by showing the effect of noradrenaline on the functional integration of different brain regions during attentional tasks[62] and the increased functional connectivity between the LC and the amygdala during the retrieval of emotional memories[91].

Conclusion and perspectives

Current theories attempting to assign a coherent overarching function to the LC noradrenaline system are based on studies elucidating the cognitive context that drives LC activity in rats and monkeys[10,26–28,37,66,67]. These studies have shown that LC neurons respond to the salience and biological significance of stimuli. LC neurons are particularly sensitive in behavioural contexts that require a shift in attention and behavioural adaptation. We know from the electrophysiological data that LC responses to changes in the significance of a stimulus occur before such responses take place in forebrain regions, and also precede behavioural adaptation to changes[10,36,37]. This reinforces the idea that the LC noradrenaline system plays an important part in mediating shifts in attention and in promoting optimal behavioural performance[26–28]. Noradrenaline released by task-responsive LC neurons acts simultaneously on multiple brain regions involved in these processes. Given that the projection regions of these systems are so widespread and that the effects at the cellular and synaptic levels are so diverse and complex, understanding their role in cognition will only be furthered by simultaneous recording of activity in the neuromodulatory nucleus and in multiple target regions engaged in the cognitive process of interest. This is particularly relevant if one adopts the theoretical framework outlined in this Review, emphasizing the interdependence of and interaction between attention, sensory perception and memory retrieval. Furthermore, simultaneous recording from dopaminergic neurons of the VTA and LC neurons during behavioural tasks would do much to further our understanding of the concerted or complementary action of these two systems in forebrain regions that mediate cognitive function. Multisite recording in behaving rodents and primates is becoming more feasible, with continuous improvements in technology for multichannel recording and data analysis[100].

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The imaging studies reviewed here suggest that an essential role of the LC noradrenaline system is to promote or even orchestrate dynamic interactions among networks involved in cognition[62,91]. fMRI studies cannot measure neuronal activity directly and in real time, but they have the advantage of being able to measure global activity in the whole brain while the subject is performing a cognitive task. Here also there are constant improvements in the technique's temporal and spatial resolution. It is now possible to combine electrophysiological recording of specific regions with more global fMRI[101], which should allow new insights into how different brain regions interact and are modulated by brainstem neurons during cognitive activity. The development of brain imaging for rodents is also progressing[102]; this will allow further functional anatomical studies to elucidate how brainstem neuromodulatory systems interact with each other and how they regulate (and, in turn, are regulated by) forebrain structures.

The literature concerning the anatomy and physiology of LC neurons and the effects of noradrenaline on target regions is extensive and has been subject to many reviews over the years. The effects of noradrenaline on target neurons are well established. The challenge now, as outlined in this Review, is to understand how these cellular effects of noradrenaline, released at a critical, well-defined moment, facilitate the dynamic reorganization of neuronal networks to promote cognition.

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Acknowledgements
The author thanks S. Bouret, M. Segal and J.-P. Tassin for helpful comments on the manuscript and the Centre National de la Recherche Scientifique for ongoing support. Supported also by grants from ACI Neurosciences Integratives, Fondation de France (NRJ) and Volkswagenstiftung.

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